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# A 12-week, double-blind, placebo-controlled trial of donepezil adjunctive treatment to risperidone in chronic and stable schizophrenia

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ABSTRACT

There is considerable incentive to develop new treatment strategies that effectively target cognitive deficits in schizophrenia. One of the theoretically promising novel treatment candidates is acetylcholinesterase inhibitors that increase the synaptic levels of cholinergic, nicotinic, and muscarinic receptor activity. The purpose of this study was to assess the efficacy of donepezil as an adjuvant agent in the treatment of chronic schizophrenia in particular for cognitive impairments. This investigation was a 12-week, double-blind study of parallel groups of patients with stable chronic schizophrenia. Thirty patients were recruited from inpatient and outpatient departments, age ranging from 22 to 44 years. All participants met DSM-IV-TR. diagnostic criteria for schizophrenia. To be eligible, patients were required to have been treated with a stable dose of risperidone as their primary antipsychotic treatment for a minimum period of 8 weeks. The subjects were randomized to receive donepezil (10 mg/day) or placebo, in addition to risperidone (4–6 mg/day). Clinical psychopathology was assessed with Positive and Negative Syndrome Scale (PANSS). Cognition was measured by a cognitive battery. Patients were assessed by a psychiatrist at baseline and after 8, and 12 weeks after the medication started. The PANSS scores and cognitive performance were used as the outcome measures. The donepezil group had significantly greater improvement in the negative symptoms over the 12-week trial. There were no differences between the donepezil and placebo groups on any neurocognitive assessments at endpoint (week 12). The present study indicates donepezil as a potential adjunctive treatment strategy for negative symptoms of chronic schizophrenia.



## 1. Introduction

Schizophrenia is usually a chronic, lifelong illness with a peak age of onset in the mid 20s. Although the severity of schizophrenia has been recognized for many years, its etiology and pathophysiology are not fully understood (Mohammadi and Akhondzadeh, 2001). The introduction of conventional antipsychotic agents almost 50 years ago heralded a major advance in the treatment of schizophrenia and other psychotic disorders but these compounds have serious limitations in terms of both efficacy and tolerability (Akhondzadeh, 2006). Patients treated with these agents often have persistent psychotic symptoms, have frequent relapses, develop prominent functional impairment and experience distressing and disabling adverse effects (Mohammadi and Akhondzadeh, 2001). There is considerable incentive to develop new treatment strategies that effectively target cognitive deficits in schizophrenia. Although the second-generation antipsychotics may improve cognition slightly more than do the first-generation compounds, the effect sizes have been found to be small and with limited clinical significance (Jann, 2004; Akhondzadeh et al., 2005; Harvey, 2006; Jones et al., 2006). One of the theoretically promising novel treatment candidates is acetylcholinesterase inhibitors that increase the synaptic levels of cholinergic, nicotinic, and muscarinic receptor activity (Karson et al., 1996; Peuskens et al., 2005; McGurk et al., 2007). Cognitive impairment is estimated to occur in 75%–85% of patients with schizophrenia and often precedes the onset of other symptoms (Bowie and Harvey, 2005; Jones et al., 2006; Keefe et al., 2007). Regarding cognitive impairments, deficits are observed in controlled and active information processing, such as speed of processing, attention/vigilance, working memory, verbal learning

*Abbreviations:* ALT, Alanine Aminotransferase; AST, Aspartate Aminotransferase; DSM, Diagnosis and Statistical Manual of Mental Disorders; ESRS, Extrapyramidal Symptoms Rating Scale; GGT, Gamma-Glutamyltransferase; PANSS, Positive and Negative Syndrome Scale; WAIS, Wechsler Adult Intelligence Scale; WCST, Wisconsin Card Sorting Test.

