A 12-week, double-blind, placebo-controlled trial of galantamine adjunctive treatment to conventional antipsychotics for the cognitive impairments in chronic schizophrenia

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The objective of the study was to study the effects of acetylcholinesterase inhibitors on cognition in patients with schizophrenia. We conducted a 12-week, double-blind, placebo-controlled trial of galantamine as adjunctive treatment to conventional antipsychotic drugs on 24 patients with schizophrenia. The 24 patients had been stabilized on conventional antipsychotic drugs (chlorpromazine equivalent dose of 1390 mg/day) for a minimum of 3 months before their enrollment into the study. The patients were evaluated at baseline, and after 6 and 12 weeks using the Korean version of Mini Mental State Examination, Brief Psychiatric Rating Scale, and a standard neuropsychological battery. Compared with placebo, galantamine produced a small and nonsignificant change in the cognitive measures, but the score for recognition on the Rey Complex Figure Test improved significantly in patients given galantamine ($P<0.05$). Of the several domains of cognitive functions assessed, galantamine tended to improve the score for recognition on the Hopkins Verbal Learning Test and for color on the Stroop Test ($P<0.1$), but these results were not statistically significant. The scores on the Korean version of Mini Mental State Examination did not change significantly in patients with galantamine, and the psychiatric symptoms did not change. The addition of galantamine to the conventional antipsychotic medication of patients with schizophrenia does not produce a change in the cognitive function or state of psychopathology. *Int Clin Psychopharmacol* 22:63–68 © 2007 Lippincott Williams & Wilkins.

International Clinical Psychopharmacology 2007, **22**:63–68

Keywords: cognitive function, galantamine, schizophrenia

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Received 18 November 2005 **Accepted** 3 October 2006

Introduction

Cognitive symptoms are considered to be important predictors of the treatment outcomes with regard to social and vocational functioning of patients with schizophrenia (Green, 1996). The treatment of cognitive deficits may be essential for improving the quality of life of these patients, and thus, cognitive impairment has been an area of focus for several decades in the research of schizophrenia. Conventional antipsychotic drugs are known to have limited beneficial or negative effects on cognitive function (Blyler and Gold, 2000), whereas atypical antipsychotic drugs have been suggested to have potential benefits on cognitive function (Keefe *et al.*, 1999). Despite the beneficial effects of atypical antipsychotics on cognitive function, these drugs do not correct the impairments of cognitive function in patients with schizophrenia to normal levels (Purdon *et al.*, 2000). Researchers have speculated that nicotinic cholinergic receptors are involved in cognitive impairment in these patients. Diminished expression of the α7 subtype of nicotinic cholinergic receptors has been reported for schizophrenic patients in several brain regions, including the hippocampus, frontal cortex, and thalamus (Adler *et al.*, 1998). Altered expression and function of the α7 nicotinic acetylcholine receptor may be responsible for the auditory sensory gating deficit in these patients owing to the diminished suppression of an auditory-evoked response (P50) to repeated stimuli (Adler *et al.*, 1998). Deficits in sensory gating are associated with attention impairment and may contribute to cognitive symptoms and perceptual disturbances (Adler *et al.*, 1998). Breese *et al.* (2000) observed abnormal regulation of the density of high-affinity nicotinic receptors in schizophrenic patients. Consequently, pharmacological interventions that enhance central cholinergic function may have an enhancing function on the cognition of these patients.

Galantamine is a combined acetylcholinesterase inhibitor (Thomsen *et al.*, 1991) and allosteric potentiator of the nicotinic receptor (Schrattenholz *et al.*, 1996; Samochocki *et al.*, 2003). Galantamine interacts with the nicotinic receptor at sites that are different from those for acetylcholine and nicotine, and it modulates ion channel activity and potentiates the actions of nicotinic receptors

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in the presence of acetylcholine. Overall, galantamine provides the requisite cholinergic stimulation without producing desensitization. Galantamine may be the acetylcholinesterase inhibitor of choice as an adjunct to antipsychotic treatment to target the cognitive impairment associated with schizophrenia. To our knowledge, however, there is only one unpublished study that investigated the effect of adjunctive galantamine on risperidone treatment in schizophrenia (Allen *et al.*, 2003). Hence, the goal of this study was to determine whether galantamine given as an adjunctive treatment to conventional antipsychotic drugs could enhance cognitive function compared with a placebo in schizophrenic patients.

