

NCT01621737

Antipsychotic Effects of Oxytocin

Document Date: 7/22/2013

**UCSD Human Research Protections Program
New Biomedical Application
RESEARCH PLAN INSTRUCTIONS**

These instructions are for completing the Research Plan that is available in MS Word format from the [HRPP website](#).
The headings on this set of instructions correspond to the headings of the Research Plan.
General Instructions: Enter a response in for all topic headings.
Enter "Not Applicable" rather than leaving an item blank if the item does not apply to this project.

Version date: 05/11/2011

1. PROJECT TITLE

Project # 111017
Antipsychotic Effects of Oxytocin

2. PRINCIPAL INVESTIGATOR

David Feifel, M.D., Ph.D.
Professor, Department of Psychiatry
Director, Neuropsychiatry and Behavioral Medicine Program
UC San Diego Medical Center

3. FACILITIES

UCSD Medical Center, Department of Psychiatry
200 West Arbor Drive
San Diego, CA 92103-8620

4. ESTIMATED DURATION OF THE STUDY

Study enrollment will occur over approximately a two year period. Completion of the entire protocol, including subject recruitment, study procedure execution, and statistical analysis is anticipated to take no longer than four years.

Each subject will be enrolled for a 7 week period, including a screening phase. Study procedures involve weekly clinic visits as an outpatient. Approximately 72 patients will be randomly assigned to either 84 IU of oxytocin (equivalent to 42 IU BID), 168 IU of oxytocin (84 IU BID) or vehicle placebo. The doses of oxytocin are based upon previous studies in humans showing improvement in schizophrenia related changes in behavior and brain function (Kosfeld et al, 2005; Kirsch 2005; Heinrich M 2003).

The total study duration for each individual subject will be approximately 7 weeks, which includes a 7-day screening period, a baseline (randomization) visit, and the six-week treatment phase.

Participants will remain on their current antipsychotic medication and dose throughout the study.

5. LAY LANGUAGE SUMMARY OR SYNOPSIS (no more than one paragraph)

The purpose of this study is to test whether or not people with schizophrenia feel improvement in their symptoms when oxytocin nasal spray is added to their current medications. Volunteers will be randomly assigned to one of three groups; a higher dose group, a lower dose group, or a group who receives a nasal spray with no medication in it (placebo). Volunteers will be asked questions about their mental and physical health as well as take several computer tests to track any changes over the 7 weeks of the study.

6. SPECIFIC AIMS

The proposed study is a randomized, double-blind, placebo-controlled dose-ranging, pilot study intended to replicate and extend the promising results from an earlier proof of concept study testing intranasal oxytocin in schizophrenia. This second-stage pilot study will seek to obtain information not obtained in the limited proof-of-concept study; specifically, the optimal dose of oxytocin for efficacy and tolerability, the time to optimal efficacy and the effects of longer term exposure (6 weeks) to daily intranasal oxytocin. It is expected that the information obtained from this pilot study will provide indispensable information for the design and execution of future full scale parallel arm studies to test the efficacy and safety of intranasal oxytocin. It may also provide valuable information for other pilot studies that may test oxytocin in other clinical populations, and ultimately for the development of new treatment strategies for psychosis and other mental disorders based upon the use of oxytocin or oxytocin analogs.

Specific Aim #1: To replicate the promising positive findings from the pilot study in a larger and more diverse sample of subjects recruited from more than one site. In the recent pilot-study mentioned, 80 IU of intranasal oxytocin significantly improved positive and negative symptoms of schizophrenia and short term memory recall. However that study was conducted in a small number of subjects using a crossover experimental design. These findings are very promising but need to be replicated with a larger number of subjects representing more than one recruitment site.

Specific Aim #2: To investigate the efficacy and safety of higher doses of oxytocin. The original study used 80 IU of intranasal oxytocin and this was found to be well tolerated and effective. However the effect size in this study was moderate. It is possible that higher doses of oxytocin would produce stronger therapeutic effects; therefore, this study proposes to test a higher dose of oxytocin, 168 IU, in addition to the approximate dose tested in the pilot study.

Specific Aim #3: Establish the time needed to reach peak efficacy. Duration of treatment in the original study was three weeks, and significant therapeutic benefit was observed only at the three-week endpoint but not earlier. In the proposed study, subjects will receive study drug for 6 weeks and we expect that the size of the therapeutic benefit of oxytocin will increase from 3 to 6 weeks.

Specific Aim #4: Investigate the possible cognitive effects of intranasal oxytocin. In the pilot study, oxytocin significantly improved short term recall performance in the California Verbal Learning Test. This raises the possibility that chronic oxytocin will improve cognitive deficits associated with schizophrenia. This study will test this hypothesis using the Computerized Multiphasic Interactive Neurocognitive DualDisplay™ System (CMINDS®) and Mayer-Salovey-Caruso Emotional Intelligence Test: Managing Emotions (MSCEIT™ ME).

Specific Aim #5: To determine if daily intranasal oxytocin is sufficiently safe, feasible and acceptable to patients to warrant further clinical development. Information derived from this study will inform development of oxytocin not only for schizophrenia but other potential neuropsychiatric disorders.

Specific Aim #6: The objective of the study is to compare the efficacy of intranasal oxytocin versus intranasal placebo to improve symptoms in schizophrenia patients who have residual symptoms despite being on adequate treatment with antipsychotic medication. Improvement will be measured by total score in the Positive and Negative Syndrome Scale (PANSS).

Specific Aim #7: To determine if oxytocin-induced enhancement of mu-rhythm suppression of 'mirror' neurons in schizophrenia patients can serve as a predictive biomarker of individual clinical response to this neurohormone.

Secondary objectives include:

- To evaluate the efficacy of intranasal Oxytocin as measured by change in the total CGI-Severity and Improvement scores

- To evaluate the efficacy of intranasal Oxytocin as measured by change in the total GAF score
- To evaluate the efficacy of intranasal Oxytocin as measured by change in the total scores of HAM-A.
- To evaluate the efficacy of intranasal Oxytocin on self-rated social anxiety as measured by change in the total Social Phobia Inventory (SPIN).
- To evaluate the efficacy of intranasal Oxytocin as measured by change in the total Calgary Depression Scale for Schizophrenia (CDSS) scores.
- To evaluate the safety of intranasal Oxytocin as measured by reported Adverse Events
- To evaluate the safety of intranasal Oxytocin as measured by collected safety measures to include blood tests, witnessed and reported adverse events
- To evaluate changes in ability to infer the mental state of others from emotion differentiation by their performance with the Penn Emotion Recognition Test (ER-40).
- To evaluate the possible correlation between the response to intranasal Oxytocin and biological markers, specifically endogenous oxytocin levels (tested via blood and saliva sample). Using saliva to test hormone levels has become a preferred method. Many hormone levels can fluctuate throughout the day. Using saliva allows for convenient specimen collection at multiple times (ie, pre and post dose). There is a believed correlation between the "bioavailable" (or active) amount of hormone in the blood and the levels found in saliva. We will collect both blood and saliva samples to confirm or reject the proposed correlation which may lead to a more convenient way of collection in future trials. Determining hormone bioavailability is critical with hormones and saliva as the specimen medium is ideal for this.
- To assess the differential effect of oxytocin on early environment and social parameters based on scores on the Childhood Trauma Questionnaire (CTQ) and Experience Close Relationships (ECR).
- To detect and monitor any changes in sexual functioning as rated by the Arizona Sexual Experience Scale (ASEX)
- To determine if expected deficits in neural processing of socially relevant visual stimuli (mu-rhythm suppression of mirror neurons) in schizophrenia patients correlates with the severity or nature of their symptoms
- To determine if intranasal oxytocin can improve mu rhythm suppression in schizophrenia patients

7. BACKGROUND AND SIGNIFICANCE

Schizophrenia is a devastating chronic mental disorder reported to affect more than 2.4 million Americans (Kessler et al, 2005). Patients treated with even the best currently available antipsychotic medications typically continue to experience significant symptoms. Thus, there is a compelling need for novel treatments that are efficacious and safe.

Oxytocin is a nine amino acid neuropeptide best known for its involvement in parturition and lactation. In addition to these well-established peripheral effects, there is a compelling body of converging evidence indicating that oxytocin plays a critical role in the regulation of a number of diverse centrally-mediated behavioral and cognitive processes that are highly relevant to schizophrenia (see Argiolas and Gessa 1990; McCarthy and Aaltemus 1997; Lee, Brady, Shapiro, Dorsa, & Koenig, 2005). Furthermore, several lines of research suggest that oxytocin receptors may be an important target for the development of novel treatments for schizophrenia. Oxytocin and its receptors exist in several areas of the brain which have been heavily implicated in the pathophysiology of schizophrenia, such as the nucleus accumbens and the hippocampus (van Leeuwen, van Heerikhuizen, van der Meulen, & Wolters, 1985). Oxytocin administered peripherally inhibits dopamine transmission in the mesolimbic pathway (Sarnyai et al, 1990). Moreover, antipsychotics have been found to elevate the secretion of oxytocin in rats (Uvnas-Moberg, Alster, & Svensson, 1992), suggesting that endogenous oxytocin may play a role in the therapeutic effects of antipsychotic drugs.

