Article

Galantamine for the Treatment of Cognitive Impairments in People With Schizophrenia

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Objective: People with schizophrenia are characterized by a broad range of cognitive impairments. Despite appropriate treatment with conventional or second-generation antipsychotics, they continue to exhibit pronounced impairments. The current study was designed to examine the efficacy and safety of galantamine, an acetylcholinesterase inhibitor that also acts as an allosteric modulator at the $\alpha_4\beta_2$ and α_7 nicotinic receptors, for the treatment of these impairments.

Method: Eighty-six people with schizophrenia were entered into a 12-week double-blind, placebo-controlled, randomized clinical trial. Forty-two subjects were assigned to galantamine and 44 were assigned to placebo. The efficacy of galantamine for cognitive impairments was evaluated with neuropsychological measures of attention, motor speed, processing speed, verbal and visual memory, and working memory.

Results: The treatment effect for the overall composite score was not significant, but the heterogeneity of treatment effect analysis was significant. Follow-up analyses revealed that the subjects taking galantamine exhibited significant improvements on the WAIS-III digit symbol and verbal memory measures. In contrast, the subjects taking placebo showed a significant improvement on the GDS distractibility test. The group differences on the WAIS-III digit symbol and GDS distractibility test remained significant after correction for multiple comparisons. There were no significant between-group differences in motor speed or working memory. In general, safety analyses revealed that galantamine was well tolerated.

Conclusions: Study results suggest that galantamine may have selective benefits for aspects of processing speed and verbal memory but interferes with practice effects during the performance of an attention task.

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Schizophrenia is characterized by a broad range of cognitive impairments, including abnormalities of attention/information processing, problem solving, processing speed, verbal and visual learning and memory, and working memory (1). Despite treatment with either conventional or second-generation antipsychotics (2), people with schizophrenia continue to exhibit pronounced cognitive impairments, which have led to the investigation of adjunctive cotherapy of these impairments.

Acetylcholine acts at muscarinic and nicotinic cholinergic receptors. These receptors are distributed throughout the brain; their locations include the neocortex, hippocampus, thalamus, and basal ganglia (3), regions that have been implicated in the neural substrate for cognitive processes. The cholinergic system has been implicated in the regulation of attention, memory, processing speed, and sensory gating (4, 5), processes that are impaired in schizophrenia. Several lines of evidence suggest that the cholinergic system may be disrupted in schizophrenia. Postmortem studies have demonstrated alterations in muscarinic receptor and nicotinic receptor availability or expression (6–9). In a study using single photon emission computed tomography, the number of muscarinic receptors was significantly lower than normal in the cortex, thalamus, and basal ganglia of people with schizophrenia (10). Acute nicotine administration has been shown to improve attention, verbal and visual memory, and working memory in people with schizophrenia (11, 12). Furthermore, in a recent study, acute challenge with an α_7 nicotinic receptor partial agonist, DMXB-A, was shown to improve cognitive function and sensory gating (13). In combination, these studies suggest that people with schizophrenia may have multiple abnormalities of the cholinergic system and that agents that enhance cholinergic function may act as cognitive enhancers.

Galantamine is an acetylcholinesterase inhibitor that also acts as an allosteric modulator at the $\alpha_4\beta_2$ and α_7 nicotinic receptors (14–16). Two previous studies with small numbers of subjects have reported potential benefits of galantamine for attention, memory, and psychomotor speed in schizophrenia (17, 18). An unpublished study from Johnson and Johnson failed to find an advantage for galantamine on a measure of global cognition (clinicaltrials.gov, trial number: NCT 00077727).

The current 12-week placebo-controlled, double-blind, parallel-group, randomized clinical trial was designed to

examine the efficacy and safety of galantamine for the treatment of cognitive impairments in people with schizophrenia.

