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The effects of oxytocin and galantamine on objectively-defined vocal and facial expression: Data from the CIDAR study

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Keywords

schizophrenia; negative; computer; galantamine; oxytocin; acoustic; prosody

Dear Editor

As part of the Centers for Intervention Development and Applied Research (CIDAR) initiative funded by the National Institute of Mental Health, galantamine and oxytocin were included in a three-arm, six week randomly controlled trial (ClinicalTrials.gov NCT01012167). Both medications are associated with mild side effect profiles (Hansen et al., 2008; Oya et al., 2016), are relatively inexpensive, and have shown efficacy in at least some studies (Lee et al., 2013). Unfortunately, data from the CIDAR trial failed to find significant improvements in negative symptom severity or cognitive functioning with either galantamine or oxytocin compared to placebo using standard clinical rating scales or neuropsychological test batteries (Buchanan et al., 2016). The present study reanalyzed these data using computerized measures of natural speech and facial expressions as the dependent variables; measures with potentially superior reliability, sensitivity and precision than clinical rating scales for measuring blunted affect and alogia (Cohen and Elvevag, 2014; Cohen et al., 2016; Cohen et al., 2013).

Participants in the study met criteria for schizophrenia or schizoaffective disorder as confirmed by structured clinical interview and a) were between 18 and 64 years old, b) were rated at moderate negative symptom severity or greater using a modified Scale for the Assessment of Negative Symptoms (Buchanan et al., 2007), and c) showed minimal levels of potential “secondary negative symptoms and extra-pyramidal symptoms (see Buchanan et al., 2016 for details). Fifty participants were included in the original study. Due to technical issues with audio or video recordings, data were available for 40 participants (15 Placebo; 10 oxytocin; 15 galantamine).

Vocal and facial expression was analyzed from a modified version of the Maryland Assessment of Social Competence (Bellack et al., 1994) using two conversational role-play situations enacted with female confederates whose responses were standardized and trained to be affiliative in their affect, rather than neutral. Data were averaged across the two situations. Assessments were administered at baseline and then repeated six weeks later. The Computerized assessment of Affect from Natural Speech protocol (Cohen et al., 2016) and FaceReader version 4.0, a commercially-available program developed by Noldus Information Technology (2010), were used to measure vocal and facial expressions respectively. Summary variables, selected based on recent studies (Cohen et al., 2016; Cohen et al., 2013), included: mean pause time (i.e., average voiceless epoch bounded by speech > 150ms in length), intonation (i.e., standard deviation of the fundamental frequency values computed within a voiced epoch [i.e., an “utterance”], then averaged across utterances), and emphasis (i.e., standard deviation of the volume computed within an utterance, then averaged across utterances), as were neutral, happy and negative (sum of sad, anger, scared) facial expressions. Extreme values were “winsorized” (i.e., replaced with values 3.5 SD from the overall means).

There were no statistically significant differences across treatment arms in sex, ethnicity, age, education, parental education or baseline negative symptom scores (p's > .10). Treatment differences in average recording time and percentage of video frames analyzed by FaceReader also were also not statistically significant. In our main analyses, no statistically significant condition, treatment or interaction effects were noted for any of the six computerized measures. Interestingly, participants in the oxytocin arm showed a non-statistically significant increase in negative facial expressions pre- to post-treatment at a medium effect size level, compared to a negligible increase in the placebo and galantamine arms.

Consistent with data from symptom rating scales reported elsewhere from this medication trial (Buchanan et al., 2016), no significant treatment effects were observed. The reasons for this are unclear, though possible explanations include noncompliance or incomplete dosing (but see Lee et al 2013), insufficient power due to small sample size, short half-life and potential tolerance. Individuals in the oxytocin arm did show an increase in negative facial expressions across the two role-play tasks at a medium effect size (in contrast to negligible changes in the other arms). This finding is not entirely surprising given that the effects of oxytocin on prosocial behavior are context-dependent and can contribute to "antisocial" effects when an individual perceives themself or their "in group" members to be threatened in some manner (Kemp and Guastella, 2011). Given the confederates were established as unfamiliar people (e.g., neighbors), and in fact were largely unknown to the participants, they may have been viewed as "out group" members. Hence, oxytocin may have engendered feelings of suspicion or defensiveness in some fashion. However, confederates were trained and monitored to be affiliative during the role-plays. For this reason, and because the effects were not statistically significant, they should be viewed cautiously. In sum, the present study used highly sophisticated and sensitive computerized assessments, but failed to find significant improvements in vocal or facial expressions as a result of either galantamine or oxytocin.

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Table 1

Descriptive statistics between baseline and post-intervention treatment arms for computerized vocal and facial measures.

	Pre-Treatment	Post-Treatment	Condition F	Treatment F	Interaction F	Cohen's d[a]
Vocal: Pause times						
Placebo	2694.19 (1486.06)	2611.03 (1554.43)	0.67	0.76	0.67	−0.05
Oxytocin	2303.19 (1306.69)	1958.76 (1150.16)				−0.28
Galantamine	2434.51 (1049.42)	2300.88 (951.35)				−0.13
Vocal: Intonation						
Placebo	2.22 (0.87)	1.87 (0.48)	2.15	2.04	2.15	−0.52
Oxytocin	2.53 (1.30)	1.93 (0.63)				−0.62
Galantamine	2.51 (1.17)	2.67 (0.84)				0.16
Vocal: Emphasis						
Placebo	4.32 (3.93)	3.07 (1.23)	2.05	0.26	2.05	−0.48
Oxytocin	4.84 (4.34)	3.54 (0.96)				−0.49
Galantamine	4.02 (1.70)	4.01 (1.31)				−0.01
Facial: Neutral						
Placebo	0.32 (0.11)	0.30 (0.15)	0.06	0.06	0.06	−0.15
Oxytocin	0.32 (0.15)	0.33 (0.19)				0.06
Galantamine	0.32 (0.13)	0.31 (0.12)				−0.08
Facial: Happy						
Placebo	0.08 (0.09)	0.12 (0.11)	0.14	0.68		0.40
Oxytocin	0.06 (0.08)	0.07 (0.10)			0.14	0.11
Galantamine	0.10 (0.11)	0.08 (0.09)				−0.20
Facial: Negative						
Placebo	0.16 (0.13)	0.16 (0.13)	1.10	0.08	1.10	0.00
Oxytocin	0.14 (0.11)	0.20 (0.10)				0.57
Galantamine	0.16 (0.13)	0.18 (0.12)				0.16

[a] *d* values computed pre to post within each treatment arm.