These findings raise the possibility that exogenous oxytocin may have therapeutic potential as an antipsychotic drug. The first direct preclinical proof-of-principal test of this notion was conducted by Feifel et al. (1999), who measured the effects of oxytocin on prepulse inhibition (PPI) in rats. In that study, oxytocin administered subcutaneously in male rats produced a robust antipsychotic-like reversal of PPI deficits induced by amphetamine and the NMDA antagonist, MK801, an analog of PCP. This pattern of the reversal of drug-

induced PPI deficits is consistent with the activity of atypical antipsychotics (Geyer, 2001). Since then, other investigators have reported findings supporting an antipsychotic role for oxytocin. Lee et al. (2005) found that centrally administered oxytocin ameliorated chronic PCP-induced behavioral withdrawal, an established animal model for negative symptoms of schizophrenia. Caldwell et al. (2009) found that mice genetically lacking oxytocin were more sensitive to PCP-induced PPI disruption. Additionally, Feifel et al. (in preparation) recently found that subcutaneous oxytocin increased PPI in rats with naturally low PPI (see Preliminary Findings).

Studies in humans provide further support for the contention that oxytocin may have antipsychotic properties. Schizophrenia patients have been found to have disturbed oxytocinergic function (Linkowski et al. 1984; Beckmann et al., 1985; Legros et al., 1992; Mai et al., 1993; but see Glovinshy et al., 1994). In addition, two small and uncontrolled studies conducted in Russia evaluated the effect of intravenous oxytocin in schizophrenia and found promising results suggesting that it may reduce some symptoms of this disorder (Bujanow, 1974; Bahkarev et al., 1984).

Recent research has shown that neuropeptides such as oxytocin cross the blood-brain barrier after intranasal administration (Born, 2002), providing a useful way of studying the central nervous system effects of neuropeptides like oxytocin that might otherwise not enter the CNS. Several studies have demonstrated CNS behavioral and brain imaging effects following intranasal administration of oxytocin (See MacDonald and MacDonald, 2010 for review; Garner et al. 2010) Oxytocin is commonly administered intravenously (Pitocin®, Novartis) to stimulate parturition and an intranasal formulation of oxytocin (Syntocin®, Novartis) was approved by the FDA as a treatment for lactation aid. Though no longer available commercially in the U.S., this intranasal product remains available in other countries and has been used in a significant number of recent human studies (see MacDonald and MacDonald, 2010). Intranasal oxytocin doses ranging up to 320 IU/day have been shown to be safe and highly tolerated (Epperson, 1996; Kosfeld et al., 2005). In a recent landmark study, Kosfeld et al. (2005) demonstrated that oxytocin administered intranasally to healthy human subjects in a double blind, placebo-controlled study increased levels of trust. Furthermore, it has been shown that intranasal oxytocin reduced activation of brain circuits involved in fear in human subjects (Kirsh et al, 2005; Gamer et al, 2010) suggesting that intranasal oxytocin may reduce paranoia.

Recently, Feifel et al. (2010) conducted a small proof-of-concept, randomized, double blind, placebo-controlled crossover study comparing intranasal oxytocin to intranasal placebo added to stable doses of antipsychotic medication in patients with schizophrenia and found that oxytocin significantly reduced psychosis and improved short-term memory compared to placebo (see Preliminary Findings). This finding supports the notion that oxytocin may be a novel therapy for schizophrenia. This application proposes a pilot clinical trial that will extend the findings of the initial study and provide critical information for planning a subsequent definitive clinical trial.

Treatment for schizophrenia and related psychotic disorders is at an impasse. Recent studies have revealed that the advantage of second generation (atypical) antipsychotic over first generation (typical) antipsychotics, once thought to be substantial, is limited or non-existent. Thus treatments for this disorder have made little gains in the five decades since chlorpromazine was approved as the first antipsychotic. While currently available antipsychotics produce important improvement in symptoms of schizophrenia and related disorders, few patients experience a total remission of symptoms and a large proportion are left with debilitating residual symptoms. Thus, positive findings emanating from this study investigating effects of intranasal oxytocin as augmentation to antipsychotic drugs will have a significant impact in a number of ways, not least of which will be generation of strong interest in development of new compounds targeting the oxytocin system.

Mu rhythm suppression is a candidate biomarker in schizophrenia: Biological motion as depicted in point light animations is a well-studied construct in cognitive neuroscience, where videos are created by filming a person in the dark with lights on major body joints, while performing a repetitive motion such as walking or jumping. These displays provide sparse visual input that requires “filling-in” to recover object information to identify the kind of motion being produced (e.g., walking, jumping, dancing) (Keri, et al, 2009). It has been suggested that neural processing of biological motion is an evolutionarily conserved mechanism that plays a fundamental role in social adaptation (Keri, et al, 2009). A number of studies have associated biological motion with neural activity in the mu (8-13Hz) range (Perry, et al, 2010) over the right sensorimotor cortex, and are

thought to index the activity of 'mirror' neurons. Mu rhythms, measured from this brain region show reliable, dose dependent, suppression when the subject perceives biological motion (but not non-biological motion). Thus, mu wave suppression is an easily quantifiable operational measure of the neural processing of biological motion. In a recently published study conducted in Dr. Cadenhead's laboratory, the applicant showed that neural mu wave suppression induced by biological motion is impaired in first-episode of psychosis subjects, and that the neural impairment is inversely correlated with negative symptoms and social adjustment, providing construct validity for the mu suppression paradigm as an operational measure of social cognition in patients with psychosis (Singh, et,al, 2010).

Given OT's strong implication in social perception, it would be reasonable to expect that exogenous OT affects mu wave suppression in the context of biological motion. This has been in fact, confirmed in a recent study by Keri et al. using a well-established paradigm of biological motion similar to that used by our group. Keri et al, demonstrated that intranasal OT significantly enhanced detection of biological motion (human form) but not non-biological motion (rotating circle) compared to intranasal placebo. Taken together, the applicant's study and that by Keri et al, demonstrate that patients with psychosis have impaired biological motion induced mu suppression compared to normal subjects and that intranasal OT enhances this neural process in normal subjects. It is reasonable to expect that intranasal oxytocin will improve mu suppression in schizophrenia patients and we expect to demonstrate this. We also expect to find that subjects with the greatest enhancement in mu suppression are more likely to experience clinical improvement in response to 6-weeks of oxytocin treatment.

Hypothesis: We hypothesize that augmentation of antipsychotics with intranasal oxytocin will significantly improve psychopathology ratings as compared to placebo and an improvement in certain cognitive functions may be also observed.

8. PROGRESS REPORT

Oxytocin is a peptide neurohormone that has demonstrated effects on brain pathways and on behaviors relevant to schizophrenia. Recent studies demonstrate that oxytocin has robust antipsychotic-like effects in animal models predictive for antipsychotic efficacy (Feifel et al, 1999; Lee et al, 2005). Small uncontrolled studies conducted found that oxytocin produced antipsychotic effects in schizophrenia patients (Bujanow 1974; Bahkarev et al. 1984). Intranasal oxytocin is commercially available as a lactation aid and has a good safety and tolerability profile (see Risk Section of this research plan). Recently, Kosfeld et al (2005) reported that oxytocin administered intranasally, a route of administration thought to allow good access to the CNS for peptides like oxytocin, significantly increased trust in healthy subjects, a finding which may have relevance to symptoms seen in schizophrenia, such as paranoia. To date no randomized, placebo-controlled study of the efficacy of has been conducted to investigate the efficacy of oxytocin for symptoms of schizophrenia. The objective of the study is to compare the efficacy of intranasal oxytocin versus intranasal placebo to improve symptoms in schizophrenia patients who have residual symptoms despite being on adequate treatment with antipsychotic medication.

The Principal Investigator examined the antipsychotic potential of oxytocin in an animal model of schizophrenia that has good predictive validity for drugs with antipsychotic efficacy based upon prepulse inhibition (PPI) of the startle reflex. PPI is a measure of sensorimotor gating. PPI deficits are well documented in schizophrenia patients and are thought to reflect core dysregulation in circuits mediating sensorimotor gating and that are implicated in the pathophysiology of schizophrenia. That study demonstrated that oxytocin, administered peripherally in male rats produced a robust antipsychotic-like reversal of PPI deficits induced by amphetamine and the PCP analog, MK801 (Feifel et al 1999). This profile of effects is most consistent with atypical antipsychotics (Geyer 2001). In addition, a recent study showed that centrally administered oxytocin ameliorated chronic PCP induced behavioral withdrawal (Lee et al, 2005), an established animal model for negative symptoms of schizophrenia.

A metaanalysis by Sprong et al. (2007) indicated that participants with schizophrenia perform well below healthy controls in tests of "theory of mind". According to these authors, "theory of mind" refers to the cognitive

ability to attribute mental states to people which helps a person explain and predict behaviors of others. Domes et al (2006) found that oxytocin improved the ability to infer the mental state of others from eye region cues by testing their performance on the RMET. In addition, the Penn Emotion Recognition Test - 40 is an affective picture test that determines the subject's ability to infer another person's internal state from subtle affective facial expressions (Sachs et al 2004). This test has been incorporated into the current project as a secondary measure to investigate whether oxytocin may improve the ability of patients with schizophrenia to read the emotions of others.