Method

Subjects

Participants who met the DSM-IV criteria for schizophrenia or schizoaffective disorder were selected for entry into the study. They were diagnosed by using a best-estimate diagnostic approach that utilized information from the Structured Clinical Interview for DSM-IV (19), direct assessment, family informants, and past medical records. The subjects were judged by their primary treating clinicians to be clinically stable and in a nonacute (chronic) phase of their illness. They were required to have at least a minimal level of cognitive impairment, defined by a total score of 90 or less on the Repeatable Battery for the Assessment of Neuropsychological Status (20). The mean total score for normal subjects is 100 (SD=15). Subjects could be treated with a second-generation antipsychotic other than clozapine or a low-dose conventional antipsychotic, in the absence of concomitant anticholinergic treatment and significant extrapyramidal symptoms (defined as a total score of 4 or less on the Simpson-Angus Rating Scale [21]). Subjects who met the criteria for a DSM-IV diagnosis of alcohol or substance abuse (other than for nicotine) within the last month or the criteria for DSM-IV alcohol or substance dependence (other than for nicotine) within the last 6 months were excluded. Subjects with second-degree A-V block, CNS disorder (e.g., seizure disorder, stroke), or mental retardation were excluded.

The University of Maryland School of Medicine institutional review board approved the study protocol and informed consent procedures. Written informed consent was obtained for all subjects after the study procedures had been fully explained and before study participation. Each subject's ability to provide valid informed consent was documented by using study-specific procedures.

Neuropsychological Assessments

An eight-test neuropsychological test battery was administered at baseline and at the end of the study. The tests for working memory included WAIS-III letter-number sequencing (22) and Brief Assessment of Cognition in Schizophrenia number sequencing (23). Verbal memory was tested with the California Verbal Learning Test (24). Visual memory was assessed with the Brief Visuospatial Memory Test (25). Motor speed was tested with the Grooved Pegboard (26). Processing speed was evaluated with the WAIS-III digit symbol and symbol search (22). Attention was evaluated with the distractibility version of the Gordon Diagnostic System (GDS) Continuous Performance Test (27). Alternate forms of the California Verbal Learning Test and Brief Visuospatial Memory Test were used for the two test occasions.

Clinical Assessments

The Brief Psychiatric Rating Scale (BPRS) (28) positive symptom score was used to assess the change in positive symptoms. The BPRS positive symptom items are conceptual disorganization, hallucinations, unusual thought content, and suspiciousness. The BPRS anxiety/depression factor was used to assess changes in affective symptoms. BPRS item scores range from 1 to 7. The modified Scale for the Assessment of Negative Symptoms (SANS) (29) total score was used to assess negative symptom change. The SANS total score included all items except inappropriate affect, poverty of content of speech, social inattentiveness, inattentiveness during mental status testing, and all global items. SANS item scores range from 0 to 5. The CGI item for severity of illness was used to assess global changes. The BPRS, SANS, and CGI ratings were obtained biweekly. Intraclass correlation coefficients for these instruments ranged from 0.76 to 0.90. All raters were blind to treatment assignment. The Fagerström Test of Nicotine Dependence (30) and expired carbon monoxide were used to assess smoking status. Subjects were classified as smokers if they had a baseline level of expired carbon monoxide equal to or greater than 8 ppm.

Safety Assessments

The Simpson-Angus Rating Scale and the Abnormal Involuntary Movement Scale (AIMS) (31) were used to assess extrapyramidal symptoms and dyskinetic movements, respectively. These scales were administered biweekly. A standard chemistry panel, CBC, urinalysis, and ECG were collected at baseline and the end of the study. The Side Effect Checklist was developed at the Maryland Psychiatric Research Center to assess side effects and monitor vital signs. The Side Effect Checklist includes 22 common side effects, which are rated on a scale of 1 (none) to 4 (severe). These biweekly ratings were conducted by a nonblind pharmacist.

