

Protocol Title:  
**Investigation of intranasal oxytocin on  
relapse risk in cocaine-dependent patients**

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Clinic:  
**Substance Treatment And Research Services  
(STARS)**

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## Cover Sheet

Choose from the following that is applicable to your study

I am submitting a new protocol

## Division & Personnel

### Division

What Division/Department does the PI belong to?

Division on Substance Abuse, Department of Psychiatry

Within the division/department, what Center or group are you affiliated with, if any?

n/a

### Unaffiliated Personnel

List investigators, if any, who will be participating in this protocol but are not affiliated with New York State Psychiatric Institute or Columbia University. Provide: Full Name, Degrees and Affiliation.

Dr. Sarah Church, Executive Director, Division on Substance Abuse, Department of Psychiatry,  
Albert Einstein College of Medicine

## Procedures

To create the protocol summary form, first indicate if this research will include any of the following procedures

- ✓ Psychiatric Assessment
- ✓ Collection of Biological Specimens
- ✓ Medication Trial
- ✓ Use of Placebo or Sham Treatment
- ✓ Biological Challenge Procedure
- ✓ Use of Investigational Drug or Device

## Population

Indicate which of the following populations will be included in this research

- ✓ Medically and Psychiatrically Healthy Subjects
- ✓ Adults
- ✓ Adults over 50
- ✓ Substance Users

## Research Support/Funding

Will an existing internal account be used to support the project?

No

Is the project externally funded or is external funding planned?

Yes

Select the number of external sources of funding that will be applicable to this study

Funding Source #1

Is the PI of the grant/contract the same as the PI of the IRB protocol?

Yes

Select one of the following

The grant/contract application is a pending review or a funding decision

Source of Funding

Federal

Institute/Agency

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National Institute on Drug Abuse

**Grant Name**

Neuropeptide modulation of stress: a novel approach to cocaine relapse

**Grant Number**

pending+

**Select one of the following**

Multicenter (NYSPI is a participating site)

**Business Office**

RFMH

**Does the grant/contract involve a subcontract?**

No

**Study Location**

**Indicate if the research is/will be conducted at any of the following**

NYSPI

**This protocol describes research conducted by the PI at other facilities/locations**

Yes

Hospital, clinics and other healthcare facilities

**Hospitals, clinics and other healthcare facilities**

**Select from the list  
or type in location(s)..**

Next Step Program, Wellness Center at Waters Place, Division on Substance Abuse, Albert Einstein College of Medicine, 1510 Waters Place, Bronx, NY, 10451

**Lay Summary of Proposed Research**

**Lay Summary of Proposed Research**

This proposal describes a combined laboratory and clinical trial preliminary investigation to advance medication development for cocaine dependence. The main objective is to test whether intranasal oxytocin could reduce relapse risk by reducing stress sensitivity. To measure stress sensitivity, this study will evaluate a new stress challenge: a) intranasal desmopressin, a vasopressin analog, will be used as an endocrine stressor; its effects will be evaluated by serial measurements of serum Adrenocorticotropin hormone

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(ACTH), and self reports; b) if pretreatment with intranasal oxytocin dampens the ACTH and subjective response to intranasal desmopressin. These measures will be tested during a 7-day inpatient abstinence induction hospitalization. For those patients with family and work obligations, an outpatient abstinence induction procedure is available. The response to the desmopressin challenge will be compared to a cohort of matched control subjects. After abstinence induction, cocaine dependent patients enter a 6-week, double-blind, randomized, placebo-controlled trial of 24 IU of intranasal oxytocin vs. placebo, to monitor if this reduces the relapse risk.

This study is based on the findings that chronic stress, caused in these patients by cocaine dependence, increases the sensitivity of the Hypothalamo-Pituitary-Adrenal (HPA) axis and CNS stress pathways to vasopressin. For their part, oxytocin systems, in chronic stress, acquire an increasing moderating effect on CNS stress systems and the HPA axis. Cocaine dependence generates increased responsivity of stress systems to oxytocin in the face of depleted oxytocin stores; thus creating an environment where exogenous oxytocin could exert a strong regulatory effect. Intranasal administration provides a convenient to deliver these small peptides to the brain. Studying the feasibility of this approach, and its applicability to the treatment of cocaine-dependent patients, will be a goal of this study.

The main outcome of this study will be the number of consecutive days of abstinence from cocaine after abstinence induction. A secondary outcome will be whether the acute effect of intranasal oxytocin on desmopressin-induced ACTH secretion is associated with the number of days of continued abstinence.

## **Background, Significance and Rationale**

### **Background, Significance and Rationale**

Human laboratory studies have reliably shown that stress induced by psychological, endocrine, or cue-related challenges cause craving for cocaine that predicts relapse (Sinha et al., 2006; Brady et al., 2009; Back et al., 2010). The conditioning tying together stress and relapse to cocaine use hinges on new patterns of stress regulation provoked by repeated use of the drug (Koob, 2008). Cocaine-dependent patients experiencing stress report greater anxiety, restlessness, cravings

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(Bergquist et al., 2010), and secrete more ACTH and cortisol than control subjects (Sinha et al., 2006). These adaptations sustain the addiction and undermine efforts by patients to end it.

Attempts to develop medications of sufficient efficacy to treat cocaine addiction have so far failed (Taylor & Gold, 1990; Bisaga et al., 2005; Bisaga et al., 2010). Given the role of stress in perpetuating cocaine dependence, medications that corrode the conditioned link between stress and cocaine use could be prototypes for medication developments. Such a prototype may involve Vasopressin (VP) and Oxytocin (OT), neuropeptides physiologically and anatomically poised to influence the stress response. The relevance of VP and OT to cocaine addiction relates to their role in the sensitization of stress and reward brain circuits to chronic cocaine exposure.

### *1.1 Neuropeptides, Vasopressin, Oxytocin: basic concepts.*

The history of neuropeptides begins with VP and OT. Du Vigneaud and his team deduced the structure of VP and OT, and synthesized each in 1954 (du Vigneaud, 1954). These peptides are old in phylogeny (going back 500 million years), have evolved together, are found in all vertebrates, and are early joint regulators of homeostasis; which required that the effect of one could counterpoise the effect of the other (Van Kesteren et al., 1992). OT and VP are synthesized within neurons from a single precursor: then, a cascade of processes determine its biological activity through size, form, and derivation of the end product, generating peptides with different, and at times, opposite effects (de Wied et al., 1993).

VP is the hormonal regulator of water homeostasis (Arimura et al., 1967). With Angiotensin, it governs drinking behavior (Severs et al., 1977). The hormone OT regulates parturition and lactation (Higuchi et al., 1986). It also promotes sexual, reproductive, social, and nurturing behaviors (Pedersen et al., 1979), on which VP exerts mostly a temporizing effect (de Wied et al., 1993). This intricate webbing of behavioral and physiological effects is a feature of hypothalamic neuropeptides. Another feature is reflected in their effect on single neurons: VP and OT can exert lasting influences (Kombian et al., 2002) on neurons at CNS sites controlling homeostasis (Buijs et al., 1983). For example, OT or VP affect 2<sup>nd</sup> messenger systems (Manning et al., 2008), influence the effects or the release of primary neurotransmitters such as glutamate (Joels and Urban, 1982; Van den Hooff and Urban, 1990), and can generate ionic currents (Dreifuss and Raggenbass, 1992) that induce Long-Term-Potential, an inducible neuronal activity that underlie behavioral adaptations and learning (Teyler and Discenna, 1987). Many of these effects outlast the functional half-lives of OT or VP.]

### *1.2. Vasopressin, stress, cocaine dependence, and why a new stress challenge?*

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Vasopressin and OT are nonapeptides that differ from each other by only 2 amino acids. Yet, this small difference imparts VP and OT with greatly demarcated effects on the stress response involving the Hypothalamo-Pituitary-Adrenal axis (HPA). The HPA response begins with Corticotropin Releasing Factor (CRF) containing neurons in the Paraventricular Nucleus of the hypothalamus (PVN). These CRF neurons receive stimuli from afferents that signal physiological, sensory, or behavioral disturbances. Upon release of CRF, corticotrophs in the adenohypophysis secrete Adrenocorticotrophic Hormone (ACTH) that stimulates the adrenal glands to secrete glucocorticoids, which moderate the secretion of CRF and ACTH (Koob, 2008).

