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Donepezil for negative signs in elderly patients with schizophrenia: an add-on, double-blind, crossover, placebo-controlled study

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ABSTRACT

Objective: Cognitive impairment and negative signs are common in patients with schizophrenia. Up to 35% of elderly patients with schizophrenia fulfill the diagnostic criteria of dementia. Donepezil inhibits cholinesterase, thus enhancing cholinergic neurotransmission. We tested the efficacy of donepezil in elderly patients with chronic schizophrenia and severe cognitive impairment.

Method: Following baseline assessment, patients were randomly assigned to receive either donepezil or placebo. The dose was 5 mg daily for the first week and 10 mg for an additional 11 weeks. The procedure was repeated using the crossover compound. The Positive and Negative Symptom Scale (PANSS), Clinical Global Impression Scale (CGI) and Alzheimer Disease Assessment Scale – Cognitive subscale (ADAS-Cog) were used to assess the severity of symptoms, cognitive status and intervention effects.

Results: Twenty subjects were enrolled (15 females, five males), mean age 70.2 years (SD 6.5) and mean duration of disease 38.5 years (SD 9.3). A modest treatment effect was found for both placebo and donepezil treatment periods. No crossover effect was found. No statistical differences were demonstrated between the two treatment groups (CGI $p = 0.37$, PANSS $p = 0.71$, ADAS-Cog $p = 0.86$). Two patients died during the study period due to unrelated causes and one patient discontinued participation due to increased agitation.

Conclusion: Donepezil does not seem to improve negative signs and cognitive impairment in elderly patients with chronic schizophrenia.

Key words: schizophrenia, negative signs, donepezil, elderly patients

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Introduction

It is estimated that 85% of patients with schizophrenia demonstrate negative signs of the disease (Gold and Harvey, 1995; Palmer *et al.*, 1997; Park and Holzman, 1992). Cognitive impairment is common in patients with schizophrenia, reducing functional ability and adversely affecting quality of life (Green, 1996). Cognitive impairment can occur in the early stages of the disease (Hoff *et al.*, 1992), and may continue to increase with time, with some patients developing frank dementia (Davidson *et al.*, 1996). Up to two-thirds of elderly, chronically hospitalized patients with schizophrenia fulfill the diagnostic criteria for dementia (Arnold *et al.*, 1995).

Cholinergic activity might play a role in the pathophysiology of schizophrenia. Decreased choline acetyltransferase has been found post-mortem in brains of patients with schizophrenia compared to normal controls (Arnold *et al.*, 1995; Karson *et al.*, 1993; 1996). A possible mechanism for the cholinergic dysfunction might be a reduced number of postsynaptic nicotinic receptors (Freedman *et al.*, 1995). Alterations in the central cholinergic system of patients with schizophrenia, such as reduced numbers of muscarinic receptors in the cortex and hippocampus, may contribute to their cognitive impairment. Thus, pharmacological treatments that enhance central cholinergic function may be useful as cognitive enhancers in schizophrenia.

Donepezil inhibits cholinesterases, thus enhancing cholinergic neurotransmission. It is widely used in patients with Alzheimer's disease (AD), with beneficial effects on cognition, behavior and activities of daily living (Rogers and Friedhoff, 1996), and reports have suggested its possible effectiveness in treating other neuropsychiatric disorders (Cummings, 2000).

Few studies have examined the efficacy of donepezil in treating cognition and psychotic features of schizophrenia. One controlled study could not find any positive effect of donepezil as an adjunctive treatment to risperidone (Friedman *et al.*, 2002). Another study found no significant difference between donepezil and placebo as augmentation to clozapine regarding the positive and negative signs of the disease (Stryjer *et al.*, 2003). A single blind trial reported a beneficial effect of add-on donepezil in six patients with comorbid schizophrenia and dementia (Stryjer *et al.*, 2004). The role of pharmacological treatments that enhance central cholinergic function needs further testing in schizophrenia.

The aim of our study was to examine the possible benefit of the use of donepezil on the negative signs and the cognitive state of elderly patients with chronic schizophrenia and severe cognitive impairment.

Patients and methods

Hospitalized patients aged 60 years or older participated in the study, all diagnosed with schizophrenia according to DSM-IV criteria. The patients

or their legal guardians provided informed consent for participation in the study.

Inclusion criteria for the study were:

1 Diagnosis of schizophrenia according to DSM-IV.
2 Prominent negative signs on the Positive and Negative Symptom Scale (PANSS; Kay *et al.*, 1987): a subscale score of 21 or higher.
3 Prominent cognitive decline on the Alzheimer Disease Assessment Scale – Cognitive subscale (ADAS-Cog; Mohs *et al.*, 1983): a score of 14 or higher.
4 Age 60 years or more.
5 Long-stay inpatients (minimum duration of present hospitalization 2 years) to reflect a low level of independence.