9. RESEARCH DESIGN AND METHODS

OVERVIEW:

The proposed study is a randomized, double-blind, placebo-controlled study of the value of adjunctive intranasal oxytocin added to existing antipsychotic treatment compared with adjunctive placebo in subjects with schizophrenia. Enrolled subjects will be randomized and receive 6 weeks of treatment with one of the following adjunctives to a stable antipsychotic regimen: 1) intranasal oxytocin (84 IU/day), intranasal oxytocin (168 IU/day) or intranasal placebo. The study will be conducted over 2 years. Approximately seventy-one subjects will be entered into the study, on average 35/36 at each site each year.

PRIMARY OUTCOME MEASURE:

Positive and Negative Syndrome Scale (PANSS): The three subscales of the PANSS include the Positive scale (7 items), the Negative scale (7 items), and the General Psychopathology scale (16 items). The total PANSS score is the sum of all 30 items of which each item is scored on a 1-7 rating system (7 indicating the worst symptoms). The items on the PANSS focus on symptoms that are common in patients with psychotic disorders and include hallucinations, delusions and disorganization as well as mood disturbances.

SECONDARY OUTCOME MEASURES WILL INCLUDE:

Global Assessment of Functioning (GAF): The GAF considers psychological, social, and occupational functioning on a hypothetical continuum of mental health illness. Scores on the GAF range from 1 (extremely severe) to 100 (superior functioning).

Clinical Global Impression-Severity of Illness (CGI-S): The CGI-S is used to evaluate changes in overall severity of illness. Scores range from 1 (not at all) to 7 (among the most extremely ill).

Clinical Global Impression-Global Improvement (CGI-I): The CGI-I is a global assessment to evaluate the subject's improvement or worsening from baseline. Scores on the CGI-I scale range from 1 (very much improved) to 7 (very much worse)

Calgary Depression Scale for Schizophrenia (CDSS) is a ten item diagnostic questionnaire intended to assess the severity of depression symptoms experienced by a given patient. The CDSS will be administered by a trained and qualified rater at each scheduled study visit.

Hamilton-Anxiety Scale (HAM-A): The HAM-A is a clinician administered scale for the evaluation of anxiety symptoms. The HAM-A consists of 14 items of which each item is scored 0 (not present) to 4 (very severe).

Paranoid Thought Scale (PTS): The PTS is a self-rated scale to assess current paranoia symptoms. The PTS consists of 32 items that the subject rates from 1 (not at all) to 5 (totally).

Treatment Satisfaction Questionnaire for Medication (TSQM): This is a very short questionnaire asking patients about how satisfied they were with the ease, timing, etc. of the study medication giving a good indication of adherence (Atkinson et al, 2004).

Childhood Trauma Questionnaire (CTQ): A validated measure of adverse early experiences characterized on a measure of Anxiety Sensitivity Index and retrospective childhood maltreatment. A 5-point frequency of occurrence scale is utilized: (1) never true, (2) rarely true, (3) sometimes true, (4) often true, and (5) very often true. Each subscale score ranges from 5 (no history of abuse or neglect) to 25 (very extreme history of abuse and neglect).

Experience Close Relationships (ECR): The ECR is a self-rated questionnaire designed to assess individual differences with respect to attachment-related anxiety (i.e., the extent to which people are insecure vs. secure about the extent to which their partner's availability and responsiveness) and attachment-related avoidance (i.e., the extent to which people are uncomfortable being close to others vs. secure depending on others) (Fraley, R. C., Waller, N. G., & Brennan, K. A., 2000).

Arizona Sexual Experience Scale (ASEX): The ASEX is a self-rated scale to assess sexual functioning. The ASEX consists of 5 items that the subject will rate from 1 (Extremely strong, easily, or satisfying) to 6 (Absent or never) based on how he/she feels at the time.

Social Phobia Inventory (SPIN): The SPIN is a patient self-report scale that measures the degree of social phobia in a variety of different social situations

Penn Emotion Recognition Test (ER40): The ER-40 is a computerized emotion discrimination test presenting 40 color photographs of evoked happy, sad, anger, fear and neutral expressions balanced for poser gender and ethnicity.

The CMINDS® Computer Battery consists of the following:

Please note: The CMINDS® consists of “construct-equivalent computerized versions of the neurocognitive assessment instruments constituting the MATRICS™ Consensus Cognitive Battery (MCCB™)” (O’Halloran et al. 2007). The CMINDS® assessments achieved identical face validity and high concurrent validity with traditional paper versions of the MATRICS™ Consensus Cognitive Battery (MCCB™) (refs from above). Each of the tests listed below include the title of the CMINDS® test as well as the concurrent MATRICS™ examination. Please note the concurrent MATRICS™ assessments are listed below in italics.

<u>Cognitive Domain</u>	<u>Test</u>	<u>Description</u>
Speed of processing	Symbol Digit Association Test <i>(Brief Assessment of Cognition in Schizophrenia(BACS): Symbol-Coding)</i>	Computer-administered timed test in which respondent uses a key to decode a series of digits listed on a computer screen according to the template of non-sense symbols. The respondent verbally answers each question and it is recorded by the administrator
	Letter Fluency Test	Oral test in which the respondent names as many words

		as she/he can in 1 minute that begin with the corresponding letter presented on the computer screen
	Category Fluency Test (<i>Category Fluency: Animal Naming</i>)	Oral test in which the respondent names as many animals as she/he can in 1 minute
	Trails Making Test: Part A	Computer-administered timed test in which the respondent draws a line to connect the numbered circles that are placed irregularly on the computer screen in ascending order
	Trails Making Test: Part B	Computer-administered timed test in which the respondent draws a line to connect numbered and lettered circles that are placed irregularly on the computer screen in an ascending pattern, alternating between the numbers and letters
Attention/Vigilance	Continuous Performance Test – Identical Pairs (CPT-IP)	Computer-administered measure of sustained attention in which respondent presses a response button to consecutive matching numbers
Working memory (nonverbal)	Visuospatial Sequencing Test (<i>Wechsler Memory Scale® - 3rd Ed. (WMS®-III): Spatial Span</i>)	Using a board displayed on the respondent's computer screen in which 10 squares are irregularly spaced, the respondent is asked to tap the squares in same (or reverse) sequence as test administrator
(verbal)	Letter-Number Ordering (<i>Letter-Number Span</i>)	Orally administered test in which respondent mentally reorders strings of number and letters and repeats them to administrator
Verbal learning	Semantic Verbal Learning (<i>Hopkins Verbal Learning Test—Revised™ (HVLTR™)</i>)	Orally administered test in which a list of 12 words from three taxonomic categories is presented and the respondent is asked to recall as many as possible after each of three learning trials
	Delayed Semantic Verbal Learning (<i>Hopkins Verbal Learning Test—Revised™ (HVLTR™)</i>)	Orally administered test in which a respondent is first asked to recall as many words as possible from the list of 12 words that was presented 20-25 minutes earlier in the battery. A randomized list of 12 target words and 12 non-target words are then presented to the respondent and she/he must press one of two response buttons, reporting that she/he recognizes the word from the previous list or does not recognize the word from the previous list
Visual memory and learning	Visual Figure Learning Test (<i>Brief Visuospatial Memory Test—Revised (BVMT-R™)</i>)	A computer-administered test that involves reproducing six geometric figures from memory
	Delayed Visual Figure Learning Test	A computer-administered test that involves reproducing six geometric figures from memory after a 20-25 minute delay. A randomized list of 6 target figures and 12 non-target figures are then presented to the respondent and

		she/he must press one of two response buttons, reports that she/he either recognizes the figure from the previous task or does not recognize the figure from the previous task
Reasoning and problem solving	Maze Solving (<i>Neuropsychological Assessment Battery</i> ® (NAB®): Mazes)	Seven timed paper-and-pencil mazes of increasing difficulty that measure foresight and planning
Social cognition	<i>Mayer-Salovey-Caruso Emotional Intelligence Test</i> (MSCEIT™): Managing Emotions	Paper-and-pencil multiple-choice test that assesses how people manage their emotions
IQ	North American Adult Reading Test (NAART)	Computer-administered test in which the respondent is asked to read individually spelled words and pronounce them aloud (Letz et al., 2003)

Mu wave suppression paradigm: If subjects agree to participate in this sub-study, the informed consent for EEG collection will be obtained prior to any EEG procedures. EEG waves will be recorded over 32-sites using a standard 32-electrode cap with the Biosemi system (9), while subjects are watching 60-80 second videos. The videos will consist of experimental conditions (point light animations of biological and non-biological motion, scrambled condition) and baseline condition (2 moving balls). All videos will be presented twice, using Presentation software (10). Data from both trials will be combined prior to analysis. Filters will be set to automatically identify and block any segments with eye movements and body movements (using +/- 40 microvolt deviations). Data will only be analyzed if there is at least 2 minutes of clean EEG per condition. For each segment, integrated power in the 8–13 Hz range will be computed using a Fast Fourier Transform. Mu suppression will be calculated for central (C3, Cz and C4) and occipital (O1 and O2) sites using the equation: $\text{Mu suppression} = \log_{10} (\text{mu power of experimental condition} / \text{mu power of ball condition})$. Occipital site electrical discharges will be recorded, integrated for power and compared between groups to determine if posterior alpha activity is causing differences across conditions.