Compared to CRF, VP by itself exerts a weak effect on ACTH secretion. Once CRF had been characterized as the major factor regulating ACTH secretion (Vale et al., 1981), it was rapidly noted that exposure of corticotrophs to CRF and VP provoked greater ACTH release than either peptide alone, raising a possibility that CRF and VP may be co-localized in the same PVN neurons (Rivier & Vale, 1983). This was confirmed, and found to depend on the chronicity of stress. In animals, more VP RNA and VP was found in the soma of a greater proportion of CRF neurons, and VP was co-localized with CRF in neurosecretory axon terminals (de Goeij et al., 1991, 1992). Chronic stress thus induces a shift from CRF to VP-controlled HPA activation: in the PVN, CRF mRNA levels decrease and VP mRNA levels increase; in the adenohypophysis, CRF receptor density decreases while VP1b receptor density increases, a mechanism by which the HPA maintains its activity in the face of persistent glucocorticoid release and down regulation of CRF and CRF receptors (Scott & Dinan, 1998; Ducat et al., 2012). These adaptations in the PVN and anterior pituitary are found in human subjected to chronic stress (Araya et al., 2006), and have been reproduced in animal models of drug addiction. For example, VP facilitates the development of tolerance to morphine and alcohol (Colbern et al., 1986); withdrawing cocaine from rats exposed to a 14-day escalating "binge" cocaine dose caused secretion of high levels of ACTH and corticosterone that could be blocked by a V1b receptor antagonist. It also increased VP mRNA in the PVN without concurrent increase in CRF mRNA, and increased V1b receptors in the pituitary (Zhou et al., 1996, 2011). Hence, endocrine adaptations to cocaine dependence and other drugs involve VP-based mechanisms, and the evidence for this supports the plausibility of the endocrine challenge with the VP analog desmopressin proposed herein. In support of this approach, two reports present data showing that the VP analog desmopressin (DDAVP) provoked greater ACTH release in human subjects with another condition related to chronic stress: chronic major depression (Dinan et al., 2004; Araya et al., 2006).

Stress sensitivity and its dysregulation are subject to individual genetic, constitutional and environmental factors (Kreek and Laforge, 2007). These factors impact treatment. Cocaine-dependent patients at baseline, with an abnormal diurnal cortisol secretion profile (48% of the sample), could not become abstinent from cocaine during a lead-in of a clinical trial (Raby et al., 2013, accepted). Therefore, it is reasonable to think that some cocaine-dependent patients - with similar severity of cocaine use - differ in terms of stress sensitivity or dysregulation. Because of this, they may face very different odds of overcoming their addiction. A VP challenge might reveal a form of stress dysregulation related to cocaine use in humans, and provide some answer to this question: Is high stress sensitivity or dysregulation a necessary condition for a positive outcome from OT, from other treatments targeting stress; or could it be applied to anyone with cocaine dependence seeking treatment?]

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### *1.3. Oxytocin, the stress response, and its pertinence to cocaine dependence.*

The adaptations of the OT system in chronic stress occur in tandem with those of the VP system but differ. In animal models of HPA regulation, OT appears to act as a VP antagonist (Hartwig, 1989). Intracerebro-ventricular (icv) infusion of an OT antagonist disinhibits the HPA axis (Neuman et al., 2000b) and OT reduces stress hormone release during acute and recurrent stressors (Ditzen et al., 2009). The OT innervation and receptors responsible for restraining the stress and HPA response reside within the PVN, on and surrounding the CRF/VP neurons responsible for HPA activation (Dabrowska et al., 2011); and in more distant sites such as the amygdala and lateral septum that are richly endowed with glucocorticoid receptors (Fuxe et al., 1985). Glucocorticoid binding to these receptors induces up-regulation of OT receptors (Liberzon et al., 1997). The OT system is thus positioned to display increasing inhibitory effects on the stress response as a stressor becomes more chronic (Windle et al., 2004). However, the CNS pathology induced by drug addiction may break this process of homeostatic protection.

In one animal and one human study, recurrent cocaine or alcohol use was reported to deplete OT stores in the hypothalamus, hippocampus, and amygdala (Sarnyai et al., 1992; Sivukhina et al., 2006). Consequently, cocaine dependence may create a hormonal environment in which this regulatory mechanism cannot fully operate due to decreased OT stores. As this hormonal environment also favors upregulation of OT receptors (see above), it could be surmised that OT pathways would be especially sensitive to exogenous OT. If this were so, favorable conditions would exist to test if IN OT can reduce stress sensitivity and the relapse risk inherent to cocaine dependence. In support of this notion, effects of OT on addiction-related behaviors have been reported: exogenous OT in rodents retarded the development of alcohol or opiate tolerance (Colbern et al. 1986); it also decreased the hyperactivity, locomotor sensitization and stereotyped behavior caused by cocaine; and inhibited metamphetamine-induced place preference, facilitated its extinction, and inhibited its reinstatement by stress (Kovacs et al., 1990; Sarnyai & Kovacs, 1994; Qi et al., 2008, 2009).

Exogenous IN OT could also exploit another feature of OT systems of potential pertinence: the autocrine and paracrine effects of OT on OT neurons. Chronic stimulation of OT receptors by OT leads to anatomical and physiological changes in OT neurons that sustain OT release (Ludwig & Leng, 2006). Therefore, once OT systems are triggered with sufficient constancy, they display a proclivity to sustain OT secretion for extended periods of time. This would adequately serve instances of prolonged need such as lactation (Theodosios, 2002), and could prove advantageous for the treatment of a chronic, relapsing condition like cocaine dependence. While gender differences have been documented for some effects of OT; as a regulator of the CNS stress response and of the HPA axis, OT appears to play an equally important role in male and females (Neumann et al., 2000a, b). Nonetheless, we will investigate gender differences (exploratory aim b).

### *1.4 Intranasal administration, Desmopressin, Oxytocin, and Pharmacological Properties.*

The intranasal (IN) route of administering neuropeptides is a validated and approved method of drug administration in the pharmacological industry. The FDA has approved the medicinal use of

IN VP, and of its analogue desmopressin (DDAVP), and IN OT is approved in Europe (Syntocinon, 2012; Baumgartner et al., 2008). Although vascular brain areas devoid of blood-brain barrier (BBB) allow for some CNS penetration, systemic delivery of therapeutics to the CNS is not effective for 98% of small molecules (Pardridge, 2005). The IN route allows delivery of small peptides such as DDAVP and OT from the nasal mucosa to the brain via intraneural (olfactory and trigeminal nerves) and perivascular pathways (Dhuria et al., 2010), with sustained levels of VP, DDAVP, and OT being measured in the CSF hours after IN administration (Born et al., 2002; Dhuria et al., 2010; Linnen et al., 2011).

DDAVP will be the agonist used in this study because it is a longer-lasting agonist at the human V1b receptor (V1b > >V1a in the CNS; Bielsky et al., 2004), has little affinity for the peripheral V2 (renal) and V1a (vascular) receptors, and has no affinity for the OT receptor (Saito et al., 1997). When given IV, at recognized doses (80 IU) DDAVP does not cross the BBB, but has good CNS penetration by the IN route (Stegner et al., 1983; Manning et al., 2008). IN OT is not euphorogenic and is not reported to be distinguished from placebo in control subjects at doses proposed in this study (20 IU; Macdonald et al., 2011). Presently, there are no synthetic OT receptor agonists or V1b receptor antagonists available for human use (Manning et al., 2012). Should these become available, these would be attractive prototypes for medication development.

References for this section can be found in the uploaded grant application.

