Original Article

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Effects of Donepezil Adjunctive Treatment to Ziprasidone on Cognitive Deficits in Schizophrenia: A Double-blind, Placebo-Controlled Study

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Abstract

The objective of this study was to examine the effects of adjunctive treatment with the acetylcholinesterase inhibitor, donepezil, on cognitive deficits and psychopathology in schizophrenic patients treated with the antipsychotic, ziprasidone. The design of the study was double blind, placebo controlled, and longitudinal. Patients were treated with ziprasidone for 8 weeks, thereafter randomized to 4 months of double-blind adjunctive treatment with either donepezil (dose, 5–10 mg) or placebo. The severity of psychopathology (PANSS) and the cognitive deficits were examined at baseline and after 4 months. A total of 21 schizophrenic patients were enrolled, of whom 11 patients completed the trial (donepezil, n = 7; placebo, n = 4). There were no within- or between-group differences in changes on the Positive and Negative Syndrome Scale scores or a global cognitive score. Within-group improvements (all at trend level *P* = 0.07) were seen in the placebo group on Trail-Making Test B, immediate verbal recall, and set-shifting errors. The donepezil group showed a significant deterioration on planning efficiency (*P* = 0.04). Between-group differences were found between the lack of improvement in immediate verbal recall in the donepezil group and the improvement in the placebo group (*P* = 0.02), and between the deterioration of planning efficiency in the donepezil group and the stability in the placebo group (trend level, *P* = 0.07). Linear regression analyses showed that neither baseline psychopathology scores, baseline levels of cognitive deficits, nor psychopathology changes over time accounted for these changes in cognitive scores. The study found no evidence of improved cognition after treatment with donepezil, although the conclusions that can be drawn are limited by the small sample size.

Key Words: schizophrenia, cognition, donepezil, ziprasidone

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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.[1,2] One of the theoretically promising novel treatment candidates is acetylcholinesterase inhibitors that increase the synaptic levels of cholinergic, nicotinic, and muscarinic receptor activity.[3] In contrast with Alzheimer disease, there have been no clear neuropathologic findings implicating the cholinergic system in the pathophysiology of schizophrenia.[4,5] However, fewer muscarinic and nicotinic receptors have been found in schizophrenia, principally in the hippocampus.[6,7] Furthermore, positive correlations between reduced postmortem levels of acetylcholinetranferase and antemortem cognitive deficits have been found,[5,8] and in vivo single photon emission computed tomography studies of unmedicated schizophrenic patients have found decreased muscarinic receptor binding in both the cortical and the subcortical cortices.[9]

Studies on healthy subjects have found that short-acting cholinergic antagonists, such as scopolamine, impair cognitive functions, especially memory, whereas cholinergic agonists improve the same functions.[10–12] Similarly, cigarette smoking and other nicotinic receptor agonists improve working memory, complex reaction times (ie, attention), and

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sensory-gating deficits, and smooth pursuit eye movements impairments in schizophrenia.[13,14] Centrally active acetylcholinesterase inhibitors, such as donepezil, rivastigmine, and galantamine, all inhibit the breakdown of acetylcholine by the enzyme acetylcholinesterase, indirectly stimulating the muscarinic and the nicotinic receptors. Galantamine, in addition to this effect, also potentiates nicotinic receptor stimulation by an allosteric mode of action.[15] These compounds have been used extensively to ameliorate the cognitive deficits in mild to moderate Alzheimer disease.[16–18] Recent studies using such longer-acting acetylcholinesterase inhibitors adjunctive to antipsychotic treatment in samples with schizophrenia have found conflicting results. Positive effects have been reported on verbal fluency,[19] with modest improvements reported on verbal learning,[20] verbal recognition memory, and P50 gating, and the largest improvements were found, to date, on motor speed.[21] A lack of efficacy has been reported in larger, double-blind studies of adjunctive donepezil.[22–24] These previous studies of adjunctive acetylcholinesterase inhibitors have included patients on various antipsychotic compounds with varying degrees of anticholinergic action. The studies also differ in length and dosage of adjunctive medication, concomitant medication allowed, age and chronicity of patient samples, severity of baseline cognitive deficits in patients, and comorbidity. The objective of the present study was to examine the effects of adjunctive treatment with the acetylcholinesterase inhibitor, donepezil (placebo controlled), on cognitive deficits and psychopathology in schizophrenic patients stabilized on an atypical antipsychotic medication (ziprasidone).