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and memory, visual learning and memory, reasoning and problem solving, and verbal comprehension (Keefe et al., 2007). Although dopamine has conventionally been regarded as the key neurotransmitter involved in the pathogenesis of schizophrenic symptoms, several studies have established that the cholinergic neurotransmitter system, involving both nicotinic and muscarinic receptors, is important for the neuromodulation of cognitive processes in schizophrenia (Karson et al., 1996; Peuskens et al., 2005). Acetylcholine (ACh) acts in many cognitive functions, such as cortical modulation of sensory information processing, attention, memory and learning. This relation between Ach and cognition has been relatively well established in animals and healthy humans and in Alzheimer's disease (Karson et al., 1996; Peuskens et al., 2005). In schizophrenia, several studies have also reported anomalies in the cholinergic pathway. Therefore, drugs that act on cholinergic pathways may improve cognitive dysfunctions in schizophrenia (Roman and Rogers, 2004). The most frequently tested agent has been donepezil (Roman and Rogers, 2004; Peuskens et al., 2005). Although several open-label and small sample-controlled studies have suggested a beneficial effect on cognitive impairments and psychotic symptoms (MacEwan et al., 2001; Buchanan et al., 2002; Stryjer et al., 2003; Risch et al., 2005; Lee et al., 2007), large controlled trials have failed to demonstrate a beneficial effect (Friedman et al., 2002; Tugal et al., 2004; Mazeh et al., 2006; Stip et al., 2007). The studies also differ in length and dosage of adjunctive medication, concomitant medication allowed, age and chronicity of patients (MacEwan et al., 2001; Buchanan et al., 2002; Stryjer et al., 2003; Risch et al., 2005; Lee et al., 2007). Overall, the results are contradictory so far (McGurk et al., 2007). We conducted a double-blind, placebo-controlled trial in which we added a full therapeutic dose of donepezil to patients with stable schizophrenia. We also examined the effect of donepezil on psychosis and general psychopathology.

## 2. Methods

### 2.1. Setting

This investigation was a prospective, 12-week, double-blind study of parallel groups of patients with chronic schizophrenia and was undertaken in Roozbeh Psychiatric Hospital (Tehran, Iran) and Dr. Beheshti Hospital (Zanjan, Iran) from January 2006 to January 2008.

### 2.2. Patients

Thirty patients were recruited from both inpatient and outpatient departments, although most patients were outpatients, and some had brief periods of hospitalization during the study (11 women and 19 men) age ranging from 22 to 44 years. All participants met DSM-IV-TR diagnosis criteria for schizophrenia (American Psychiatric Association, 2000). A structured diagnostic procedure, including chart reviews, preceded a census diagnosis with a senior clinician. To be eligible, patients were required to have been treated with a stable dose of risperidone as their primary antipsychotic treatment for a minimum period of 8 weeks before entry into the study. In addition, subjects needed to demonstrate a minimum period of 4 weeks symptom stability, defined as no more than 20% change on consecutive ratings on the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987).

The level of cognitive impairment required for participation was defined as a total performance score at least 20 on Mini-Mental State Examination (Folstein et al., 1975). The 17-item Hamilton's Rating Scale for Depression was administered mainly to assess the presence of depression which could affect cognitive performance (Hamilton, 1960). Patients were excluded if they had any medical diagnoses or were receiving medications that may have affected cognitive performance or if they were abusing substances within 6 months of entry into the study. Furthermore, the following psychotropic medications were not allowed for the duration of the study: anticholinergics, sedating antihistaminics, antidepressants, mood stabilizers, or a second antipsychotic. Pregnant or lactating women and those of reproductive age without adequate contraception were also excluded.

The protocol was approved by the Institutional Review Board (IRB) of Tehran University of Medical Sciences (Grant Number: 2734). 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. The trial was performed in accordance with the Declaration of Helsinki and subsequent revisions (World Medical Association, 2000).