Methods

Subjects

Inpatients from the psychiatric wards of Sangnok, Semyoung, Dongnae, Daenam, Busan Municipal, and Dongsuh hospitals in Korea were included in this study. Informed consent was obtained for this protocol, which was approved by the Institutional Review Board of the Inje University Busan Paik Hospital. All of the patients met the *Diagnostic and statistical manual of mental disorders-IV* (American Psychiatric Association, 1994) diagnostic criteria of schizophrenia and had been stabilized with a current dose of conventional antipsychotic drugs for a minimum period of 3 months before entering into the study. The level of cognitive impairment required for participation was defined as a total performance score between 18 and 24 on the Korean version of Mini Mental State Examination (K-MMSE) (Korean Association for Geriatric Psychiatry, 2003). All of the patients complained of cognitive deficits in their clinical examinations. Patients who had any medical problem or took any medication that affected cognitive performance were excluded. Anti-parkinsonian anticholinergics and benzodiazepines were permitted if the dose did not change during the 12 weeks.

Assessments

The Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962) and the 17-item Hamilton's Rating Scale for Depression (Hamilton, 1967) were used to assess the severity of psychiatric symptoms and depressed mood. The Clinical Global Impression-Severity and Improvement Scale was also administered to all patients. A neuropsychological battery was administered together to evaluate the changes in several domains of cognitive function. The neuropsychological battery included the following measures of attention, auditory and visual memory, and executive function: the K-MMSE, Hopkins Verbal Learning Test (HVLT), Rey Complex Figure Test (RCFT), Digit Span Forward and Backward Test, Digit Symbol Substitution Test, Stroop Test, Trail Making Test Part A, Verbal Fluency Test (VFT), and Boston Naming Test. The HVLT is a test of the immediate memory span, new learning, susceptibility to interference, and delayed recall. The Trail Making Test Part A is a test of visuomotor speed and the ability to set shift. The VFT measures verbal productivity and the intactness of the lexical system, which was measured by the Category Fluency Test.

Study design

Twenty-four patients were entered into the 12-week, double-blind, parallel trial of galantamine adjunctive treatment. The severity of psychotic symptoms and cognitive impairments of the patients were evaluated at baseline. The patients were then randomly assigned under double-blind conditions to receive either galantamine or a placebo in addition to their treatment with a fixed dose of conventional antipsychotic drugs (chlorpromazine equivalent dose (Preskorn, 2005) of 1390 mg/day). Galantamine was prescribed at 8 mg once a day and increased to 16 mg/day at the end of 6 weeks. The BPRS was used at baseline and at 6 and 12 weeks after the baseline evaluation to assess any changes in the severity of psychiatric symptoms. The neuropsychological battery was administered at the same time to assess any changes in the various domains of cognitive function. A checklist for adverse events after taking galantamine was used (Wilcock *et al.*, 2000).

Analyses

Baseline comparisons between the two groups were performed with a Mann–Whitney *U*-test or Fisher's exact test, depending on the nature of the respective variable. The efficacies of galantamine and placebo were analyzed using repeated-measures analysis of variance with the group (galantamine vs placebo) as the between-subject factor and the time (baseline, week 6, and week 12) as the within-subject factor. For missing data, the last observation was carried forward for analysis. $P \leq 0.05$ was considered statistically significant.

