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High-dose galantamine augmentation inferior to placebo on attention, inhibitory control and working memory performance in nonsmokers with schizophrenia

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Abstract

Dysfunction in the neuronal nicotinic acetylcholine receptor (nAChR) system has been implicated in the pathophysiology of schizophrenia, and it has been postulated that treatments that increase nAChR activity may improve symptoms of the disorder. We investigated the effects of the acetylcholinesterase inhibitor and allosteric nAChR modulator, galantamine, on cognitive performance and clinical symptoms when added to a stable antipsychotic medication regimen in nonsmoking outpatients with schizophrenia in a double-blind, placebo-controlled, parallel-group design. Participants were randomized to receive either galantamine ($n=10$) up to 32 mg/day or identical placebo ($n=10$) for 8 weeks and completed a cognitive battery at baseline and week 8 and clinical scales at baseline, week 4 and week 8. The primary outcome measure was attentional performance as measured by the *d*' measure in the Continuous Performance Test — Identical Pairs (CPT-IP) Version. Contrary to our hypothesis, galantamine treatment was associated with inferior performance on the CPT-IP, on the three-card Stroop task, and on the Letter–Number Span task without reordering. Galantamine had no effect on clinical symptoms. In summary, galantamine treatment, at a dose of 32 mg/day, was well tolerated but was not effective as an adjunctive treatment for cognitive deficits in stable nonsmokers with schizophrenia.

Keywords: Galantamine; Schizophrenia; Attention; Nicotine; Acetylcholine

1. Introduction

People with schizophrenia are more likely to smoke and to have a higher level of nicotine dependence than those in the general population (de Leon and Diaz, 2005). It has been suggested that people with schizophrenia use nicotine to self-medicate symptoms of their disorder that are caused from abnormal nicotinic receptor structure and function (Dalack et al., 1998; Kumari and Postma, 2005). Decreased numbers of both high- and low-affinity nicotinic acetylcholine receptor (nAChR) numbers have been described in several brain regions in those with schizophrenia compared to controls (Breese et al., 2000; Durany et al., 2000; Freedman et al., 1995).

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In addition, a polymorphism in the promoter region of the alpha 7 nAChR gene is associated with reduced nAChR transcription in schizophrenia (Leonard et al., 2002) and with heavy cigarette smoking in this population (De Luca et al., 2004).

Nicotine has been shown to at least partially and transiently normalize neurophysiologic deficits of schizophrenia, including sensory gating deficits, which are linked to the gene that codes for the alpha 7 nAChR (Adler et al., 1993, 1992; Avila et al., 2003; Olincy et al., 2003) and to improve cognitive deficits associated with schizophrenia such as attention and inhibitory processing (Barr et al., in press; Harris et al., 2004; Jacobsen et al., 2004; Smith et al., 2002). Additionally, stimulation of presynaptic nAChRs on glutamatergic and dopaminergic neurons increases activity of these neurons in relevant brain regions (Kiba and Jayaraman, 1994; Mansvelder and McGehee, 2000; Nomikos et al., 2000; Sziraki et al., 1998), an effect that may have relevance for improving cognitive dysfunction and negative symptoms of the disorder (Carlsson and Carlsson, 1990; Ishimaru et al., 1994; Javitt and Zukin, 1991; Kim et al., 1980; Olney and Farber, 1995).

The abnormality in nicotinic signaling and possible reversal by nicotine has stimulated interest in a potential therapeutic role for agents that increase nicotinic signaling. Clinical studies of the acetylcholinesterase inhibitor, donepezil, in schizophrenia have been mixed with some reports of moderate improvements in memory (Buchanan et al., 2003; Howard et al., 2002; Lee et al., 2007a; Risch et al., 2001) or negative symptoms (Risch et al., 2007) and others showing no effect (Fagerlund et al., 2007; Freudenreich et al., 2005; Stryjer et al., 2004; Tugal et al., 2004) including a recent large well controlled trial showing no effect for donepezil augmentation on the CATIE cognitive battery or clinical symptoms (Keefe et al., in press).