### 2.3. Intervention

After baseline evaluation of the severity of psychotic symptoms and cognitive impairments, 30 subjects entered a 12-week, double-blind, parallel trial of donepezil adjunctive treatment. The subjects were randomized in a 1:1 pattern to receive donepezil (5 mg/day and after 4 weeks the dose was increased to 10 mg daily for another 8 weeks) or the placebo in addition to dose of risperidone (4–6 mg/day). Donepezil and placebo were prepared in identical appearing tablets, which were dispensed every 4 weeks; surplus tablets were counted each study visit. Clinical psychopathology was assessed with standard rating scales for schizophrenia: PANSS (Kay et al., 1987). Cognition was measured by a cognitive battery. Patients were assessed by a psychiatrist at baseline and after 8, and 12 weeks after the medication started. Side effects were systematically recorded throughout the study and were assessed using a checklist administered by a resident of psychiatry. A cognitive battery measuring 6 major domains (attention, working memory, executive function, verbal memory, visual memory and construction) was utilized. The Wisconsin Card Sorting Test (WCST; Heaton, 1981) was used to assess executive functions of changing categories. 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. 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, 8 weeks and at the end of the study (at 12 weeks). The findings were within the normal range.

### 2.4. Outcome

The mean total, subtotal PANSS scores and cognitive performance were used as the main outcome measure. The extrapyramidal symptoms were assessed using the Extrapyramidal Symptoms Rating Scale (ESRS) (part one: parkinsonism, dystonia, dyskinesia; sum of 11 items) (Chouinard et al., 1980).

### 2.5. Statistical analysis

A two-way repeated measures analysis of variance (time–treatment interaction) was used. The two groups as a between-subjects factor (group) and the three measurements during treatment as the within-subjects factor (time) were considered. This was done for positive, negative, general psychopathology subscales and PANSS total

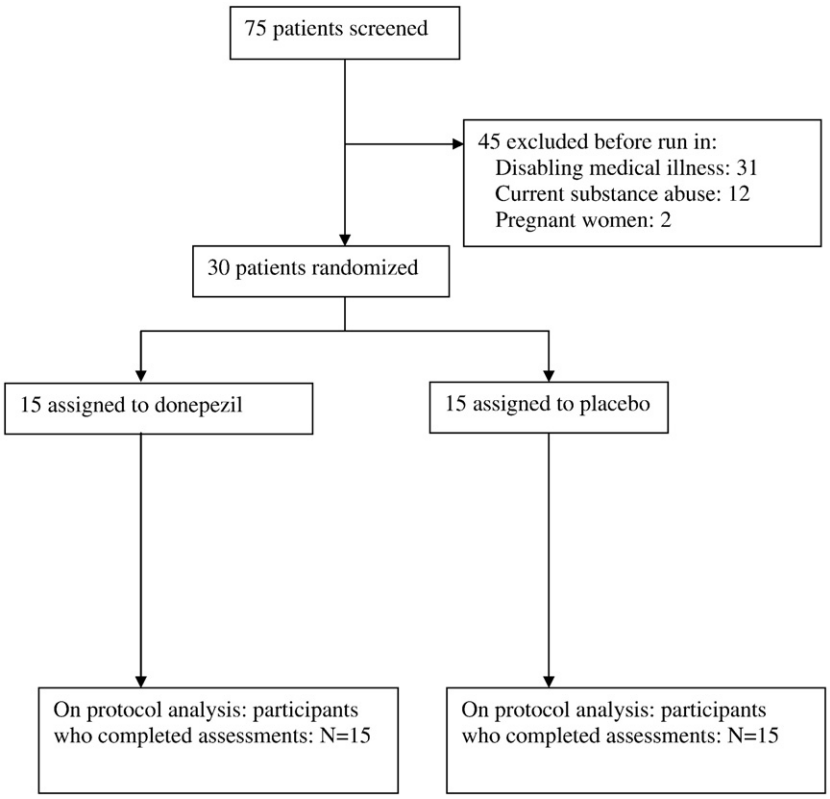


**Fig. 1.** Trial profile.

scores. The cognitive variables were analyzed using *T* tests of difference scores between baseline-donepezil and baseline-placebo and endpoint-donepezil and endpoint-placebo. To compare the demographic data and frequency of side effects between the protocols, Fisher's exact test was performed. All tests were two-tailed, with level of significance set at 0.05. Data were analyzed by using commercially available statistical packages (SPSS 13.00. Chicago, IL, USA).