Results

Demographics

Twenty-four patients agreed to participate and were all entered into the study and randomized into the galantamine ($n = 12$) or placebo ($n = 12$) groups. Two patients did not complete the 12-week trial. One of these patients received regular doses of galantamine for more than 6 weeks and completed the clinical evaluations at baseline and at week 6 before she suddenly discharged herself from the hospital. The other patient who dropped out of the study also completed the clinical evaluations at baseline and at week 6, but did not complete the study owing to a headache that was attributed to the galantamine.

Table 1 shows the demographic characteristics and baseline measures of our study population. No significant

Table 1 Baseline demographic and clinical data of the patients

	Mean (SD)		
	Galantamine ($n=12$)	Placebo ($n=12$)	*P*
Age (years)	39.5 (3.2)	41.5 (3.2)	0.11
Education	8.3 (3.8)	9.0 (2.5)	0.75
Illness duration (years)	15.8 (5.7)	18.8 (7.2)	0.26
Daily chlorpromazine equivalent dose (mg)	1279.1 (832.5)	1502.5 (1146.5)	0.67
Medication duration (months)	55.0 (51.1)	64.4 (51.6)	0.75
Clinical rating scale scores			
BPRS score	54.9 (6.2)	60.9 (5.7)	0.05
HAM-D score	3.7 (2.7)	5.0 (2.1)	0.18
K-MMSE score	21.8 (2.2)	21.8 (1.9)	0.86
CGI-S score	2.8 (0.6)	3.2 (0.4)	0.07
	Percentage (%)		
Gender (male)	66.7	50.0	0.68
Use of anticholinergics	66.7	75.0	1.00

Data were analyzed by Mann–Whitney test for continuous variables and Fisher's exact test for categorical variables.
BPRS, Brief Psychiatric Rating Scale; HAM-D, Hamilton's Rating Scale for Depression; K-MMSE, Korean version of the Mini Mental State Examination; CGI-S, Clinical Global Impression ratings-Severity.

differences on any demographic or clinical variable were seen at baseline. All patients received conventional antipsychotic drugs at a mean dose was 1390 mg/day chlorpromazine equivalent dose. The most commonly used antipsychotic was haloperidol (16 patients, 67%), followed by chlorpromazine (13 patients, 54%). Other antipsychotics were levopromazine, bromoperidol, nemonapride, and perphenazine. Thirteen patients (54.2%) received a combination of two classes of antipsychotics.

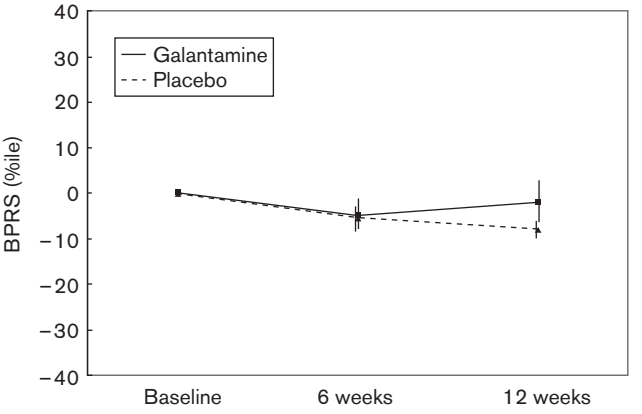
Effects of adjunctive galantamine on psychiatric symptoms

The psychiatric symptoms at baseline and after 6 and 12 weeks of treatment remained essentially unchanged. The change in the mean scores of the BPRS and Hamilton's Rating Scale for Depression did not differ between the galantamine and placebo groups. We defined a response as an improvement of 20% or more in the BPRS total score; at the end of the study, no responders remained in either group (Fig. 1). No patients improved by two points or more on the Clinical Global Impression-Severity and Clinical Global Impression-Improvement scale after adjunctive galantamine treatment. Thus, no benefit of medications was detected on any measure of psychopathology.