Study Design

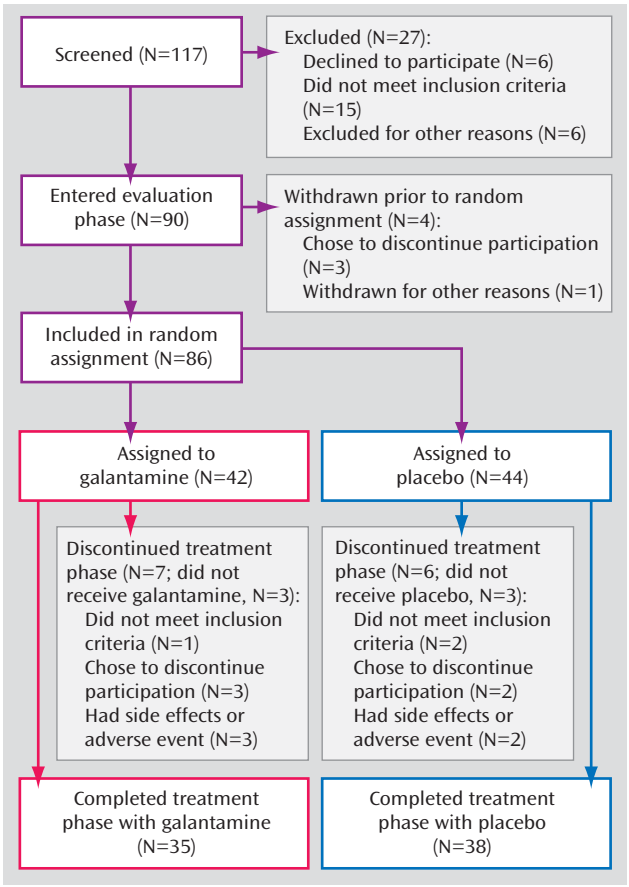
After the subjects provided written informed consent, the Repeatable Battery for the Assessment of Neuropsychological Status was administered to evaluate whether they met the minimal level of cognitive impairment. Subjects who met this criterion entered the 2-week evaluation phase, during which they underwent medical screening and baseline symptom and safety assessments. Subjects who continued to meet all inclusion criteria entered the 12-week double-blind treatment phase and were randomly assigned to galantamine or placebo. The galantamine target dose was 24 mg/day. This dose was selected because it appeared to provide the optimal risk-benefit ratio in the Alzheimer's disease registration studies (32). Subjects assigned to galantamine were given an initial dose of 4 mg twice a day, which was increased by 8-mg increments every 4 weeks. If a subject could not tolerate the study medication, he or she was instructed to skip a dose and was then rechallenged with the prescribed dose. If the participant still could not tolerate the prescribed dose, then the dose was reduced to the last tolerated dose. The subjects assigned to placebo received an equal number of matched tablets.

Medication compliance was assessed by weekly pill count and medication review. In addition, all subjects had a compliance plan that consisted of medication checks by family members and/or mental health care providers who had extensive contact with the subjects. All subjects who were judged to have received 75% or more of their assigned study medication were considered compliant.

Statistical Analyses

For each neuropsychological test, the subjects' scores were converted to z scores: z=(score–baseline mean)/baseline SD. For the primary outcome measure, an overall composite z score was computed from the average of the z scores for the individual tests. Preliminary data inspection suggested that even after transformation to z scores, many of the test scores were not normally distributed, and accordingly, the Wilcoxon rank sum test was used to compare treatments. An adaptation of the method of Pepe et al. was used to test for heterogeneity of effect across neuropsychological tests (33). In brief, the generalized estimating equations method for unbalanced repeated-measures analysis of variance (ANOVA) was used to fit the following model—change in z score= treatment+tests+treatment-by-test interaction—to the individual test z scores; a significant treatment-by-test interaction indicates heterogeneity of effect sizes among the different tests. Post hoc analyses of treatment differences on individual neuropsychological tests were performed, with p values adjusted for multiple comparisons by using the Benjamini and Hochberg procedure to

FIGURE 1. Subject Flow Through Study of Galantamine for Cognitive Impairments in People With Schizophrenia



control the false discovery rate (34). Mixed-model analysis of covariance was used to examine changes in symptoms. Longitudinal trends in repeated assessments with the Simpson-Angus scale and AIMS were evaluated by using the following procedure: for each subject, the Kendall's tau-b rank correlation was calculated for the correlation of the Simpson-Angus score and AIMS total score to time (i.e., study visit), and the distribution of these correlations was compared by using the Conover-Salsburg rank test (35). This procedure has superior power to mixed models for repeated-measures ANOVA for outcomes with nonnormal distributions, in which only a subgroup of subjects may "respond" to treatment (36). For items on the Side Effect Checklist, treatments were compared by using Fisher's exact test on presence or absence of newly incident or worsened (compared to baseline) side effects. Analysis of covariance (ANCOVA) was used to examine mean changes in laboratory measures, vital signs, and continuous ECG measures.