Galantamine is the weakest acetylcholinesterase inhibitor of those that are approved for the treatment of dementia of the Alzheimer's type. Additionally, galantamine acts as an allosterically potentiating ligand (APL) at neuronal nAChR (Maelicke and Albuquerque, 2000; Popa et al., 2006; Samochocki et al., 2003; Schrattenholz et al., 1996) and has demonstrated positive effects in animal models of schizophrenia (Csernansky et al., 2005; Deutsch et al., 2003; Hohnadel et al., 2007; Schilstrom et al., 2007; Wang et al., 2007a,b). There have been promising case reports and small studies reporting efficacy of galantamine for the treatment of cognitive dysfunction (Bora et al., 2005; Schubert et al., 2006), negative symptoms (Rosse and Deutsch, 2002) and psychotic and disorganized symptoms of schizophrenia (Allen and McEvoy, 2002), as well as a report of no significant effect (Lee et al., 2007b).

For treatment of Alzheimer's disease, a dosage of 16–24 mg/day is recommended, but up to 32 mg/day has been shown to be safe and effective (Raskind et al., 2000). Prior studies of the effects of galantamine in schizophrenia described modest effects at a dose of 16–24 mg/day (Allen and McEvoy, 2002; Bora et al., 2005; Lee et al., 2007b; Rosse and Deutsch, 2002; Schubert et al., 2006). This study aimed to test the hypothesis, in a randomized, double-blind, placebo-controlled, parallel-group design, that a relatively high dose of galantamine, 32 mg/day, would be associated with improved cognitive performance and negative symptoms in stable, nonsmoking outpatients with schizophrenia. We have recently demonstrated an effect for nicotine on attention (Barr et al., in press) and memory (Weiss et al., 2006) in nonsmokers with schizophrenia and chose to study the effect of galantamine on attention and working memory in nonsmokers with the hypothesis that those not receiving exogenous nicotinic stimulation from tobacco smoking would benefit more from galantamine than those already receiving exogenous stimulation (e.g. smokers).

2. Materials and methods

The study protocol was approved by the appropriate Institutional Review Board. All participants provided written informed consent prior to beginning study procedures.

2.1. Participants

Participants were stable, adult outpatients with schizophrenia or schizoaffective disorder depressed type who had been on a stable dose of an antipsychotic medication for at least 8 weeks prior to enrollment. Participants were excluded who were taking an anticholinergic medication or who reported use of an illicit drug or a nicotine-containing product in the past 3 months or who had expired air carbon monoxide (CO) >9 ppm or salivary drug screen positive for cotinine, cocaine, THC, ethanol, amphetamine, or benzodiazepines at screening.

2.2. Procedures

The study took place at an urban, university-affiliated community mental health clinic. Participants were randomized to receive either galantamine or identical placebo in addition to their usual medications for 8 weeks. Randomization was performed with concealed allocation with a 1:1 ratio, in blocks of 4. The following dosing

schedule was followed: 4 mg per day for 3 days; then 4 mg twice per day for 11 days; then 8 mg twice per day for 14 days; then 12 mg twice per day for 14 days; and finally 16 mg twice per day for 14 days.

2.3. Measures

The following neuropsychological tests were performed at baseline and week 8: Continuous Performance Test — Identical Pairs (CPT-IP) Version 4.0 (Biobehavioral Technologies, New York, NY, USA) to measure attention (Cornblatt et al., 1989); the Three-Card Stroop (Stoelting Co., Wood Dale, IL, USA) to measure response inhibition; Letter-Number Span (LNS) from the WAIS-III (Wechsler, 1997) to measure attention and working memory; and Grooved Pegboard (Model 32025, Lafayette Instrument Company, Lafayette, IN, USA) to measure motor speed.

The following standard clinical rating scales were performed at baseline, week 4 and week 8: Positive and Negative Syndrome Scale (PANSS), the Scale for the Assessment of Negative Symptoms (SANS), the Calgary Depression Scale for Schizophrenia (CDSS), the Abnormal Involuntary Movement Scale (AIMS), the Simpson–Angus Scale (SAS) and the Barnes Akathisia Scale.

Medication compliance was assessed weekly by self-report and pill counts. Adverse event questionnaires were performed weekly. Weekly self-report of nonsmoking status was confirmed by weekly expired air carbon monoxide (CO) measurement (Bedfont Smokerlyzer II, Bedfont Scientific, LTD, Kent, UK) of <9 ppm and by semi-quantitative salivary cotinine concentration of <10 ng/mL at baseline, week 4 and week 8 (Nicalert™, Jant Pharmacal Corporation, Endocino, CA, USA).

