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A 12-week, double-blind, placebo-controlled trial of donepezil as an adjunct to haloperidol for treating cognitive impairments in patients with chronic schizophrenia

Bong-Ju Lee *Department of Psychiatry, School of Medicine and Paik Institute for Clinical Research, Inje University, Republic of Korea.*
Jung-Goo Lee *Department of Psychiatry, Dong Suh Mental Hospital, Masan, South Korea.*
Young-Hoon Kim *Department of Psychiatry, School of Medicine and Paik Institute for Clinical Research, Inje University, Republic of Korea.*

Abstract

To study the effects of acetylcholinesterase inhibitors (AChEIs) in the management of cognitive impairments in patients with schizophrenia, we investigated the effects of 12 weeks of adjunctive therapy with donepezil on their cognitive impairments.

Twenty-four subjects stabilized on haloperidol treatment (5–30 mg/day) for a minimum of 3 months were entered into a double-blind, placebo-controlled trial of donepezil as an adjunctive treatment. Subjects were randomly assigned under double-blind conditions to receive either 5 mg/day donepezil ($N = 12$) or placebo ($N = 12$) for 12 weeks. The subjects were evaluated at baseline, and after 4, 8, and 12 weeks using the Korean version of Mini Mental State Examination (K-MMSE), Brief Psychiatric Rating Scale (BPRS), and standard neuropsychological assessment.

The K-MMSE scores improved significantly ($p < 0.05$) but the BPRS scores did not improve significantly in patients given donepezil; subjects showed slight improvement in several cognitive measures. At the end of the study, the difference in the mean K-MMSE scores between the donepezil and placebo groups approached statistical significance ($p = 0.056$). Of the several domains of cognitive functions assessed, verbal recognition and visual recall memory improved significantly ($p < 0.05$). But donepezil did not affect scores in the executive function tests.

Our findings support a potential positive effect of AChEIs in the management of cognitive impairments in patients with chronic schizophrenia. Further studies with large subjects are needed to confirm our findings.

Keywords
donepezil, cognition, schizophrenia

Introduction

Patients with schizophrenia have impairments in most domains of cognition, such as attention, visual and verbal memory, working memory and processing speed (Goldberg and Gold, 1995). Although conventional antipsychotic drugs have limited beneficial or deleterious effects on cognition (Blyler and Gold, 2000), atypical antipsychotic drugs may have modest beneficial effects on cognitive function (Keefe *et al.*, 1999). However, patients with schizophrenia continue to exhibit pronounced cognitive impairment despite adequate treatment with atypical antipsychotic drugs (Purdon *et al.*, 2000). Therefore, clinicians must consider other treatments to address the continued problem of cognitive impairment. Adjunctive pharmacotherapy may offer a viable alternative approach to treating cognitive impairment in patients with schizophrenia.

Dopamine is regarded as the key neurotransmitter involved in the pathophysiology of schizophrenia (Davis *et al.*, 1991), although the cholinergic system has also been implicated (Karson *et al.*, 1996). The brains of schizophrenic patients have fewer muscarinic receptors (Crook *et al.*, 2000) and nicotinic receptors, especially in the hippocampus (Leonard *et al.*, 1996; Freedman *et al.*, 1995), than those of healthy people. Cholinergic mechanisms have been implicated in the regulation of attention, memory, processing

Corresponding author: Young-Hoon Kim, MD, PhD, Department of Psychiatry, School of Medicine, Inje University, 633-165, Gaegum-dong, Busanjin-gu, Busan, 614-735, South Korea.
Email: npkyh@chol.com

speed and sensory gating processes (Vitiello *et al.*, 1997; Brocks *et al.*, 1998; Furey *et al.*, 2000).

Donepezil is a selective acetylcholinesterase inhibitor that improves general measures of cognitive impairment in patients with Alzheimer's disease (Rogers *et al.*, 1998). The aim of this study was to examine whether donepezil given as an adjunctive treatment to haloperidol would improve attention and memory, as compared with a placebo, in schizophrenic patients.

