Efficacy and Tolerability of Low-Dose Donepezil in Schizophrenia

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Abstract: There have been many advancements in the pharmacologic treatment of schizophrenia; however, negative symptoms and cognitive impairment remain an intractable part of this illness. Donepezil is an anticholinesterase inhibitor with cognitive enhancing effects approved for the treatment of Alzheimer disease that has shown some benefit in the treatment of schizophrenia. In this study, 15 inpatients at a state hospital with a history of schizophrenia were administered donepezil in a randomized, double-blind, crossover design. Neurocognitive testing and psychiatric ratings were completed at baseline and at regular intervals for 18 weeks. Results indicated that donepezil treatment was associated with modest improvements in psychiatric symptoms and improved verbal learning. These results suggest that donepezil may be helpful as adjunctive therapy for the treatment of psychiatric symptoms and cognitive impairment in a subgroup of schizophrenic patients.

Key Words: schizophrenia, cognition, donepezil, negative symptoms

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Despite recent treatment advances, schizophrenia remains one of the most severe and persistent forms of mental illness.[1] The most overtly disruptive symptoms of this disorder, which until recently had been the primary focus of treatment, are commonly referred to as positive symptoms (eg, hallucinations, delusions, etc.). Although current pharmacologic therapies are generally effective in controlling these symptoms, recent evidence strongly suggests that functional outcome and long-term prognosis may be more significantly related to negative symptoms (eg, affective flattening, anhedonia, etc.) and cognitive impairment.[2–4] However, significantly less research has been conducted in this area. Although second-generation antipsychotics appear to be more effective in treating negative symptoms and cognitive impairment in this population, there continues to be an absence of any clinically accepted pharmacologic interventions to treat these symptoms.[5–7]

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The dopamine hypothesis of schizophrenia has proved to be a heuristically powerful model for exploring mechanisms and treatment of the positive symptoms of this illness.[8] However, an emerging body of evidence has challenged this monochromatic schema in favor of a model of schizophrenia involving multiple neurotransmitters and receptors outside the D2 subtype.[8,9] More recent formulations have focused on other neurotransmitters with regard to etiology and treatment of schizophrenia, including glutamate, serotonin, γ-aminobutyric acid, *N*-methyl-D-aspartate (NMDA), and acetylcholine.[10] Studies have shown that administration of NMDA receptor coagonists glycine and D-serine can significantly reduce negative symptoms in schizophrenia, whereas D-cycloserine appears less robust in this effect.[11]

ROLE OF ACETYLCHOLINE IN SCHIZOPHRENIA

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.[12,13] This acetylcholine deficiency may be associated with decreased inhibition in P50 auditory-evoked response, which is thought to be a measure of sensory gating or the ability to disregard irrelevant sensory information.[14,15] Although reports using very differing methods and examining different brain regions are somewhat conflicting,[16] there is evidence to support abnormalities in nicotinic receptor density in the hippocampus,[17] choline acetyltransferase levels in the pons,[18] and basal ganglia choline levels in brains of schizophrenic patients.[19]

There is compelling evidence that nicotinic agonist administration has efficacy in reversing some neurocognitive abnormalities in schizophrenic patients,[20,21] as well as normalizing aberrant brain physiology.[22] This latter finding is bolstered by basic research showing nicotine reverses a drug-induced physiologic abnormality with face and predictive validity in an animal model.[23] These findings may help explain the extremely high rate of cigarette smoking in patients and subjective reports of symptomatic improvement after smoking.[24] Although some have posed that nicotinic agonists are effective only briefly, findings of Leven et al[20] argue against this.

Nonetheless, the endemic use of tobacco among patients with schizophrenia, and anecdotal reports of a decrease in symptoms, suggests an acetylcholine deficiency among these patients, and it has been noted that administration of nicotine reverses cognitive dysfunction induced by haloperidol.[15,20] Repeated exposure of nicotine in rats has shown an

upregulation of neuronal nicotinic acetylcholine receptors, suggesting an increased neurotransmission of acetylcholine.[25] In addition, it is known that nicotine exerts extensive cholinergic effects and the administration of nicotine results in cortical arousal mediated by acetylcholine release.[26]

Furthermore, it has been demonstrated that patients with schizophrenia have decreased blood flow to regions of the brain that are influenced by acetylcholine release, including frontal and limbic areas of the brain.[27] In addition, there is evidence of decreased hippocampal nicotinic receptor activity and reduced choline acetyltransferase in the pons, which may explain the neurovegetative symptoms seen in schizophrenia.[15,18] Similarly, patients with Alzheimer disease have a hypoprofusion of blood flow and metabolism in the heteromodal and limbic cortex of the brain.[28,29] Inhibitors of the enzyme acetylcholinesterase (ie, donepezil) are believed to improve blood flow to these areas by increasing the availability of acetylcholine.[30]