Results

Subject flow is presented in Figure 1. Eighty-six subjects were randomly assigned to treatment. Thirty-two outpatients and 10 inpatients were assigned to galantamine, and 31 outpatients and 13 inpatients were assigned to placebo. Three subjects assigned to galantamine and three assigned to placebo were treated with low doses of conventional antipsychotics. The remaining subjects were treated with second-generation antipsychotics. Seventy-three subjects (35 taking galantamine and 38 taking placebo) completed the study. All of these subjects had valid baseline and end-of-study neuropsychological assessments and were included in the primary outcome analyses. Eighty subjects received either galantamine (N=39) or placebo (N=41) and were included in the safety analyses, and 79 subjects (39 taking galantamine and 40 taking placebo) received at least one postrandomization symptom assessment and were included in the secondary efficacy analyses. There were no significant differences in the demographic, clinical, or baseline symptom characteristics of the subjects who entered the double-blind phase (Table 1).

Neuropsychological Measures

The mean baseline total scores on the Repeatable Battery for the Assessment of Neuropsychological Status for the subjects included in the analyses of neuropsychological test scores were 69.2 (SD=10.4) for galantamine and 67.5 (SD=11.1) for placebo (t=0.38, df=70, p=0.52). The mean galantamine dose at the end of the study was 23.5 mg/day (SD=2.7). The test z scores at 0 and 12 weeks for the composite and individual measures are presented in Table 2. The treatment effect for the composite score was not significant. However, the follow-up Pepe-Whitaker-Seidel test for heterogeneity of effect size for the individual test scores was significant (χ^2=17.19, df=7, p=0.02), indicating that treatment effects were not uniform across individual measures. In the unadjusted analyses, there were three significant group differences: galantamine improved performance more than placebo on the WAIS-III digit symbol test and the California Verbal Learning Test, whereas placebo was more effective than galantamine for the GDS distractibility test (Table 2). After adjustment of p values for multiple comparisons, the WAIS-III digit symbol and GDS distractibility test results remained significant, but the finding on the California Verbal Learning Test did not (Table 2).

Fifteen of 35 galantamine subjects and 21 of 38 placebo subjects were classified as smokers at baseline. ANCOVAs for the interaction between smoking status and group assignment for the composite score and for each of the individual tests were not significant (in all cases, p>0.25).

Symptom Measures

The subjects had mild to moderate baseline levels of positive and negative symptoms (Table 1). There were no significant group differences in the change in BPRS total score (F=0.16, df=1, 447, p=0.69), BPRS positive symptom item score (F=0.91, df=1, 447, p=0.34), or BPRS anxiety/depression factor score (F=0.71, df=1, 447, p=0.40). There was also no significant group difference in the change in SANS total score (F=2.76, df=1, 66.1, p=0.11). In exploratory analyses of the SANS subscales, there was a significant treatment group effect for the SANS alogia subscale,

TABLE 1. Characteristics of People With Schizophrenia Who Received Galantamine or Placebo for Cognitive Impairments

Baseline Characteristic	Galantamine (N=42)		Placebo (N=44)	
	N	%	N	%
Male sex	37	88.1	37	84.1
White race	14	33.3	18	40.9
	Mean	SD	Mean	SD
Age (years)	49.9	9.2	49.5	9.9
Age at onset (years)	24.4	7.8	25.9	7.2
BPRS scores				
Total	33.8	9.1	34.9	10.7
Positive symptoms	9.8	5.3	10.6	5.1
Anxiety/depression	5.8	2.9	5.7	2.6
Scale for the Assessment of Negative Symptoms total score	30.1	11.9	28.1	11.6
CGI severity rating	4.2	0.7	4.3	0.8
Repeatable Battery for the Assessment of Neuropsychological Status total score	70.3[a]	10.1	69.4	12.3

[a] N=41.

with galantamine subjects exhibiting a greater reduction in these symptoms (t=–2.77, df=71.2, p=0.007).