METHODS

Subjects

Patients

Schizophrenic patients were included from participating psychiatric departments in the Copenhagen catchment area. Both inpatients and outpatients were included, although most patients were outpatients, and some had brief periods of hospitalization during the study. The patients included in the study either continued their ongoing treatment with ziprasidone or had their treatment switched to ziprasidone because of insufficient efficacy or because of unacceptable adverse effects of their previous antipsychotic medication. Ziprasidone was selected because of its low in vivo and in vitro binding affinity to cholinergic receptors.[25] Treatment-refractory patients (ie, patients on whom 2 or more antipsychotic compounds had insufficient or no effect) were not included. All patients were treated with ziprasidone for a minimum duration of 8 weeks and were thereafter randomized to 4-month, double-blind adjunctive treatment with either donepezil (dose, 5–10 mg) or placebo, in conjunction with continued ziprasidone treatment (Table 1). Donepezil doses started at 5 mg and were increased to 10 mg after 4 weeks. If agitation or extrapyramidal symptoms (EPSs) appeared, the dose was reduced to 5 mg. The following medications were not allowed during the study: anticholinergics, tricyclic antidepressants, antipsychotics other than ziprasidone, and mood stabilizers. However, selective serotonin reuptake inhibitors (SSRIs) and benzodiazepines were allowed throughout the study (benzodiazepines were allowed only after cognitive assessments).

A total of 21 patients were randomly allocated to treatment with either donepezil or placebo. Of these, 10 were excluded or withdrew for the following reasons: switch to a different antipsychotic medication because of insufficient effect of ziprasidone on psychotic symptoms (n = 4), cannabis-induced psychotic symptoms (n = 1), extreme outlier on cognitive tasks (n = 1), magnetic resonance imaging scans revealed structural abnormalities, a tumor (n = 1) and an arachnoid cyst in the left temporal lobe (n = 1), patient-initiated withdrawal after subjective feeling of adverse effects after taking 1 placebo tablet (n = 1), and acutely increased EPSs after almost 3 weeks of

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donepezil treatment (n = 1). Thus, 11 patients were included in the present analysis (donepezil, n = 7; placebo, n = 4). All 11 patients were diagnosed with schizophrenia of F 20.0 paranoid subtype, according to the criteria of the *International Statistical Classification of Diseases, 10th Revision (ICD-10)*.

Healthy Controls

Healthy controls were matched to the patients in a ratio of 1:1 on the basis of sex and age. Written informed consent was obtained after complete description of the study. There were no differences between patients and controls on the basis of socioeconomic background (parental education and income, combined), or between the placebo and the donepezil groups on the basis of age, socioeconomic background, age at the onset of psychotic symptoms, or illness duration. Controls were included to establish the baseline level of cognitive deficit and to determine the retest effects.

Materials

Psychopathology

Schizophrenia diagnoses were confirmed at inclusion using the SCAN 2.1 interview, *ICD-10* criteria.[26] The severity of psychopathology was rated using the PANSS[27]; adverse effects, using the Extrapyramidal Symptom Rating Scale (ESRS), according to recent criteria[28]; depressive symptoms, using Calgary Depression Scale[29]; and global function, using the CGI (severity of illness and global improvement)[30] and GAF (Global Assessment of Function).

Cognition

The cognitive test battery consisted of computerized tests from Cambridge Neuropsychological Test Automated Battery (CANTAB) and Buschke Selective Reminding Task, Rey Complex Figure Task, and Trail-Making Tests A and B, all of which have been described in detail in other studies.[31–34] The cognitive tests were conducted by post–bachelor level psychology students, trained and supervised in administering the tests. There was no minimum level of cognitive impairment required for inclusion into the project. Psychopathology, adverse effects, and cognition were examined at baseline and after 4 months of adjunctive treatment.

Statistical Analyses

Data analyses were performed using SPSS 11.0 software. Nominal and ordinal data were analyzed using Pearson χ^2 test. Parametric statistics were used to calculate z scores, with the healthy control group as reference. A global cognitive score was calculated as primary outcome measure, averaging the z scores of the main cognitive outcome measures. Because of the small sample sizes when comparing the effects of adjunctive medication, nonparametric statistical analyses (Wilcoxon) were used for direct group comparisons, with adjunctive medication (donepezil/placebo) as the between-group variable. Logistic regression analyses (forward, conditional method) were conducted, with changes in cognitive scores, psychopathology, and adverse effects as separate predictors of adjunctive medication (donepezil/placebo). Linear regression analysis (stepwise method) was conducted on the combined patient groups (donepezil and placebo) to determine the variance in cognitive change scores, as explained by the psychopathology and the adverse effects (both baseline and change scores).

