

# A double-blind, placebo controlled, cross-over trial of adjunctive donepezil for cognitive impairment in schizophrenia

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## Abstract

Although there have been several case reports suggesting the beneficial effect of acetylcholinesterase inhibitors in the cognitive deficits seen in schizophrenia, controlled studies have revealed contradictory results. The aim of this study was to investigate if donepezil could improve cognitive functions in schizophrenia. Twelve schizophrenic patients, who were diagnosed according to DSM-IV criteria and who had been on a stable dose of a high-potency typical antipsychotic for a minimum period of 3 months, participated in this 12-wk double-blind, placebo controlled, cross-over study of donepezil adjunctive treatment. Patients were randomly assigned under double-blind conditions to receive 5 mg/d donepezil or placebo for 6 wk, and then were crossed over to the alternate condition for 6 additional weeks. At baseline, 6 and 12 wk, patients were evaluated with the Positive and Negative Syndrome Scale (PANSS), Calgary Depression Scale, the Wechsler Memory Scale – Revised (WMS-R), a test for Verbal Fluency, Trail Making Test, Parts A and B, and Wisconsin Card Sorting Test (WCST). Treatment effect was not significant in any of the cognitive measures. There were also no significant changes in the PANSS and depression scores. Nicotinic receptor desensitization may cause non-responsiveness to acetylcholine as previously suggested, but the most likely explanation appears to be that defects in other neurotransmitter systems account for the cognitive deficits seen in schizophrenic patients.

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## Introduction

Schizophrenic patients have been consistently shown to have deficits on various cognitive measures such as memory, attention, executive function, verbal fluency, and motor skills (Bilder, 1996; Goldberg and Gold, 1995; Weinberger and Gallhofer, 1997). The severity of such particular cognitive deficits have all been shown to predict functional outcome such as social skill acquisition and employment (Addington and Addington, 1999, 2000; Addington et al., 2001; Green et al., 2000; Weiss et al., 2002; Zahn et al., 1994).

There have been several hypotheses concerning the underlying neural mechanisms of cognitive deficits in schizophrenia. Dopamine, norepinephrine and acetylcholine transmitter systems are thought to be

involved (Friedman et al., 1999). With regard to the acetylcholine system, a correlation between the severity of cognitive impairments and decreased brain choline acetyltransferase levels have been shown in schizophrenia (Karson et al., 1996). Both muscarinic and nicotinic receptors show specific changes in schizophrenia and are thought to contribute to the cognitive impairment in this disorder (Hyde and Crook, 2001). For example, post-mortem studies reveal decreased binding profile of muscarinic receptors in the frontal, parietal and temporal cortices (Bennett et al., 1979), which are all involved in cognitive performance. Freedman et al. (1995) have shown that schizophrenic patients have a lower density of nicotinic receptors in the hippocampus. Neuroleptic and cigarette exposure are considered as serious confounders in the interpretation of such findings (Hyde and Crook, 2001). Anti-cholinergic agents such as scopolamine or atropine have been shown to worsen memory functions in humans that can be reversed by a choline esterase inhibitor, physostigmine. The response to physostigmine

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has been linked to normal functioning of the cholinergic receptors (Davis et al., 1978; Drachman et al., 1982). Since physostigmine has a very short half-life, it is not a viable cognitive enhancer for long-term treatment. Cholinesterase inhibitors such as donepezil or rivastigmin are better choices for this purpose and have been shown to improve cognitive functions in patients with Alzheimer's disease (Francis et al., 1999; Giacobini, 1998).

Due to the need to provide more effective cognitive enhancement, adjunctive treatment approaches have been investigated in various studies. Adjunctive treatments have so far targeted the cholinergic and dopaminergic systems. The findings described above regarding the cholinergic system have led researchers to study the effect of cholinomimetics on cognition in schizophrenia, following the first case report suggesting a beneficial effect (MacEwan et al., 2001). The cholinesterase inhibitor donepezil has recently been studied as adjunctive treatment to the atypical antipsychotic olanzapine in a pilot open-label study (Buchanan et al., 2002), and to risperidone in a double-blind, placebo-controlled study (Friedman et al., 2002). The results of the cholinomimetic adjunctive treatments are inconsistent. The findings of the 4-wk open-label study (Buchanan et al., 2002) revealed pronounced improvement in motor speed, and moderate improvements in verbal recall memory, visual memory and processing speed. However, no beneficial effects were observed in the 12-wk double-blind study (Friedman et al., 2002). Both studies utilized 5 and 10 mg donepezil.

