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A Randomized Clinical Trial of Oxytocin or Galantamine for the Treatment of Negative Symptoms and Cognitive Impairments in People with Schizophrenia

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Abstract

Purpose/Background—Negative symptoms and cognitive impairments tend to co-occur in people with schizophrenia. If their association with each other is due, in part, to shared pathophysiology, then this suggests that a single drug could potentially be effective for both domains. The current study was designed to examine this hypothesis.

Methods/Procedures—Fifty-eight participants with either DSM-IV-TR schizophrenia or schizoaffective disorder entered into a 6-week double-blind, placebo-controlled, double-dummy, randomized clinical trial of intranasal oxytocin and galantamine. Seventeen participants were randomized to intranasal oxytocin, 20 were randomized to galantamine and 21 were randomized to placebo. The Scale for the Assessment of Negative Symptoms total score was used to assess change in negative symptoms (the primary outcome measure for oxytocin). The MATRICS Consensus Cognitive Battery composite score was used to assess cognition (the primary outcome measure for galantamine).

Findings/Results—There were no significant group differences for negative symptoms (oxytocin versus placebo: F=0.19, df=2, 47.4, p=0.83; galantamine versus placebo: F=0.41, df=2, 52.5, p=0.67). There were no significant group differences for cognitive impairments (galantamine versus placebo: t= 0.71, df=40, p=0.48; oxytocin versus placebo: t= 0.50, df=40, p=0.62). There

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Conflict of Interest: Robert W. Buchanan: DSMB member: Consultant: AbbVie; Advisory Board: AbbVie; Amgen; Boehringer Ingelheim-RCV; EnVivo; Lundbeck; Takeda; Deanna L. Kelly: Advisory Board: Otsuka, XOMA and Janssen; Elaine Weiner: no competing interests or financial support to disclose; James M. Gold: Consultant: Amgen and Hoffman LaRoche; and receives royalty payments from the BACS.; Gregory P. Strauss: receives royalties and consultation fees from ProPhase LLC in connection with the commercial use of the Brief Negative Symptom Scale and other professional activities; Maju M. Koola: no competing interests or financial support to disclose; Robert P. McMahon: no competing interests or financial support to disclose; and William T. Carpenter: Consultant: HealthAnalytics and Pharmagenesis; Advisory Board: Allergen and Teva.

were also no significant group differences for the functional capacity or ancillary symptom measures.

Implications/Conclusions—The lack of an efficacy signal for either compound precluded our ability to test whether pharmacological treatment pathways for negative symptoms and cognitive impairments overlap or are independent. (clinicaltrials.gov trial number: NCT01012167)

Keywords

schizophrenia; oxytocin; galantamine; cognition; negative symptoms

Introduction

Negative symptoms and cognitive impairments tend to co-occur in people with schizophrenia[1]. However, it is not known whether the association between these two domains is based on shared pathophysiology or the effect each has on the assessment of the other[2]. If the association between negative symptoms and cognitive impairments is due, in part, to shared pathophysiology, then this suggests the hypothesis that a single drug could potentially be effective for both domains. However, if there is limited overlap in pathophysiology, then separate medications would be required.

In order to test this hypothesis, we selected two agents, for which, at the time of study initiation (2009), there was preliminary evidence for their potential efficacy for these domains. We selected intranasal oxytocin for the treatment of negative symptoms, because preclinical studies suggested that oxytocin improves social behavior, including retention of social memories[3], duration of social contacts[4,5], and social affiliation in rats exposed to maternal stress (J. Koenig et al, unpublished data). In addition, single-dose intranasal oxytocin transiently improves various aspects of social cognition in healthy human controls[6-11]. Finally, initial descriptive studies suggested oxytocin levels were abnormal in people with schizophrenia[12]. We selected galantamine for the treatment of cognitive impairments, because agents that modulate the α7 nicotinic receptor have been hypothesized to be effective for the treatment of cognitive impairments in people with schizophrenia[13]. In addition to its ability to inhibit acetylcholinesterase, galantamine is a positive allosteric modulator at the α4β2 and α7 nicotinic receptors[14-16]. In a previous study, we found that galantamine was effective for processing speed and verbal memory[17]. Similar results were observed in some[18,19], but not all[20], other studies with galantamine. In addition, two studies with the α7 nicotinic receptor partial agonist, 3-[(2,4-dimethoxy)benzylidene] anabaseine (DMXB-A), suggested that α7 nicotinic receptor agents could improve cognition[21,22].