RESULTS

Psychopathology

There were no within- or between-group differences in the changes on PANSS, GAF, CGI (neither severity of illness nor global improvement), Calgary Depression Scale, or Extrapyramidal Side-effect Rating Scale scores in the donepezil and placebo groups from baseline to follow-up. Two patients in the donepezil group and 2 patients in the placebo group received SSRIs (Table 1).

TABLE 1. Case-Level Demographics and Clinical Data

	Pt 1	Pt 2	Pt 3	Pt 4	Pt 5	Pt 6	Pt 7	Pt 8	Pt 9	Pt 10	Pt 11
Age (yrs)	43.0	32.8	39.4	28.9	23.2	39.4	25.8	27.2	40.9	38.9	33.0
Sex	Male	Male	Female	Female	Female	Male	Male	Male	Male	Male	Male
Illness duration (yrs)	17.0	6.8	1.4	4.9	2.4	8.4	5.8	0.7	14.9	9.9	7.0
Ziprasidone doses (mg)	160	120; 80 (reduced because of EPSs)	160	120	160; 140; 100 (reduced because of EPSs)	200	80; 120; 160 (increased because of increased psychotic symptoms)	160	60; 80; 120 (increased because of increased psychotic symptoms)	160	80
Adjunctive medication	Donepezil (5 mg)†	Donepezil (5 mg)†	Donepezil (10 mg)	Donepezil (10 mg)	Donepezil (10 mg)	Donepezil (10 mg)	Donepezil (10 mg)	Placebo	Placebo	Placebo	Placebo
Smoking	Smoker	Smoker	Smoker	Nonsmoker	Nonsmoker	Smoker	Smoker	Occasional smoker	Smoker	Nonsmoker	Nonsmoker
Additional medication during the study*	Oxazepam (15 mg/d)	None	Effexor (225 mg/d) + Truxal (75 mg max/d pn) + Rivotril (0.5 mg max × 3 pn)	Oxazepam (30 mg max/pn) + Imovane (7.5 mg max/d pn)	Zoloft (50 mg × 1/d) + oxazepam (45 mg max/d pn)	None	None	Effexor (75 mg/d)	Effexor (225 mg/d)+ oxazepam (22.5 mg/d + 45 mg max/d pn)	Oxazepam (max 15 mg/d pn)	None

	Base-line	16 wks	Base-line	16 wks	Base-line	16 wks	Base-line	16 wks	Base-line	16 wks	Base-line	16 wks	Base-line	16 wks	Base-line	16 wks	Base-line	16 wks	Base-line	16 wks	Base-line	16 wks
PANSS positive symptoms	9	12	10	11	9	11	16	11	13	11	8	8	16	12	10	10	10	15	10	9	8	9
PANSS negative symptoms	11	16	15	11	19	17	11	13	20	16	17	10	18	20	12	11	17	19	23	20	16	16
PANSS general symptoms	21	24	19	18	28	25	21	20	34	23	21	21	24	34	21	27	20	31	28	24	21	19
PANSS total symptoms	41	52	44	40	56	53	48	44	67	50	46	39	58	66	43	48	47	65	61	53	45	44
CGI severity	3	3	3	3	4	4	4	4	5	4	4	4	4	4	3	3	4	3	5	4	3	3
CGI global improvement	3	4	1	1	2	2	4	3	4	3	4	3	3	2	2	1	2	2	4	3	2	2
GAF	65	65	63	68	59	53	61	85	50	58	61	69	60	51	70	68	60	55	51	60	65	65
Calgary depression scale	0	0	0	0	4	4	0	0	4	0	0	0	0	0	0	2	1	10	5	1	1	0

*Zoloft is sertaline hydrochloride (SSRI); Effexor, venlafaxine hydrochloride (phenethylamine monoamine reuptake inhibitor); Truxal, chlorpromazine hydrochloride (aliphatic phenothiazine); oxazepam, 3-hydroxy benzodiazepine; Rivotril, clonazepam (3-hydroxy benzodiazepine); Imovane, zopicolne (γ-aminobutyric acid-t inhibitor).

†Reduced from 10 to 5 mg because of emerging adverse effects.

Pt indicates patient; PANSS, Positive and Negative Syndrome Scale; CGI, Clinical Global Impression; GAF, Global Assessment of Function.