Stryjer et al. (2002) reported three schizophrenic patients with comorbid dementia showing 6–9 points of improvement on the Mini-Mental State Examination (MMSE). The same group also conducted a 4-wk single blind study, again on schizophrenic patients with comorbid dementia, with 5 mg donepezil added to ongoing antipsychotic treatment, consisting mostly of atypical antipsychotics (Stryjer et al., 2003). Significant improvement was noted in MMSE, although no improvement was observed on the Alzheimer's Disease Assessment Scale–Cognitive subscale and the Positive and Negative Syndrome Scale (PANSS).

Galantamine, which acts both as a cholinesterase inhibitor and nicotinic receptor modulator (allosterically potentiating ligand), has also recently been reported to improve verbal fluency and reduction of commission errors in schizophrenic patients treated with risperidone (Allen et al., 2003).

The use of cholinomimetic agents in schizophrenia might have clinical implications other than changes in cognitive functioning of schizophrenic patients.

Tandon et al. (1992) studied the effect of anticholinergic treatment on positive and negative symptoms in 40 drug-free schizophrenic patients. Anticholinergic treatment resulted in an increase of positive and a reduction of negative symptoms. Tandon (1999) later reviewed the evidence that cholinergic modulation affects both positive and negative symptoms, and that neuroendocrine and polysomnographic data suggest an increased muscarinic cholinergic activity in schizophrenia. The interactions between the dopaminergic and cholinergic systems were suggested to occur especially in regions that are thought to be relevant in schizophrenia. In addition, clozapine's partial agonist effect on  $M_1/M_4$  cholinergic receptors and high affinity to muscarinic receptors is thought to be related to its superior clinical effectiveness in treatment-resistant schizophrenia, which further underlines the importance of cholinergic modulation regarding psychopathology. However, evidence indicates that the pathology in the cholinergic systems may be more relevant to cognitive deficits associated with schizophrenia, rather than positive symptoms (Hyde and Crook, 2001).

To our knowledge, there has been no published double-blind study investigating the cognitive-enhancing effects of cholinomimetic agents in chronic non-demented schizophrenic patients receiving typical antipsychotics. The aims of the study were to ascertain donepezil's effects on cognitive functions in schizophrenic patients, to assess whether donepezil treatment would exert an effect on positive and negative symptoms, and finally to evaluate the correlation between probable cognitive changes and alterations in symptomatology.

## Method

### Subjects

Twelve patients with a DSM-IV diagnosis of schizophrenia at the Department of Psychiatry at Hacettepe University Faculty of Medicine were included in the study. The patients had been followed at the outpatient clinic for at least 2 yr before inclusion. The project was approved by the local Ethics Committee. All patients and a first-degree relative provided informed consent before being admitted to the study. The inclusion criteria were: an age range of 18–45 yr, treatment with high-potency typical antipsychotics, no changes in symptomatology or drug dosage during the last 3 months and a minimum education of high-school graduation (11 yr). [As an inclusion criterion, the minimum level of education was determined as high-school graduation, due to the fact that education

has been reported as an important parameter affecting the level of performance on neurocognitive tests (Anil et al., 2003).] The typical antipsychotics used by the patients were either fluphenazine or pimozide. Exclusion criteria were: the use of atypical antipsychotics, concomitant psychotropic or anticholinergic treatments, alcohol and substance dependence and/or abuse, mental retardation, presence of serious and unstable medical and/or neurological disorders, history of head trauma and a Calgary Depression Scale (Addington et al., 1992) score above 6. All patients completed the study and the treatment was well tolerated.

### Procedures

The study was conducted in a double-blind, placebo-controlled, cross-over design. Patients were randomly assigned under double-blind conditions to receive 5 mg donepezil by mouth once a day or placebo for 6 wk, and then were crossed over to the alternate condition for an additional 6 wk.

All patients went through a physical examination before entering the study. As safety measurements, laboratory evaluations, consisting of complete blood count and creatinine, GGT (gamma-glutamyltransferase), ALT (alanine aminotransferase), AST (aspartate aminotransferase), total bilirubin and fasting serum glucose levels, were performed for each patient at baseline, 6 wk and at the end of the study (at 12 wk). The findings were within the normal range.

The clinical syndromes and cognitive skills were assessed at baseline, at 6 wk before the cross-over procedure and at 12 wk. The symptom ratings were done by utilizing the Turkish versions of the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987; Kostakoglu et al., 1999) and Calgary Depression Scale (Addington et al., 1992; Oksay et al., 2000). The Calgary Depression Scale was administered mainly to assess the presence of depression which could effect cognitive performance. A cognitive battery consisting of 11 tests measuring 7 major domains (attention, working memory, executive function, verbal memory, visual memory, verbal fluency and construction) was utilized. The Wisconsin Card Sorting Test (WCST; Heaton, 1981) and the Trail Making Test, Parts A and B (Reitan and Wolfson, 1985) were used to assess executive functions of changing categories and resisting interference respectively. From the Wechsler Memory Scale – Revised (WMS-R; Wechsler, 1987), three subtests including figural memory, visual reproduction and visual paired associates were administered to assess visual memory, and two subtests