In the current randomized clinical trial, we tested whether similar or different pathways were associated with the treatment of negative symptoms and cognitive impairments by determining the effect of intranasal oxytocin and galantamine on these two domains. We hypothesized that intranasal oxytocin would improve negative symptoms and galantamine would selectively improve cognitive function in people with schizophrenia.

Materials and Methods

Participants

Inpatients or outpatients, between 18 and 65 years, who met DSM-IV-TR criteria for schizophrenia or schizoaffective disorder were selected for study entry. Participants were diagnosed using a best estimate diagnostic approach, which utilized information from the Structured Clinical Interview for DSM-IV[23], direct assessment, family informants, and past medical records. Participants were required to be clinically stable, in the non-acute phase of their illness, and meet retrospective and prospective criteria for persistent negative symptoms[24,25]. The retrospective determination of persistence was based on the best-estimate diagnosis and/or therapist report. The prospective definition of persistence used negative symptom assessments completed at the beginning and end of a 4-week Evaluation Phase. Participants were required to demonstrate a minimum level of negative symptoms, defined as a modified Scale for the Assessment of Negative Symptoms (SANS) total score ≥ 20 or alogia global score ≥ 3[25]. They were also required to not exceed specified levels of positive symptoms (i.e., Brief Psychiatric Rating Scale (BPRS)[26] positive symptom total score ≤ 16); affective symptoms (i.e., BPRS Anxiety/Depression factor score ≤ 14); and extrapyramidal symptoms (i.e., Simpson-Angus Extrapyramidal Symptom Rating Scale (SAS)[27] total score ≤ 10).

In addition, participants were required to have been on the same antipsychotic(s) for 2 months and the same dose(s) for one month. If prescribed other psychotropic medications, they were required to have been on the same drug and dose for at least 30 days. Participants with a DSM-IV-TR diagnosis of alcohol or substance abuse (other than nicotine) within the last month, alcohol or substance dependence (other than nicotine) within the last 6 months, or mental retardation; or who had an unstable medical condition were excluded. Pregnant and lactating female participants were excluded.

The University of Maryland School of Medicine and the State of Maryland Department of Health and Mental Hygiene IRBs approved the study protocol and informed consent procedures. Written informed consent was obtained from all participants after study procedures had been fully explained and prior to study participation. Participant ability to provide valid informed consent was documented using study specific procedures.

Clinical Assessments

The modified SANS total score was the primary measure used to assess negative symptom change[25]. The BPRS positive symptom item total score was used to assess positive symptom change. The four BPRS positive symptom items are: conceptual disorganization, hallucinatory behavior, unusual thought content, and suspiciousness. The Calgary Depression Scale (CDS)[28] total score was used to assess depressive symptom change. The Clinical Global Impression (CGI) severity of illness item was used to assess global clinical changes. The SANS, BPRS, CDS, and CGI were obtained at the beginning and end of the Evaluation Phase and biweekly during the Double-Blind Treatment Phase. Intraclass correlation coefficients for these instruments ranged from 0.76 to 0.90. All raters were blind to treatment assignment.

Neuropsychological and Functional Capacity Assessments

The MATRICS Consensus Cognitive Battery (MCCB) and the Rapid Visual Information Processing Test (RVIP) were used to assess neuropsychological test performance. The MCCB is comprised of 10 tests, which assess seven cognitive domains[29]. The MCCB composite score is a standardized mean of the seven domain scores. T-scores are standardized to normative data, and have an estimated mean of 50 and SD of 10 in the general healthy population[30]. The RVIP is a computerized measure of sustained attention[31], which requires participants to respond when they see a target sequence of 3 odd or 3 even digits in a stream of single digits (from 1 to 9) presented at a rate of 1/600ms.