Effects of adjunctive galantamine on the Korean version of Mini Mental State Examination

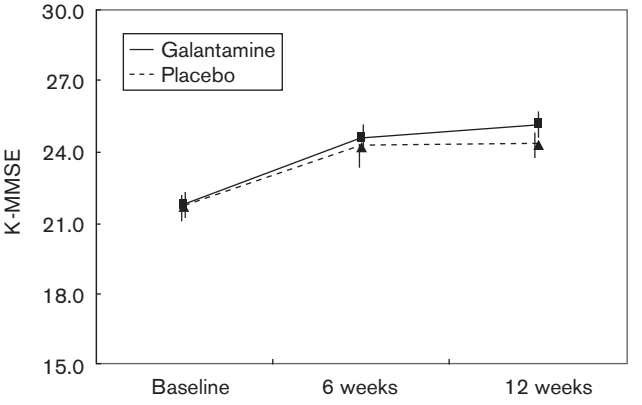
In the galantamine group, the mean (SD) K-MMSE score was 21.8 (2.2) at baseline and increased to 25.2 (2.1) after 12 weeks (Fig. 2). In the placebo group, the mean K-MMSE score was 21.8 (1.9) at baseline and 24.3 (2.2) after 12 weeks. The changes in the galantamine group, however, did not differ from those of the placebo group at the end of study.

Fig. 1



The changes from baseline scores on the Brief Psychiatric Rating Scale (BPRS) in the galantamine and placebo groups during the 12 weeks for patients with chronic schizophrenia.

Fig. 2



The total scores on the Korean version of the Mini Mental State Examination (K-MMSE) in the galantamine and placebo groups during the 12 weeks for patients with chronic schizophrenia.

Effects of adjunctive galantamine on impaired cognitive functions

Table 2 provides the results of the cognitive tests for both groups. No statistically significant differences were observed between the two groups for any of the cognitive measures except the score for recognition on the RCFT.

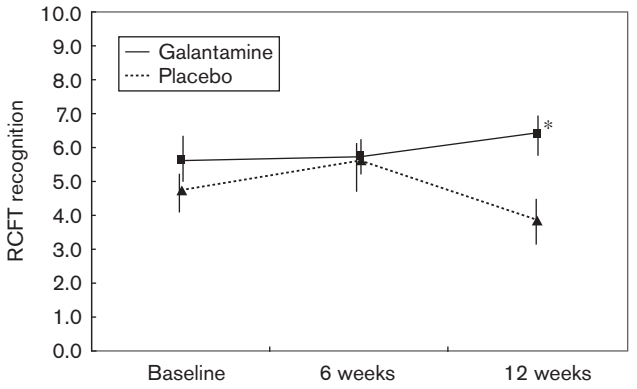
RCFT: In the galantamine group, the mean score for recognition increased significantly after 12 weeks compared with the placebo group ($P < 0.05$; Fig. 3). The mean scores for immediate and delayed recall improved more from the baseline to week 12 in the galantamine group than in the placebo group. The between-group difference in immediate and delayed recall, however, was not significant.

Table 2 Changes from baseline to week 12 in the cognitive assessment scores in the galantamine and placebo groups