STUDY PROCEDURES

Visit	Screen ^a	Baseline	Midweek	3	4	5	6	7	8/ET
Week	-1	0	0	1	2	3	4	5	6
Days	-7 to -1	0	3/4	7	14	21	28	35	42
General Procedures									
Informed Consent	x								
Assess Inclusion/Exclusion	x	x		x	x	x	x	x	x
Medical History	x								
Physical Exam	x								
SCID/Psychiatric History	x								
Urine Drug Screen ^b	x								
Urine Pregnancy Screen ^c	x	x							
Vital signs/ weight	x	x		x	x	x	x	x	x
Blood chemistry ^d /Urine osmolality	x								x
Oxytocin Levels ^e		xx							x
EEG	xx								x

Clinician-Rated Scales									
PANSS ^f	(x)	x		x	x	x	x	x	x
HAM-A/ CDSS/ CGI:S ^g / CGI:I/ GAF		x		x	x	x	x	x	x
Cognitive tests (CMINDS® and MSCEIT™ ME) ^h	x	x							x
Patient-Rated Scales									
CTQ	x								
TSQM		x		x	x	x	x	x	x
PTS/ SPIN/ ASEX/ ER-40/ ECR		xx		x	x	x	x	x	x
Other Procedures									
Mid-Week Safety Call ⁱ			x						
Dispense study drug		x		x	x	x	x	x	
Single Challenge Dose ^k	x								
Concomitant Meds		x	x	x	x	x	x	x	x
Adverse Events		x	x	x	x	x	x	x	x
1-hr safety monitoring following in- clinic dose		x							

^aScreening procedures can be done over a week period if needed to complete all procedures such as confirmation of diagnosis. The screening and baseline visits can occur on the same day.

^b In addition to Visit 1, an optional urine drug screen or blood chemistry may be performed at any point during the study at the discretion of the Principal Investigator or study coordinators if it is suspected the subject is not abstaining from illegal substances or have general health concerns.

^cPremenopausal women will be queried regarding their menstrual cycles and data correlated with clinical findings. Patients are instructed to use a medically accepted form of birth control through their study participation, and are also questioned about their birth control method at each visit. If a pregnancy is suspected at any time during the study, the patient will be asked to complete a urine pregnancy test.

^d Basic Metabolic Panel includes Glucose, BUN, Creatinine, Bicarbonate, Chloride, Sodium, Potassium, Calcium, osmolality

^eOxytocin Levels will be collected via saliva and blood draw twice during the Baseline Visit. One blood draw and passive drool will be collected at the beginning of the visit (pre-dose) and a second blood draw and passive drool collection will be taken 30 minutes after the in-clinic dose. The third Oxytocin level will be taken at the patient's last visit (either Visit 8 at the conclusion of the protocol or the Early Termination visit).

^f PANSS must be done at baseline, but it may be completed at screening in addition at the discretion of the investigator if he feels that the subject may not meet entry criteria

^gThe CGI-S will be completed twice at the Baseline Visit, once prior to dosing and a second time at least 50 minutes after the in-clinic dose of the study drug or placebo.

^h Practice improvement is expected with repetition of some MATRICS tests. While the parallel group design will determine any improvement beyond the practice effect, neuropsychologists Richard Keefe and Philip Harvey have pointed out the majority of practice effect occurs between the first and second administrations of the MATRICS battery (personal communications). This finding by Keefe and Harvey regarding paper versions of the MATRICS™ should translate to the computerized versions of the CMINDS® as O'Halloran et al. (2007) found that standard paper administration versions and computerized administration versions of neurocognitive assessment instruments are substantially equivalent. These computerized versions yielded highly equivalent measures of absolute agreement throughout all the test batteries when compared to the standard paper versions. The group comparison will be between baseline (after the majority of practice effect has occurred) and 6 weeks. While this strategy may miss transient improvement between these timepoints it will decrease the practice effect. Transient improvements in cognition are not clinically meaningful.

ⁱAll patient-rated scales except the ASEX will also be given 50 minutes after the in-clinic dose at the Baseline Visit.

^jA Mid-Week Safety Call to Study Site - The subject will be instructed to contact study staff on day 3 or day 4 of taking study drug. This call will be a brief open ended question and answer discussion to find out the subject's experiences with the study medication over the past few days and answer any questions that may arise.

^kA challenge dose will be administered between screening EEG paradigms. This dose will only be administered after all other inclusion/exclusion criteria have been verified. All subjects will receive 24IU as a challenge dose.

Study Procedure Details

Visit 1 – Screening (approximately 4-5 hours)

During Visit 1 of the study the volunteer will:

- Be asked questions about medical and psychiatric history
- Participate in a clinical interview called a Structured Clinical Interview for DSM-IV-TR (SCID) which is a structured question and answer discussion. This will be performed by a trained study staff who will ask a series of questions about behaviors and mood symptoms over time
- Be given a physical examination by one of the study doctors
- Have weight, pulse and blood pressure measured
- If the volunteer is a woman capable of having children, a urine test will be done to ensure she is not pregnant
- Give a urine sample for testing to make sure there are no illegal or controlled substances in his/her body. The results of any urine drug screen will remain confidential and be disclosed only as required by law
- Blood draw (about one teaspoon or 5 mL) and urine sample will be collected that will include standard tests to make sure volunteers are healthy
- Be asked questions about health and any current illnesses or medications (including over-the-counter medications, herbal remedies, alcohol consumption, and substances of abuse).

Be asked a series of questions about how s/he was feeling within the past few weeks such as whether there were anxious feelings, feelings of depression or difficulty concentrating. The volunteer will also possibly be asked about symptoms that are commonly associated with schizophrenia using a clinical interview called the SCI-PANSS (Structured Clinical Interview – Positive and Negative Syndrome Scale).

The SCI-PANSS will be completed at the discretion of the investigator if he feels that the subject may not meet entry criteria

- Complete a series of activities which will be used to measure process of thought called the CMINDS® and MSCEIT™ ME
- Premenopausal women will be queried regarding their menstrual cycles and data correlated with clinical findings
- Once all inclusion/exclusion criteria have been met subjects will have a baseline EEG performed
- Subsequently subjects will receive a, one time, challenge dose of 24 or 48 IU oxytocin followed by the EEG paradigm

Visit 2-Baseline (approximately 2 hours)

During Visit 2 – Baseline, the volunteer will:

- Have weight, pulse and blood pressure measured
- Be asked questions about health and any current illnesses or medications (including over-the-counter medications, herbal remedies, alcohol consumption, and substances of abuse)
- Be asked a series of questions about how s/he was feeling within the past few weeks such as whether there were anxious feelings, feelings of depression or difficulty concentrating. The volunteer will also be asked about symptoms that are commonly associated with schizophrenia using a clinical interview called the SCI-PANSS (Structured Clinical Interview – Positive and Negative Syndrome Scale)
- Complete a series of activities which will be used to measure process of thought called the CMINDS® and MSCEIT™ ME
- Complete a test on ability to recognize emotions called the Penn Emotion Recognition Test (ER-40) both pre and post in-office dose.
- Will be randomized to Group 1, 2, or 3 (described above) to receive either 84IU, 168IU of oxytocin or placebo
- Fill out questionnaires about mood at the time, **experience with close relationships**, and symptoms of paranoia both before and at least 50 minutes after the in-office dose of the study drug or placebo.
- Complete a questionnaire about sexual functioning
- The volunteer will be asked to stay at the clinic for one hour after taking the study drug so that the study doctor and study staff can monitor the first experience with the study drug. The study staff will ask questions about how the study drug affects the individual.
- When the study doctor decides the volunteer is ready to go, study drug will be dispensed along with written instructions on how and when to take the study drug.
- Have a blood and saliva sample taken at the beginning of the visit as well as 30 minutes after the in-office dose for monitoring of study drug levels within the body.

Mid-Week Call to Study Site (Day 3 or 4)

The volunteer will be instructed to contact study staff on day 3 or day 4 of taking study drug or the study staff will attempt to contact the volunteer. This information is also on the diary card. We will ask if the volunteer has had any unusual experiences since starting the study drug and if s/he has taken any medications other than the study drug and antipsychotic medication.

Visits 3-8 (weeks 1-6); (approximately 2-3 hours);

During Visits 3-8 of the study the volunteer will:

- Have weight, pulse and blood pressure measured
- Be asked questions about health and any current illnesses or medications (including over-the-counter medications, herbal remedies, alcohol consumption, and substances of abuse).
- Be asked a series of questions about how the volunteer is feeling within the past few weeks such as whether s/he has had anxious feelings, feelings of depression or difficulty concentrating. The staff will also

ask about symptoms that are commonly associated with schizophrenia using a clinical interview called the SCI-PANSS (Structured Clinical Interview – Positive and Negative Syndrome Scale)

- Study drug dispensed along with written instructions on how and when to take the study drug (except at Visit 8)
- Be asked a series of questions inquiring into any occurrences or events of note
- Complete a questionnaire about symptoms of paranoia and sexual functioning
- Complete a test on ability to recognize emotions called the Penn Emotion Recognition Test (ER-40).

