International Journal of Neuropsychopharmacology (2004), **7**, 117–123. Copyright © 2004 CINP
DOI: 10.1017/S1461145703004024

ARTICLE

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

Önder Tuğal, Kâzım M. Yazıcı, A. Elif Anıl Yağcıoğlu and Ahmet Göğüş

Hacettepe University Faculty of Medicine, Department of Psychiatry, Ankara, Turkey

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.

Received 21 May 2003; Reviewed 14 September 2003; Revised 9 October 2003; Accepted 26 October 2003

Key words: Acetylcholine, cognitive, donepezil, schizophrenia.

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). Anticholinergic 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

Address for correspondence: Dr K. M. Yazıcı, Associate Professor of Psychiatry, Hacettepe University Faculty of Medicine, Department of Psychiatry, Ankara 06100, Turkey.
Tel.: (90) 312 305 1873 *Fax*: (90) 312 310 1938
E-mail: kyazici@hacettepe.edu.tr

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 comission 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 (Anıl et al., 2003).] The typical antipsychotics used by the patients were either fluphenazine or pimozide. Exclusion criteria were: the use of atypical antipsychotics, concominant 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 Weschler 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 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.

Table 1. Characteristics of the patient population

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

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 2×2 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 2. The psychopathological assessments

	Baseline (followed by)		6 wk		12 wk		Results of statistical analysis				
							Effect size				
	Donepezil	Placebo	Donepezil first	Placebo first	Donepezil first	Placebo first	6 wk	12 wk	Treatment effect	Period effect	Carry-over effect
	(mean ± S.D.)		(mean ± S.D.)		(mean ± S.D.)		(*r*)		[*F*(d.f. = 1, 2), *p** or *z*, *p***]		
PANSS Total	61.8 ± 12.4	56.2 ± 14.0	62.7 ± 11.3	57.8 ± 13.3	55.0 ± 13.6	59.7 ± 9.8	0.8	0.2	0.02, 0.889	0.62, 0.439	0.01, 0.906
PANSS Positive	14.0 ± 7.0	12.7 ± 4.3	14.2 ± 5.3	12.7 ± 5.2	11.0 ± 3.4	12.2 ± 4.8	0.2	0.3	**−1.14, 0.253**	**0.99, 0.325**	**0.0, 1.0**
PANSS Negative	15.0 ± 5.1	14.0 ± 6.2	17.0 ± 8.0	13.5 ± 4.0	14.8 ± 5.2	16.3 ± 6.6	2.5	2.0	**−0.75, 0.455**	**0.20, 0.844**	**0.32, 0.746**
PANSS General	32.8 ± 5.6	29.5 ± 8.3	31.5 ± 5.1	29.7 ± 6.5	29.2 ± 7.5	31.2 ± 6.2	1.5	0.2	0.33, 0.573	0.04, 0.850	0.13, 0.723
Calgary Depression	4.3 ± 1.5	2.2 ± 1.5	2.7 ± 1.8	2.7 ± 2.4	2.3 ± 2.7	3.0 ± 0.6	2.2	0.7	1.94, 0.179	0.01, 0.916	0.46, 0.504

* Analysis of variance.
** Figures in bold indicate Wilcoxon test.

the first 6 wk and donepezil in the second 6 wk of the study, and the second group received donepezil in the first 6 wk and placebo in the second 6 wk of the study. There were no significant differences between the age, sex, education level, duration of illness and the mean chlorpromazine-equivalent daily dose of current antipsychotic treatment between the groups. The characteristics of the population can be seen in Table 1.

Psychopathological assessments

Regarding the PANSS total score, the PANSS Positive, Negative and General subscale scores and the Calgary Depression Scale scores, there were no significant treatment, period or carry-over effects at any period (Table 2).

Neurocognitive assessments

There were no significant treatment, period or carry-over effects on any neurocognitive measurements at any period, except a significant period effect for figural memory ($z = 2.07$, $p = 0.038$) (Table 3).

Discussion

In this double-blind, placebo-controlled study, adjuvant treatment with a cholinesterase inhibitor, donepezil, has not affected cognitive performance on a variety of neurocognitive tasks. These results are in accordance with the results of another double-blind, placebo- controlled trial of donepezil adjunctive treatment to risperidone (Friedman et al., 2002). In our study, although not statistically significant, the observed improvement in most categories of neurocognitive tests could be explained by retest effect, regardless of the donepezil or placebo treatment.