	Galantamine ($n=12$)		Placebo ($n=12$)		
	Baseline	12 weeks	Baseline	12 weeks	*P* value
HVLT					
Immediate recall	13.1 ± 4.2	17.3 ± 3.4	12.3 ± 3.5	14.3 ± 5.7	0.2601
Delayed recall	3.8 ± 2.2	5.3 ± 1.8	2.8 ± 1.4	3.8 ± 2.4	0.5350
Recognition	6.8 ± 2.3	7.3 ± 2.2	7.1 ± 2.6	5.8 ± 3.2	0.0833
RCFT					
Immediate recall	9.6 ± 6.0	13.4 ± 8.4	5.8 ± 3.9	8.0 ± 6.0	0.5205
Delayed recall	8.6 ± 5.7	13.0 ± 8.3	4.9 ± 5.1	8.5 ± 5.4	0.8665
Recognition	5.7 ± 2.4	6.4 ± 2.1	4.8 ± 2.1	3.9 ± 2.3	0.0284*
Digit span					
Forward	4.8 ± 1.1	4.9 ± 0.9	5.5 ± 0.8	5.9 ± 1.3	0.6335
Backward	2.8 ± 0.8	2.8 ± 0.7	3.2 ± 1.2	3.5 ± 1.0	0.4621
DSST	23.9 ± 6.2	26.8 ± 7.5	18.3 ± 6.3	19.8 ± 6.0	0.6704
Stroop					
Letter	104.0 ± 16.0	103.4 ± 16.0	101.8 ± 14.4	104.9 ± 9.9	0.3799
Color	59.0 ± 23.9	66.3 ± 25.8	49.8 ± 12.5	49.2 ± 13.2	0.0789
Trail making part A (s)	88.8 ± 34.0	82.0 ± 32.3	113.8 ± 39.6	112.8 ± 52.3	0.8715
Verbal fluency	15.0 ± 3.9	14.6 ± 4.5	11.0 ± 3.2	10.6 ± 2.6	0.9964
Boston naming test	39.4 ± 6.2	42.5 ± 7.5	39.4 ± 11.0	44.2 ± 10.9	0.2543

Data were analyzed by repeated-measures analysis of variance.
HVLT, Hopkin's Verbal Learning Test; RCFT, Rey Complex Figure Test; DSST, Digit Symbol Substitution Test.
*$P<0.05$.

Fig. 3



The scores on the Rey Complex Figure Test (RCFT) recognition in the galantamine and placebo groups during the 12 weeks for patients with chronic schizophrenia.

HVLT: The mean change in the scores for immediate and delayed recall on the HVLT did not differ between the galantamine and placebo groups during the 12-week study period. Of the mean scores for recognition, the between-group difference at week 12 approached significance ($P = 0.083$).

Stroop test: The mean change in the color test between both groups approached significance at week 12 ($P = 0.079$).

Other tests: The two groups did not differ in any other outcome as measured by the Digit Span Forward and Backward Test, Digit Symbol Substitution Test, Trail Making Test Part A, VFT, or Boston Naming Test.

Table 3 Adverse events occurring during the study

Adverse events	Total ($n=24$)	Galantamine ($n=12$)	Placebo ($n=12$)
Dizziness	6 (25)	2 (16.7)	4 (33.3)
Headache	5 (20.8)	1 (8.3)	4 (33.3)
Diarrhea	5 (20.8)	3 (25)	2 (16.7)
Nausea	2 (8.3)	1 (8.3)	1 (8.3)
Vomiting	2 (8.3)	0 (0)	2 (16.7)
Weight decrease	1 (4.2)	1 (8.3)	0 (0)

Data are given as number (%) of each group.

Adverse events of adjunctive galantamine

The incidence of adverse events was similar between the galantamine group and the placebo group. The most common adverse events were dizziness, headache, diarrhea, nausea, and vomiting (Table 3). Adverse events generally were transient and of mild-to-moderate intensity. No serious adverse events were seen in any of the patients from either group. Galantamine was relatively well tolerated. Only one galantamine patient did not complete the study because of headache, which was related to the galantamine because the headache disappeared while the galantamine treatment was interrupted.