## Specific Aims and Hypotheses

### Specific Aims and 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.

## Description of Subject Population

### Sample #1

#### Specify subject population

cocaine-dependent sample

#### Number of completers required to accomplish study aims

50

#### Projected number of subjects who will be enrolled to obtain required number of completers

75

#### Age range of subject population

18-60

### Sample #2

#### Specify subject population

control sample

#### Number of completers required to accomplish study aims

50

#### Projected number of subjects who will be enrolled to obtain required number of completers

75

#### Age range of subject population

18-60

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### **Gender and Ethnic Breakdown**

Based on our previous studies at the Substance Treatment and Research Service, it is expected that 50% of participants entering this trial will be African-American, 25% Hispanic-American, 20% Caucasian, and less than 5% Asian. Similar race/ethnicity statistics are found at the Division on Substance at the Albert Einstein College of Medicine. We expect gender percentages of 55% for men, and 45% for women. To establish our comparator control group, we will keep a table of demographic characteristics of cocaine-dependent samples.

### **Description of subject population**

Cocaine-Dependent sample: Men and women, aged 18 to 60, who meet DSM-IV criteria for current cocaine dependence, and who is seeking treatment. Cocaine-dependence has to be verified by at least one cocaine positive urine toxicology. The patients must use at least 4 days within a month, with at least weekly use. Binge patterned use can be considered if they occur at least 2x/month, and involved the use of at least \$200. The patients should read, speak and write english sufficiently to adequately consent to participate, and be able to adequately perform study procedures. They must be able to pass the scent test, a test that determines if their sense of smell is intact.

Control sample: Men and women, aged 18 to 60, without presents drug dependence. The patient should read, speak, and write english sufficiently to adequately consent, and be able to perform study procedures. They must be able to pass the scent test, a test that determines if their sense of smell is intact.

### **Recruitment Procedures**

#### **Describe settings where recruitment will occur**

Cocaine-dependent patients: Most of the recruitment through the STARS clinic occurs through the media. For patients at the Division on Substance Abuse (DOSA) at Albert Einstein College of Medicine, they may participate if they are patients already attending treatment at the Next Step program, or respond to advertisement and present themselves to participate in the study at Waters Place location (affiliated with Albert Einstein College of Medicine). The Next Steps Program is the outpatient substance abuse treatment program affiliated with the Division on Substance Abuse at the Albert Einstein College of Medicine.

#### **How and by whom will subjects be approached and/or recruited?**

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As they are no clinical service at the STARS clinic, all patients that may be eligible to participate in this study will present to STARS in response to media advertising.

For potential patients contacting the STARS clinic or the Division on Substance Abuse at the Albert Einstein College of Medicine (DOSA), a standardized telephone interview is conducted at the first call. Prospective participants who do not present with immediate exclusion criteria are scheduled for a first screening visit. **We have a request for a Waiver of Documentation of Consent for the phone screen under reference 45 CFR 46.117 (c), (1) (2).**

For patients already enrolled in the Next Step program at DOSA, screening may be arranged for patients deemed eligible by their counsellors, or after the patient has voluntarily initiated contact with the investigators. The screening process consists of a psychiatric diagnostic evaluation and a medical evaluation of the candidate to rule out any condition that may make participation in this study hazardous.

The consent procedure for the baseline evaluation differs between the two sites. For patients enrolled through the STARS clinic, they must first read and agree to the general screening consent (NYPI IRB# 4436R) describing the evaluation process in detail. For patients enrolling through DOSA, the screening process is included in the consent form for the study (Einstein IRB# 2014-3568).

The screening process begins with completion of the following forms: locator form; demographic form, drug history questionnaire, concomitant medication form. The locator form indicates the patient's name, address, phone number, as well as names, addresses and phone numbers of family members and close friends, along with a permission to contact them. The demographic form records information about education, marital status, employment, income, social support, housing, gender and racial category. The drug history questionnaire reviews lifetime use of drugs by category, as well as any previous treatment attended.

The psychiatric diagnostic evaluation follows, conducted by a member of the research staff (LCSW, CASAC, MD, PhD) trained in the administration of the Mini International Neuropsychiatric Interview (MINI; Lecrubier et al., 1997), a treatment/drug use history, and a Hamilton Depression Scale – 25 (Williams, 1988).

The psychiatric evaluation is conducted by a research psychiatrist (MD). It includes a psychiatric and medical review of systems, a mental status examination, a review of inclusion/exclusion criteria, and of the diagnostic evaluation. A consensus diagnosis is reached, which must include cocaine dependence, and not include any exclusion diagnoses.

The MD then conducts the medical evaluation, including: medical history, review of systems, physical examination including vital signs, olfactoscopic examination of the nasal cavity, screening blood test (chem-20, CBC, urinalysis, urine toxicology, urine pregnancy test for women patients), and an electrocardiogram. The Scent test is conducted at this point.

When completed, and the laboratory reports received, the assembled information is reviewed by the principal investigator or a research MD familiar with the study protocol. This information is reviewed against the inclusion/exclusion criteria of the study to determine eligibility to participate. For control participants, the screening process is the same as described for cocaine-dependent patients. For potential control participants entering through the STARS clinic, they will sign the

screening consent form (IRB# 4436R). Those entering through DOSA, they will sign the study consent form for control participants (Einstein IRB# pending)

**How will the study be advertised/publicized?**

This study will be advertised through print media such as the village voice, Metro AM, AM NY. Once prospective patients or control participants call, they will be offered to screen either at DOSA, or at STARS. AT DOSA, Albert Einstein College of Medicine IRB-approved flyers will be posted in the clinic.

**Do you have ads/recruitment material requiring review at this time?**

Yes

**Does this study involve a clinical trial?**

Yes

**YOU MUST REGISTER AT [ClinicalTrials.gov](http://ClinicalTrials.gov) IMMEDIATELY UPON RECEIPT OF IRB APPROVAL AND PRIOR TO ENROLLMENT OF THE FIRST SUBJECT. YOU WILL BE PROVIDED WITH A NCT REGISTRATION NUMBER ON REGISTRATION. PLEASE REVISE THIS SECTION OF THE PROTOCOL SUMMARY FORM TO INCLUDE THE NCT NUMBER AND RE-SUBMIT AS AN AMENDMENT TO THE IRB.**

**Concurrent Research Studies**

**Will subjects in this study participate in or be recruited from other studies?**

No

**Inclusion/Exclusion Criteria**

**Name the subject group/sub sample**

cocaine-dependent sample

**Create or insert table to describe the inclusion criteria and methods to ascertain them**

INCLUSION CRITERION	METHOD OF ASCERTAINMENT
1.Age 18 to 60.	MINI interview, self-report, ID confirmation
2. Meets DSM IV criteria for current cocaine	MINI Interview, self

dependence and is seeking treatment.	report
3. Displays at least one cocaine-positive urine toxicology during screening.	Urine Toxicology
4. Use of cocaine at least 4 days in the past month, with at least weekly use, or reports episodic binges of large amounts of cocaine (at least \$200) at least 2x/month.	Self report
5. Able to give informed consent and comply with study procedures.	MINI, Self-report, MSE
6. Can pass the blindfolded scent test recognizing the scent of cinnamon or coffee.	Scent test

**Create or insert table to describe the exclusion criteria and methods to ascertain them**

EXCLUSION CRITERIA	METHOD OF ASCERTAINMENT
1. Meets DSM IV criteria for bipolar disorder, schizophrenia or any psychotic disorder other than transient psychosis due to drug abuse. Substance Induced Mood Disorder with Hamilton Depression Scale score $\geq 15$ will be excluded. Patients with Major Depressive Disorder will be eligible to participate, provided they are in remission (Hamilton Depression Scale-25 Score < 8), whether receiving treatment or not.	MINI interview, self-report
2. History of allergic, dermatological, or adverse event related to oxytocin or desmopressin. Patient using oxytocin or vasopressin-based products cannot participate.	Self report
3. Chronic organic mental disorder, insufficient proficiency in English, or any condition or status (illiteracy) that would render an individual incapable of giving informed consent.	Psychiatric evaluation
4. Significant current suicidal risks, suicide attempt within the past year.	Psychiatric evaluation
5. Unstable physical disorders, which might make participation hazardous: hypertension (>140/90), hepatitis (patients with chronic	Medical evaluation

mildly elevated transaminase levels (2-3 X upper limit of normal will be considered acceptable if PT/PTT is normal), serum sodium (Na) < 133 mEq/L, renal failure (creat >2; BUN > 40. History of hyponatremia. Patients on medication (\*) (see partial list below) that may induce hyponatremia will not be excluded, provided no evidence of hyponatremia is found at screening.