Method

Subjects

The subjects were inpatients from the psychiatric wards of Dong Suh Mental Hospital, Masan, Kyeung-Nam Province, South Korea. The protocol was approved by the Institutional Review Board (IRB) of Busan Paik Hospital, Busan, South Korea. Patients were screened as potential participants in a 12-week double-blind study of donepezil as adjunctive treatment. The patients provided informed consent in accordance with the procedures outlined by the local IRB, and were informed that they could withdraw from the experiment at any time. All 24 subjects met the DSM-IV diagnostic criteria for schizophrenia, and had been stabilized with a current dose of haloperidol for a minimum period of 3 months before entering into this study. The level of cognitive impairment required for participation was defined as a total performance score between 15 and 24 on the K-MMSE (Park *et al.*, 1990; Park *et al.*, 1991; Kang *et al.*, 1997). The patients who had clinically significant physical abnormalities based on the physical and laboratory examination, and had a history of CNS stimulating drug misuse were excluded from our study. However, antiparkinsonian anticholinergics and benzodiazepines were allowed if their doses did not change during the 12 weeks.

Study design

After baseline evaluation of the severity of psychotic symptoms and cognitive impairments, 24 subjects entered a 12-week, double-blind, parallel trial of donepezil adjunctive treatment. The dosage of donepezil was 5 mg/day because authors wanted to find out the minimal effective dosage of donepezil. The subjects were randomized in a 1:1 pattern to receive donepezil (5 mg/day) or the placebo in addition to a fixed dose of haloperidol (5–30 mg/day) for 12 weeks.

Assessments

The BPRS and the HAM-D were used to assess the severity of psychiatric symptoms and depressed mood at 4, 8, 12 weeks after baseline evaluation. The Clinical Global Impression-Improvement (CGI-I) was completed to assess the effectiveness of donepezil on the cognitive impairments. Several neuropsychological tests were administered together as a cognitive assessment battery to evaluate the changes in several domains of cognitive function. The cognitive assessment battery included measures of attention, auditory and visual memory, and executive function: the K-MMSE, Hopkins Verbal Learning Test (HVLT), Rey Visual Learning Test (RVLT), Digit Span Forward and Backward, Digit Symbol Substitution Test (DSST), Stroop Test, Trail Making Tests Part A, Verbal Fluency Test (VFT) and the Boston Naming Test (BNT). HVLT is a test of immediate memory span, new learning, susceptibility to interference and delayed recall (Brandt, 1991). RVLT is a test for assessment of a variety of cognitive processes, including planning, organizational skills and problem-solving strategies, as well as perceptual, motor and memory functions (Poulton and Moffitt, 1995). The Stroop colour and word test is a measure of executive function that is commonly used in neuropsychological evaluations (Moering *et al.*, 2004). The Trail Making Tests Part A is a test of visuomotor speed and the ability to set shift (Reitan, 1958). VFT measures verbal productivity and the intactness of the lexical system, which was measured by the Category Fluency Test (Crowe, 1998). The Boston Naming Test is commonly viewed as a measure of language ability, particularly, confrontational naming, and word-retrieval problems (Mitrushina and Satz, 1995).

Subjects were encouraged to report any spontaneous adverse events after taking their dose of donepezil, and an adverse events checklist was completed.

Analyses

Epidemiological and clinical data between the two groups at baseline were compared using the t-test for continuous variables and *Chi* square analysis for categorical variables. The efficacy on the clinical and cognitive performances between donepezil and the placebo was compared at the difference times using the t-test. Analysis of variance (ANOVA) was used to compare the clinical and cognitive performances at the different times (baseline, week 4, week 8 and week 12). α for the outcome measures was set to 0.05.

Results

Demographics

Twenty-four subjects entered the study and were randomized to donepezil ($N = 12$) or placebo group ($N = 12$). Twenty-three subjects completed the entire protocol without any significant violation. One patient received regular doses of donepezil for more than 8 weeks and completed the clinical evaluations at baseline, week 4 and week 8 before he discharged and dropped out from the study.

Table 1 shows the subjects' demographic and clinical data. The baseline scores of MMSE are over 21, except 5 subjects (2 subjects in the placebo group, 3 in the donepezil group).

The donepezil and placebo groups did not differ significantly at baseline on any demographic or clinical variable. No subject was identified as having remarkable depressive symptoms.