## 3. Results

### 3.1. Patients disposition and characteristics

Seventy five patients were screened for the study and 30 were randomized to trial medication (15 patients in each group) (Fig. 1). No significant differences were identified between patients randomly assigned to the group 1 or 2 condition with regard to basic demographic data including age, age of first onset of illness, gender, marital status, level of education, mean duration of illness and number of life-time hospitalization (Table 1). All 30 patients completed the trial.

**Table 1**
Baseline data

| | Donepezil group | Placebo group | *P* |
|---|---|---|---|
| Gender | Male: 9, female: 6 | Male: 10, female: 5 | ns |
| Age (mean±SD) | 32.33±6.47 (years) | 33.86±6.05 (years) | ns |
| Marital status | Single: 8, married: 5, divorced: 2 | Single: 9, married: 4, divorced: 2 | ns |
| Level of education | Under diploma: 6, diploma: 7, higher diploma: 2 | Under diploma: 8, diploma: 5, higher diploma: 2 | ns |
| Time since diagnosis | 85.6±46.6 (months) | 89.2±50.2 (months) | ns |
| Number of life-time hospitalization (mean±SD) | 4.53±2.10 | 4.2±1.56 | ns |

### 3.2. PANSS subscales and overall scale

#### 3.2.1. Positive symptoms

The mean±SD scores of two groups of patients are shown in Fig. 2. There were no significant differences between the two groups at week 0 (baseline) on the PANSS ($t$=1.29, $df$=28, $P$=0.20). The difference between the two treatments was not significant as indicated by the effect of group, the between-subjects factor (Greenhouse–Geisser