6. Coronary vascular disease as indicated by history, or suspected by abnormal ECG. Electrocardiogram, medical history

7. Currently meets DSM-IV criteria for another substance dependence or abuse disorder other than nicotine, or alcohol. If alcohol dependent, must not be in need of detoxification. MINI, medical eval, utox

8. Participants who cannot comply with study procedures during the inpatient or outpatient abstinence induction (phase 1) will not proceed to phase 2. Study performance

9. Pregnancy, positive urine pregnancy test, or breastfeeding. Women who wish to participate must agree to use a method of contraception during the study and sign a written commitment to that effect, and submit to a urine pregnancy test every two weeks of phase 2 History, medical monitoring.

10. History of transphenoidal surgery or sinus surgery in the past month. Simple nasal congestion is not exclusionary. History, medical screening.

## Inclusion/Exclusion Criteria #2

### Name the subject group/sub sample

control sample

Create or insert table to describe the inclusion criteria and methods to ascertain them

#### INCLUSION CRITERIA

1. Age 18 to 60

#### METHOD OF ASCERTAINMENT

MINI interview,

- |   |                                     |
|---|-------------------------------------|
|   | self-report, ID confirmation        |
| 2. Able to give informed consent and comply with study procedures                   | Self-report, Psychiatric Evaluation |
| 3. Can pass the blindfolded scent test recognizing the scent of cinnamon or coffee. | Scent test                          |

**Create or insert table to describe the exclusion criteria and methods to ascertain them**

EXCLUSION CRITERIA	METHOD OF ASCERTAINMENT
1. DSM-IV Axis 1 psychiatric diagnosis. Patients with Major Depressive Disorder will be eligible to participate, provided they are in remission (Hamilton Depression Scale Score < 8), whether receiving treatment or not.	MINI interview, self-report
2. Unstable physical disorders, which might make participation hazardous. Serum sodium (Na) < 133 mEq/L, renal failure (creat > 2, BUN > 40) is exclusionary. Patients on medications* (see partial list below) that may cause hyponatremia will not be excluded provided there is no evidence of hyponatremia at screening.	medical and physical examination
3. Diagnosis of Substance Abuse or Dependence disorder, with exception of nicotine dependence. Patients in remission may participate if its duration is greater than 2 years preceding participation.	Self-report, treatment history.
4. History of allergic, dermatological, or adverse event related to oxytocin or desmopressin. Patient using oxytocin or vasopressin-based products cannot participate.	Self-report, medical history.
5. Chronic organic mental disorder, insufficient proficiency in English that would render an individual incapable of giving informed consent.	Psychiatric evaluation
6. History of transphenoidal surgery, sinus surgery in the past month. Simple nasal congestion is not exclusionary.	History, medical screening.

## Waiver of Consent/Authorization

Indicate if you are requesting any of the following consent waivers

**Waiver of consent for use of records that include protected health information (a HIPAA waiver of Authorization)**

No

**Waiver or alteration of consent**

No

**Waiver of documentation of consent**

Yes

**Waiver of parental consent**

No

## Consent Procedures

**Is eligibility screening for this study conducted under a different IRB protocol?**

Yes

**Indicate NYSPI IRB #**

NYSPI IRB# 4436R

**Describe Study Consent Procedures**

1. Baseline Evaluation For potential patients contacting the STARS clinic or the Division on Substance Abuse at the Albert Einstein College of Medicine (DOSA), a standardized telephone interview is conducted at the first call. Prospective participants who do not present with immediate exclusion criteria are scheduled for a first screening visit. For patients already enrolled in the Next Step program at DOSA, screening may be arranged for patients deemed eligible by their counsellors, or after the patient has voluntarily initiated contact with the investigators. The screening process consists of a psychiatric diagnostic evaluation and a medical evaluation of the candidate to rule out any condition that may make participation in this study hazardous. The consent procedure for the baseline evaluation differs between the two sites. For patients enrolled through the STARS clinic, they must first read and agree to the general screening consent (NYPI

IRB# 4436R) describing the evaluation process in detail. For patients enrolling through DOSA, the screening process is included in the consent form for the study (Einstein IRB# 2014-3568). The screening process begins with completion of the following forms: locator form; demographic form, drug history questionnaire, concomitant medication form. The locator form indicates the patient's name, address, phone number, as well as names, addresses and phone numbers of family members and close friends, along with a permission to contact them. The demographic form records information about education, marital status, employment, income, social support, housing, gender and racial category. The drug history questionnaire reviews lifetime use of drugs by category, as well as any previous treatment attended. The psychiatric diagnostic evaluation follows, conducted by a member of the research staff (LCSW, CASAC, MD, PhD) trained in the administration of the Mini International Neuropsychiatric Interview (MINI; Lecrubier et al., 1997), a treatment/drug use history, and a Hamilton Depression Scale – 25 (Williams, 1988). The evaluation is conducted by a research psychiatrist (MD). It includes a psychiatric and medical review of systems, a mental status examination, a review of inclusion/exclusion criteria, and of the diagnostic evaluation. A consensus diagnosis is reached, which must include cocaine dependence, and not include any exclusion diagnoses. The MD then conducts the medical evaluation, including: medical history, review of systems, physical examination including vital signs, olfactoscopic examination of the nasal cavity, screening blood test (chem-20, CBC, urinalysis, urine toxicology, urine pregnancy test for women patients), and an electrocardiogram. The Scent test is conducted at this point. When completed, and the laboratory reports received, the assembled information is reviewed by the principal investigator or a research MD familiar with the study protocol. This information is reviewed against the inclusion/exclusion criteria of the study to determine eligibility to participate. For control participants, the screening process is the same as described for cocaine-dependent patients. For potential control participants entering through the STARS clinic, they will sign the screening consent form (IRB# 4436R). Those entering through DOSA, they will sign the study consent form for control participants (Einstein IRB# 2014-3568) 2. Informed Consent For patients from DOSA, they signed the consent form for the study at the time of screening. If the patient is found eligible to participate in the research study, they will be informed of this, and arrangements will be made with them (and with their counselor if applicable) to begin. For patients from the STARS clinic not meeting any exclusion criteria, we inform the patient about their eligibility to participate. If the patient agrees to participate, a consent appointment is set. The consent form for the study is presented to the patient to read. After reading, the patient answers a consent quiz to verify their understanding of the study they are about to begin. For control participants entering through DOSA, they will have signed the consent form written for control participants at the time of screening. For control participants entering through the STARS clinic, they will sign the consent form for control participants.

**Indicate which of the following are employed as a part of screening or main study consent procedures**

✓ Consent Form

**Waiver of Documentation of Consent**

**Would the consent form signature be the only link between the subject's identity and the**

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**research data?**

Yes

**Is breach of confidentiality the main study risk?**

No

**Persons designated to discuss and document consent**

**Select the names of persons designated to obtain consent/assent**

Levin, Frances, MD

Nunes, Edward, MD

Raby, Wilfrid, MD

**Type in the name(s) not found in the above list**

**Study Procedures**

**Describe the procedures required for this study**

**Design Overview:**

This is a 2 phases, 7-weeks, prospective, double-blind, placebo-controlled, randomized clinical trial of comparing intranasal oxytocin to placebo in cocaine-dependent patients. The principal aim of the study is to examine if intranasal oxytocin can reduce the relapse risk. Cocaine-dependent and control patients will be recruited through IRB-approved advertising in public media, and from the STARS clinic of the Division on Substance Abuse at the New York State Psychiatric Institute, and the Division on Substance Abuse at the Albert Einstein College of Medicine. Prior to the 6-week outpatient phase, cocaine-dependent patients will be required to become abstinent. To achieve this, patients will opt for either an inpatient or an outpatient approach. During the inpatient approach, patients will be hospitalized at the New York State Psychiatric Institute (5-South) for 7 days to establish abstinence, participate in the stress challenge over 2 separate days which evaluates baseline stress sensitivity, investigate if oxytocin can exert an acute effect on stress parameters, and begin on randomized medication (IN oxytocin 24 IU/day vs. IN placebo). There will not be a placebo lead-in.