Additionally at Visit 8 (week 6 or Early Termination);

- Complete a series of activities which will be used to measure process of thought called the CMINDS® and MSCEIT™ ME
- Have an additional blood sample taken (about 1 tablespoon) to monitor study drug levels in the blood
- EEG paradigm will be conducted

Follow Up Call

The volunteer will be asked to contact the study site one week after the last study drug dose to report taking any new medications or any unusual experiences since stopping the study drug.

Administration and dispensing of the study medication:

Except the one time challenge dose, this is a double-blind study, participants will be randomized to receive one of three possible intranasal study medications adjunctive to their antipsychotics: oxytocin 84 IU, oxytocin 168 IU or placebo (vehicle without oxytocin). Randomization will be performed stratifying gender groups, type of antipsychotic (typical versus atypical) and severity of symptoms based upon PANSS score (≤ 90 versus >90) so that gender, symptom severity and antipsychotic type are distributed relatively evenly across treatment groups. Bottles containing placebo or two different concentrations of oxytocin will be formulated (See Study Drug Formulation below) so that the concentration of oxytocin in the high dose (168 IU) will be double that of the low dose (84 IU). All subjects will be instructed to spray 7 pumps of the spray bottle (one in each nostril, alternating nostrils) to achieve correct dose in the morning and again in the afternoon. Subjects will be given enough study drug at the time of the visit to last until the next visit with extra to cover approximately three additional days. Each pump bottle has 5 ml (300 IU) which is enough for 2.5 days of study drug. Therefore, subjects will be given one spray bottle supply at the time of each visit. The weight of each bottle will be recorded prior to dispensing. After all procedures are performed on baseline visit and study drug is randomly assigned, a dose of the study drug will be taken at the study site, in the presence of a staff member to insure correct administration.

Study Drug Compliance

1. Subjects will be instructed on proper use of the nasal device from study staff.
2. Subjects will be given a diary card by the study staff to mark each use of the study drug in between site visits to the study site. This is to help subjects track study drug use. Subjects will be instructed to return study drug nasal spray bottles, used or unused, to the site at each visit along with the diary card.
3. Each bottle will re-weighed after return to estimate the amount of fluid remaining

STUDY DRUG:

Intranasal oxytocin is FDA approved as a lactation aid and was commercially marketed (Syntocinon®, Novartis) in the US up to the 1990's. It continues to be marketed commercially by Novartis in Europe and elsewhere. Oxytocin powder (Pictocin, Novartis) is readily available in the US and is used for intravenous

administration as a paruition stimulant in pregnant women. Both intravenous and intranasal oxytocin are well tolerated and safe (Hoover RT 1971) (see risk section of this Research Plan).

This study will use oxytocin powder supplied by Spectrum Laboratories and UCSD Investigational Drug Service (IDS) will make formulate both the Oxytocin and Placebo.

-Chlorbutanolhemihydrat	2.5mg
-Methyl-4-hydroxybenzoat	0.4mg
-Propyl-4-hydroxybenzoat	0.2mg
-Dinatriumphosphatanhydricum	1.9mg
-Acidumcitricumanhydricum	2.56mg
-Na-Sorbit	5.0mg
-Sorbitol 70%	25.0 mg
-Glycerin 85%	25.0mg
-Aqua pur.	q.s.

Comment: 1 IU is 1.7 micrograms oxytocin and 1 puff is 12 IU (=20.4 micrograms oxytocin)

STATISTICAL CONSIDERATION

Our primary analysis will be the comparison of subjects on oxytocin with subjects on placebo using a mixed model repeated measures analysis (MMRM). If this comparison is statistically significant then we use a linear contrast to investigate the dose-response between 84 IU (42 IU bid) and 168 IU (84 IU bid). We also have introduced an adaptive design that is consistent with FDA guidance for phase 2 studies when dosing groups are unclear (2010).

Sample Size Calculation. The primary efficacy measure will be change in PANSS total score from baseline to each visit. Based upon a preceding proof-of-concept study (Feifel et al. Biological Psychiatry, in press) with effect sizes (cross-over design) range from .40 to .53. An estimated sample size of 24 in the placebo group and 48 in the oxytocin group (24 in each dose group) is required to achieve 85% power to detect an effect size of 0.3 for time-averaged main treatment effect (Cohen's d for standardized mean difference between oxytocin and placebo treatment groups) using 6 repeated measurements having a AR(1) (first order autoregressive) covariance structures and assuming the correlation between observations on the same subject is 0.5, and the alpha level (Type I error rate) is 0.05 in a 2-sided test (Hintze, 2008). If we ignore the repeated measures design, an effect size of 0.5 will be detected with the same alpha and beta for the same sample size of 80 patients in the ratio of 2:1 for oxytocin:placebo.

The proposed sample size includes considerations for a single pre-specified, planned interim analysis for futility stopping based on conditional power (CP) (stochastic curtailing method) (Halperin et al., 1982; Lan et al., 1982) or an equivalent stopping boundary on interim Z-test value (B-value) (Lan and Witts, 1988). This interim futility analysis will be performed and reviewed by an external statistical consultant Cynthia Siu, PhD when 50% of the enrolled patients complete 6 weeks of follow-up. The adjusted critical value for an overall alpha of 0.05 (2-sided) in the final analysis is 0.0515 with resulting power 84.6% to detect a specified effect size of 0.3 or greater with 80 patients in the ratio of 2:1 for oxytocin:placebo (See Interim Analysis Plan below).

Futility Interim Analysis Plan. This randomized, double-blind study adopts an adaptive design with a single pre-specified, planned, unblinded interim analysis for futility stopping based on conditional power (CP) (stochastic curtailing method) (Halperin et al., 1982; Lan et al., 1982) or an equivalent stopping boundary on interim Z-test value (B-value) (Lan and Witts, 1988). The purposes of this formal interim analysis are to assess CP levels which are the probability of reaching statistically significant treatment difference at study end given the interim results. To avoid inflation of Type I error, no early stopping for efficacy is planned in this study. The unblinded data will be only available to external statistician Dr. Siu and not the PIs or other study staff.

It is well known that futility termination will reduce the Type I error rate (α) and inflate the Type II error rate ($\beta = 1 - \text{power}$ of the test), with the level of beta inflation bounded by P_{L0} , the probability of stopping for futility under the null hypothesis of no treatment effect (Lan et al., 1982; Lachin 2005). In order to maintain the design Type I error rate (α) at 5% and power close to 85%, we use an iterative procedure to determine the CP utility boundary values and the adjusted Z-test critical value in the final analysis, with 60% (P_{L0}) chance of stopping for futility under the null hypothesis. This provides: 1) a CP futility stopping boundary value equal to 0.3 at 50% enrollment (i.e. stop the trial if CP observed < 0.3) under the original design assumption (see Sample Size Calculation), 2) an adjusted Z-test critical value of 1.947 (ZF) for declaring significant treatment effect in the final analysis (or $P \leq 0.0515$), and 3) an overall power of 84.6%, i.e. 15.4% overall Type II error rate with 3.1% false negative error rate at interim look and 12.3% probability of continuing the trial and failing to reject the null hypothesis (false negative error rate) at study end.

In summary, we provide the following futility stopping rule for assessing interim results at 50% enrollment:

1. A recommendation to stop the trial for futility if CP value for comparing combined oxytocin vs. placebo (i.e. the probability that final study results will be statistically significant given interim data) is less than 30% under the original design assumption. An equivalent boundary for interim Z-test value is 0.253 (interim $P > 0.800$), interim B-value ≤ 0.179 , or if equivalently interim drift parameter estimate ≤ 0.358 .
 - a. If futility stopping criteria are met for the combined oxytocin group, we will examine CP and interim Z-test value for each dose (vs. placebo) to check if both dose groups meet a similar stopping criterion CP < 0.3 (or $P > 0.800$) for an overall α of 5% and an adjusted power of 80%.
 - b. In case of dropping only 1 dose arm and reallocation of remaining subjects to another arm we will use a fixed weighted Z-test method to protect the Type 1 error (Cui et al., 1999; Lan et al., 2005).
2. To declare the treatment effect significant if p-value computed at study end ($N=72$) is less than 0.0515.

This futility interim monitoring plan will include a vigorous data quality control to ensure successful signal detection in potential treatment effects. In addition to verifying validity of study design assumptions using the unblinded interim data, we will perform blinded, ongoing assessments of inconsistencies in the efficacy outcome measures, inter-relationships between efficacy variables, missing data patterns, and will implement a data management plan that has real-time capability to detect, query, and address data issues in the study.