For an assessment of compliance, the presence or absence of galantamine in previously frozen patient serum samples was determined using high-performance liquid chromatography (HPLC) and photo-diode-array absorbance (PDA) detectors in a subset of participants. A working internal standard was created using intermediate solution and previously frozen drug-free serum. A galantamine standard was created by extracting galantamine from the pill form of the drug with a hexane containing solvent. Galantamine was found to elute at approximately 2.6 min on both the 214-nm and 230-nm chromatograms. Peaks <0.0015 A were considered to be below the detection limits for this method, and therefore clinically insignificant (Puopolo et al., 1991). Each peak >0.0015 A, with a retention time between 2.60 min and 2.67 min was examined and the presence of galantamine was confirmed by matching the retention time and the ultraviolet spectra to the galantamine standard. If no peak >0.0015 A was observed then the sample was considered negative for galantamine. This method was used to generate the qualitative presence or absence of galantamine. Quantitative analysis was not performed because pure galantamine compound was not available to create the galantamine standard.

2.4. Data analysis

Baseline characteristics were compared by randomization status with Student's *T* tests and Exact tests for continuous and dichotomous variables, respectively. The data were examined for distributional properties. The random errors variable of the CPT-IP was transformed to a natural logarithm. Linear regression models were performed to evaluate the effect of medication status on change in cognitive performance, controlling for baseline scores. Point estimates and 95% confidence intervals of medication effect were calculated from these regression models. The five-factor subscale structure was used to analyze PANSS scores (Lindenmayer et al., 1994). The use of covariates was limited to medication status and baseline score due to sample size considerations. For cognitive tests and for the SANS total score, effect estimates (Cohen's *d*) were also calculated. SAS Version 9.1 statistical software was used for all analyses.

3. Results

Thirty-five potential participants were screened, 23 signed informed consent and 20 met entry criteria, were randomized, took at least one dose of study medication and are included in the analysis. Of the 20 participants who enrolled in the study, 18 (9 placebo, 9 galantamine) completed 8 weeks of treatment. Data from the final visit of the two participants who discontinued study procedures prior to week 8 are included in the LOCF analysis. Baseline demographic and clinical characteristics are presented by randomization status in Table 1. There were no significant differences between the treatment groups at baseline. All participants were taking a stable dose of a second-generation antipsychotic medication. Two participants in the galantamine group were taking two different antipsychotics.

3.1. Cognitive performance

3.1.1. Attention

As shown in Fig. 1a, galantamine treatment was associated with worsened performance on the *d*' measure of the CPT-IP, the primary outcome measure, compared with placebo ($\beta = -10.4$, $p = 0.035$). This is

Table 1
Baseline demographic characteristics

	Galantamine	Placebo
	(*n*=10)	(*n*=10)
Age	44.3 (11.9)	50.5 (4.7)
Male/female	7/3	6/4
Ethnicity		
Caucasian	8	9
African–American	2	1
Marital status		
Single	10	9
Divorced or separated	0	1
IQ	95.3 (12.1)	98.9 (13.3)
Years of education	12.9 (2.6)	13.0 (3.6)
Antipsychotic medication[a]		
Clozapine	2	3
Risperidone	0	4
Aripiprazole	2	1
Olanzapine	4	2
Ziprasidone	3	0
Quetiapine	1	0
CO[b] at screening (ppm)	0.9 (0.6)	0.8 (1.0)
Clinical symptoms		
PANSS total score	65.4 (14.3)	68.1 (19.5)
SANS total score	30.5 (16.1)	23.3 (9.7)
CDSS total	3.7 (3.4)	3.9 (3.7)

[a]Number of participants in each group on the antipsychotic medication; some participants were taking more than one antipsychotic medication.
[b]Carbon monoxide.

an overall measure of ability to detect signal to noise. Galantamine treatment was associated with a trend toward an increase in ln random errors compared with placebo (β=17, p= 0.0740). There was no medication effect on reaction time or variability in reaction time. Data are given in Table 2.

3.1.2. Executive function/inhibitory control

Galantamine treatment was associated with worsened performance compared with placebo on the Stroop task, as assessed by the interference *T*-score, (higher *T*-score reflects greater inhibitory control) (β=−50, p=0.035). See Table 2 and Fig. 1b.

3.1.3. Memory

Galantamine treatment was associated with worsened performance compared with placebo on the LNS task without reordering (β=−13, p<0.03; Cohen's d=−0.92), but had no significant effect on performance on the reordering portion of the task (β=−0.6, p=0.43)

3.1.4. Motor speed

There was no effect of galantamine relative to placebo on motor performance as assessed with the Grooved Pegboard task (β=0.2, p=0.74).