Friedman et al. (2002) have discussed that the negative results of their study could be related to the baseline severity of cognitive impairment of their subjects. On average, their patients had performed 3.5 standard deviations below age and education-matched normative standards on the California Verbal Learning Test (CLVT), indicating severe impairment. We have normative data for the neurocognitive battery utilized in this study, except for the Trail Making and the Block Design tests (Demir et al., 2000; Ertugrul and Ulug, 2002). Our patients performed in the range of 0.4 (Visual Paired Associates) and 2.2 (WCST) standard deviations below the normal population within a similar age range and education level. This result also indicates that donepezil does not lead to cognitive enhancement in relatively less severely impaired schizophrenic patients.

Table 3. The neurocognitive assessments

	Baseline (followed by)		6 wk		12 wk		Results of statistical analysis				
							Effect size				
	Donepezil	Placebo	Donepezil first	Placebo first	Donepezil first	Placebo first	6 wk	12 wk	Treatment effect	Period effect	Carry-over effect
	(mean ± S.D.)		(mean ± S.D.)		(mean ± S.D.)		(*r*)		[*F*(d.f. = 1, 2), *p** or *z*, *p***]		
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.

Acknowledgements

We thank the Pfizer Pharmaceutical Company for donating the study medication and providing the financial support for the statistical analyses. We also thank Dr Oktay Özdemir, an independent statistician, for conducting the statistical analyses.

Statement of Interest

None.

References

Addington D, Addington J, Maticka-Tindale E (1992). Reliability and validity of a depression rating scale for schizophrenics. *Schizophrenia Research 6*, 201–208.

Addington J, Addington D (1999). Neurocognitive and social functioning in schizophrenia. *Schizophrenia Bulletin 25*, 173–182.

Addington J, Addington D (2000). Neurocognitive and social functioning in schizophrenia: a 2.5 year follow-up study. *Schizophrenia Research 44*, 47–56.

Addington J, Addington D, Gasbarre L (2001). Neurocognitive and social functioning in schizophrenia and other diagnoses. *Schizophrenia Research 48*, 367–368.

Allen T, McEvoy JP, Keefe R, Levin E, Wilson W (2003). Galantamine improves cognition in patients with schizophrenia. Poster presented at the biennial meeting of the International Congress on Schizophrenia Research, Colorado Springs, Colorado.

Anıl AE, Kıvırcık BB, Batur S, Kabakçı E, Kitiş A, Güven E, Başar K, Turgut Tİ, Arkar H (2003). The Turkish Version of the Auditory Consonant Trigram Test as a measure of working memory: a normative study. *Clinical Neuropsychologist 17*, 159–169.

Bennett JP, Enna SJ, Bylund DB, Gillin C, Wyatt RJ, Snyder SH (1979). Neurotransmitter receptors in frontalcortex in schizophrenia. *Archives of General Psychiatry 36*, 927–934.

Bilder RM (1996). Neuropsychology and neurophysiology in schizophrenia. *Current Opinions in Psychiatry 9*, 57–62.

Buchanan RW, Summerfelt A, Tek C, Gold J (2002). An open labeled trial of adjunctive donepezil for cognitive impairments in patients with schizophrenia. *Schizophrenia Research 59*, 29–33.

Davis KL, Mohs R, Tinklenberg J, Pfefferbaum A, Hollister L, Kopell B (1978). Physostigmine: improvement of long-term memory in normal humans. *Science 201*, 272–274.

Demir B, Göğüş A, Savaşır I (2000). Cognitive functions in depressed patients [in Turkish]. *Turkish Journal of Psychiatry 11*, 179–189.

Drachman D, Glosser G, Fleming P, Longenecker G (1982). Memory decline in the aged: treatment with lecithin and physostigmine. *Neurology 32*, 944–950.

Ertugrul A, Ulug B (2002). The influence of neurocognitive deficits and symptoms on disability in schizophrenia. *Acta Psychiatrica Scandinavica 105*, 196–201.

Fleiss JL (1986). *The Design and Analysis of Clinical Experiments* (pp. 279–281). New York: John Wiley and Sons.

Francis PT, Palmer AM, Snape M, Wilcock GK (1999). The cholinergic hypothesis of Alzheimer's disease: a review of progress. *Journal of Neurology, Neurosurgery, and Psychiatry 66*, 137–147.

Freedman R, Hall M, Adler LE, Leonard S (1995). Evidence in post mortem brain tissue for decreased numbers of hippocampal nicotinic receptors in schizophrenia. *Biological Psychiatry 38*, 22–33.

Friedman JI, Adler DN, Howanitz E, Harvey PD, Brenner G, Temporini H, White L, Parella M, Davis KL (2002). A double blind placebo controlled trial of donepezil adjunctive treatment to risperidone for cognitive impairment of schizophrenia. *Biological Psychiatry 51*, 349–357.