Table 1 presents an overview of phase 1 for cocaine-dependent and control patients.

see up-loaded table 1.

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Because of professional, personal, or financial reasons, some patients may choose *the outpatient abstinence-induction procedure*. During this week, patients will need to attend the clinic on three consecutive days and provide a negative urine toxicology for cocaine at each visit. Following this, they must complete all the study procedures prescribed in the in-patient Phase 1 procedure: essentially the stress challenges as described in section 4A3 below. If a patient cannot remain abstinent during this week, the patient will be offered another attempt to become abstinent during following week and complete the phase 1 procedures. If a patient cannot achieve abstinence during either week, then the inpatient phase will be mandatory for continued participation. If the patient cannot do this, we will offer referrals for treatment in another setting.

Control patients will participate only in phase 1. They will not be hospitalized, but the structure of the testing will be such as to reproduce the conditions under which the cocaine-dependent patients will be tested. When the two consecutive days of testing are completed, their participation ends. These will be matched for age and gender.

Phase 2 follows to study the effects of intranasal oxytocin on relapse risk to cocaine use after abstinence is induced. This phase of the study will be carried out identically at the STARS clinic, or at the Division on Substance Abuse at Albert Einstein College of Medicine. During this phase, patients must attend the clinic three times a week. At these visits, the randomized medication will be taken under supervision of research staff, from a bottle kept at the research site. On the days when the patient is not at the research site, the medication is taken as instructed from an at-home bottle. Compliance with at-home administration will be monitored by a single-blind weighing of the at-home bottle at each visit. At each visit, vital signs, adverse events, urine toxicology, and drug use are reviewed. At one visit, the patient will meet with a counselor for compliance enhancement therapy. At another visit, the patient will meet with a research MD for ratings, monitor progress, and review side-effects.

**Phase 3 involves the repeat to the DDAVP stress challenge and a repeat salivary cortisol collection.**

Table 2 schematizes the structure of the whole protocol.

see uploaded Table 2

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Week 1, phase 1: In-hospital phase, cocaine-dependent patients.

The purpose of the in-hospital phase is to allow abstinence to begin, and provide an environment amenable to stress sensitivity testing. Patients from either sites can be admitted to the General Research Unit on PI-5 for this phase, during which the following procedures will take place:

1) Establish controlled abstinence.

2) Complete baseline assessments, including Time Line Follow-Back (Litten & Allan, 1992) to quantify drug use, Cocaine Craving Scale (Weiss et al., 1997), Clinician Global Impression-Observer (Guy, 1976), Perceived Stress Scale (Cohen et al., 1983), Hamilton Depression Scale-25 items (Williams, 1988).

3) Upon the 1<sup>st</sup> negative urine toxicology for cocaine, we will collect baseline salivary cortisol samples at these approximate times: 8-9am, 11-12pm, 2-3pm, 5-6pm.

4) Stress Challenges. These consist of two tests performed on separate days in counterbalanced order, as illustrated below. The test itself will be performed in the Biological Studies Unit. Patients will have breakfast in the morning prior to testing.

**see uploaded Figure 1**

Each testing period will begin with the insertion of a saline lock. Following the saline lock insertion, there will be a 2-hour habituation interval before any testing begins. The testing will begin around noon to 1 pm, when the diurnal secretion of ACTH usually falls to allow easier detection of ACTH variation due to the experimental variations.

After habituation, baseline levels of ACTH, **BP, HR, subjective ratings of anxiety, restlessness, cravings for cocaine (Likert scales) are obtained. Research staff complete a behavioral activation scale during the endocrine challenge at those same specific time points (R. Sinha, personal communications). The patient is then asked to insufflate 40 IU (10 ug or 0.1cc) of desmopressin in each nostril.** At each of the specified time points in figure 1, repeat measurements of ACTH, BP, HR, subjective ratings, and **staff observer ratings are also obtained.** A relaxation procedure (specific muscle group tension and relaxation) used in protocol NYSPI IRB 6013, will also be used to close the day of testing. **At the next day of testing, the procedure begins by placement of a saline lock and habituation for two hours. Baseline levels of ACTH, BP, HR, subjective ratings and staff observer ratings are drawn. Then the patient is asked to insufflate 12 IU (16 ug or 0.3cc) of oxytocin in each nostril. Repeat measurements are obtained as during baseline occur at specified time points. Forty minutes later, patients insufflate 40 IU of desmopressin in each nostril, and all**

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**measurements are repeated at specified time points.**

5) After baseline stress testing is completed, begin randomized administration of intranasal Oxytocin 20 IU per day in the morning, for each remaining day of phase 1. This will serve also as an opportunity to train patients on how to administer intranasal solutions. The steps are as follows: 1) exhale through the nose, head bent forward; 2) while inhaling, spray once into one nostril; 3) repeat step 1 & 2 for the other nostril; 4) repeat steps 1 to 3 again to reach the daily dose of 24 IU of randomized medication. The patients will be instructed by a member of the research staff to ensure proper technique and optimal absorption of the medication. The Oxytocin solution is stable at room temperature for one month after being opened. Nonetheless, the manufacturer recommends that the bottle be kept refrigerated between uses and we will recommend this to the patients as well. Its stability should ensure that transportation to the clinic should not cause degradation, provided it is not exposed to extreme heat (> 100 Fahrenheit), direct sunlight, or frozen.

Phase 1, control participants.

The purpose of Phase 1 for control participants without psychiatric, medical, or addiction disorders is to test their stress sensitivity with the same procedure as cocaine-dependent patients. This is to study if stress dysregulation is more prevalent among cocaine users than normal controls, and to study if vasopressin-based stress mechanisms bear some specificity to the stress dysregulation observed in cocaine-dependent patients.

For control participants, the procedure will be carried out over two days as outpatients. They will be instructed to present themselves between 9 to 10 am on a testing morning, having eaten breakfast. A saline lock will be inserted, and a 2-hour habituation period will follow before testing begins at approximately 1 pm. The procedure will be the same as described for cocaine-dependent patients, and will be administered in counterbalanced order (**see above, stress procedures**). Completion of phase 1 ends their participation in this study.

Phase 1, week 1, cocaine-dependent patients, outpatient version.

This procedure is based on our previous experience acquired during protocol NYSPI IRB 6013 (mifepristone study for cocaine dependence) with patients who cannot participate in the inpatient procedure. Over a period of 7 days, not counting Saturdays and Sundays, a participant will have to produce at least three consecutive cocaine negative urine toxicologies at daily visits. Once abstinence is established the phase 1 procedures begin (Table 1), with verification of negative toxicology before each testing day. Randomized medication will begin after completion of all the physiological tests.

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If a urine toxicology test emerges positive for cocaine once Phase-1 procedures have begun, the testing will stop. The patient can then attempt another period of seven days to reach abstinence, complete the baseline testing, and begin randomized medication. If abstinence cannot be reached during this two-week window, the patient will be offered to carry out phase 1 as an inpatient. If the patient cannot participate as an inpatient, referrals to other treatment options will be offered.

Phase 2, outpatient phase, week 2 to 7, cocaine-dependent patients only

During this phase in which only cocaine-dependent patients participate, they will continue randomized medication while participating in a structured program to support and promote continuing abstinence and completion of the study.