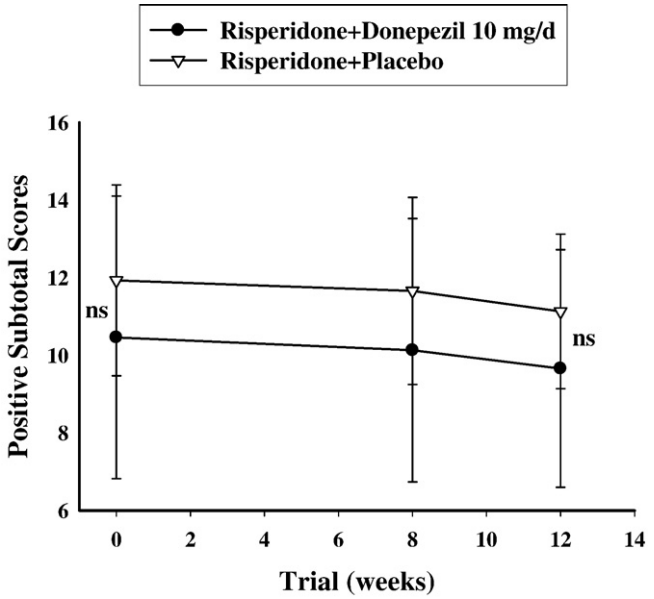


**Fig. 2.** Mean±SD of the two protocols on the positive subtotal scores of the PANSS. ns = non-significant.

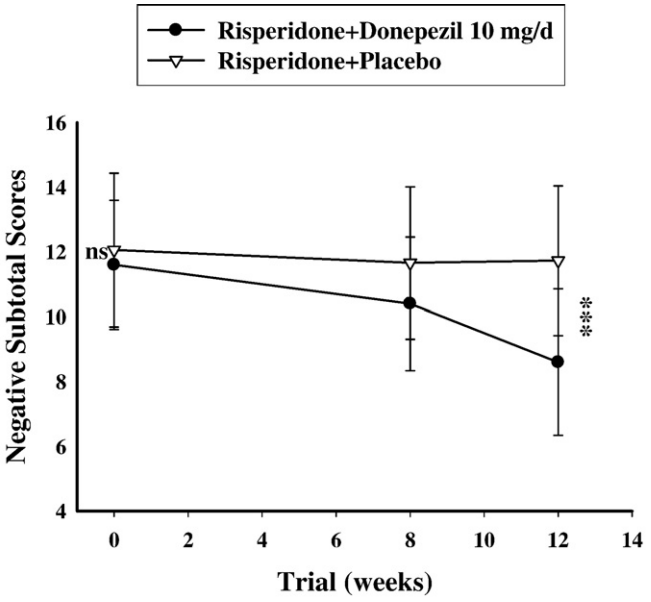


**Fig. 3.** Mean ± SD of the two protocols on the negative subtotal scores of the PANSS. ns = non-significant and ***<0.001.

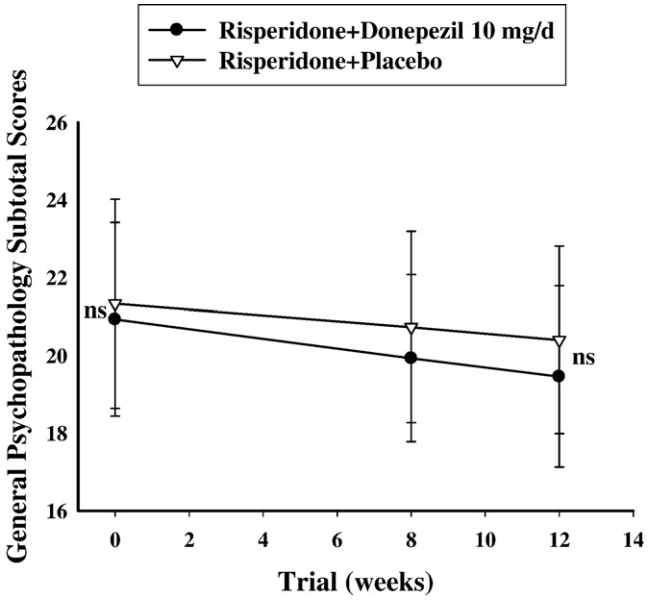


**Fig. 4.** Mean ± SD of the two protocols on the general psychopathology subtotal scores of the PANSS. ns = non-significant.

corrected: $df$=1 and $F$=0.04; $P$=0.16). The behavior of the two treatment groups was similar across time (groups-by-time interaction, Greenhouse–Geisser corrected: $F$=0.04, $df$=1.50, $P$=0.92). The difference between the two treatments was not significant at the endpoint (week 12) ($t$=0.71, $df$=28, $P$=0.48).

*3.2.2. Negative symptoms*

The mean ± SD scores of two groups of patients are shown in Fig. 3. There were no significant differences between the two groups at week 0 (baseline) on the PANSS ($t$=0.58, $df$=28, $P$=0.56). The difference between the two treatments was significant as indicated by the effect of group, the between-subjects factor (Greenhouse–Geisser corrected: $df$=1 and $F$=4.37; $P$=0.04). The behavior of the two treatment groups was not similar across time (groups-by-time interaction, Greenhouse–Geisser corrected: $F$=20.22, $df$=1.84, $P$<0.001). The difference between the two treatments was significant at the endpoint (week 12) ($t$=3.75, $df$=28, $P$<0.001). The changes at the endpoint compared to baseline were: −3.00 ± 1.73 (mean ± SD) and −0.33 ± 0.72 for donepezil and placebo, respectively. A significant difference was observed on the negative subscale of PANSS at week 12 compared to baseline in the two groups ($t$=5.50, $df$=28, $P$<0.001).