Table 1 Baseline demographic and clinical data of the subjects

	Mean (SD)		
	Donepezil (N = 12)	Placebo (N = 12)	*p*
Age (years)	42.2 (5.7)	44.2 (4.0)	0.37
Education (years)	9.8 (3.7)	7.5 (2.0)	0.09
Illness duration (years)	13.1 (4.7)	15.9 (5.7)	0.34
Daily haloperidol dose (mg)	14.4 (9.6)	17.0 (8.9)	0.49
Clinical rating scale scores			
BPRS score	33.1 (4.9)	36.8 (4.5)	0.11
HAM-D score	5.4 (2.1)	6.8 (3.0)	0.23
K-MMSE score	22.0 (1.9)	21.8 (3.4)	0.46
	Percentage		*p*
Sex (male)	66.7	58.3	0.67
Use of anticholinergics	100	91.3	0.31
Smoking	66.7	50.0	0.40

Data were analysed using the t-test for continuous variables and *Chi* square analysis for categorical variables.
Abbreviations: BPRS, Brief Psychiatric Rating Scale; HAM-D, Hamilton's Rating Scale for Depression; K-MMSE, Korean version of the Mini Mental State Examination.

Effects of adjunctive donepezil on psychiatric symptoms

The change in the mean scores of the BPRS did not differ between the donepezil and placebo groups (Fig. 1). Donepezil adjunctive therapy produced no significant improvements in the BPRS total score. When we defined a response as an improvement of 20% or more in the BPRS total score, there were no responders in either group at the end of the study. No subjects improved by two points or more on the CGI-Improvement after adjunctive donepezil treatment.

Effects of adjunctive donepezil on the K-MMSE

In the donepezil group, the mean K-MMSE score at baseline was 22.0 (1.9); this score increased significantly to 25.1 (3.5) after 12 weeks ($p < 0.05$) (Fig. 2). In the placebo group, the mean K-MMSE score at baseline was 21.8 (3.4) and 22.7 (3.7) after 12 weeks. After 12 weeks, the difference between groups in the K-MMSE score approached statistical significance ($p = 0.059$).

Effects of adjunctive donepezil on impaired cognitive functions

HVLT: The mean change in the scores for immediate and delayed recall on the HVLT did not differ between the donepezil and placebo groups during the 12-week study period. In the donepezil group, the mean scores for recognition were 5.2 (3.6) at baseline, 5.9 (3.1) at week 4, 7.3 (2.7) at week 8 and 9.4 (1.4) at week 12 (Fig. 3). In the placebo group, the means scores were 6.5 (2.6) at baseline, 6.5 (3.2) at week 4, 6.1 (2.8) at week 8 and 7.5 (2.0) at week 12. The increase in the mean score for recognition from baseline to 12 weeks was significant in the donepezil group ($p < 0.01$). The recognition score differed significantly between groups at week 12 ($p < 0.05$) (Fig. 3).

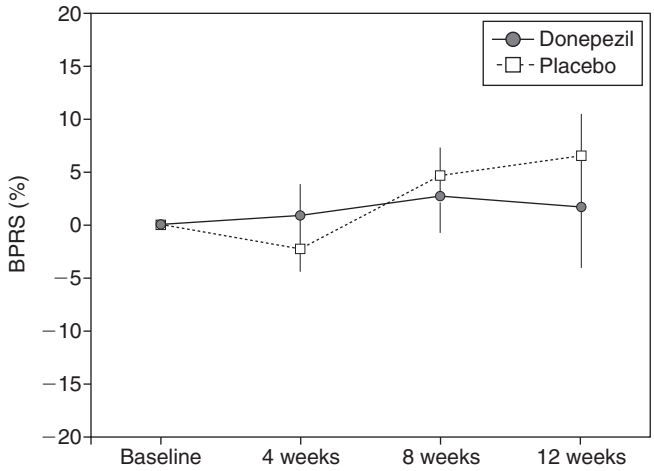

Figure 1 The changes form baseline scores on the BPRS in the donepezil and placebo groups during the 12 weeks in patients with chronic schizophrenia

*Donepezil baseline vs. placebo at 12 weeks ($p < 0.5$), and donepezil vs. placebo at 12 weeks ($p = 0.059$).