Analysis Methods: The primary population for efficacy analyses includes all randomized subjects based on the intention-to-treat principle. The population for safety analyses will include all subjects who receive at least one dose of study medication. In the primary analysis, we test the hypothesis of difference in PANSS total change score (Week 6) between the combined oxytocin and placebo groups with adjustment for baseline score using a likelihood-based mixed-effects model for longitudinal data analysis (MMRM LDA) (Fitzmaurice and Ware, 2004). The MMRM LDA model can accommodate incomplete data under the assumption of ignorable attrition (see below under Missing Data). The same MMRM LDA model will be applied to evaluate the dose-response relationship using a linear contrast for the placebo and oxytocin dose groups, comparisons of treatment groups over time using treatment-by-visit (categorical visit variable) interaction term, and the trajectories of treatment responses over time based on time slope computed for each subject (continuous time variable).

Secondary efficacy measures will be the PANSS positive symptom and negative symptom subscales, PANSS general psychopathology subscale, CGI-S, CGI-I HAM-A, CCDS, GAF, cognitive scales as with the primary endpoint using the same MMRM LDA analyses. No multiplicity adjustment will be made in the secondary analyses. Appropriate descriptive statistics with 95% confidence intervals will be provided within and across treatment groups. Normal assumption will be checked and nonparametric alternatives will be considered if the assumption is seriously violated.

Mediators and baseline moderators of treatment effects on efficacy outcome measures will also be explored (Kraemer et al., 2006). The significance of moderator effects due to baseline characteristics (age, gender, initial

PANSS scores, duration of illness, class of medication) will be tested using treatment-by-baseline characteristic interaction terms in the MMRM LDA and/or ANCOVA models. To assess impact of improvement in one domain (e.g. positive symptoms) on the efficacy of a related symptom domain (e.g. negative symptoms), a mediator analysis model with terms for treatment, baseline, and positive symptoms improvement will be applied to determine significance of oxytocin effect on reductions in negative symptoms after adjustment for potential positive symptom improvement. We will perform similar mediator analysis for assessing inter-relationships between cognitive improvement and symptom improvement in positive and/or negative symptoms. In addition, cross-sectional baseline and longitudinal change score associations between treatment outcome measures and mediator effects will be assessed by including mediators as time-varying covariates in the MMRM LDA models (Diggle et al., 2001).

MU-Suppression. Data will be analyzed in two ways. Pearson rank correlations will be used to examine correlations between mu wave suppression in response to a single dose of OT and symptom severity at the end of 6 weeks of treatment. In additional exploratory analyses, mu suppression values will be split at the median into High suppressors and Low suppressors and followed up by correlations with symptom measures to determine if initial high suppression is correlated with greater improvement in symptom severity. Secondly, Pearson rank correlations will be conducted between mu wave suppression and symptom severity at baseline, and between mu wave suppression and symptom severity after administration of a single dose of oxytocin.

Safety Endpoints. The safety dataset will contain all subjects who take at least one dose of oxytocin. All adverse events will be coded using the most current version of the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of subjects reporting treatment-emergent adverse events will be tabulated within each dose group by treatment, system organ class (SOC) and MedDRA-preferred term. Treatment-emergent adverse events will be those adverse events that begin or worsened following the first dose of study drug. Adverse events will be further classified by severity and investigator-assigned relationship to study drug.

Clinical laboratory values and vital signs measured at the end of each treatment period will be analyzed using ANOVA, with factors sequence, period and treatment. Dose-response relationships will be explored and any laboratory values that fall outside normal ranges will be identified.

Missing Data. Some observations may be missing after baseline assessment. Individual missing items in all scales will not be imputed. All subjects expressing the desire to discontinue the study will be asked to come in for a final assessment, prior to stopping their medications. The primary analysis will be based on the likelihood based mixed-effects model (MMRM LDA) which provides valid estimates of treatment effect under the missing at random (MAR) assumption. The assumptions about random dropout and MAR can be tested using methods proposed by Diggle et al. (2001) and dropout cohort visualization as in Potkin et al, (2009). Two sensitivity analyses will be conducted to evaluate the robustness of results: one based on a mixed-effects model for missing not at random (MNAR) data with covariate adjustment for dropout measures (Wu and Follmann, 1999; Wu et al., 2001), and the other based on the usual LOCF-ANCOVA method with missing data following dropout imputed by an individual's last observed measurement. Further details are provided in the Statistical Analysis Plan, which will clearly specify the mixed-effects model methodology, sensitivity analyses, and evaluation of the assumptions.

10. HUMAN SUBJECTS

The proposed study will involve participants meeting DSM-IV-TR criteria for Schizophrenia. After completing a screening process, eligible participants will complete weekly study visits during a 7 week time period.

Approximately 71 subjects will be entered into the study at this site. Patients will be recruited from the outpatient services at UCSD Medical Center, a large program with over 2000 active patients and serving a large area in mid-town San Diego. Participants will be 21 years and older and will be in good general health.

Subjects will be selected according to the following inclusion/exclusion criteria:

Inclusion Criteria:

1. Adult men or women, 21 years of age or older.
2. Meet DSM-IV criteria for Schizophrenia
3. Women of childbearing potential must test negative for pregnancy at the time of enrollment based on urine pregnancy test and agree to use a reliable method of birth control during the study.
4. Must be on a therapeutic dose of 1 or 2 atypical or typical antipsychotic medications (for example, but not limited to: Clozapine, Olanzapine, Risperidone, Ziprasidone, Aripiprazole, Seroquel) with no major dose changes for at least 4 weeks.
5. A minimum PANSS total score of 55 at baseline and a score of at least 4 (moderate) on the subscale of the PANSS (suspiciousness/persecution) at screening.
6. Have a Clinical Global Impressions-Severity (CGI-S) scale score of at least 4 (moderately ill) at baseline.
7. Must be able to communicate effectively with the investigator and study coordinator and have the ability to provide informed consent.
8. Must be able to use nasal spray.
9. Must demonstrate an acceptable degree of compliance with medication and procedures in the opinion of the investigator.

Exclusion Criteria:

Subjects will be excluded from the study if they meet any of the following criteria:

1. Are pregnant or are breastfeeding
2. A urine drug screen performed at screening must not show evidence of recent use of drugs of abuse
3. Any active medical condition that in the opinion of the investigator will interfere with the objectives of the study
4. Are unsuitable in any way to participate in this study, in the opinion of the investigator.
5. Another current DSM-IV diagnosis other than Schizophrenia

Vulnerable populations will not be involved in this study.

Permitted:

Subjects taking up to two sleep medications (diphenhydramine, zolpidem, zaleplon, or diazepam), at a reasonable dose as judged by the investigator, are permitted in this study.

Minor adjustments in sleep medication are acceptable. Patients will be asked to notify the study doctor of any changes to sleep aids.

Discontinuation Criteria

The criteria for enrollment must be followed explicitly. If a subject who does not meet enrollment criteria is inadvertently enrolled, that subject should be discontinued from the study. In addition, subjects will be discontinued from the study and/or from the study in the following circumstances:

1. If Exclusion Criteria, as listed above, are observed or develop after entry or enrollment, the subject will be discontinued from the drug/study at the next visit or sooner in the event of a safety exclusion criterion.
2. The subject or attending physician requests that the subject be withdrawn from the study.

No subjects will be excluded from participation based on race, ethnicity or gender.

If patients need to be discontinued due to lack of efficacy or intolerance from study medication a study psychiatrist will meet with them and assess their clinical status. Additionally, addressing the patient's ongoing treatment needs (once out of the study) is proactively addressed with the patient on study entry, as in many cases anxiety disorders are chronic conditions in need of ongoing care. Study psychiatrist will discuss non-investigational options for controlling subjects anxiety taking into account treatments subjects has been on in the past, if any. In collaboration with subject, study physician will initiate any treatment of anxiety as deemed appropriate. A referral plan will be developed with subject for him/her to continue treatment with an outpatient psychiatrist. Subject will be followed and cared for by study physician without cost to subject until subject has been able to transfer care to another provider or until patient is deemed stable and has chosen not to pursue care by another provider. After study care of subject will be documented in a medical record.

Sources of Materials

-Data that will be collected from human subjects for this project includes ratings scales interviews and responses to patient self-rated scales. In addition, blood and urine samples will be collected to perform routine laboratory tests and drug screens.

-Access to individually identifiable private information about human subjects will be limited to research staff affiliated with the project. Research records will be kept confidential to the extent provided by law. The collection and submission of medical information will be accomplished with strict adherence to professional standards of confidentiality. Patients' medical information will be held in a secure location.

-Data regarding schizophrenia symptom severity will be collected via interviews with a staff clinician and via patient self-rated scales. Study coordinators will also conduct an interview to establish a medical and psychiatric history for each patient. Blood and urine samples will be collected via the UCSD Medical Center Outpatient Phlebotomy Center. All data will be collected specifically for the proposed research project.

11. RECRUITMENT

Potential subjects will be recruited through several sources. Ads/flyer will be posted in adult clinics, day treatment programs in the county and distributed to colleagues. Approval may be sought from San Diego County Mental Health for recruitment from county run facilities. Recruitment Flyer is included with this application.