For patients continuing at the STARS clinic and DOSA at Waters Place (150 Waters Place, Bronx, NY, 10461), the structure of the program during this phase will be as follows:

- 1: Patients continue to receive intranasal Oxytocin (24IU/day) vs. intranasal placebo. During their visits to either clinic, they will administer the randomized medication under supervision from a bottle kept at the clinic. Each witnessed administration will be recorded. Since they "self-administer" the medication, it can be witnessed by any member of the research team.
- 2: On the days when patients do not attend the clinic, they will be asked to administer the randomized medication from an "at-home" bottle. They will be asked to bring the bottle at each visit to the clinic. In a single-blind fashion, it will be weighed as a measure of compliance. The metered bottle delivers 4 IU/0.1cc or per puff. Each daily dosing requires 6 puffs, or 0.6cc. The weight of each puff or 0.1 cc is approximately 0.1g. Hence, for each at-home insufflation, the bottle weight is expected to change by 600 mg. The expected change in weight will be plotted against the recorded change in weight, and this will be used to estimate at-home compliance.
- 3: At each visit, vital signs are recorded, and an inquiry is made about adverse events. The Time-Line-Follow-Back is completed to review drug use by calendar date. This allows a day-to-day review of reported drug use for each day of participation.
- 4: At week 2, 4, and 6, a thorough medical review will be carried out to ensure patient safety. This will include a review of systems, with a focus on lethargy, fatigue, nausea, and weakness, which are the usual symptoms of hyponatremia. Although the risk is remote, hyponatremia would be the major metabolic complication that could arise from intranasal oxytocin. Of note is the fact that it has been reported when oxytocin is used in the induction of labor with continuous intravenous infusion (Pitocin, PDR, 2014), a condition vastly different from those of this study. A blood draw will be done to monitor electrolytes and

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blood counts. For women, a urine pregnancy test will also be done. Detection of pregnancy ends participation in the study.

5: Self-reports that will be completed weekly at one of the visits: Perceived Stress Scale, Cocaine Craving Scale.

6: The vital sign form, the review of system form (including blood results) will be dated and will refer to a calendar date of the clinical trial week it was performed to ensure proper recording.

7: At one of the visit, patients will meet with a research psychiatrist to review participation, whether progress or regress is being made, and to complete clinical ratings that will include a Substance Use Inventory, the Clinical Global Impression scale, a medical review, and completion of all clinical notes. All these forms are dated. These are then recorded in the clinical trial week form that corresponds to the calendar dates for that week.

8: At one of the visits, the patients will meet with a STARS or DOSA therapist for compliance enhancement therapy aimed at sustaining compliance with participation in all aspects of the study.

9: If a patient misses a visit, every attempt is made to make contact and reschedule as soon as possible. Significant others reported in the locator form may also be contacted if direct contact with the participant cannot be made. The research team continues this effort until contact is made. If a patient cancels a visit, the patient will be instructed to continue the medication with the "at-home" bottle until the next rescheduled visit.

10: Vouchers for completing all procedures of the study (bringing in the bottle, attending all visits, completing all assessments, attending appointments with the therapist and psychiatrist) will be offered (see Compensation section below).

11: At the end of Phase 2 (week 7), patients are rated as responders or non-responders on the end-of-study (EOS) form. To be a responder, frequency or quantity of cocaine use must have decreased by at least 75% compared to the baseline estimate of the 30 days prior to participation in the study. This is estimated by the results of urine toxicology and self-report recorded on the Time-Line-Follow-Back. If the toxicology does not correspond to the self-report, active use of cocaine is recorded. Missed visit will be recorded as days of use. A secondary measure will be time to relapse of cocaine use after completion of the abstinence induction procedure. They also repeat the salivary cortisol collection, and the stress challenge with intranasal desmopressin.

12: Patients are removed from the trial if they miss one week of medication (3 witnessed administration). Patients may elect to stop their participation at any time. Reasons for cessation will be recorded on the end-of-study form. We will attempt to complete end-of-study assessments. Patients may be removed by the investigator under several circumstances: 1) emergence of a medical condition unrelated to the study that would render continued participation

unsafe; 2) psychiatric worsening, such as emergence of depression (HamD score >17), psychosis (HamD item 22 >3), or of other significant psychiatric symptoms such as suicidality (HamD item 15 > 3), culminating in a CGI score > 6 for two consecutive weeks; 3) substance abuse worsening as assessed by clinicians on the research team during weekly visits, as evidenced by a CGI score >6 for two consecutive weeks; 4) emergence of hyponatremia during the study as indicated by a sodium concentration < 133 mEq/L or early symptoms such as asthenia, fatigue, nausea, vomiting, and weakness; 5) missing one week of supervised clinic-based administration of IN oxytocin or placebo.

**The study will be stopped if 3 patients develop hyponatremia during the course of the study.**

**Phase 3 is a repeat of the DDAVP stress challenge and saliva cortisol collection**

Below is a table of measures by week and clinic visits (Table 3).

Table 3: Weekly measures

	<b>Study assessments</b>	<b>Screening</b>	<b>Wk 1 Phase 1</b>	<b>Wk 2 to Wk 7 Phase 2</b>
<b>Physiological measures</b>	Blood studies: chem. 20, CBC. Urinalysis, Urine drug toxicology, urine pregnancy test	XX		
Monitoring blood studies: chem20, CBC.				XX (wk 2,4,6)
EKG		XX		XX (wk 7)
Medical Hx		XX		XX
Physical examination		XX		XX
Urinalysis		XX		XX (wk 2,4,6)
Urine toxicology		XX	XX (daily)	XX (3x/week)
Endocrine Stress Challenge with observed and		XX		XX

subjective ratings			
Supervised IN Oxytocin		XX	XX (3x/week)
BP, Pulse, Temp	XX	XX (daily)	XX (3x/week)
<b>Interviews</b>		XX	XX (3x/week)
TLFB-cocaine	XX	XX	XX (3x/week)
CGI-O	Adverse Symptoms Report (ASR)	XX	XX (1x/week)
Ham-D, 25 items		XX	XX (1x/week)
QSUI		XX	XX (1x/week)
MINI		XX	
<b>Self-Reports</b>		XX	XX (3x/week)
PSS		XX	XX (1x/week)
Cocaine craving scale (CCS)	CGI-self	XX	XX (3x/week)
Locator Form		XX	
Demographic form		XX	
Drug history questionnaire		XX	

**You can upload charts or diagrams if any**

- Table1PSF%OTVP%.pdf
- Table2PSF%OTVP 14 (1).pdf
- Figure 1 PSF%OTVPDay 1version2.pdf
- Study assessmentstable4PSF%OTVP.pdf

**Criteria for Early Discontinuation**

**Criteria for Early Discontinuation**

Removal from participation from the study can take place under several circumstances: 1) emergence of a medical condition unrelated to the study that would render continued participation unsafe; 2) psychiatric worsening, such as emergence of depression (HamD score >17), psychosis (HamD item 22 >3), or of other significant psychiatric symptoms such as suicidality (HamD item 15 > 3). **Each of these conditions, presenting separately or together, in any combination, which would lead the reviewing clinical to rate a CGI score > 6 for two consecutive weeks;**

3) substance abuse worsening as assessed by clinicians on the research team during weekly visits, as evidenced by a CGI score >6 for two consecutive weeks; 4) emergence of hyponatremia during the study as indicated by a sodium concentration < 133 mEq/L or early symptoms such as asthenia, fatigue, nausea, vomiting, and weakness; 5) missing one week of supervised clinic-based administration of IN oxytocin or placebo. Participation in the study is voluntary and patients can withdraw at any time. In each instance, they will be offered referrals for ongoing treatment.

The study will be stopped if 3 patients develop hyponatremia during the course of the study.

## Blood and other Biological Samples

**Please create or insert a table describing the proposed collection of blood or other biological specimens**

Blood draws for this study are as follows:

1: During screening, approximately 12 .5 ccs (one tablespoon) of blood is drawn for electrolytes, hepatic panel, blood counts analyses for both cocaine dependent patients and controls.

2: During phase 1, blood samples are taken as part of the stress challenge testing. Day 1 testing involves 64 ccs of blood (8 tubes) for measurement of ACTH. Day 2 involves 88 ccs of blood (11 tubes) for measurement of ACTH. This applies for control and cocaine-dependent participants. These samples are drawn through a saline catheter.

3: During Phase 2, at weeks 2, 4, and 6, medical monitoring involves a blood draw to review electrolytes, hepatic function, blood counts. This equals 24 ccs of blood (3 tubes). This applies only to cocaine-dependent patients.

4: At the end of phase 2, Day 1 of the stress challenge is repeated. This involves 64 ccs of blood (8 tubes) for analysis of ACTH. This applies only to cocaine dependent patients. These samples are drawn through a saline catheter.

5: For control participants, the total volume of blood drawn during their participation in screening and phase 1 would be 164.5 ccs of blood, approximately 17 tablespoons.