**Table 1.** Characteristics of the patient population

Group	Group 1 (Placebo–donepezil) (mean $\pm$ s.d.)	Group 2 (Donepezil–placebo) (mean $\pm$ s.d.)
Age (yr)	38.0 $\pm$ 10.2	29.2 $\pm$ 5.9
Education (yr)	13.2 $\pm$ 1.8	11.0 $\pm$ 0.0
Duration of illness (yr)	16.0 $\pm$ 9.0	6.3 $\pm$ 3.1
Chlorpromazine equivalent antipsychotic dose (mg/d)	216.7 $\pm$ 157.1	137.5 $\pm$ 49.4
Sex		
Male	33.3%	66.7%
Female	66.7%	33.3%

including logical memory and verbal paired associates were administered to assess verbal memory. Although all of the tests utilized assess attention to a certain degree, the digit-span subtest from the WMS-R was particularly administered to evaluate attention and working memory. The Wechsler Adult Intelligence Scale (WAIS; Wechsler, 1987) block design subtest was used to evaluate construction ability. Finally, the Verbal Fluency (WHO, 1993) test was used to evaluate verbal fluency.

### Statistical analysis

Age, education, illness duration and medication dose of the groups were compared utilizing Mann–Whitney *U* test, sex ratios were compared utilizing Fisher's exact test.

Analysis of the outcome variables were carried out using the ANOVA model for 2  $\times$  2 cross-over studies described by Ratkowsky et al. (1992) to determine the presence of treatment, period and carry-over effects after their distribution was verified to be normal (by Shapiro–Wilk's test). Otherwise, the approach for non-normal quantitative response variables described by Fleiss (1986) was used to test for the residual effects of treatment. In the absence of a residual treatment effect, the Wilcoxon test was used to assess the period and treatment effects for non-normal distributions. Effect sizes were also calculated.

## Results

### Characteristics of the patient population

The whole sample of patients was divided into two groups. The first group of patients received placebo in



**Table 3.** The neurocognitive assessments

	Baseline (followed by)		6 wk		12 wk		Results of statistical analysis				
			Donepezil first	Placebo first	Donepezil first	Placebo first	Effect size		Treatment effect	Period effect	Carry-over effect
	Donepezil (mean ± S.D.)	Placebo (mean ± S.D.)					6 wk (r)	12 wk (r)			
WCST – categories completed	1.8±0.8	2.8±2.6	2.7±1.8	3.3±2.9	3.8±2.5	2.5±2.2	0.3	0.7	−0.91, 0.363	0.45, 0.752	0.58, 0.565
WCST – perseverative errors	36.5±14.8	26.2±14.6	21.7±9.1	18.3±13.3	17.0±9.0	25.5±14.8	7.0	5.2	0.99, 0.332	2.74, 0.113	0.03, 0.856
Trail Making – A (sec)	55.3±23.6	48.3±14.8	47.5±28.4	45.0±12.4	39.5±8.0	42.5±19.4	2.5	0.5	0.11, 0.742	0.05, 0.826	0.04, 0.852
Trail Making – B (sec)	141.3±85.0	128.2±36.1	113.7±55.4	97.3±25.3	77.2±12.9	95.5±35.8	3.2	2.0	0.04, 0.853	0.57, 0.460	0.05, 0.83
Figural memory	6.5±1.1	6.7±1.2	8.3±1.9	7.0±1.7	6.7±2.1	8.3±1.9	1.5	0.3	−0.72, 0.473	2.07, 0.038	−1.55, 0.122
Visual paired associates – 1	8.2±5.1	10.5±4.4	10.8±6.4	14.3±5.4	15.7±5.2	13.7±6.0	1.2	1.5	0.19, 0.671	0.14, 0.715	0.01, 0.931
Visual paired associates – 2	2.8±1.6	5.3±1.6	3.8±2.4	5.7±0.8	6.0±0.0	4.5±2.5	0.7	0.3	−0.35, 0.723	0.35, 0.723	−1.33, 0.183
Visual reproduction – 1	34.7±3.8	34.3±4.9	34.5±3.8	33.2±7.2	35.8±3.4	33.5±6.7	1.0	3.7	0.21, 0.651	0.01, 0.940	0.75, 0.397
Visual reproduction – 2	29.3±9.6	29.5±5.0	32.2±8.1	33.7±3.9	33.5±4.0	33.8±7.8	1.3	1.8	0.98, 0.326	1.46, 0.146	0.32, 0.748
Logical memory – 1	18.2±5.1	21.5±7.3	22.7±6.5	27.3±7.8	29.3±6.0	25.8±6.3	1.3	1.2	0.32, 0.579	1.27, 0.273	0.0, 0.961
Logical memory – 2	16.0±6.1	18.0±8.8	20.2±7.6	24.8±7.7	27.2±7.7	25.0±6.2	2.7	2.5	1.0, 0.330	0.56, 0.463	0.0, 0.965
Verbal paired associates – 1	17.0±2.8	18.3±3.6	18.8±4.5	22.0±2.4	21.7±2.7	20.0±5.0	1.8	1.5	0.61, 0.445	1.13, 0.301	0.01, 0.921
Verbal paired associates – 2	6.8±1.0	7.3±0.8	7.2±1.6	7.8±0.4	8.0±0.0	7.5±1.2	0.2	0.2	0.37, 0.711	0.78, 0.435	0.0, 1.0
Digit span forward	6.3±1.6	6.8±1.7	7.3±1.4	7.8±1.6	7.3±2.5	6.8±1.0	0	0	0.0, 1.0	4.9, 0.057	0.0, 1.0
Digit span backward	4.5±2.4	5.3±1.5	5.3±2.6	5.8±1.6	5.7±1.5	5.5±2.7	0.3	0.3	0.24, 0.631	0.24, 0.631	0.48, 0.498
Block design	27.2±11.5	26.5±9.2	30.8±12.0	27.7±10.6	30.7±13.0	32.0±12.4	2.5	1.8	0.86, 0.365	0.0, 1.0	0.03, 0.863
Verbal fluency	28.3±8.3	23.7±6.5	29.3±12.6	31.2±5.8	35.0±7.0	32.5±20.0	6.5	0.7	2.06, 0.167	0.91, 0.351	1.25, 0.277