12. INFORMED CONSENT

Prior to entry in the trial, the investigator(s) will explain to the potential subjects the aims, methods, reasonably anticipated benefits, and potential hazards of the trial and any discomfort it may entail. Subjects will be informed that they are free to not participate in the trial and that they may withdraw consent to participate at any time. They will be told what alternative treatments are available if they refuse to take part and that such refusal will not prejudice future treatment. Finally, they will be told that competent physicians/lab personnel may examine their records but that personal information will be treated as strictly confidential and will not be publicly available. Subjects will be given the opportunity to ask questions about the study. After this explanation and before entry to the trial, the subject's consent will be obtained. If signed informed consent cannot be obtained, the subjects will not be included in the trial. Subjects who are conservatorized will be able to participate in this study if their conservator signs consent.

13. ALTERNATIVES TO STUDY PARTICIPATION

In order to receive treatment for this disorder it is not necessary to participate in this clinical trial. There is a large variety of FDA approved antipsychotic medications available by prescription from the patient's physician/psychiatrist.

Alternative treatments for schizophrenia include the use of conventional antipsychotic medications, such as, but not limited to, risperidone, olanzapine, quetiapine, or haloperidol. Each of these medications carries their own risk of side effects which can include transient or permanent tardive dyskinesia. Potential benefit of these alternate treatments may include the availability of greater scientific information regarding the medications because these medications are FDA-approved and readily available.

14. POTENTIAL RISKS

All medications have side effects and some of these can be unexpected and unforeseen. Subjects will be closely monitored throughout the trial duration and subjects will be provided emergency contact numbers to ensure 24-hour monitoring.

Nasal Inhalation Oxytocin

The FDA (see appended letter) notes “lack of safety concerns” associated with the clinical use of oxytocin despite “the length of marketing history of this product in the U.S., the continued availability of the injectable oxytocin in the US and the IN form outside the US” A drug insert provided with IN nasal oxytocin in Europe where it continues to be marketed for lactation lists the following risks; painful uterine contracts; in rare occasions, allergic skin reactions, nausea or headache. Several published studies have used various doses (18- 360 IU) of IN oxytocin administered once to more than a week (e.g. Anseau et al, 1987; Epperson 1996 ; Fehm-Wolfsdorf et al , 1988; Westenberg ,1992; Kosfeld et al 2005; Ruis et al, 1981; Heinrichs et al 2003; Fewtrell et al 2005; Bruins et al 1992.) Most studies do not report any adverse effects. One case (Anseau et al, 87) of a patient developing reversible memory loss, psychosis, and a decrease in plasma sodium and osmolality is reported which is consistent with a picture of SIADH. Some studies reported decreases in verbal recall and memory whereas others did not find this. Other rare mild and transient effects were reported in some studies including, dry mouth, mild dizziness, mild headache, and mild nasal irritation. No effect on blood pressure has been noted.

Risks of Blood Draw

During the study, blood will be drawn 8 times for chemistry basic panel. Some problems from this are: pain, bleeding, bruising, swelling, dizziness, fainting, in rare cases, infection at the insertion site.

Additional Risks

Since this is an experimental treatment there may be some unknown risks that are currently unforeseeable. Subjects will be informed of any significant new findings.

Symptoms of schizophrenia may not improve or may worsen. There is also the possibility that there may be unforeseen risks associated with this test article, which are not yet known.

Allergy Risks

As with any drug, there is a chance that the subjects may have an allergic reaction to the drug. Symptoms of an allergic reaction may be a skin rash, hives or more serious problems like trouble breathing and shock. It is not possible to predict in advance who will develop these problems.

Female subjects will be instructed to use one of the following acceptable methods of birth control throughout the study:

- oral or patch contraception
- Depo-Provera® or other intramuscular injection
- implantation of levonorgestrel (Norplant®) system or an IUD
- barrier methods (combination of diaphragm and spermicide or condom and spermicide)

Risk of Disclosure

Subjects will be asked to provide a urine sample to be tested for certain types of controlled substances that may be regulated by law. Additionally, information about subjects' mental and physical health collected

throughout the study will also be kept with research records. Disclosure of this kind of information is a risk of being in the study. Disclosure of this kind can affect a subjects' ability to get a job, obtain life or health insurance, employment or ability to adopt children. Confidentiality risk will be managed by keeping subjects' information completely confidential, stored in a secured location and disclosed only as required by law.

Other Risks

Participation includes a urine toxicology and pregnancy test. It is possible that a positive drug screen may become known outside of the research setting and it could potentially jeopardize the subjects' ability to acquire a job or insurance.

EEG mu suppression paradigm exposes subjects to the application of electrodes. The possibility of skin irritation from application of paste exists, however, is unlikely given that the salt concentration of the paste is similar to that of human sweat.

As with any drug, participants are faced with the possibility of side effects. Other studies of oxytocin report side effects such as dry mouth, mild dizziness, mild headache, and mild nasal irritation. Because the treatment proposed in the study is investigational, there is a risk that participants' symptoms of schizophrenia may stay the same or worsen. There may also be other risks or side effects which are currently unknown. Possible side effects from venipuncture include faintness, inflammation of the vein, pain, bruising, or bleeding at the site of puncture. There is also a slight possibility of infection as a result of the blood draw procedure. Women of child-bearing potential are asked to utilize an approved method of birth control during study participation as risks to a fetus are unknown. Urine and blood samples collected during this study will be utilized to screen for illicit chemical substances. The results of these tests will be kept confidential and may be disclosed as required by law. It is possible that positive drug screen results may become known outside of the research setting; if this information were disclosed, it could potentially jeopardize a subject's ability to obtain employment or insurance. Additionally, some of the information to be collected for this study includes information on patient diagnosis. There is a risk that this information can become known outside of the research setting. This information, if disclosed, could also potentially jeopardize a patient's ability to obtain employment or insurance. The study staff will manage this risk by storing all study information in a secure location in a locked facility. No information about subject participation will be provided to anyone outside of the necessary research staff without subject's written permission.

Potential subjects will be recruited through several sources in the community surrounding the UCSD Medical Center. Flyers will be posted in adult clinics, day treatment programs, and distributed to colleagues. Advertisements will be placed in local community publications and online forums, and a local press release will be made.

Prior to entry in the trial, the investigator(s) or study coordinator(s) will explain to the potential subjects the aims, methods, reasonably anticipated benefits, and potential hazards of the trial and any discomfort it may entail. Subjects will be informed that they are free to not participate in the trial and that they may withdraw consent to participate at any time. They will be told what alternative treatments are available if they refuse to take part and that such refusal will not prejudice future treatment. Finally, they will be told that competent physicians/lab personnel may examine their records but that personal information will be treated as strictly confidential and will not be publicly available. Subjects will be given the opportunity to ask questions about the study. After this explanation and before entry to the trial, the subject's consent will be obtained and documented via signature of an informed consent form by both the patient and the person conducting the informed consent discussion. If signed informed consent cannot be obtained, the subjects will not be included in the trial. Subjects who are conservatorized will be able to participate in this study if their conservator signs a consent form on their behalf.

15. RISK MANAGEMENT PROCEDURES AND ADEQUACY OF RESOURCES

A staff that is highly qualified in the assessment and treatment of schizophrenia in adults will closely monitor subjects in this study. This monitoring includes the frequent periodic assessments involved in the study protocol, which occur at intervals of 1 week long. Study drug will be administered on site following both baseline visits. Mid-week calls are set up following both baseline visits along with a study treatment follow up visit. In addition, subjects will be monitored throughout the study for any adverse events. Subjects will be instructed by the Investigator to report the occurrence of any adverse events immediately. At the beginning of each treatment period, the Investigator will query the subjects, in a generalized fashion, whether any clinical adverse events have occurred since the last visit. Any serious or unexpected event, including death due to any cause, whether or not related to the study drug or procedures, will be reported to the UCSD HRPP within 10 days.

After a thorough literature search was performed and confirmed the relative safety profile of this drug, the following additional safety measures were added in an attempt to be thorough.

Biological safety measures include blood chemistry and urine osmolality to monitor for SIADH. These tests will be done at screening and at every visit after randomization. In addition a blood metabolic assay (glucose, liver enzymes) will be conducted at each visit.

If any clinical worsening or serious adverse event is detected during the course of the trial that cannot be managed by a dose adjustment, the subjects will be discontinued from the protocol.

It is my intention to provide contact information for study staff to the subjects and reiterate this information at the time of each visit. Contact information for PI, and Drs. MacDonald and Becker, are listed on the diary form that will be provided to the subject at each visit. Study subjects will be encouraged, as documented in the consent and on the separate diary form, to contact the study team with medical concerns, reactions, and experiences. Subjects will be given a diary form to complete upon each use for administrations that are done between site visits. This diary form includes 24 hour emergency contact information (including PI, sub-Is and study staff), nearest emergency department from subject's residence and concomitant medication diary.

At the termination of the project or in the event that any subjects will need to be discontinued from the study due to lack of efficacy or an adverse event, one of the study doctors will arrange for subjects to receive appropriate treatment for any symptoms that require stabilization. The study staff will also help arrange routine follow-up for subjects' symptoms of schizophrenia (e.g., referral if required) and will provide standard medication treatment of schizophrenia to subjects until such follow up is available.