6: For cocaine-dependent patients, the total volume of blood drawn during screening, phase 1 and phase 2 would total 198.5 ccs of blood, approximately 20 tablespoons.

## Assessment Instruments

**Create a table or give a brief description of the instruments that will be used for assessment**

Mini Neuropsychiatric Interview (MINI)	45 minutes
Time Line Follow Back (TLFB)	5 minutes
Behavioral Activation Scale (BAS)	2 minutes
Clinician Global Impression-Observer (CGI-O)	1 minute

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Hamilton Depression Scale-25 items (HAM-D)	5 minutes
Perceived Stress Scale (PSS)	2 minutes
Cocaine Craving Scale (CCS)	2 minutes
Lickert Scales for cocaine craving, agitation during Stress challenge (0 to 10, 10 = worse)	1 minute

**Please attach copies, unless standard instruments are used**

### Off label and investigational use of drugs/devices

**Choose from the following that will be applicable to your study**

Drug

**Select the number of drugs used in this study**

2

**Drug #1**

**Name of the drug**

desmopressin

**Manufacturer and other information**

Part of the relevant information is already described in the uploaded PSF

Desmopressin is a synthetic vasopressin analog, with greatest affinity to the V1b receptor. It will be used to test a form of stress adaptation that we think might be present in cocaine-dependent patients.

The main reported side effects of intranasal desmopressin is abdominal pain (2%), headache (2%), epistaxis (3%), nostril pain (2%), rhinitis (8%), and conjunctivitis (2%) (PDR, 2014). There is remote possibility of hyponatremia. How this will be monitored and approached is discussed in the risk section.

The manufacturer is Apothec or Sanofi Aventis Inc. It will be ordered by our research pharmacy and dispensed from there.

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The use of desmopressin is being reviewed by the FDA under a single IND also involving the use of intranasal oxytocin: IND#: 122630.

**Approval Status**

IND is approved

**IND#**

122630

**Who holds the IND/IND sponsor?**

IND is held by PI/CU Investigator

Raby, Wilfrid, MD

**Drug #2**

**Name of the drug**

oxytocin

**Manufacturer and other information**

Part of the relevant information is already uploaded in the PSF

Intranasal oxytocin is being tested in cocaine-dependent patients to see if it would mitigate a form of stress that they may develop, which contribute to increasing their relapse risk.

In published reports on the use of intranasal oxytocin, noted side-effects were: light-headedness, anxiety, clouded thinking, and transient nasal cavity irritation. There is a remote possibility of hyponatremia. In the published reports on the investigational use of intranasal oxytocin, there has not been one instance of this complication. How this will be monitored and approached is discussed in the risk section

Intranasal oxytocin is not available by prescription, hence not approved by the FDA for clinical use. We will use Syntocinon prepared by Novartis, Switzerland. Victoria Pharmacy Zurich Switzerland will the packaging for international shipment. They will also prepare matching placebo solutions.

**Approval Status**

IND is approved

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**IND#**

122630

**Who holds the IND/IND sponsor?**

IND is held by PI/CU Investigator  
Raby, Wilfrid, MD

**Research Related Delay to Treatment**

**Will research procedures result in a delay to treatment?**

Yes

**Maximum duration of delay to any treatment**

What is maximum duration of delay due to research procedures before patient begins a treatment of any kind?

The delay to treatment is the delay required for baseline workup; once a cocaine-dependent patient enters the trial, it begins with an in-hospital phase, guaranteeing abstinence, or participates in an outpatient version of phase 1 should it not be possible to be hospitalized for 5 to 7 days. The baseline workup can easily be completed when a patient attends their first screening appointment. Delays extending beyond this are usually due to scheduling conflicts, or further evaluations being needed to clarify medical or psychiatric issues. In more complicated cases, at the most, two to three weeks may be required to complete the work-up and determine eligibility.

**Maximum duration of delay to standard care or treatment of known efficacy**

What is maximum duration of delay before active treatment (medication or psychotherapy) that is part of routine care or of known efficacy is offered? (Include time period described in B. above.)

The delay for effective treatment for cocaine dependence is the time for baseline work-up as noted in 4B. The first part of the trial is an in-hospital stay, or an outpatient version, during which breaking the cycle of addiction to cocaine is attempted. Being unable to do so is the very situation that often brings people to treatment. They also participate in extensive testing, which highlights some of their precipitants to cocaine use. This material can be integrated into the supportive therapy in the trial. Compliance Enhancement is a behavioral therapy with demonstrated efficacy for substance dependence disorders (Carroll & O'Malley, 1996; Pettinati et al., 2005). Patients will be monitored at all times for clinical worsening, and can be removed from the trial at any point to be offered treatment as clinically indicated.

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### **Treatment to be provided at the end of the study**

Describe treatment to be provided (if any, including duration) at the end of the study.

At the end of phase 2, the patient will have the opportunity to meet with their therapist for 3 more sessions to help with the transition of ending the study, and if they wish, continue treatment at another location. STARS or DOSA staff will continue to work with patients until alternative treatment is found. Patients participating in the NEXT STEP program at DOSA can continue in this program.

### **Clinical Treatment Alternatives**

#### **Clinical treatment alternatives**

This proposal offers procedures that themselves are part of recognized treatment approaches to cocaine dependence. The procedures described here are based in part on protocol 6013, which studies the effects of mifepristone in humans to treat cocaine dependence.

We have used in hospital treatment for detoxification as a well-established method of first intervention in cocaine dependence. It is readily appreciated by most patients that if they could stop on their own, in their own home, they would have done so. Compliance enhancement therapy (Carroll et al., 1994), coupled with voucher incentives (Higgins et al., 1994) provide behavioral treatments with demonstrated efficacy.

If patients contacting STARS cannot qualify, we will offer referrals to clinical treatment. For patients contacting DoSA, participation in the Next Steps program is an option, with or without participation in the study. Patients completing the study can continue at Next Steps.

### **Risks/Discomforts/Inconveniences**

#### **Risks that could be encountered during the study period**

Risks to subjects.

1. We expect few side effects and adverse events from the medication tested in this clinical trial, given the total dosing and frequency of administration.
  
2. More common side effects encountered with IN administration are nasal irritation, nasal congestion, nasal discharge, and potentially atrophic rhinitis. This may be particularly so for intranasal cocaine users with damaged nasal mucosa. This will be specifically monitored for during clinic visits.
  
3. Desmopressin (Vasopressin analog): Desmopressin is used to treat central diabetes insipidus. Daily dosing can be up to 0.8 mg po/day (or up 3200 IU). The most severe complication that can arise from use of desmopressin (PO or IN) on a daily basis for a prolonged period of time is excessive renal water reabsorption and hyponatremia. Signs and symptoms of emerging hyponatremia include: headache, nausea/vomiting, decreasing serum sodium, weight gain, fatigue, lethargy, depressed reflexes, muscle weakness, spasms, or cramps, change in mental status, disorientation, and coma. This rarely develops from administration of a single or a few consecutive daily doses. During their participation, control participants will receive 2 consecutive doses of IN desmopressin (total = 160 IU); cocaine-dependent patients receive 3 doses of IN desmopressin (total = 240 IU), two during phase 1 and one at the end of phase 2. In the one publication where a somewhat comparable approach was used (Araya et al., 2006), no side effects from desmopressin IV was noted.
  
4. Oxytocin: Oxytocin is used during labor and delivery to promote uterine contraction. In this instance, doses vary, but far exceed the daily dose of 24 IU/day used in this study. Administered intravenously as Pitocin, it can also lead to hyponatremia, arrhythmia, convulsions, chest pain, shortness of breath, confusion, swelling, headache, nausea/vomiting, cardiac arrhythmia. During their participation, control participants will receive 2 consecutive doses of IN oxytocin (40 IU in total) during phase 1. Cocaine-dependent patients receive 47 doses of IN oxytocin (940 IU) over a period of 7 weeks. No serious adverse events arose in a study during which 40 IU were administered daily for one week, then 80IU/day for another 7 weeks (Modabbernia et al., 2013). Feeling too relaxed, light-headedness, anxiety, clouded thinking, and nasal cavity irritation are the most common side effects reported in protocols approximating the one presented here (Rodrigues et al., 2009; Ditzen et al., 2009).
  