*3.2.3. General psychopathological symptoms*

The mean ± SD scores of two groups of patients are shown in Fig. 4. There were no significant differences between the two groups at week 0 (baseline) on the PANSS ($t$=0.70, $df$=28, $P$=0.67). The difference between the two treatments was not significant as indicated by the effect of group, the between-subjects factor (Greenhouse–Geisser corrected: $df$=1 and $F$=0.70; $P$=0.41. The behavior of the two treatment groups was similar across time (groups-by-time interaction, Greenhouse–Geisser corrected: $F$=0.93, $df$=1.59, $P$=0.30). The difference between the two treatments was not significant at the endpoint (week 12) ($t$=1.09, $df$=28, $P$=0.28).

*3.2.4. PANSS total scores*

The mean ± SD scores of two groups of patients are shown in Fig. 5. There were no significant differences between the two groups at week 0 (baseline) on the PANSS ($t$=1.12, $df$=28, $P$=0.26). The difference between the two treatments was not quite significant as indicated by the effect of group, the between-subjects factor (Greenhouse–Geisser corrected: $df$=1 and $F$=3.51; $P$=0.07). The behavior of the two treatment groups was not similar across time (groups-by-time interaction, Greenhouse–Geisser corrected: $F$=9.27, $df$=1.83, $P$<0.001). The difference between the two treatments was significant at the endpoint (week 12) ($t$=2.65, $df$=28, $P$<0.01). The changes at the endpoint compared to baseline were: −5.46 ± 2.41 (mean ± SD) and −2.06 ± 1.62 for donepezil and placebo, respectively. A significant difference was observed on PANSS total score at week 12 compared to baseline in the two groups ($t$=4.52, $df$=28, $P$<0.001).

*3.3. Neurocognitive assessments*

Table 2 shows the results of cognitive tests for both groups at week 0 and week 12. No statistically significant differences were observed between the two groups at week 0 for any of the cognitive measures. In addition, there were no differences between the donepezil and placebo groups on any cognitive deficits at endpoint (week 12).