TABLE 2. Cognitive Deficits at Baseline (Compared With Controls [N = 11]) and Within- and Between-Group Differences (Baseline to Follow-up)

	Patients at Baseline (N = 11)			Within-Group Differences (Baseline to Follow-up)			Between-Group Differences (Baseline to Follow-up)		
Cognitive Tests	**Z score**	***df***	***P***	**Donepezil (n = 7)**	**Placebo (n = 4)**	**Controls (n = 11)**	**Donepezil vs Placebo**	**Donepezil vs Controls**	**Placebo vs Controls**
Global cognitive score	−1.4	20	0.001	NS	NS	NS	NS	NS	NS
Rey complex figure test (copy)	−2.5	20	0.06	NS	NS	NS	NS	NS	NS
Buschke selective reminding task, Supraspan	−1.0	20	0.07	NS	$P = 0.07$	NS	$P = 0.02$	NS	NS
Buschke selective reminding task, long-term recall	−2.4	20	0.06	NS	NS	NS	NS	NS	NS
CANTAB spatial span	−0.8	20	0.08	NS	NS	NS	NS	NS	NS
CANTAB IED total errors (adjusted)	−0.2	20	NS	NS	$P = 0.07$	NS	NS	NS	$P = 0.08$
CANTAB stockings of Cambridge mean no. of moves	−0.7	20	NS	$P = 0.04$*	NS	NS	$P = 0.07$	$P = 0.03$	NS
CANTAB choice movement time	−2.0	20	0.01	NS	NS	NS	NS	NS	NS
Verbal semantic fluency (animals)	−1.6	20	0.03	NS	NS	NS	NS	NS	NS
Symbol digit modalities test	−1.1	20	0.01	NS	NS	NS	NS	NS	NS
Trail-making test B	−1.4	20	0.09	NS	$P = 0.07$	NS	NS	NS	NS

*The only within-group change that reflected deterioration from baseline.
P indicates 2-sided significance; NS, not significant.

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Cognition

There were no differences between the donepezil and the placebo groups on any cognitive deficits at baseline, nor were there any significant within- or between-group changes on the global cognitive score (Table 2). In exploratory analyses, within-group improvements (all at trend level P = 0.07) were seen in the placebo group on Trail-Making Test B, immediate verbal recall (Supraspan from Buschke Selective Reminding Task), and set-shifting errors (Total errors [adjusted] from CANTAB IED Set-shifting Task). The donepezil group showed a significant deterioration on planning efficiency (mean number of moves from CANTAB Stockings of Cambridge; P = 0.04). Exploratory analyses found between-group differences between the lack of improvement in immediate verbal recall in the donepezil group and the improvement in the placebo group (P = 0.02), and between the deterioration of planning efficiency in the donepezil group and the stability in the placebo group (at trend level P = 0.07). There were no within-group changes in the healthy control group, but there was a significant between-group difference (compared with healthy controls) regarding the deterioration on planning efficiency in the donepezil group (P = 0.03) and a tendency toward a between-group difference from the improvement in the placebo group on set-shifting errors (P = 0.08; Table 2). Linear regression analyses showed that neither baseline psychopathology scores, baseline levels of cognitive deficits, nor psychopathology changes over time accounted for the changes in cognitive scores. In exploratory analyses, when logistic regression (forward, conditional model) was applied using cognitive change scores to predict the type of adjunctive medication (donepezil/placebo), the difference scores in Supraspan from Buschke Selective Reminding task resulted in a significant model (excluding other change scores), with χ^2_1 = 9.244, df = 1, P = 0.002, accounting for between 56.8% and 77.8% of the variance, with an overall correct prediction rate of 90.9%. When examined in separate analyses, the only other significant cognitive predictor (mean number of moves from CANTAB Stocking of Cambridge) resulted in a significant model (χ^2_1 = 5.086, df = 1; P = 0.024), accounting for between 37% and 50.7% of the variance, with an overall correct prediction rate of 72.7%.

Tolerability

One patient was excluded from the project because of EPSs that emerged in mild form approximately 1 week after donepezil treatment (dose, 5 mg) was initiated, with acute worsening after an additional 10 days on 5-mg treatment. His symptoms were acute dystonia with dysarthria, moderate to moderately severe parkinsonian bilateral rigidity, marked facial masking, moderately stiff posture, and mild to moderate bradykinesia. Four weeks after the donepezil dose was increased to 10 mg, 2 patients experienced emerging EPSs. After the dose was reduced to 5 mg, the EPSs were ameliorated. Two patients had their ziprasidone doses decreased to ameliorate the EPSs. One patient had completed the project on 10-mg donepezil but, at the end of the project, had symptoms of oligomimi, bradykinesia, and sialorrhea that improved considerably within days of stopping the donepezil treatment.