Safety Measures

There was a significant treatment group effect for the total score on the Simpson-Angus Rating Scale; for the galantamine group, the mean score fell from 1.4 (SD=1.8) at baseline to 1.1 (SD=1.8) at the end of the study, and for the placebo group the mean score was 1.6 (SD=2.1) at baseline and 1.6 (SD=1.9) at the end of the study (Conover-Salsburg test for treatment effect: t=2.03, df=77, p=0.05). The group treatment effect for AIMS total score was not significant. For galantamine the mean score was 2.0 (SD=3.1) at baseline and 2.1 (SD=3.0) at the end of the study, and for placebo the mean score was 2.1 (SD=3.1) at baseline and 1.6 (SD=3.0) at the end of the study (Conover-Salsburg test for treatment effect: t=0.35, df=77, p=0.73).

There were no significant group differences on the chemistry panel measures, including glucose, triglyceride, and cholesterol indices. The mean change in hemoglobin was significantly greater in the subjects assigned to galantamine (galantamine: mean change=0.29 g/dl, SD=0.69; placebo: mean change=–0.17, SD=1.06; t=2.19, df=72, p=0.03), with a similar but nonsignificant difference for hematocrit values (galantamine: mean change=0.81%, SD=2.17; placebo: mean change=–0.34, SD=2.98; t=1.89, df=72, p=0.06). There were no significant group results for the urinalysis, except for glucose. Three subjects receiving galantamine went from normal baseline values to abnormal values at the end of the study, whereas two subjects receiving placebo went from abnormal baseline values to normal values at the end of the study (χ^2=7.06, df=3, p=0.05). All three of the galantamine subjects had a previous history of type II diabetes mellitus.

ECG results were remarkable for significant group differences in the mean change in PR interval (galantamine: mean change=25.7 msec, SD=56.0; placebo: mean change=–3.0, SD=12.0; t=3.00, df=71, p=0.004) and the mean change in the QRS interval (galantamine: mean change=11.4 msec, SD=25.1; placebo: mean change=–1.6, SD=11.7; t=2.86, df=72, p=0.006) but not the mean change in QTc interval (galantamine: mean change=3.03 msec, SD=28.89; placebo: mean change=3.03, SD=27.68; t=0.00, df=71, p=0.99).

There were no significant group differences on vital signs or on any of the items of the Side Effect Checklist, including nausea, vomiting, and change in weight. Three galantamine subjects withdrew because of adverse events. One subject developed pneumonia and was hospitalized, one subject had a worsening of positive symptoms and required adjustment of antipsychotic medications, and one subject resumed drinking alcohol. Two placebo subjects withdrew because of adverse events. One subject reported dizziness and attributed this to the study medication, and one subject had a worsening of positive symptoms.

Discussion

The study results suggest that galantamine does not exhibit significant global benefit for cognitive impairments in people with schizophrenia. Rather, galantamine appears to have a heterogeneous effect on neuropsychological test measures. Specifically, in unadjusted analyses galantamine was associated with improved performance on the WAIS-III digit symbol test and the California Verbal Learning Test. The treatment effect for the WAIS-III digit symbol test remained significant after correction for multiple comparisons. The effect on the California Verbal Learning Test was nonsignificant after adjustment but suggestive (i.e., p=0.06). In contrast, there was greater improvement on the GDS distractibility test in the subjects who received placebo. There was no effect of baseline smoking status on treatment outcome.

Galantamine had the most pronounced effect on WAIS-III digit symbol performance, a processing speed measure, although it had no effect on WAIS-III symbol search, another measure of processing speed. The digit symbol result is consistent with findings from two previous studies. Schubert and colleagues (17) observed that, compared to placebo, galantamine had a significant effect on the attention index of the Repeatable Battery for the Assessment of Neuropsychological Status (20), which comprises a digit

TABLE 2. Neuropsychological Test Scores of People With Schizophrenia Who Received Galantamine or Placebo Over 12 Weeks for Cognitive Impairments