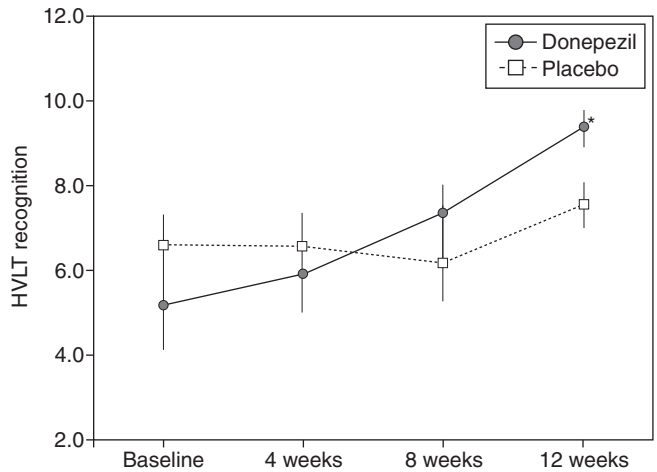

Figure 2 The total scores on the K-MMSE in the donepezil and placebo groups during the 12 weeks in patients with chronic schizophrenia

*Donepezil baseline vs. placebo at 12 weeks ($p < 0.01$), and donepezil vs. placebo at 12 weeks ($p < 0.05$).

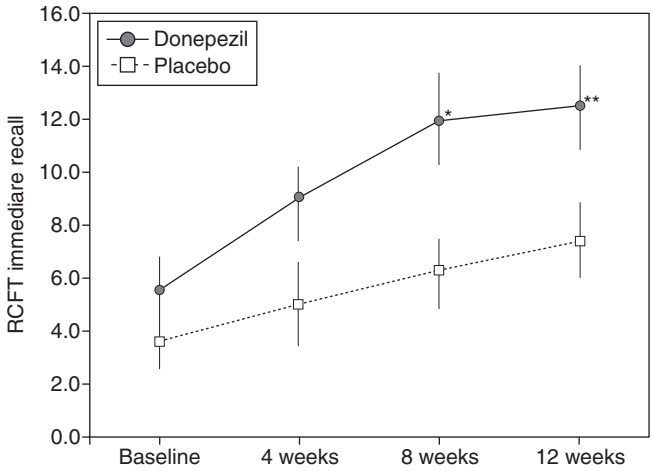

Figure 3 The scores on the HVLT recognition in the donepezil and placebo groups during the 12 weeks in patients with chronic schizophrenia

*Donepezil baseline vs. placebo at 8 weeks ($p < 0.05$).
**Donepezil baseline vs. placebo at 12 weeks ($p < 0.01$), and donepezil vs. placebo at 12 weeks ($p < 0.056$).

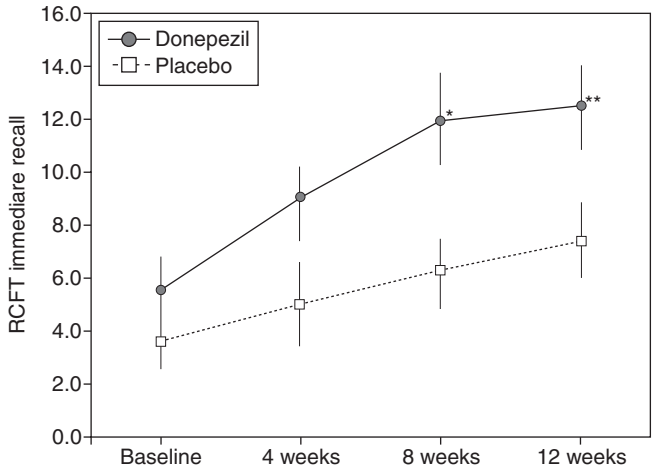

Figure 4 The scores on the RCFT immediate recall in the donepezil and placebo groups during the 12 weeks in patients with chronic schizophrenia

*Donepezil baseline vs. placebo at 8 weeks ($p < 0.05$).
**Donepezil baseline vs. placebo at 12 weeks ($p < 0.01$), and donepezil vs. placebo at 12 weeks ($p < 0.056$).