A modified version of the UCSD Performance-Based Skills Assessment (UPSA)[32], the UPSA-2, was used to assess functional capacity. In comparison to the UPSA, the UPSA-2 contains a sixth component: Medication Management, and the content complexity and number of items required to be remembered are increased for the Comprehension/Planning, Financial Skills, and Transportation components to reduce potential for ceiling effects. The MCCB, RVIP, and UPSA-2 were administered at the end of the Evaluation and Double-blind Phases.

Safety Assessments

A standard blood chemistry panel, complete blood count, urinalysis, and EKG were obtained in the Evaluation Phase and at the end of the Double-Blind Treatment Phase. Female participants of child-bearing potential had a biweekly pregnancy test. The SAS, the Abnormal Involuntary Movement Scale (AIMS)[33] and the Barnes Akathisia Scale (BAS)[34] were used to assess extrapyramidal symptoms (EPS), dyskinetic movements and akathisia, respectively. The SAS, AIMS and BAS were administered at the end of the Evaluation and Double-blind phases. The Side Effect Checklist (SEC) was used to assess side effects and monitor vital signs. The SEC is comprised of 32 common side effects, which are rated on a 1 (none)-4 (severe) scale. The SEC ratings were conducted at the end of the evaluation phase and weekly through the study.

Oxytocin Levels

Plasma oxytocin levels were determined via radioimmunoassay using a magnetic bead kit from Phoenix Pharmaceuticals, Inc. Samples were assayed in duplicate; the average of these samples was taken as the final oxytocin value. Assay sensitivity was 5 pg/ml with minimal cross reactivity with vasopressin. The coefficient of variation averaged 5-8% across the assays. Plasma oxytocin levels were obtained at the end of the Evaluation and the Double-blind Phases.

Study Design

The study consisted of a 4-week Evaluation Phase and a 6-week Double-Blind Treatment Phase. After participants signed consent, they entered the Evaluation Phase, during which they underwent medical screening and baseline symptom, safety and cognitive assessments. Participants who met inclusion criteria entered the 6-week Double-Blind Treatment Phase and were randomized to one of three treatment regimens: active intranasal oxytocin and placebo galantamine; placebo intranasal oxytocin and active galantamine; or placebo

intranasal oxytocin and placebo galantamine. The intranasal oxytocin dose was 24 IU twice a day. Victoria Apotheke Zuerich (Pharmaworld.com) provided the intranasal oxytocin (Syntocinon® from Novartis Pharmaceuticals) and matching intranasal placebo oxytocin. The intranasal oxytocin concentration was validated by the University of Maryland School of Pharmacy GMP facility. All participants were educated and received a practice intranasal saline dispenser to ensure proper use of the intranasal oxytocin. The galantamine target dose was 12 mg twice a day; the following titration schedule was used: 4 mg twice a day for 1 week, then 8 mg twice a day for 1 week, then 12 mg twice a day for 4 weeks. The galantamine was purchased from Value Drug Company, Duncansville, PA and blinded by Zonetak Pharmacy, Owings Mills, MD. Participants were assigned study treatment from a list of random assignments generated using permuted block randomizations with variable block sizes. In response to a randomization request, the biostatistician sent a code number to the unblinded pharmacist, which identified the next treatment selection to be dispensed from the treatment sequence.

If a participant could not tolerate their study medication, they were instructed to skip a dose and then resume treatment with the prescribed dose. If the participant was still unable to tolerate their study medication, then the dose could be lowered to alleviate side effects.

Medication compliance was assessed by weekly pill count and weight of returned intranasal bottles. All participants who received 75% or more of their assigned study medication were considered compliant.

Statistical Analyses

The Hedeker and colleague method to estimate power for linear contrasts in longitudinal data with attrition was used to calculate sample size for the oxytocin versus placebo SANS total score comparison[35]. We found that 40 participants per group would provide power=0.80 (testing at alpha=0.025 to allow for multiple primary outcomes) to detect a 6 point group difference in the SANS total score (an effect size of 0.5 s.d.). Prior clinical trial data was used to estimate the correlations among baseline and post-randomization SANS total scores[25,36].