	Galantamine			Placebo			Wilcoxon Test for Between-Group Difference in Change Score		
Measure and Week	N	Mean	SD	N	Mean	SD	χ^2 (df=1)	Unadjusted p	Adjusted p[a]
Overall test battery z score							0.82	0.37	0.66
Week 0	35	0.03	0.64	38	–0.03	0.61			
Week 12	35	0.15	0.68	38	0.05	0.55			
Brief Assessment of Cognition in Schizophrenia number sequencing score							0.43	0.52	0.66
Week 0	35	12.2	3.6	38	12.3	3.5			
Week 12	35	12.9	3.5	38	12.5	3.5			
WAIS-III letter-number sequencing score							0.46	0.50	0.66
Week 0	35	8.1	2.8	38	7.9	2.9			
Week 12	35	8.1	2.2	38	7.5	2.5			
WAIS-III digit symbol score							9.48	0.002	0.02
Week 0	35	5.8	2.2	38	5.6	1.7			
Week 12	35	6.7	2.7	38	5.5	1.8			
WAIS-III symbol search score							0.02	0.89	0.90
Week 0	35	6.1	2.9	38	5.7	2.1			
Week 12	35	6.2	3.1	38	5.9	2.1			
Grooved Pegboard score							0.52	0.48	0.66
Week 0	35	114.0	44.6	37	117.5	38.1			
Week 12	35	110.9	38.9	37	114.7	38.6			
California Verbal Learning Test score							5.53	0.02	0.06
Week 0	35	7.1	2.3	38	7.7	2.2			
Week 12	35	7.8	2.7	38	7.6	2.6			
Brief Visuospatial Memory Test score							0.02	0.90	0.90
Week 0	35	4.6	2.1	38	5.0	1.8			
Week 12	35	4.8	1.7	38	5.3	2.3			
GDS distractibility test score							6.66	0.01	0.05
Week 0	34	0.9	0.1	36	0.8	0.1			
Week 12	35	0.9	0.1	36	0.9	0.1			

[a] Adjusted for multiple testing by using the method of Benjamini and Hochberg (34).

symbol analogue and a digit span measure. Olincy and colleagues reported that acute challenge with DMXB-A also significantly improved performance on the attention index (13). We note that the digit symbol task requires cognitive and motor processes in addition to those needed for the symbol search, which suggests that the current results reflect the differential sensitivity of these two processing speed measures to treatment effects, rather than random error. Lending support to this conclusion is the finding from a recent meta-analysis, which compared the performance of people with schizophrenia and healthy comparison subjects on 37 neuropsychological measures, that the largest impairment was observed for digit symbol coding tasks (37).

Processing speed, as measured by digit symbol coding tasks, may be central to our understanding of the neuropsychology of schizophrenia. Not only do people with schizophrenia show severe impairment, but their relatives also show impaired performance on digit symbol tasks (37). Moreover, coding task performance is related to vocational outcome, independent living, and other expected community roles (37, 38). These studies suggest that measures of processing speed, particularly digit symbol coding tasks, are strongly predictive of functional outcome. In the current study, we did not include functional outcome or other coprimary outcome measures, so we could not directly address this issue. Future studies are required to test whether galantamine, with or without concomitant psychosocial intervention, is effective in improving community outcomes.

Galantamine appeared to improve verbal memory performance, although this effect showed greater interindividual variation than the digit symbol effect and was nonsignificant after adjustment for multiple comparisons. It is interesting that Schubert and colleagues also reported marked but variable improvement in immediate verbal memory (17). They did find significant improvement in delayed memory, which was not assessed in the current study. This combination of findings suggests that positive treatment effects on verbal memory may result for some subjects with galantamine treatment. Understanding the validity of such effects will require further study.

The GDS distractibility test was the only test for which there was a marked placebo effect. The significant performance improvement probably reflects a practice effect. The lack of similar improvement in distractibility for the galantamine group suggests the possibility that galantamine may block the practice effect on this measure. Partial support for this explanation is provided by the results of our open-label donepezil study, in which we found

donepezil to have a similar adverse effect on GDS distractibility test performance (39). On the other hand, a large number of subjects in the current study performed near the test ceiling, which limits confidence in the finding. Additional study will be required to determine if the negative galantamine effect was an artifact or an unexpected but reliable result.

Galantamine had limited effects on symptoms. There was no evidence of an effect on positive or affective symptoms. Galantamine also did not result in global negative symptom improvement, but it did have a significant effect on the SANS alogia subscale. Future studies designed to specifically address the potential value of galantamine for negative symptoms are required.

Galantamine was well tolerated. Galantamine treatment was associated with a small but significant improvement in extrapyramidal symptoms. Galantamine also significantly increased hemoglobin levels, but not into the abnormal range. Finally, consistent with its known vagotonic properties, galantamine was associated with significant increases in the PR and QRS intervals, but not with prolongation of the QTc interval.