RCFT: In the donepezil group, the mean score for immediate recall from baseline to 12 weeks increased significantly ($p < 0.01$) (Fig. 4). The between-group difference in immediate recall was significant only at week 8 ($p < 0.05$), and approached significance at week 12 ($p = 0.056$).

Digit Span (DS) Forward and Backward: In both groups, the scores for the DS Forward and Backward did not change significantly over the 12 weeks. However, the between-group difference of the score for DS Backward Test at week 12 approached significance ($p = 0.066$) (Fig. 5).

Executive function and other tests: The two groups did not differ in any other outcome measures such as the Stroop Tests (letter and colour), Trail Making Tests Part A, Verbal Fluency Test, Boston Naming Test and Digit Symbol Substitution Test (DSST) (Table 2).

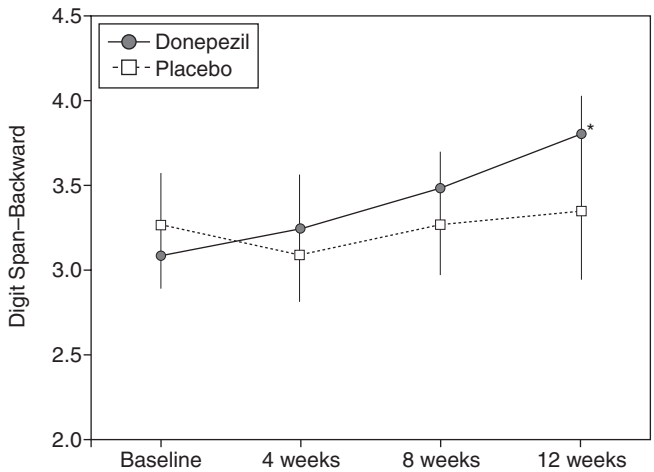

Figure 5 The scores on the Digit Span – Backward test in the donepezil and placebo groups during the 12 weeks in patients with chronic schizophrenia

*Donepezil baseline vs. placebo at 12 weeks ($p < 0.066$).

Adverse events of adjunctive donepezil

We found no serious adverse events that led to subject withdrawal. All except one subject reported no emerging adverse events after adding donepezil. One patient in the donepezil group complained of mild abdominal pain and diarrhoea for 2 days between weeks 4 and 8, but this did not seem to be related to the drug effects.

Discussion

Cognitive impairment is a core symptom and an enduring feature of schizophrenia, and has been identified recently as an important measure of its long-term outcome (Cuesta *et al.*, 1998). Cognitive impairment is probably a more important consideration than the characteristic psychotic symptoms in treating this disorder. The effects of cognitive decline after the onset of the illness may have

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

	Median change in score				
	Donepezil		Placebo		
Test and test item	Baseline ($N = 12$)	12 weeks ($N = 11$)	Baseline ($N = 12$)	12 weeks ($N = 12$)	p value
HVLT					
Immediate recall	12.0±2.95	21.0±4.85	13.0±2.18	19.5±3.98	0.310
Delayed recall	2.5±3.00	8.0±2.20	3.0±1.23	6.5±2.14	0.560
Recognition	4.0±5.17	9.0±1.43	7.0±2.61	7.5±2.02	0.047
RCFT					
Immediate recall	4.8±4.66	14.0±5.24	2.8±3.28	6.3±5.07	0.054
Delayed recall	6.5±4.41	140±5.24	2.8±3.28	6.85±4.07	0.160
Recognition	4.0±2.61	7.0±2.02	3.5±2.93	4.5±1.95	0.180
Digit span					
Forward	5.0±1.07	5.0±0.82	5.5±1.56	5.0±1.00	0.670
Backward	3.0±0.79	4.0±0.75	3.0±1.14	3.0±1.44	0.066
DSST	18.5±6.43	23.0±10.88	17.0±9.10	20.0±8.90	0.300
Stroop					
Letter	107.5±21.91	110.0±19.14	108.5±20.80	107.5±18.82	0.670
Colour	38.5±13.16	51.0±14.66	45.5±16.08	49.0±14.96	0.230
Trail making part A (s)	139.5±56.42	78.0±33.63	120.5±85.19	78.0±73.59	0.280
Verbal fluency	9.5±4.02	12.0±2.75	11.5±3.65	12.0±2.47	0.200
Boston Naming Test	40.0±11.14	47.0±11.33	35.0±10.22	43.0±9.13	0.690