In the primary analysis, a post hoc contrast from a mixed model for repeated measures analysis of covariance (MM-ANCOVA): follow-up SANS total score = baseline SANS total score + week + treatment + treatment × week, where the correlation between repeated follow-up measurements was modeled using an unstructured covariance matrix, was used to test for SANS total score final study visit group differences. In this model, the treatment term estimates the average group difference (across weeks), and the treatment × week interaction term allows post hoc group comparisons at particular weeks. SAS® PROC Mixed was used to fit these models, using the Kenward-Rogers approximation to calculate degrees of freedom for hypothesis tests. All participants with post-baseline SANS data were included in these models, without imputation for missing data points. Results of such mixed models have been shown to give very similar results to multiple imputation, and to be superior to completed case or last observation carried forward methods of coping with missing data[37,38]. The same model was used to examine the secondary outcome of the effect of galantamine versus placebo on the SANS total score.

The primary cognitive outcome measure was a composite measure comprised of two MCCB subtests: the Brief Assessment of Cognition in Schizophrenia (BACS) Symbol Digit test and the Hopkins Verbal Learning Test (HVLT) and the RVIP. These measures were selected based on previous studies with nicotinic agents, which suggest that these agents should have their maximum effect on memory and attention measures. We used the formula: $E^2 = 2*((z_a+z_b)^2)(1-(r_0^2))/(2n)$, to estimate the effect size, E, for the galantamine-placebo comparison. We used prior data to estimate the correlation between baseline and week 6 Z-scores for each of the three components of the primary cognitive outcome (r=0.6) and to calculate the average correlation across all three measures (r_0= 0.77)[39]. We assumed a group size of 40 participants per group based on the sample size analysis for the negative symptom outcome. In the context of these assumptions, E= 0.65 z-score units.

In the primary analysis for cognition, the cognitive composite measure was the mean of BACS Symbol Digit test, HVLT, RVIP z-scores, with the z-scores for each test = (individual participant score - pooled baseline mean)/(pooled baseline s.d.). Analysis of covariance (ANCOVA) was used to estimate treatment differences on the mean of the test z-scores at week 6, adjusting for the baseline mean of the z-scores. The same model was used to examine the secondary outcome of the effect of oxytocin versus placebo on the cognitive composite score. An ANCOVA model was used to examine treatment group differences for the secondary cognitive outcomes: MCCB composite and domain scores and UPSA-2 total score. The covariate for these analyses was the baseline score.

The MM-ANCOVA model used for the primary negative symptom outcome was used for analyses of other symptom measures. Since the purpose of these analyses was to confirm that observed negative symptom changes were not secondary to changes in other symptom measures, we included all three groups in the “treatment” term, and only conducted follow-up analyses if the overall treatment × week term was significant.

For each SEC item, Fisher's exact test was used to compare the number of participants who had new or worsened (compared to baseline) side effect severity. The Wilcoxon rank sum test for differences in change scores was used to compare treatments on SAS total score; the Mantel-Haenszel test for difference in change score was used to compare treatments on AIMS and BAS total scores[40]. ANCOVA was used to examine mean changes in laboratory measures and vital signs.

Results

The study was conducted between March 2010 and January 2014. Eighty-six participants were consented; of these 26 did not meet inclusion/exclusion criteria, and 2 withdrew prior to randomization (see Supplemental Figure 1: CONSORT Flow Chart). Fifty-eight were randomized, of whom 2 (1 assigned to oxytocin, 1 to placebo) withdrew prior to receipt of study medication. Six of the remaining 56 participants withdrew prior to the end of study treatment: 2 from the galantamine group; 1 from the oxytocin group; and 3 from the placebo group. Three of these participants withdrew prior to the collection of any efficacy data, which left 53 for whom at least some efficacy data were obtained, and 50 who completed the entire trial. Demographic and baseline clinical characteristics are presented in Table 1.