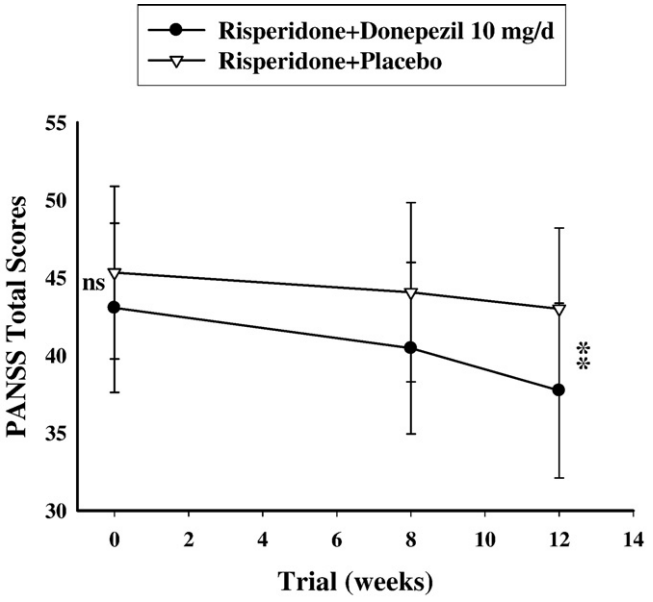


**Fig. 5.** Mean ± SD of the two protocols on the total scores of the PANSS. ns = non-significant and **<0.01.

**Table 2**
The neurocognitive assessments

| | Donepezil week 0 ($n$=15) mean±SD | Placebo week 0 ($n$=15) mean±SD | $P$ | Donepezil week 0 ($n$=15) mean±SD | Placebo week 0 ($n$=15) mean±SD | $P$ |
|---|---|---|---|---|---|---|
| WCST—categories completed | 2.12±0.66 | 2.10±0.74 | 0.95 | 2.18±0.67 | 2.28±0.65 | 0.68 |
| WCST—perseverative error | 37.20±15.10 | 38.00±18.05 | 0.84 | 35.33±18.8 | 32.46±14.28 | 0.64 |
| Figural memory | 5.56±1.25 | 5.33±1.26 | 0.61 | 6.53±1.20 | 6.26±1.10 | 0.09 |
| Visual paired associates 1 | 8.73±3.67 | 8.33±3.92 | 0.77 | 8.60±3.99 | 9.16±3.72 | 0.69 |
| Visual paired associates 2 | 3.30±1.67 | 4.03±1.83 | 0.26 | 4.23±1.64 | 3.63±1.36 | 0.28 |
| Visual reproduction 1 | 33.00±4.47 | 31.06±4.59 | 0.25 | 31.20±4.28 | 33.93±4.85 | 0.11 |
| Visual reproduction 2 | 27.86±5.35 | 28.20±4.73 | 0.85 | 29.73±3.93 | 30.00±5.27 | 0.87 |
| Logical memory 1 | 18.40±2.94 | 20.66±5.40 | 0.16 | 22.13±4.61 | 21.60±3.24 | 0.46 |
| Logical memory 2 | 17.33±2.38 | 19.66±4.77 | 0.10 | 20.80±3.96 | 19.66±2.94 | 0.38 |
| Verbal paired associates 1 | 16.26±2.81 | 16.06±2.52 | 0.83 | 16.93±2.15 | 17.26±2.18 | 0.67 |
| Verbal paired associates 2 | 6.26±1.47 | 6.60±2.07 | 0.61 | 6.90±1.97 | 6.83±1.34 | 0.91 |
| Digit-span forward | 5.76±1.08 | 6.03±1.51 | 0.58 | 6.43±1.41 | 6.33±1.04 | 0.82 |
| Digit-span backward | 5.20±0.94 | 5.40±0.94 | 0.56 | 5.86±0.99 | 5.70±0.88 | 0.63 |
| Block design | 27.33±5.15 | 28.26±5.21 | 0.62 | 29.06±3.67 | 29.53±5.19 | 0.77 |

### 3.4. Hamilton's Rating Scale for Depression

Table 3 provides the score of Hamilton's Rating Scale for Depression for both groups at weeks 0 and 12. There were no differences between the donepezil and placebo groups on Hamilton's Rating Scale for Depression at weeks 0 and 12.

### 3.5. Extrapyramidal Symptoms Rating Scale

There were no significant differences between the means ESRS both groups at weeks 0 and 12 (Table 4).

### 3.6. Clinical complications and side effects

Six side effects were observed over the trial. The difference between the donepezil and placebo in the frequency of side effects was not significant (Table 5).