3.2. Clinical scales

Linear regression models that included change in clinical score as the dependent variable and medication status and respective baseline clinical as independent variables revealed no significant effect of medication on PANSS, SANS and CDS total scores. The data are presented in Table 2 with confidence intervals for the point estimates. While the effect of galantamine was not significant compared with placebo, the SANS total score in the galantamine group decreased by more than 10% (baseline mean score 30.5; week 8 mean score 26.5). The effect size for galantamine on

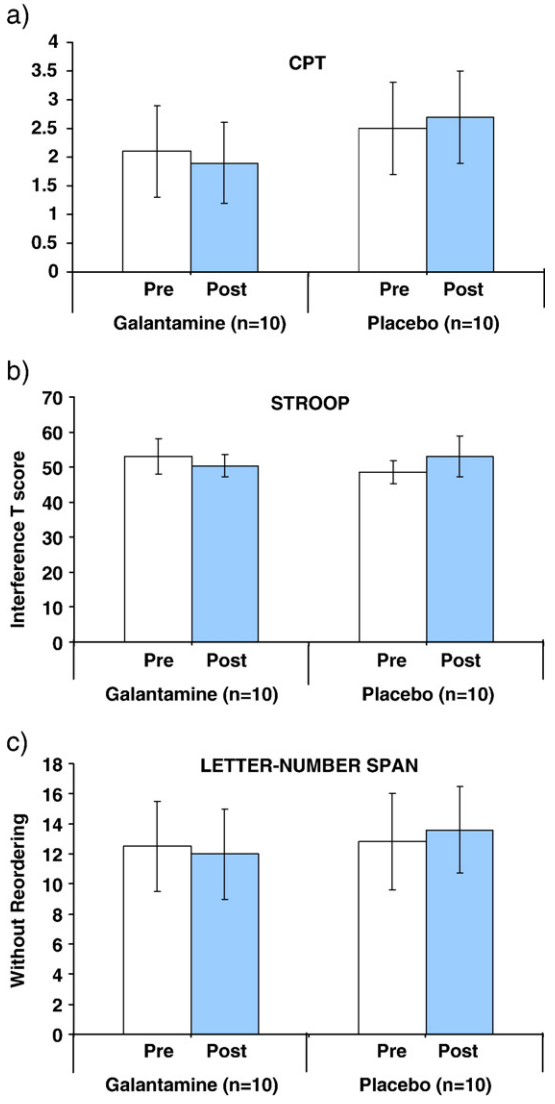

Fig. 1. Galantamine effect on measures of cognitive performance in nonsmokers with schizophrenia. a) Cognitive Performance Test – Identical Pairs (CPT), *d*'; b) Three-Card Stroop, Interference T-score; c) Letter-Number Span, without reordering.

Table 2
Effect of galantamine and placebo on neuropsychological and clinical symptoms

	Galantamine (n=10)			Placebo (n=10)			Effect estimate [a]	95% CI effect estimate	p
	Pre	Post	Change	Pre	Post	Change			
Neuropsychological									
CPT									
d'	2.1 (0.8)	1.9 (0.7)	−0.2 (0.5)	2.5 (0.8)	2.7 (0.8)	0.1 (0.4)	−10.4	−0.9, 0.0	0.03
Random errors (ln)	−3.9 (1.4)	−3.6 (1.4)	0.3 (1.2)	−2.9 (2.2)	−3.4 (2.0)	−1.6 (2.4)	7.3	−0.2, 3.5	0.07
Reaction time	563.1 (97.7)	550.5 (77.9)	−12.6 (61.2)	555.7 (57.5)	555.7 (71.5)	−0.1 (42.9)	1.7	−56.9, 36.0	0.64
Reaction time SD	161.4 (34.6)	158.3 (44.8)	−3.07 (28.4)	149.9 (36.1)	140.4 (39.4)	−9.4 (25.5)	−0.4	−19.2, 33.7	0.57
Stroop									
Interference *T*-score	53.1 (5.0)	50.4 (3.1)	−2.7 (3.7)	48.5 (3.2)	53.0 (5.8)	4.5 (5.3)	−5.0	−9.6, −0.4	0.04
Letter-number span									
Without reordering	12.5 (3.0)	12.0 (3.0)	−0.5 (1.4)	12.8 (3.2)	13.6 (2.9)	0.8 (1.2)	−1.3	−2.5, −0.1	0.03
With reordering	8.8 (4.2)	8.9 (3.4)	0.1 (2.1)	8.7 (2.5)	9.4 (2.9)	0.7 (1.1)	−0.6	−2.1, 0.9	0.43
Grooved pegboard									
Average pegs	15.2 (2.8)	15.9 (3.1)	0.7 (1.8)	15.8 (3.4)	16.1 (3.4)	0.4 (1.4)	0.2	−1.3, 1.8	0.74
Clinical symptoms									
PANSS									
Total score	65.4 (14.3)	65.4 (16.3)	0.0 (10.5)	68.1 (19.5)	70.4 (20.7)	2.3 (10.9)	−2.6	−12.9, 7.7	0.50
SANS									
Total score	30.5 (16.1)	26.5 (17.3)	−4.0 (9.2)	23.3 (9.7)	25.6 (12.3)	2.3 (10.9)	−5.7	−14.7, 3.3	0.20
CDSS									
Total score	3.7 (3.4)	3.6 (3.3)	−0.1 (2.3)	3.9 (3.7)	6.9 (5.2)	3.0 (5.4)	−3.2	−6.9, 0.5	0.09