Data were analyzed using the t-test for continuous variables.
Abbreviations: HVLT, Hopkin's Verbal Learning Test; RCFT, Rey Complex Figure Test; DSST, Digit Symbol Substitution Test.

a greater effect on the level of functioning (Green, 1996) than the initial severity of cognitive impairment or the degree of symptoms. Discounted in the past as an unimportant factor, cognitive impairment is now recognized as a central feature and not an epiphenomenon of other aspects of the illness or its treatment. Many pharmacological strategies have been proposed to augment cognitive performance, including serotonin 1A agonists, glutamatergic agonists, noradrenergic α_2 receptor agonists and cholinomimetics (M1/M4 muscarinic receptor agonists and acetylcholinesterase inhibitors) (Friedman *et al.*, 1999; Sumiyoshi *et al.*, 2001).

Although controlled studies have revealed contradictory results, several reports have suggested that AChEIs have beneficial effects on the cognitive impairments associated with schizophrenia (Table 3). In this study authors wanted to find out the potential cognitive enhancing effect of AChEIs in patients with schizophrenia. It was based on the assumption that reduced cholinergic activity could improve the cognitive impairment of schizophrenia. Previous studies have employed a cross-sectional design comparing first-episode patients, chronic patients and, occasionally, normal control subjects. However, medication and institutionalization can confound the results of cross-sectional studies. Longitudinal designs may overcome this problem. So authors deigned this study as a longitudinal study.

In our study, subjects had mild to moderate levels of cognitive impairment at baseline (e.g., K-MMSE scores ranged from 15 to 24). The subjects were treated for 12 weeks with donepezil and the typical antipsychotic haloperidol instead of atypical antipsychotics, which are thought to improve cognitive impairment in schizophrenia. The effects of this treatment on the attention were significant compared with that observed in other studies.

In summary, the results of this double-blind, placebo-controlled study suggest that adjunctive donepezil has beneficial effects on selected cognitive functions in patients with schizophrenia. The extent and eventual clinical utility of this pharmacological approach should be evaluated by other studies using long-term follow-up and controlling several confounding factors.

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Table 3 Controlled clinical trials of adjunctive donepezil to antipsychotics in patients with schizophrenia and schizoaffective disorder

Authors	Diagnosis of subjects	Number of subjects	Concomitant antipsychotics	Duration of study (weeks)	Results	Study design
Tugal *et al.*, 2004	Schizophrenia	12	Typical antipsychotics	6	No improvement in PANNS and HAM-D No improvement in the cognitive measures	Double-blind placebo-controlled cross-over study
Friedman *et al.*, 2002	Schizophrenia	36	Risperidone	12	No improvement in the cognitive measures	Double-blind placebo-controlled parallel study
Buchanan *et al.*, 2003	Schizophrenia	15	Olanzapine	6	Modest improvement in verbal recall memory and processing speed with smaller changes in verbal recognition memory. No effect on attention. No changes in either positive of negative symptoms	Open-labeled study
Risch *et al.*, 2001	Schizoaffective disorder	1	Olanzapine	6	Significant improvement in several cognitive measures. Reduction in depressive symptoms.	Double-blind placebo-controlled cross-over study
Freudenreich *et al.*, 2005	Schizophrenia	36	Atypical, typical antipsychotics	8	No improvement in the cognitive measures	Double-blind placebo-controlled parallel study
Present study	Schizophrenia	24	Haloperidol	12	No improvement in BPRS Significant improvement in verbal recognition memory and attention measures	Double-blind placebo-controlled parallel study

Abbreviations: PANNS, The Positive and Negative Syndrome Scale; HAM-D, Hamilton Depression Rating Scale; BPRS, Brief Psychiatric Rating Scale.

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