5. Another potential risk, especially for intranasal cocaine users, is whether the use of the intranasal approach would serve as a trigger for cocaine use. As this pharmacological approach has not been investigated before, this will be specifically queried for during clinic-based administration.
  
6. No data exists examining the risk of cocaine use is enhanced by concomitant intake of oxytocin. We

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do not anticipate that it would increase the risk of cocaine use. As change in cocaine use is a main outcome of the study, evidence of increased cocaine use will be monitored closely.

7. The stress challenge may cause patients to experience cravings for cocaine. After each procedure, a gradual muscle relaxation procedure will be used to reduce these.
  
8. Vouchers could be exchanged for drugs, or their monetary value could serve as a trigger to procure cocaine. Expending vouchers is a major topic of the counseling during the study to promote a drug-free lifestyle.
  
9. The structured interviews, self-reports, and questionnaires should not pose a physical risk. Their disadvantage is the time to complete them. Our past experience using these measures indicates that patients find them acceptable.
  
10. The risk of the blood tests is the discomfort associated with venipuncture, and a possibility of slight bruising. For the stress challenge, a saline lock will be placed to avoid repeated venipuncture.
  
11. Patients applying for, or admitted to treatment divulge information, such as drug use, which is sensitive and may have adverse social consequences if released. This would include information released to insurance companies, family members, or made public in any way. All clinical and research records will be treated with the confidentiality accorded any medical record in a substance abuse treatment setting. We will also apply for a certificate of confidentiality for this trial.

### **Describe procedures for minimizing risks**

Procedures to minimize risk.

The exclusion criteria are designed to minimize the medical and psychiatric risks to participants. Potential participants will not enter the study should they present with a psychiatric disorder,

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suicidality risk; except major depression provided it is in remission as attested by a HamD score <8. The baseline medical evaluation includes a history, review of systems, a physical examination, blood chemistry profile including electrolyte (Na, K, Cl, Ca, CO<sub>3</sub>), liver function test, blood count, urinalysis, urine pregnancy test, and electrocardiogram. It is designed to detect unstable medical conditions that would be prejudicial to participation in the study. Since the most serious potential adverse event is water toxicity and hyponatremia (Na < 133 mEq/L), the screening will focus closely on any signs and symptoms of hyponatremia, which include: nausea, vomiting, headache, confusion, loss of energy, fatigue, restlessness and irritability, muscle weakness, spasms, or cramps, seizures, unconsciousness, and coma. The medical, psychiatric, and laboratory screening is such that hyponatremia, or risks of hyponatremia (medications, renal failure), will be brought forth. Should hyponatremia emerge (Na < 133 mEq/L), whether symptoms are present or not, during the clinical trial, clinic-based and at-home administration of randomized medication will be interrupted, and the patient monitored by daily blood draws to monitor progress, together with encouragement to consume salt containing fluids. Should symptoms and signs appear or worsen, the patient will be referred to an emergency room for electrolyte management. Feeling too relaxed, light-headedness, anxiety, clouded thinking, and nasal cavity irritation are the most common side effects reported in protocols approximating the one presented here (Rodrigues et al., 2009; Ditzen et al., 2009). Symptoms of nasal irritation can occur from nasal administration. We will monitor this during clinic-based administration. This irritation may be more likely in intranasal cocaine users because of pre-existing irritation and damage to the nasal mucosa. No specific intervention is contemplated for this, except that nasal mucosa with preserved olfaction regenerates rapidly. Reduction in consumption or abstinence from cocaine may reduce this problem. Intranasal administration could be a trigger for further cocaine use. The Cocaine Craving Scale will be administered after clinic-based administration. Should cravings be reported, relaxation exercises (as performed in IRB protocol 6013) conducted with the patient by a member of the research staff can assuage the cravings. Whether the intranasal route is itself a trigger in cocaine-dependent patients is an important measure of the feasibility of this approach. The screening, consent, and study visit procedures are designed to safeguard the patient's welfare during their participation. The principal investigator and research staff extensively review and explain procedures, monitor the patient's status to review progress, side-effects, and adverse events. The purpose and procedures of the stress sensitivity testing will be thoroughly explained. Studying stress parameters can help determine if targeting these represents a valid approach to the treatment of cocaine dependence. Post-stress challenge relaxation exercise (already used in Protocol 6013) can help reduce the induced stress. This is especially important for patients choosing the outpatient abstinence induction procedure. We ask patients to give us names of person whom they trust who we can contact during the study should not be able to contact them through their regular number. We emphasize to them that although not mandatory, it is an important safety issue, in case we need to contact them urgently, or reschedule missed appointments. Removal from participation from the study can take place under several circumstances: 1) emergence of a medical condition unrelated to the study that would render continued participation unsafe; 2) psychiatric worsening, such as emergence of depression (HamD score >17), psychosis (HamD item 22 >3), or of other significant psychiatric symptoms such as suicidality (HamD item 15 > 3), culminating in a CGI score > 6 for two consecutive weeks; 3) substance abuse worsening as assessed by clinicians on the research team during weekly visits, as evidenced by a CGI score >6 for two consecutive weeks; 4) emergence of hyponatremia during the study as indicated by a

sodium concentration < 130 mEq/L or early symptoms such as asthenia, fatigue, nausea, vomiting, and weakness; 5) missing one week of supervised clinic-based administration of IN oxytoxin or placebo. Participation in the study is voluntary and patients can withdraw at any time. In each instance, they will be offered referrals for ongoing treatment. The study will be stopped if 3 patients develop hyponatremia during the course of the study.

## **Methods to Protect Confidentiality**

### **Describe methods to protect confidentiality**

We will apply for a certificate of confidentiality for this study (pending).

Patient's records are kept in locked files and released only with the patient's consent. Contact with family members or significant others will only be with the patient's expressed consent. All computer data is stored without names or other coded identification. Data files are protected by passwords. Should data be transmitted electronically, it will be encrypted. Research data will be accessible to the PI, co-PIs, and staff hired to assist with the study. Dr. Raby is the sponsor of this study, and holder of the IND (# pending). Dr. Raby assumes all responsibility concerning data integrity and confidentiality. The FDA has a right of access to all data gathered during the study as part of their review process. The FDA will also receive an annual report on progress and difficulties encountered during the study. NYSPI, Columbia University, New York state will have access to the data as part of quality control procedures.

No identifiers will be used in published reports.

### ***Will the study be conducted under a certificate of confidentiality?***

Yes, we will apply for the Certificate of Confidentiality

## **Direct Benefits to Subjects**

### **Direct Benefits to Subjects**

Participants will receive a free medical and psychiatric evaluation at baseline, and may benefit from improved symptoms of drug use from the behavioral treatment offered as part of the protocol, or from the medication. Patients will also be offered referrals upon completion of the study, or when they choose to leave. Patients found not to be eligible will also be offered referral opportunities should they wish.

## Compensation and/or Reimbursement

### Will compensation or reimbursement for expenses be offered to subjects?

Yes

**Please describe and indicate total amount and schedule of payment(s).**

**Include justification for compensation amounts and indicate if there are bonus payments.**

Incentive payments are provided to favor study retention and encourage participation in all aspects of the study, except medication intake.

Collection of vouchers will be contingent on attendance to all study appointments, the provision of a urine sample at every visit, completion of all self reports, and bringing the at-home medication for single-blind weighing.

For phase 1,

control participants will receive \$150 for their participation after they complete testing. After completion of Phase 1, they receive no further compensation.

cocaine-dependent patients will receive \$20/day, or will receive \$150 if they complete the whole week. Because availability of money can be a trigger to cocaine use, cocaine dependent patients will receive their reimbursement for phase 1 at the end of that week in a form of a voucher for services that can promote a drug-free lifestyle.

For Phase 2:

cocaine-dependent patients accumulate vouchers for completing all study procedures as described above. Each visit with completion of all study procedures will earn them \$5. They can also receive an extra \$20/week for each week of consecutive and complete participation. If