PANSS = Positive and Negative Affect Scale, SANS = Schedule for Assessment of Negative Symptoms, CDSS = Calgary Depression Scale for Schizophrenia.

[a] Effect estimates presented are unstandardized coefficients (β) calculated with linear regression analyses with change from baseline to week 8 as the dependent measure, and medication status and baseline measure as independent variables.

negative symptoms as assessed by SANS total score was moderate (Cohen's d=−0.675). An exploratory analysis was conducted for PANSS and SANS subscale scores at week 8 and for total scores at week 4; there were also no significant effects on subscale scores at week 8 or for total scores at week 4 (data not shown).

3.3. Safety and tolerability

One participant on galantamine withdrew consent at week 6, at a dose of 24 mg/day, due to muscle cramps in feet and abdomen. One participant randomized to the placebo group discontinued study medication at week 5, stating she no longer wanted to take study medication. Both of these participants completed endpoint assessments at the time of discontinuation of study medication, and these clinical assessments, collected at study weeks 5 and 6, respectively, were used in the LOCF analyses for week 8 endpoint scores. One subject on placebo completed 8 weeks of study medication but did not increase her dose beyond the equivalent of 16 mg/day due to mild nausea, moderate fatigue and insomnia and increased alertness. All other participants completed the dose titration to 32 mg/day.

A total of 43 adverse events (defined here as an increase in any symptom, even if mild) were reported in the galantamine group; 46 were reported in the placebo group. The most common events (5 or more people) reported in the galantamine group were fatigue, nausea and somnolence; the most common in the placebo group was depression, fatigue, dizziness and somnolence. Repeated measures ANOVA of extrapyramidal symptom scales revealed no significant effect of medication on adverse event frequency or severity (data not shown).

For the 18 participants who completed the 8 week study, the average number of missed doses of study medication was 1.35 doses per two week interval, 1.13 in the galantamine group and 1.56 in the placebo group, by self report, confirmed by pill count. For an additional assessment of compliance, the presence or absence of galantamine in serum samples was determined in 8 of the 20 participants, 5 assigned to galantamine and 3 assigned to placebo. Galantamine was present in serum of all 5 participants randomized to galantamine and in none of the 3 assigned to placebo.

4. Discussion

In this eight-week, double-blind, placebo-controlled trial of galantamine augmentation, at a maximum dose of 32 mg/day, of antipsychotic treatment in stable outpatient

nonsmokers with schizophrenia, the effect of galantamine was inferior to placebo on attention as assessed by the CPT-IP *d'* (signal to noise detection), on inhibitory control as assessed by the Stroop Interference *T*-score, and on one measure of memory, the LNS without reordering. There was also a trend for galantamine to be inferior to placebo for random errors in the CPT-IP measure of attention. Galantamine did not separate from placebo on measures of working memory or psychomotor speed, as assessed with the LNS with reordering and Grooved Pegboard. Galantamine also did not separate from placebo on clinical measures, although the study may have been underpowered to detect an effect on negative symptoms.

These findings are consistent with a recent report of a large, randomized, placebo-controlled study of donepezil for cognitive performance in schizophrenia (Keefe et al., in press) in which few beneficial effects of donepezil were observed and placebo was superior to the cholinesterase inhibitor in some cognitive measures. The present study fails to replicate reports of beneficial effects of lower doses of galantamine (16–24 mg/day) in schizophrenia in case series (Allen and McEvoy, 2002; Bora et al., 2005; Rosse and Deutsch, 2002) and in one small, double-blind, placebo-controlled trial in patients taking risperidone (Schubert et al., 2006).