Subjects will have 24-hour access to emergency psychiatric care and will be provided with a means of contacting the on-call study doctors and research staff at the UCSD Medical Center. Subjects will be informed and encouraged to contact study physicians and staff immediately with medical concerns or unusual reactions. This information will also be listed on the diary cards provided to subjects at every visit along with the identification of the closest Emergency Department location to their residence. PI and sub-investigator phone numbers for 24-hour access has been listed in the consent form.

Confidentiality risk will be managed by keeping all of each subjects' data completely confidential, and stored in a secured filing cabinet and on Clinical Conductor, a secure, password protected clinical trials administration database. The data collected for this investigation will be used for research and treatment purposes only. Data will be available only to those directly involved with the study, HRPP, and the FDA.

Research records will be kept confidential to the extent allowed by law. The following people will have access to the study data collected for this study: Dr. Feifel and study staff listed below, UCSD HRPP, the grant funding agency, National Institute of Mental Health, representatives of the grant funding agency and government agencies where permitted or required by law (such as the Food and Drug Administration (FDA) and the United States Department of Health and Human Services).

Research records will be kept confidential to the extent provided by law. The National Institute of Mental Health, including its agents and contractors, the United States Food and Drug Administration or other regulatory authorities, and similar ethics committees and regulatory agencies in other countries, as well as the UCSD Institutional Review Board, may review original medical and research records in connection with this study. Medical records that contain subject identity will be treated as confidential and will be shared only with these agencies, or as required by law. Medical information may be held and processed on a computer. The results of this research may be published in scientific journals or presented at medical meetings, however subject name will not appear in any publications or reports produced from this study.

16. PRIVACY AND CONFIDENTIALITY CONSIDERATIONS INCLUDING DATA ACCESS AND MANAGEMENT

In order to maximize patient privacy, all consenting will be done in a private room in an office, where the participant can ask questions without feeling uncomfortable or embarrassed. If and when the study doctor needs to perform a physical exam, the patient will be provided with a private room to undress and dress. While receiving the physical exam the only person who will be in the room other than the patient will be the study doctor conducting the exam. If, however, the study doctor is of the opposite gender to the patient, a staff member of the same gender as the patient will also be in the room during the physical exam.

Confidentiality will be maintained through physical and electronic security measures. The study office where patient files are maintained is kept locked, and only authorized research staff are allowed access. Research participant information stored electronically is maintained on computers with appropriate UCSD approved security firewalls, password protection, and other data storage safety measures.

Once a subject has enrolled in the study, a sequential Subject Identification (SubID) Number will be assigned. The SubID number is to be recorded on all study documents and will link the study treatment and the study documents to the subject's name and medical record. To maintain confidentiality, the subject's name will not be recorded on any study document other than the informed consent.

Patient's blood or urine sample will be tested for certain types of drugs (known as controlled substances in the United States) that may affect behavior and that may be regulated by law. If test results show that they have taken these types of drugs, they will be notified. The results of this test will be kept confidential and disclosed only as required by law. It is possible that positive drug screen results may become known outside of the research setting. If this information was disclosed, it could potentially jeopardize their ability to get a job or insurance.

17. POTENTIAL BENEFITS

No direct benefit can be guaranteed to the individual subjects. The subjects may benefit from the formal diagnostic procedures, required assessments, and increased scrutiny during the study, which are more rigorous than the community standard for diagnosis and assessment. A more general benefit of this study will be a greater understanding of the benefits of intranasal oxytocin augmentation.

18. RISK/BENEFIT RATIO

The potential benefits of this investigation outweigh the risks involved. Subjects will continue on their current regimen of antipsychotic therapy. If intranasal oxytocin is found to decrease associated symptoms, it could potentially benefit many people. All subjects will be receiving close medical supervision and an active antipsychotic. The health and safety of individual subjects will be the top priority of all study investigators.

Current treatments available for schizophrenia are unsatisfactory, and many patients continue to suffer from their symptoms even with treatment. Information obtained as a result of this trial may assist in the

development of superior treatments for schizophrenia and related illnesses.

19. EXPENSE TO PARTICIPANT

There is no expense to the subjects for any of the research activities.

20. COMPENSATION FOR PARTICIPATION

Subjects will receive \$80 per visit (paid at each visit) to compensate them for time, travel and inconvenience.

If a separate visit is required to complete the Mu-suppression paradigm subjects will be compensated an additional \$50 per extra visit.

21. PRIVILEGES/CERTIFICATIONS/LICENSES AND RESEARCH TEAM RESPONSIBILITIES

Dr. David Feifel is a board certified Psychiatrist and Director at the UCSD Neuropsychiatry and Behavioral Medicine Unit, with privileges at UCSD Medical Center and is eligible to practice in California. William Perry, PhD and Arpi Minassian, PhD will oversee the cognitive measures included in the study and the study as a whole. Dr. Fiza Singh is a board eligible Psychiatrist with privileges at UCSD Medical Center and is eligible to practice in California and will oversee EEG and mu-suppression procedures. Allison Hadley, MD, Kaimana MacDonald, MD and Dr. Alexandar Papp are psychiatrists here at UCSD Medical Center working within the NBMU. Physicians in the trial will be responsible for reviewing safety data for patients, perform GAFs, perform physical exams, review lab results, review a subject's appropriateness based on study inclusion / exclusion criteria and diagnostic measures, dosing decisions and performing some study rating scales. Rebecca McKinney, BA and Patrice Cobb, BA have extensive experience in administration of standardized psychoeducational scales, diagnostic instruments, and ratings that will be utilized. Patrice Cobb, BA will be lead coordinator for this study. She will be responsible for collecting adverse event and concomitant medication information through open ended questions that will be reviewed with the physician. In addition, she has received training on the outcome measures and cognitive evaluations to be used in this study. She will assist with vitals collection and lab collection, coordinating procedures such as scheduling patients for visits, evaluating a subject's appropriateness for the study with inclusion/exclusion criteria, reviewing diary cards and instructing patients on proper dosing, doing accountability, helping to recruit subjects and dispensing study drug from Investigational Drug to subjects. She has also been trained to administer informed consent for this study. Nicholas Schaffner, BA will be assistant coordinator for this study. They will help follow patients through the study and correspond with the grant institution, clinicaltrial.gov, and assist with communication with HRPP.

Additional research staff that may assist in following patients, querying patients for AEs, conduct ratings and patient interviews, instruct patients on proper dosing, conduct cognitive testing, do drug accountability, performing vitals and collecting labs as outlined in this study, reviewing diary cards, schedule patients, and help recruit subjects are the following: Travis Gault, and Katie Wheeler.

De-identified data will be shared with Dr. Steven Potkin and the University of California, Irvine's fBIRN laboratory as a part of an approved National Institute of Mental Health collaborative grant. This data will be stripped of any identifying information and will be used for analysis purposes only.

22. BIBLIOGRAPHY

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23. FUNDING SUPPORT FOR THIS STUDY

A grant of \$250,000 (over two years) was approved by the National Institute of Mental Health for this research project. This grant will not be awarded until the final HRPP approval is given.

24. BIOLOGICAL MATERIALS TRANSFER AGREEMENT

Not applicable as all scheduled blood lab work for this study will be processed on site. All urine testing will be performed by clinical trial staff.

25. INVESTIGATIONAL DRUG FACT SHEET AND IND/IDE HOLDER

See Appendix for intranasal Oxytocin drug fact sheet. Access to study drug, appropriate licensing, dispensing, accountability and storage will be closely regulated throughout the course of this study. The investigational drugs will be received, dispensed and accounted for by the Investigational Drug Service at UCSD Medical Center located at the following address:

Investigational Drug Service, RM 1-317

UCSD Medical Center
Department of Pharmacy

200 West Arbor Drive
San Diego, CA 92103-8765

26. IMPACT ON STAFF

All members of the clinical research staff are experienced in conducting protocols of this nature and have all the necessary resources and training. There will be no impact on in-patient or other non-research hospital staff as this is an out-patient protocol.

27. CONFLICT OF INTEREST

No conflict of interest between PI and Sub-Investigators and the granting institution, National Institute of Mental Health.

28. SUPPLEMENTAL INSTRUCTIONS FOR CANCER-RELATED STUDIES

Not applicable

29. OTHER APPROVALS/REGULATED MATERIALS

Not applicable

30. PROCEDURES FOR SURROGATE CONSENT AND/OR DECISIONAL CAPACITY ASSESSMENT

Subjects who have impaired intellectual capacity to comprehend the informed consent as demonstrated using the "Capacity to Consent Form" (included with this submission) will not be enrolled in this study. Patients who are conservatorized will only be included if they consent to be in the study and their designated conservator consents. In many instances, conservatorized patients have the cognitive capacity but not the legal capacity to consent to treatment. If a conservatorized patient demonstrates cognitive capacity to provide consent based upon the "capacity to consent form" AND consents to participating in this study, then the potential subject's conservator will be contacted, informed of the subject's consent. Informed consent for the subject's participation will then be sought from the legal conservator as described in item 11 above (without "capacity to consent form") and he/she will be asked to sign the "Legal Conservator" signature line below the subjects signature. Thus, conservatorized subjects will only be enrolled if they demonstrate (cognitive) capacity to consent, consent to participate, and their legal conservator provides informed consent.

Version date: May 11, 2011