There have been a number of previous studies of acetylcholinesterase inhibitors in schizophrenia (40). Donepezil has been the most frequently tested agent. Although initial open-label trials and small controlled studies suggested a potential benefit (40), a large multicenter study (N=245) failed conclusively to demonstrate any beneficial effects of donepezil on a comprehensive neuropsychological battery (41). Similarly, positive findings with open-label rivastigmine (40) were not replicated in a double-blind, placebo-controlled study (42). Two small published double-blind studies examined the efficacy of galantamine for cognitive impairments in people with schizophrenia (17, 18). Schubert and colleagues (N=14) reported significant benefits of galantamine for the attention and delayed memory indices of the Repeatable Battery for the Assessment of Neuropsychological Status (17). Lee and colleagues (N=24) observed a significant improvement in visual recognition in galantamine-treated subjects (18). These subjects also showed nearly significant improvements in verbal recognition and attention, which may not have reached significance because of the small number of subjects (18). Finally, in an industry-sponsored study, there was no significant difference between galantamine and placebo on a global measure of cognition (clinicaltrials.gov, trial number: NCT00077727). The results for individual measures were not provided.

If the results of the Schubert, Lee, and current studies accurately reflect the cognitive benefits of galantamine, then the question arises of why galantamine has a beneficial effect but donepezil and rivastigmine apparently do not. In addition to acting as an acetylcholinesterase inhibitor, galantamine, in contrast to donepezil and rivastigmine, is also a positive allosteric modulator of the $\alpha_4\beta_2$ and α_7 nicotinic receptors (14–16). The allosteric properties of galantamine could lead directly to increased release of acetylcholine and activation of postsynaptic nicotinic receptors (15) or act indirectly through its effects on the release of other neurotransmitters, especially glutamate and dopamine (16, 43). Schilström and colleagues found that galantamine increases dopaminergic activity and release in the prefrontal cortex in a dose-dependent manner (16). Wang and colleagues demonstrated that galantamine increased dopamine release in the hippocampus and that this effect was related to its ability to improve cognition in a mouse model of Alzheimer's disease (43).

There are several potential limitations of the current study. First, the participants were relatively old. Second, the subjects' mean total score on the Repeatable Battery for the Assessment of Neuropsychological Status was markedly lower than that in the study by Schubert et al. (17) and suggests that the subjects were moderately cognitively impaired. These two factors may have limited the ability to detect the full range of benefit of galantamine treatment. A third potential limitation is the galantamine dose. Galantamine is an allosteric modulator at low concentrations, but at high concentrations the main effect of galantamine is mediated through its acetylcholinesterase inhibitor actions (15). In addition, at higher doses galantamine may act as an inhibitor of nicotinic receptors (15). In the current study, only one dose of galantamine was evaluated. If the cognition-enhancing effects of galantamine are mediated through its allosteric actions at the nicotinic receptors and if the current dose was above or below the maximum effective dose for these effects, then the observed results may underestimate the potential benefit of adjunctive galantamine treatment. Finally, there is the possibility that the acetylcholinesterase inhibitor activity of galantamine may have interfered with the potential benefits of its allosteric actions (16).

In summary, the current study results suggest that galantamine may have heterogeneous effects on cognitive performance. If the beneficial effects of galantamine are mediated through its allosteric actions at the nicotinic receptors, then future studies of more specific and potent allosteric modulators may be of considerable value.

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Dr. Buchanan has served on data safety monitoring boards for Pfizer and Wyeth; has been a consultant to Memory Pharmaceuticals and Organon; and has served on advisory boards of AstraZeneca, GlaxoSmithKline, and Pfizer. Dr. Conley has served on advisory boards of AstraZeneca, Bristol-Meyers Squibb, Janssen, Johnson & Johnson, Eli Lilly, Organon, Pfizer, Solvay, and Wyeth. Ms. Ball has received grant support from Eli Lilly. Dr. Gold has served as a consultant to Pfizer and has received royalty payments for the Brief Assessment of Cognition in Schizophrenia. Dr. Dickinson, Ms. Feldman, and Dr. McMahon report no competing interests.

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