Discussion

Even though adjunctive galantamine was associated with significant improvement in recognition by the RCFT, the results of other measures in the RCFT were not significant. The addition of galantamine to the antipsychotic medication did not produce positive effects in the cognitive function of patients with schizophrenia in the present study. Therefore, the results of this trial do not support the assertion that galantamine adjunctive treatment is beneficial to cognitive functions including

visual memory. Allen *et al.* (2003), however, reported that galantamine improved a measure of attention and verbal fluency in a 4-week, double-blind, placebo-controlled trial, but this study differed from our trial in concomitant antipsychotics. Whereas Allen *et al.* (2003) treated their patients with galantamine and risperidone, our patients were treated with galantamine and conventional antipsychotics instead of atypical antipsychotics. Therefore, the methodological difference of the studies should be considered. Our trial is consistent with the negative results of several other double-blind trials that used an anticholinesterase inhibitor as the augmenting medication. Tugal *et al.* (2004) treated 20 patients with donepezil and typical antipsychotics in a 12-week, double-blind, placebo-controlled, cross-over study, but their sample population was not large enough to confirm benefits on cognitive function. Furthermore, their patients were treated with donepezil for only 6 weeks, which might be too short to show the effect of donepezil on cognitive function. Friedman *et al.* (2002) treated patients with donepezil and risperidone for 12 weeks, and their sample population of disabled patients who had severe cognitive impairment at baseline may have been particularly refractory to the intervention. Freudenreich *et al.* (2005) also did not allow enough time to reveal the effects of donepezil. They included smokers who might be treating their putative cholinergic dysfunction with nicotine. Kumari *et al.* (2006) treated patients with rivastigmine and atypical antipsychotics. Cholinergic facilitation with rivastigmine in schizophrenic patients treated with atypical antipsychotics may not produce clinically meaningful cognitive improvement.

The results of the current study were negative, but we do not rule out a more subtle or complicated role of the cholinergic system in schizophrenia. First, our patients were treated with anti-parkinsonian anticholinergics during the study. A large body of evidence in animals and humans has established that the cholinergic neurotransmitter system is important for attention, memory, and learning (Furey *et al.*, 2000; Friedman, 2004). Anticholinergic drugs interact with the cholinergic augmentation and are known to impair cognitive and information processing functions in both normal (Kumari *et al.*, 2001; Zachariah *et al.*, 2002) and schizophrenic populations (Strauss *et al.*, 1990; Kumari *et al.*, 2003a, b). The administration of scopolamine or atropine induces memory dysfunction in rats, primates, and humans (Blozovski *et al.*, 1977; Drachman, 1977; Aigner and Mishkin, 1986). This drug-induced impairment is subsequently reversed after displacement of the blocking agent (Dawson *et al.*, 1992), and by the use of acetylcholinesterase inhibitors. Irrespective of the use of antiparkinsonian anticholinergics, the results of our trial did not support the addition of galantamine for the improvement of cognition or psychopathology. Smoking is perhaps one of the biggest confounders, and smokers were included in our study group. Smoking is considered to desensitize nicotine receptors in patients with schizophrenia who do not show normal upregulation following chronic nicotine use (Kumari *et al.*, 2006). This might have prevented the cholinesterase inhibitor from reaching the full therapeutic potential, influencing changes in brain activity and improvements in behavioral performance or clinical status. Future studies might examine the cognitive effects of galantamine in nonsmoking schizophrenic patients. Most of the patients in this study were chronic and institutionalized; therefore, they may be unresponsive to the galantamine treatment in particular. In addition, the use of high-dose antipsychotics might have caused insensitivity to the intervention.

The duration of the study was 12 weeks and may not have been sufficiently long. Although it does not exclude the possibility of a task-learning effect, the results of this study tended to have more positive effect on cognition as time progressed. Comparable with the results at week 6, the results at week 12 showed more improvement on cognitive functions from the baseline. Galantamine significantly benefits cognitive function in Alzheimer's dementia for up to 6 months (Lilienfeld, 2002), and many studies investigating the effects of galantamine on cognitive function were conducted for 6 months (Raskind *et al.*, 2000; Ritchie *et al.*, 2004).

In summary, the results of this double-blind, placebo-controlled study do not support the adjunct use of galantamine in patients with schizophrenia and failed to show beneficial effects on cognitive functions or psychopathology.

Acknowledgements

The authors acknowledge the study investigator, Young-Ran Hwang, and the staff at each center.

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