Negative Symptoms (see Table 2)

In the oxytocin versus placebo comparison, the MM-ANCOVA treatment × week interaction was not significant (F=0.19, df=2,47.4, p=0.83). The oxytocin versus placebo week 6 SANS total score comparison was also not statistically significant (Cohen's d = -0.10, estimated mean difference in total scores ± s.e.: -1.02±1.55; t= -0.66, df=46.9, p=0.51). In the galantamine versus placebo comparison, the MM-ANCOVA treatment × week interaction was not significant (F=0.41, df=2,52.5, p=0.67), nor was the week 6 galantamine versus placebo contrast (Cohen's d= -0.15, estimated mean difference in total scores ± s.e.: -1.45±1.39; t= -1.04, df= 46.9, p=0.30).

Cognition (see Table 3)

In the primary outcome analysis, the ANCOVA estimate of the week 6 galantamine versus placebo difference in the composite z-score was 0.11±0.15 (t= 0.71, df=40, p=0.48). In the oxytocin versus placebo comparison, the ANCOVA estimate of the week 6 group difference in the composite z-score was 0.08±0.15 (t= 0.50, df=40, p=0.62). In exploratory analyses, there were no significant galantamine/placebo or oxytocin/placebo group differences for any of the individual measure that comprised the composite measure (see Supplemental Table 1).

In the analyses of the secondary cognition outcome measure: MCCB composite score (see Supplementary Table 2), there were no significant galantamine/placebo (t=0.49; df=42.0; p=0.63; Cohen's d=0.09) or oxytocin/placebo (t=0.78; df=42.0; p=0.44; Cohen's d=0.15) group differences. In the pairwise comparisons of the individual MCCB domains; only one domain was nominally significant (unadjusted $p<0.05$), which was not strong enough to survive adjustment for multiple comparisons (see Supplemental Table 2). There were also no significant group differences in the UPSA-2 total score: galantamine versus placebo: t= -0.69; df=44; p=0.49; and oxytocin versus placebo: t= 1.25; df=44; p=0.22 (see Supplemental Table 3).

Other symptoms (see Supplemental Table 4)

The MM-ANCOVA treatment × week interaction for BPRS total score was: F=0.46; df=4,82.2; p=0.77; for BPRS positive symptoms was: F=0.44; df=4,83.4; p=0.78; and for CDS total score was: F=1.02; df=4,82.5; p=0.40. In addition, none of the study participants had a CDS suicide item score greater than 1 (Mild) at any visit, and only 4/56 participants had a rating of 1 at one or more visits. There were also no significant group differences in the CGI severity of illness item (data available upon request from the authors).

Plasma Oxytocin Levels (see Table 4)

After adjustment for baseline oxytocin levels, there were no significant week 6 group differences in oxytocin levels (F=0.42; df=2,36; p=0.66).

Side Effects (see Table 5)

One study participant assigned to galantamine was hospitalized for several days, presenting with shortness of breath and suspected pneumonia, and was also treated for a urinary tract infection during the hospitalization. The serious adverse event was judged to not be related

to study medication. Only one SEC side effect was significantly different among treatment groups: new onset or worsening of enuresis was reported by 1/20 participants assigned to galantamine, 4/16 participants assigned to oxytocin, and 0/20 participants assigned to placebo (Fisher's exact test, p=0.028). There were no statistically significant treatment group differences in the SAS, AIMS or BAS total scores (data available upon request from the authors). There were no trends toward QTc prolongation in the active treatment groups, and no participants had excessive prolongation (QTc>500 msec). There were no significant group differences in vital sign changes (data available upon request from the authors). On 21 blood chemistry measurements, pairwise treatment comparisons with placebo, using analysis of covariance, suggested possible treatment effects (for potassium, triglycerides, VLDL and glucose; data available upon request from the authors). However, only two of these comparisons (galantamine versus placebo: triglycerides and oxytocin versus placebo: glucose) had p-values <0.05, unadjusted for the 42 pairwise comparisons performed. Notably, in both cases, the active treatment group exhibited a shift in the healthier direction.

Discussion

In contrast to our study hypotheses, we found no evidence for the efficacy of intranasal oxytocin for negative symptoms or galantamine for cognitive impairments; nor was galantamine superior to placebo for negative symptoms or oxytocin superior to placebo for cognitive impairments. In addition, there was no effect of either medication on any of the other cognitive or symptom measures.