\* Analysis of variance.

\*\* Figures in bold indicate Wilcoxon test.

Unlike our study, both the Friedman et al. (2002) and Buchanan et al. (2002) studies have investigated the effect of adjunctive treatment to atypical antipsychotics. In fact, Buchanan et al. (2002) have suggested that the improvement observed in their investigation could be the result of the enhancement of the beneficial effect which olanzapine already provided. Unlike these trials, any beneficial effect which might have been observed in our study would directly have had to rely on donepezil, as typical neuroleptics do not improve cognitive performance in general. The Stryjer et al. (2003) study results are also not comparable with the results of the reported study, as their group consisted of patients with comorbid dementia and all patients except one received atypical antipsychotics.

The most pronounced effect of adjunctive donepezil treatment has been observed in the area of motor speed in the study of Buchanan et al. (2002), and the benefit was explained through the role of nicotinic receptors on basal ganglia function. This parameter has not been directly investigated in our study nor in the study of Friedman et al. (2002). Further exploration, with emphasis on this measure definitely has merit, however it is possible that typical neuroleptic usage might interfere with this possibly beneficial effect, with a high propensity for extrapyramidal (EPS) side-effects.

We have used donepezil in the lower dosing regimen of 5 mg to avoid side-effects. It is possible that the higher dosing of 10 mg as used in two previously mentioned adjunctive treatment trials could have provided different results. However, Friedman et al. (2002) reported that half of their patients received 10 mg donepezil for 8 wk, but the outcome was not different from the group who received 5 mg donepezil.

One reason that cholinomimetics do not enhance cognitive functions in schizophrenic patients could be nicotinic receptor desensitization due to chronic tobacco use seen in the majority (80–90%) of these patients (Hughes et al., 1986; Lohr and Flynn, 1992). One other reason could be that cognitive impairment in schizophrenia is more likely to be related to other transmitter systems. Since our study did not control for smoking we cannot further speculate on receptor desensitization. The roles of the dopaminergic, serotonergic and noradrenergic systems, as discussed earlier, should be further studied. It should also be borne in mind that alterations in the cholinergic system may be a downstream effect from pathology in other neurotransmitter systems or structures (Hyde and Crook, 2001).

In this study, no significant change has been observed in the positive and negative symptoms of the patients during adjunctive donepezil treatment. This

result is in accordance with the findings of Friedman et al. (2002) and Buchanan et al. (2002). The clinical stability of the patients in this study who had been receiving neuroleptic treatment could explain the unchanging nature of the positive and negative symptoms.

Our study duration of 6 wk might be considered short to provide strong evidence for the lack of efficacy of donepezil for cognitive enhancement in schizophrenia. Nevertheless, the two open studies (Buchanan et al., 2002; Stryjer et al., 2003) shown as the major evidence for the benefit of donepezil augmentation on neurocognition in schizophrenic patients were both conducted with a shorter study period of 4 wk.

Finally, our results should be interpreted with caution because the sample size is relatively small. Further controlled studies with larger sample sizes are needed before concluding that cholinomimetics are not effective as a cognitive enhancer in this group of patients.

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### Statement of Interest

None.

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