At low doses, galantamine acts as an allosteric potentiator of nAChRs, increasing the probability of agonist induced nAChR channel opening, and at higher doses, galantamine acts primarily as an acetylcholinesterase (AChE) inhibitor (Samochocki et al., 2003; Samochocki et al., 2000; Schrattenholz et al., 1996). At low doses, unlikely to inhibit AChE, galantamine, like nicotine, increases burst firing activity of dopaminergic cells in the ventral tegmental area and increases dopamine levels in the pre-frontal cortex, via activation of nAChRs, an effect that is blocked by inhibitors of alpha 4 beta 2 and alpha 7 nAChRs, as well as by an *N*-methyl-D-aspartate receptor (NMDAR) antagonist (Schilstrom et al., 2007). Phasic cortical dopamine release has been implicated as important to cognitive performance and as a possible mechanism for a beneficial effect of galantamine on cognitive function and negative symptoms. Galantamine at concentrations of 0.1–1 μM, corresponding to cerebrospinal fluid concentrations in humans on galantamine 16–24 mg daily, appears to act as an APL, but at concentrations >1 μM galantamine does not potentiate nAChR channel opening in the presence of ACh (Schrattenholz et al., 1996) and at concentrations >10 μM, galantamine, like the selective AChE inhibitor donepezil, may inhibit nAChR-mediated currents in dopaminergic cells (Schilstrom et al., 2007). It is likely that at high doses, galantamine's nAChR allosteric modulation effect may be masked by a stronger direct nAChR inhibitory effect. It is not known what oral doses of galantamine in humans would produce such inhibition of nAChR activity.

Our findings are limited by the small sample size, limiting our power to detect medication effects and to control for potential confounders. Smokers were excluded with the hypothesis that any medication effects would be greater in nonsmokers. It is possible, however, that nonsmokers and those who have been able to quit smoking represent a subset of patients with schizophrenia who are less responsive to nicotinic agonist treatment. Additionally, it is possible that upregulation of nAChRs by smoking may potentiate clinical effects of the allosteric potentiating ligand, galantamine. Inclusion of only nonsmokers limits generalizability of the findings to nonsmokers, currently a minority of patients with schizophrenia. The findings are also limited by measurement of cognitive function at only two time points, baseline and endpoint, when most subjects were taking 32 mg/day of galantamine, as positive clinical effects may be greater at lower doses. It is important to note two limitations with regard to SANS scores. First, baseline SANS scores were relatively low, possibly causing a floor effect. Second, SANS scores were decreased by more than 10% in the galantamine group and increased in the placebo group. While it is possible that SANS scores in each group regressed to the mean, narrowing baseline differences between groups, it is also possible that the study simply lacked the power to detect an effect of galantamine on negative symptoms.

In summary, in this double-blind, placebo-controlled trial, galantamine, 32 mg/day, had a directionally opposite effect from placebo on measures of cognitive performance and indeed significantly worsened performance on measures of attention and inhibitory processing compared with placebo, while there was no medication effect on motor speed or clinical symptoms. It is therefore possible that galantamine augmentation at this dose may worsen cognitive functioning in patients with schizophrenia. Future studies should therefore test the effects of galantamine across several levels of smoking and several doses of galantamine.

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Contributors

Dr. Evins designed the study and wrote the protocol. Drs. Freudenreich, Deckersbach and Goff contributed to study design and

editing of the manuscript. Mr. Dyer, Ms. Culhane and Dr. Pachas recruited participants and conducted subject assessments. Dr. Murphy performed the galantamine assays. Dr. Evins and Ms. Culhane performed data analysis. All authors contributed to and have approved the final manuscript.

Conflict of interest

Dr. Evins has received or has pending research grant support from Pfizer, Inc. and Janssen Pharmaceutica, and Speakers' Honoraria from Primedia. Dr. Freudenreich has received research grant support from Cephalon and Speakers' Honoraria from Primedia. Dr. Goff has received research grant support from Cephalon, Janssen Pharmaceutica, and Pfizer, Inc. and Speakers' Honoraria from Bristol-Myers Squibb, Eli Lilly and Company, Letters and Science, Primedia, SG Cowen, and Verus Med. Dr. Goff also reports Advisory/Consultative Relationships with Bristol-Myers Squibb, GlaxoSmithkline, Merck, Organon, Pfizer, Inc. and Solvay/Wyeth. Mr. Dyer, Ms. Culhane and Drs. Pachas and Deckersbach report no conflicts of interest.

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