The lack of an efficacy signal for either compound precluded our ability to test whether pharmacological treatment pathways for negative symptoms and cognitive impairments overlap or are independent. The most rigorous test of this hypothesis would be to examine the comparative efficacy of known effective medications for these domains. Unfortunately, despite years of drug development, there are no known effective pharmacological agents for either of these illness components.

Our study is one of multiple studies, which has examined the efficacy of multi-dose intranasal oxytocin for schizophrenia. In contrast to single dose studies, which found oxytocin benefits for social cognition in people with schizophrenia[41-46, but see 47], there is less clear-cut evidence to support the efficacy of repeated intranasal oxytocin administration in this population. In two small sample pilot projects, oxytocin was observed to improve Positive and Negative Syndrome Scale total score[48,49]; Feifel and colleagues also found a significant oxytocin effects for positive and negative symptoms. In a third study, there was a significant oxytocin effect for negative symptoms in inpatients, but not outpatients, with schizophrenia[50]. In contrast, two studies, which combined oxytocin with social cognition training, failed to find any significant benefit of oxytocin for positive or negative symptoms[51,52].

There are a number of possible explanations for the lack of negative symptom efficacy. In addition to the simple conclusion that oxytocin is not effective for these symptoms, our knowledge of the pharmacodynamics, pharmacokinetics and optimal dosing strategy for oxytocin may be inadequate[53,54]. Our selected dose was based on the dosage used in single

dose challenge studies with healthy controls[6-11]. These studies suggested that the central nervous system effects of oxytocin, despite its short half-life, persist up to two hours. However, there is little information on how best to translate the dose used in these studies to either the dose or the frequency of administration in a multi-dose clinical trial. Second, in the previous multi-dose studies, Feifel and colleagues used an intranasal oxytocin of 40IU, twice a day[48]; whereas Lee and colleagues used a dose of 20IU, twice a day[50] and the other three studies used a dose of 24IU, twice a day[49,51,52]. Since the most pronounced clinical effects were observed with the highest dose, perhaps our use of a lower dose contributed to the lack of observed effect. A third issue relates to the intranasal route of oxytocin administration. Despite our attempts to educate participants on the use of the nasal spray dispenser, they may have had difficulty in the proper administration of oxytocin. The multiple observations of functional and behavioral effects from single dose intranasal challenge studies, in which the administration of oxytocin was directly monitored[6-11,55], and the evidence of efficacy in inpatients, but not outpatients[50], provide indirect evidence to support this proposition.

In contrast to our earlier galantamine study[17], we did not find a significant effect of galantamine for cognitive impairments. This failure to replicate may have been related to either the markedly smaller sample size in the current study and/or the shorter duration of exposure. Since galantamine does not act selectively through positive allosteric modulation of the α4β2 and α7 nicotinic receptors, it may not have been an optimal choice to test the potential utility of the α7 nicotinic receptor target. However, other recent studies with α7 nicotinic receptor partial agonists or agonists have failed to demonstrate efficacy for cognitive impairments[56,57]. Although these results are discouraging for the α7 nicotinic receptor target, no studies have examined the efficacy of a pure positive allosteric modulator of this receptor.

The major study limitation involves the relatively small number of participants, which limits the power to detect an efficacy signal. However, we failed to find even statistically uncorrected evidence of efficacy for any of our primary or secondary endpoints. A larger sample would make the negative results more compelling, but additional cases would not support the efficacy hypotheses unless results were remarkably different from those observed in this clinical trial.

In summary, in the context of the limitations of this clinical trial, the efficacy hypotheses for oxytocin and negative symptoms and for galantamine and cognitive impairments were not supported.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Demographic and Baseline Clinical Characteristics