## 4. Discussion

Studies to improve the cognition impairments of community-based patients with schizophrenia are particularly important to facilitate their continued remission (Akhondzadeh et al., 2005; Jones et al., 2006). The role of acetylcholine in schizophrenia remains elusive, but it has been reported that there is a decrease in the level of α7 acetylcholine receptors in the hippocampus of patients with schizophrenia (Karson et al., 1996). In this double-blind, placebo-controlled trial, adjuvant treatment with donepezil has not improved cognitive performance on a variety of neurocognitive tasks. Our results are in line with the results of other double-blind, placebo-controlled trials of donepezil adjunctive treatment to risperidone (Friedman et al., 2002; Tugal et al., 2004; Keefe et al., 2008). The baseline level of cognitive deficits may be important for the expected efficacy of increased cholinergic transmission on cognition. Previous studies have found that poorer performers show the largest beneficial effects of cholinergic agonists (Friedman et al., 2002; Tugal et al., 2004). The level of cognitive deficits in the present study was moderate (score at least 20 on Mini-Mental State Examination). Nevertheless, this was not a negative trial since the donepezil group had significantly greater improvement in the negative symptoms over the 12-week trial. No significant differences were observed between the means of the two groups on the positive and general psychopathology scores. Clinical characteristics of the schizophrenic patients, such as sex, age and duration of illness, did not differ between groups and cannot explain differences in the therapeutic outcome. Moreover, there were no differences between the donepezil and placebo groups on Hamilton's Rating Scale for Depression over the period of trial. A review of the literature of other studies of cholinesterase inhibitor augmentation of antipsychotics in schizophrenic patients shows mixed results with respect to benefits for psychotic symptoms (Mazeh et al., 2006; Risch et al., 2007). Extrapyramidal side effects measured by the ESRS did not show any differences between the two groups over the trial. We have used donepezil in the higher dosing regimen of 10 mg whereas, the majorities of previous studies used 5 mg/day, but the outcome was not different from our study (Tugal et al., 2004). Nevertheless, donepezil with this dosage was well tolerated in our patients. The most rational reason that donepezil did not improve cognition deficit in our patients, could be that cognitive impairment in schizophrenia is more likely to be related to other transmitter systems compared to Alzheimer's disease (Peuskens et al., 2005). Our results should be considered with caution because the sample size is relatively small and our patients were chronic. Therefore, further controlled studies with larger sample sizes and non-chronic patients are needed. Generally, the present study indicates donepezil as a potential adjunctive treatment strategy for negative symptoms of chronic schizophrenia.

**Table 3**
The severity of depression based on the Hamilton Depression Scale in the donepezil and placebo groups at week 0 (baseline) and week 12 (endpoint)

| | Hamilton Depression Rating Scale Score week 0 (mean±SD) | $P$ | Hamilton Depression Rating Scale Score week 12 (mean±SD) | $P$ |
|---|---|---|---|---|
| Donepezil | 8.33±1.83 | 0.38 | 7.60±1.88 | 0.34 |
| Placebo | 7.73±1.90 | | 8.20±1.52 | |

**Table 4**
Extrapyramidal symptoms based on Extrapyramidal Symptoms Rating Scale

| | Extrapyramidal Symptoms Rating Scale score week 0 (mean±SD) | $P$ | Extrapyramidal Symptoms Rating Scale score week 12 (mean±SD) | $P$ |
|---|---|---|---|---|
| Donepezil | 1.92±1.37 | 0.57 | 1.53±1.06 | 0.87 |
| Placebo | 1.66±1.17 | | 1.46±1.18 | |

**Table 5**
Number of patients with side effects

| Side effects | Risperidone+donepezil 10 mg/day | Risperidone+placebo | $P$ |
|---|---|---|---|
| Nausea | 1 (6.66%) | 2 (13.33%) | ns |
| Insomnia | 1 (6.66%) | 2 (13.33%) | ns |
| Dizziness | 3 (20%) | 1 (6.66%) | ns |
| Muscle cramp | 3 (20%) | 1 (6.66%) | ns |
| Diarrhea | 2 (13.33%) | 2 (13.33% | ns |
| Vomiting | 1 (6.66%) | 1 (6.66%) | ns |

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*The trial group*

Shahin Akhondzadeh: principal investigator and statistical support, clinical neuropsychopharmacologist from Jan. 2006 to Jan. 2008. Maryam Gerami: resident of psychiatry, trialist from Jan. 2006 to Jan. 2008. Maryam Noroozian: clinical coordinator, neurologist from Jan. 2006 to Jan. 2008. Narges Karamghadiri: clinical psychologist, from Jan. 2006 to Jan. 2008. Aboulfazl Ghoreishi: clinical coordinator, psychiatrist from Jan. 2006 to Jan. 2008. Seyed-Hesameddin Abbasi: methodologist from Jan. 2006 to Jan. 2008. Sams-Ali Rezazadeh: pharmacist, from Jan. 2006 to Jan. 2008.

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