Exclusion criteria were:

1 Diagnosis other than schizophrenia according to DSM-IV (e.g. schizophrenia-like psychosis, cerebrovascular accident, AD).
2 Lack or paucity of negative signs (PANSS negative subscale score of 20 or less).
3 Preserved cognitive status (ADAS-Cog score less than 13).
4 Young patients with schizophrenia (age less than 60 years).
5 Patients with schizophrenia who could function independently or patients with a short time of hospitalization (less than 2 years).

Patients underwent a comprehensive physical assessment, including physical examination, body weight, pulse, and blood pressure monitoring, electrocardiogram (ECG) and routine laboratory tests at baseline. Patients continued their prescribed antipsychotic treatment. They were randomly assigned to receive either add-on donepezil or placebo (see Table 1 for baseline variable scores).

Treatment was initiated at a starting dose of 5 mg for the first week and increased to 10 mg for an additional 11 weeks. The procedure was then repeated using the crossover compound. The PANSS, the Clinical Global Impression Scale (CGI; Guy, 1976), and the ADAS-Cog were used as primary measures to assess the severity of symptoms and cognitive status. These tests were administered by a clinical neuropsychologist (H.Z.) who was blind to the patients' treatment status. Assessments were performed at baseline, before crossover (at 12 weeks) and upon completion of the study.

Statistical analysis and methods

Baseline comparisons between groups were performed using a two-sample *t*-test for continuous variables and the χ^2 test or Fisher's exact test for categorical variables. Comparative efficacy was analyzed with analysis of variance (ANOVA) to examine the differences between treatment groups. All tests applied were

two-tailed, and a *p*-value of 5% or less was considered statistically significant. The data were analyzed using SAS software (SAS Institute, Cary, NC, U.S.A.).

Results

Twenty elderly patients (15 females, five males) diagnosed with schizophrenia (DSM-IV) were recruited. Mean age was 70.2 years (S.D. 6.51) and mean duration of disease was 38.5 years (S.D. 9.34). All patients had early onset of the disease except for one patient in whom the disease started at age 50 years. During the trial patients continued with their antipsychotic drugs: olanzapine (4), risperidone (3), clozapine (3), ziprasidone (1), haloperidol (1), zuclopenthixol (1), perphenazine (1), penfluridol (1) and fluphenazine (1). Four patients did not receive antipsychotic treatment.

Three subjects did not complete the study: two patients had died due to unrelated causes (one due to congestive heart failure and one due to acute myocardial infarction). In one patient treatment was discontinued because of increased agitation.

The analysis did not reveal any carryover effect, therefore a classic crossover analysis was performed to compare the change in each of the efficacy endpoint measures; that is the mean differences between the two treatment groups at the endpoint were calculated and compared using the paired *t*-test procedure.

A modest treatment effect that did not reach statistical significance was found in both placebo and donepezil treatment arms (mean CGI change: 1.7 with

Table 1. Baseline variables scores

	VARIABLE	MEAN	S.D.	MINIMUM	MEDIAN	MAXIMUM
Donepezil	CGI	4.9	0.7	4.0	5.0	6.0
	PANSS general	43.8	10.3	34.0	40.0	65.0
	PANSS total	88.8	22.1	63.0	82.0	132.0
	PANSS negative	26.9	9.7	13.0	28.0	45.0
	PANSS positive	18.0	7.2	9.0	16.0	33.0
	ADAS-COG	32.4	12.9	14.0	35.5	57.0
Placebo	CGI	5.1	0.8	4.0	5.0	6.0
	PANSS general	48.5	9.3	34.0	48.5	61.0
	PANSS total	102.3	22.9	59.0	105.5	132.0
	PANSS positive	32.8	9.6	12.0	35.0	41.0
	PANSS negative	21.1	8.8	13.0	18.0	34.0
	ADAS-COG	30.8	10.4	14.0	32.5	47.0

PANSS = Positive and Negative Symptoms Scale; CGI = Clinical global Impression; ADAS-Cog = Alzheimer Disease Assessment Scale – Cognitive subscale.