	Galantamine			Oxytocin			Placebo		
Measure	**N**	**Mean**	**S.D.**	**N**	**Mean**	**S.D.**	**N**	**Mean**	**S.D.**
Age, Yrs.	20	45.8	12.4	16	47.4	11.2	20	42.2	11.7
Age at 1st Psychotic Symptoms	15	20.0	7.6	14	21.7	9.0	13	19.2	3.7
Participant Education, years	20	11.9	1.8	16	12.6	1.7	20	12.1	2.3
Max. Parental Education, years	17	12.2	2.7	16	13.2	3.5	20	14.3	3.2
Measure	n	N	%	n	N	%	n	N	%
Sex, (% female)	6	20	30	2	16	12.5	3	20	15.0
Race									
African-American	10	20	50.0	8	16	50.0	7	20	35.0
White	10	20	50.0	7	16	43.8	13	20	65.0
Native American	0	20	0.0	1	16	6.2	0	20	0.0
Diagnosis (% schizophrenia)	17	20	85.0	15	16	93.8	18	20	90.0
Baseline Antipsychotics									
Aripiprazole	1	19*	5.3	1	16	6.2	3	20	15.0
Clozapine	5	19	26.3	4	16	25.0	6	10	30.0
Haloperidol	0	19	0.0	1	16	6.2	2	20	10.0
Olanzapine	4	19	21.0	3	16	18.8	3	20	15.0
Quetiapine	1	19	5.3	2	16	12.5	1	20	5.0
Risperidone	5	19	26.3	5	16	31.2	5	20	25.0
Polypharmacy**	3	19	15.8	3	16	18.8	3	20	15.0
Mood Stabilizers	1	19	5.3	2	16	12.5	2	20	10.0
Antidepressants	3	19	15.8	2	16	12.5	8	20	40.0

*Baseline psychotropic medication use was missing for one participant assigned to galantamine

**Participants on polypharmacy are included in the total number of users reported for each medication. One participant assigned to galantamine used both risperidone and olanzapine, and two used both risperidone and clozapine; one participant assigned to oxytocin used both haloperidol and olanzapine, one used both risperidone and quetiapine, and one used both risperidone and clozapine; one participant assigned to placebo used both haloperidol and clozapine, and two used both risperidone and clozapine.

Table 2

SANS Total Score by Treatment and Week

	Galantamine			Oxytocin			Placebo		
Week	**N**	**Mean**	**S.D.**	**N**	**Mean**	**S.D.**	**N**	**Mean**	**S.D.**
0	19	36.63	10.97	15	33.23	6.91	19	36.63	10.61
2	19	35.22	10.26	15	30.07	6.93	19	35.05	10.52
4	18	34.06	10.64	15	31.27	7.53	18	34.22	9.61
6	18	33.22	11.27	15	31.40	6.85	17	33.47	8.47
Δ2*	19	-1.41	3.32	15	-3.17	4.20	19	-1.58	4.84
Δ4*	18	-1.69	3.46	15	-1.97	4.48	18	-1.47	5.64
Δ6*	18	-2.53	4.34	15	-1.83	3.74	17	-1.00	4.41

*Δx= change from week 0 at week x.

SANS total score comparison at week 6 (post hoc tests from MM-ANCOVA):

Oxytocin versus placebo: estimated mean difference in total scores ± s.e.: -1.02 ± 1.55; t= -0.66; df=46.9; p=0.51; Cohen's d = -0.10.

Galantamine versus placebo: estimated mean difference in total scores ± s.e.: -1.45 ± 1.39; t= -1.04; df= 46.9; p=0.30; Cohen's d= -0.15.

Table 3

Mean Z-Scores for Composite Cognitive Primary Outcome* by Treatment Group and Week

	Galantamine			Oxytocin			Placebo		
Week	**N**	**Mean**	**S.D.**	**N**	**Mean**	**S.D.**	**N**	**Mean**	**S.D.**
0	15	-0.22	0.47	14	0.23	0.92	16	0.21	0.83
6	15	-0.05	0.68	14	0.33	1.00	15	0.18	0.69
Change	15	0.17	0.44	14	0.10	0.37	15	0.03	0.41

*Composite Cognitive Primary Outcome = mean of z-scores from BACS Symbol Digit T-score, HVLT T-score, and Rapid Visual Information Processing (RVIP) test z-score.