Friedman JI, Temporini H, Davis KL (1999). Pharmacologic strategies for augmenting cognitive performance in schizophrenia. *Biological Psychiatry 45*, 1–16.

Giacobini E (1998). Invited review: Cholinesterase inhibitors for Alzheimer's disease therapy: from tacrine to future applications. *Neurochemistry International 32*, 413–419.

Green MF, Kern RS, Braff DL, Mintz J (2000). Neurocognitive deficits and functional outcome in schizophrenia: are we measuring the 'right stuff'? *Schizophrenia Bulletin 26*, 119–136.

Goldberg TE, Gold JM (1995). Neurocognitive functioning in patients with schizophrenia. In: Bloom FE, Kupfer DJ (Eds.), *Psychopharmacology: The Fourth Generation of Progress* (pp. 1245–1257). New York: Raven Press.

Heaton RK (1981). Wisconsin Card Sorting Manual. Odessa, Florida, Psychological Assessment Resources.

Hughes JR, Hatsukami DK, Mitchell JE, Dahlgren LA (1986). Prevalance of smoking among psychiatric outpatients. *American Journal of Psychiatry 143*, 993–997.

Hyde TM, Crook JM (2001). Cholinergic systems and schizophrenia: primary pathology or epiphenomena. *Journal of Chemistry and Neuroanatomy 22*, 53–63.

Karson CN, Mrak RE, Husain MM, Griffin WS (1996). Decreased mesopontine choline acetyltransferase levels in schizophrenia. Correlations with cognitive functions. *Molecular Chemistry and Neuropathology 29*, 181–191.

Kay SR, Fiszbein A, Opler LA (1987). The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophrenia Bulletin 13*, 261–276.

Kostakoglu E, Batur S, Tiryaki A, Göğüş A (1999). Reliability and validity of the Turkish version of the positive and negative syndrome scale. *Turkish Journal of Psychology 14*, 23–32.

Lohr JB, Flynn K (1992). Smoking and schizophrenia. *Schizophrenia Research 8*, 93–102.

MacEwan GW, Ehmann TS, Khanbhai I, Wrixon C (2001). Donepezil in schizophrenia – is it helpful? An experimental design case study. *Acta Psychiatrica Scandinavica 104*, 469–472.

Oksay S, Aksaray G, Kaptanoğlu C, Bal C (2000). Validity and reliability of the Turkish version of Calgary Depression Scale in schizophrenic patients [in Turkish]. *Turkish Journal of Psychiatry 11*, 278–284.

Ratkowsky DA, Evans MA, Allredge JR (1992). In: *Cross-over Experiments: Design, Analysis and Application* (pp. 77–120). New York: Marcel Dekker.

Reitan RM, Wolfson D (1985). *The Halstead–Reitan Neuropsychological Test Battery*. Tucson, AZ: Neuropsychology Press.

Stryjer R, Bar F, Strous RD, Baruch Y, Rabey JM (2002). Donepezil management of schizophrenia with associated dementia. *Journal of Clinical Psychopharmacology 22*, 226–229.

Stryjer R, Strous RD, Bar F, Werber E, Shaked G, Buhiri Y, Kotler M, Weizman A, Rabey JM (2003). Beneficial effect of donepezil augmentation for the management of comorbid schizophrenia and dementia. *Clinical Neuropharmacology 26*, 12–17.

Tandon R (1999). Cholinergic aspects of schizophrenia. *British Journal of Psychiatry 37*, 7–11.

Tandon R, DeQuardo JR, Goodson J, Mann NA, Greden JF (1992). Effect of anticholinergics on positive and negative symptoms in schizophrenia. *Psychopharmacology Bulletin 28*, 297–302.

Wechsler D (1987). *Wechsler Memory Scale – Revised*. New York: The Psychological Corporation.

Weinberger DR, Gallhofer B (1997). Cognitive function in schizophrenia. *International Clinical Psychopharmacology 12*, 29–36.

Weiss EM, Bilder RM, Fleischhacker WW (2002). The effects of second-generation antipsychotics on cognitive functioning and psychosocial outcome in schizophrenia. *Psychopharmacology* (*Berlin*) *162*, 11–17.

WHO (1993). *WHO/MNH Battery of Cognitive Assessment Instrument Pre-pilot Battery*. Geneva: World Health Organization.

Zahn T, Pickar D, Haier R (1994). Effects of clozapine, fluphenazine, and placebo on reaction time measures of attention and sensory dominance in schizophrenia. *Schizophrenia Research 13*, 133–144.