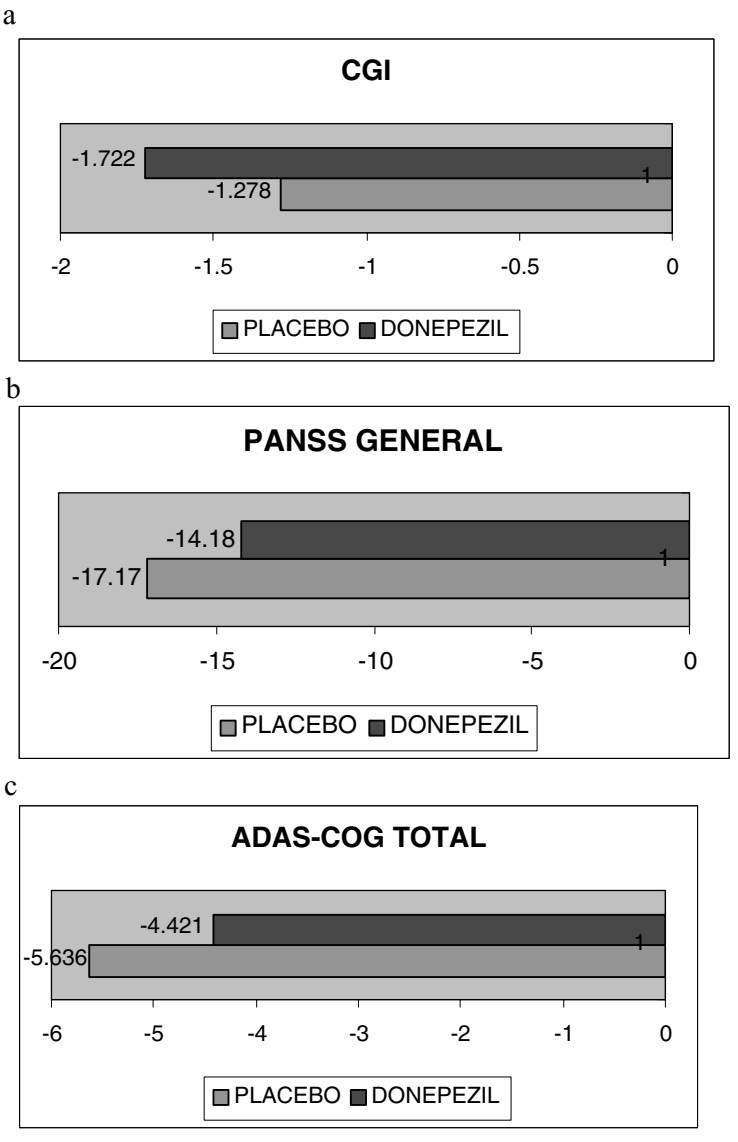

Figure 1. Mean change from baseline in efficacy variables after 12 weeks of donepezil or placebo treatment. (a) CGI; $p = 0.37$; (b) PANSS; $p = 0.71$; (c) ADAS-Cog; $p = 0.87$.

donepezil and 1.3 with placebo; mean PANSS total change: 14.2 with donepezil and 17.2 with placebo; mean ADAS-Cog change: 5.6 with donepezil and 4.4 with placebo).

No statistical differences were demonstrated between the two treatment groups (Figure 1). No significant effect of donepezil treatment was found on any measure (CGI: $p = 0.37$; PANSS general: $p = 0.71$; negative signs of

schizophrenia, PANSS negative: $p = 0.84$; positive signs of schizophrenia, PANSS positive: $p = 0.83$). No significant difference was found on any cognitive measure (expressive and receptive language functions: $p = 0.87$; word recall task: $p = 0.77$, word recognition: $p = 0.62$).

Side-effects

One patient on donepezil complained of moderate weakness and fatigue that remitted spontaneously after 10 days. Another patient on donepezil exhibited increased agitation and discontinued participation. No other significant side-effects were noted.

Discussion

Our data do not support the theory that cholinergic enhancement may be a useful augmentation strategy in elderly patients with schizophrenia and cognitive decline. These findings are similar to previous controlled studies in which donepezil was used as an adjunct to antipsychotic treatment (Friedman *et al.*, 2002; Stryjer *et al.*, 2004).

There are several possible explanations for the lack of effect of donepezil treatment in elderly patients with schizophrenia. First, brain acetylcholine levels in patients with schizophrenia who were treated with donepezil at a maximal dose of 10 mg/day may not have been high enough to achieve a clinical effect. Second, the nonspecific increase in cholinergic activity at nicotinic and muscarinic receptors produced by the drug might interact with the cholinergic alterations that occur in schizophrenia differently than in AD. Third, most schizophrenia patients are heavy smokers (Ripoll *et al.*, 2004). Chronic tobacco use might desensitize the nicotinic receptors (Adler *et al.*, 1998) and counteract the beneficial effect of the acetylcholine enhancer drug.

This study has some limitations: the small sample size means that a type 2 error is possible; and the study population may have been particularly impaired and thus less responsive to pharmacological treatments.

In conclusion, donepezil did not improve the negative signs or the cognitive impairment in our small sample of elderly patients with chronic schizophrenia. Our study is in line with other studies (Friedman *et al.*, 2002; Stryjer *et al.*, 2004) that enrolled different cohorts of patients. Larger sample sizes and different cohorts of patients with chronic schizophrenia should be investigated to confirm or refute our results.

Conflict of interest

None.

Description of authors' roles

Doron Mazeh was the principal investigator, defined the research question and wrote the paper. Hanna Zamishlani supervised the data collection. Yoram Barak assisted in formulating the research question, interpreting the data and commented on the draft paper. Ilona Mirecki provided methodological advice. Diana Paleacu coordinated the research, helped to interpret the data and commented on the draft paper.

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