ANCOVA estimate of treatment differences on z-scores at Week 6, adjusted for baseline values of the corresponding z-score:

Galantamine versus placebo: 0.11 ± 0.15; t= 0.71, df=40, p=0.48

Oxytocin versus placebo: 0.08 ± 0.15 ; t= 0.50, df=40, p=0.62

Table 4

Blood Oxytocin Levels (pg/ml) by Treatment and Visit

	Galantamine			Oxytocin			Placebo		
Week	**N**	**Mean**	**S.D.**	**N**	**Mean**	**S.D.**	**N**	**Mean**	**S.D.**
Baseline	20	13.76	6.96	16	18.22	15.52	17	14.69	7.99
Week 6	15	10.11	3.42	14	17.22	17.02	13	13.21	9.32
Change	15	-2.99	5.20	14	-1.88	14.09	11	-1.73	3.95

Analysis of covariance (ANCOVA) tests for treatment effects on week 6 oxytocin levels, adjusted for baseline oxytocin: F=0.42; df=2,36; p=0.66.

Table 5

Participants with New Onset or Worsening Compared to Baseline of Signs or Symptoms on Side Effect Checklist (SEC), by Treatment Group

	Galantamine			Oxytocin			Placebo			P-value*
SEC Item	**N**	**n**	**%**	**N**	**n**	**%**	**N**	**n**	**%**	
Abdominal Pain	20	1	5.0	16	2	12.5	20	2	10.0	0.85
Anorexia	20	2	10.0	16	3	18.8	20	3	15.0	0.89
Bruising Easily	20	2	10.0	16	0	0.0	20	0	0.0	0.32
Constipation	20	0	0.0	16	0	0.0	20	0	0.0	1.00
Diarrhea	20	6	30.0	16	3	18.8	20	1	5.0	0.13
Dizziness	20	6	30.0	16	3	18.8	20	1	5.0	0.13
Dry Eye	18	0	0.0	15	1	6.7	17	1	5.9	0.53
Dry Mouth	20	1	5.0	16	3	18.8	20	2	10.0	0.48
Enuresis	20	1	5.0	16	4	25.0	20	0	0.0	**0.03**
Excessive Tearing	18	1	5.6	15	1	6.7	17	1	5.9	1.00
Fever	20	1	5.0	16	0	0.0	20	0	0.0	1.00
Headache	20	5	25.0	16	2	12.5	20	3	15.0	0.68
Hyperhydrosis	18	0	0.0	15	0	0.0	17	0	0.0	1.00
Hypersalivation	20	3	15.0	16	3	18.8	20	5	25.0	0.78
Insomnia	20	2	10.0	16	3	18.8	20	1	5.0	0.48
Malaise	20	0	0.0	16	3	18.8	20	2	10.0	0.18
Mucosal Ulceration	20	1	5.0	16	1	6.3	20	0	0.0	0.74
Nasal Irritation	18	3	16.7	15	5	33.3	17	4	23.5	0.60
Nausea	20	3	15.0	16	3	18.8	20	1	5.0	0.47
Rash	20	2	10.0	16	2	12.5	20	2	10.0	1.00
Restlessness	20	2	10.0	16	3	18.8	20	3	15.0	0.89
Sedation	20	3	15.0	16	2	12.5	20	2	10.0	1.00
Sore Throat	20	2	10.0	16	1	6.3	20	1	5.0	1.00
Stiffness	20	2	10.0	16	1	6.3	20	2	10.0	1.00
Tinnitus	20	0	0.0	16	0	0.0	19	2	10.5	0.20

	Galantamine			Oxytocin			Placebo			P-value*
SEC Item	**N**	**n**	**%**	**N**	**n**	**%**	**N**	**n**	**%**	
Tremor	20	3	15.0	16	1	6.3	20	2	10.0	0.87
Urticaria	20	3	15.0	16	3	18.8	20	3	15.0	1.00
Uterine Contractions	6	0	0.0	2	0	0.0	3	0	0.0	1.00
Vomiting	20	1	5.0	16	2	12.5	20	2	10.0	0.85
Weight Loss	20	1	5.0	16	3	18.8	20	5	25.0	0.22
Wheezing	18	1	5.6	15	2	13.3	17	2	11.8	0.72

* Fisher's exact test p-value for any difference among treatments