DISCUSSION

Psychopathology

It is possible that the presence of clinical depression in a few of the patients had an impact on their cognitive function, as has been found in several studies.[35,36] However, only one of the patients had scores on Calgary Depression Scale that was within levels usually interpreted as impacting cognition. The lack of significant effects on psychopathology scores is in line with most previous studies,[21–24,37] although modest effects have

been reported in 1 group study[20] and in a few of the cases in the studies of Stryjer et al.[37,38] Both preclinical and clinical studies have found that muscarinic agonists reduce psychotic symptoms,[39–41] although negative symptoms have been found to be adversely affected.[42] However, case studies using adjunctive galantamine (which is a positive allosteric modulator of nicotinic receptors, in addition to being an indirect-action muscarinic and nicotinic agonist,[43,44]) have shown to ameliorate negative symptoms and disorganized thinking, with negligible efficacy on other positive symptoms.[45–47]

Tolerability

Donepezil treatment was not as well tolerated in the present study as in some previous reports.[20,23,38] One of the patients in the donepezil group experienced sialorrhea, which is a rare adverse effect in conjunction with newer atypical antipsychotics,[28] but which was also present in some of the donepezil-treated patients in the study by Freudenreich et al.[22] One of the patients had to be excluded because of acute EPSs, whereas the treatment dose of 2 patients had to be reduced from 10 to 5 mg because of adverse effects. This problem was also present in one of the studies that did find beneficial effects of physostigmine on cognition in patients with schizotypal personality disorder, where adverse effects such as nausea and vomiting occurred.[48] Studies suggest an inverted U-shaped curve in the dose and the efficacy of acetylcholinesterase inhibitors in which increased doses increase the beneficial effects until a point after which the effects become detrimental.[49]

Cognition

The baseline level of cognitive deficits may be important for the expected efficacy of increased cholinergic transmission on cognition. Studies have found that poorer performers show the largest detrimental effects of cholinergic antagonists and the beneficial effects of cholinergic agonists.[10–12] Friedman et al[23] only included patients with cognitive impairments (on a verbal learning task) of more than 2 SD, and suggested that this could have contributed to the lack of efficacy in that study. The level of cognitive deficits in the present study was less severe than in most previous studies of adjunctive acetylcholinesterase inhibitors[20,23] but in line with the level of deficits in the study of Tugal et al.[24] The fact that only paranoid, schizophrenic patients (*ICD-10*; F.20.0) were included in the present analyses may indicate an unintended selection bias toward the better-functioning patients because this subgroup of patients tends to have less severe cognitive deficits than do other schizophrenic subgroups. However, the overall level of cognitive impairments was similar to that generally found in schizophrenia.[50,51] The patients in this sample were younger than those in previous studies, which tentatively suggests that younger patients do not have more advantageous effects from donepezil treatment than do older patients.

Clearly, because of the small sample size, the present study was not powered to detect medium effect sizes in between-group comparisons, and the risk of both types 1 and 2 errors is considerable. However, some within- and between-group differences were observed in exploratory analyses, suggesting not only the mainly stable cognitive deficits but also the detrimental effects of donepezil on especially immediate verbal learning; in addition, it also suggests detrimental effects on planning efficiency (which was supported by logistic regression analyses). It is possible that treatment with ziprasidone in the present study had already optimally increased the synaptic availability of acetylcholine in these patients because atypical antipsychotics in preclinical studies have been found to increase acetylcholine release in the medial prefrontal cortex[52] and the hippocampus.[53]

The present results tentatively support the contention that the various acetylcholinesterase inhibitors may differ in their effects

on psychopathology and cognition because of their different receptor affinity profiles. This has been indicated in preclinical studies, in which physostigmine, galantamine, and donepezil have been found to improve different *N*-methyl D-aspartate antagonist–induced behavioral deficits (ie, of learning and memory) in mice.[54] Cigarette smoking may also have rendered the potential nicotinic augmentation of donepezil ineffective because of desensitization (and the low density of nicotinic receptors). It is possible, as suggested by Friedman et al,[23] that acetylcholinesterase inhibitors with dual actions, such as galantamine (which also acts as an allosterically potentiating ligand that can sensitize nicotinic receptors[43]), may be more promising candidates, compared with donepezil, when targeting the cholinergic system as a treatment strategy for schizophrenia.

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