ADJUNCTIVE THERAPY WITH DONEPEZIL

Donepezil is a reversible inhibitor of the enzyme acetylcholinesterase, indicated for the treatment of symptoms of Alzheimer disease. It is hypothesized that donepezil improves cognition by increasing the amount of acetylcholine in the synaptic cleft, which results in improved memory, attention, vigilance, and executive functioning. The choice of donepezil for this study was based on its proven efficacy as a cognitive enhancement intervention in Alzheimer disease, its more tolerable side effect profile compared with other acetylcholinesterase inhibitors, and its lack of hepatotoxicity.[31,32] There is also evidence that these agents do not pose a risk of increased psychosis, but instead appear to reduce psychotic symptoms in dementia patients.[33] Similar to the theory that the mechanism for hallucinations and delusions may derive from similar pathologic pathways despite the heterogeneity of different diagnostic groups, likewise negative symptoms and cognitive dysfunction in differing diagnostic groups may share some of the same pathophysiology.[34] More critically, effective treatment of cognitive deficits may be similar despite different diagnoses, as is obvious for positive symptoms of psychosis.

There have been a handful of studies that have examined the efficacy of donepezil in the treatment of cognitive impairment in schizophrenia. Buchanan et al[35] found that donepezil in conjunction with olanzapine was associated with improved manual dexterity, verbal recall, verbal memory, and processing speed during a 6-week open trial. There was no observed improvement in attention or psychiatric symptoms as measured by the Brief Psychiatric Rating Scale or the Scale for the Assessment of Negative Symptoms. Similarly, another study indicated that donepezil may be helpful in improving cognition and psychiatric symptoms in patients with schizophrenia and comorbid dementia.[36]

Additional studies have shown that donepezil improves left frontal lobe and cingulate activity in patients with schizophrenia[37] and is associated with strong improvements in verbal fluency.[38] Interestingly, a double-blind, placebo-controlled study by Friedman et al[39] examined 36 subjects who received donepezil (5 mg or 10 mg) for 12 weeks and found no significant improvements in cognition. The authors postulated that the lack of efficacy might be related to nicotine receptor desensitization related to chronic tobacco use; however, the exact effect of nicotine on acetylcholine receptors in humans remains unknown. Further studies with donepezil have demonstrated substantial improvements in tardive dyskinesia (TD) or the suppression of TD, specifically in the orofacial and upper extremities in patients with schizophrenia.[40]

The aim of the current study was to examine the efficacy of low-dose donepezil in the treatment of psychotic symptoms and cognitive impairment in patients with schizophrenia. It was hypothesized that donepezil treatment would enhance subjects' performance on neurocognitive assessments as well as lower overall psychiatric symptomology in comparison with placebo.

METHOD

Subjects

Twenty-four inpatients meeting criteria for a DSM-IV diagnosis of schizophrenia were recruited for the study at the Rochester Psychiatric Center, a state-run psychiatric facility affiliated with the University of Rochester. The local institutional review board (IRB), as well as the New York State Office of Mental Health Research Foundation IRB approved the study. All subjects gave written informed consent before being involved in the study. Patients were between 20 years and 60 years of age, and if female and of childbearing age, not pregnant and using a reliable form of birth control. Subjects were excluded if they had electrocardiogram conduction abnormalities, active peptic ulcer disease, a primary diagnosis of neurologic disorder, or an active seizure disorder. Patients were not involved in the study if they were taking anticholinergic medication and had been stabilized on their major psychotropic medications for 4 weeks prior to participation in the study.

Design of Medication Trial

This was an 18-week, double-blind, crossover study, with all patients assessed at baseline and biweekly throughout the active phase of the study (Fig. 1). After baseline testing, patients were assigned by simple randomization to 1 of 2 groups defined by the order in which donepezil or placebo was added to their medication regimens (group A, placebo first, donepezil second; group B, donepezil first, placebo second). One group received placebo for 8 weeks prior to being switched to donepezil for the second 8-week phase (group PD). The second group received donepezil for the first 8 weeks, followed by 8 weeks of placebo (group DP). Patients had a 2-week medication washout period between the first and second 8 weeks. During the donepezil phase, patients received 5 mg/day donepezil in addition to their current medication regimen in a single daily morning dose. This dose was chosen due to reports of relatively minimal side effects, the modest effect size that might be expected, and the lower potential for psychomotor excitement.

Subjects were assessed at baseline, throughout treatment, and at the end of treatment with measures of psychotic symptoms, general symptoms, and cognitive functioning (Table 1). The measures were designed to test for the efficacy

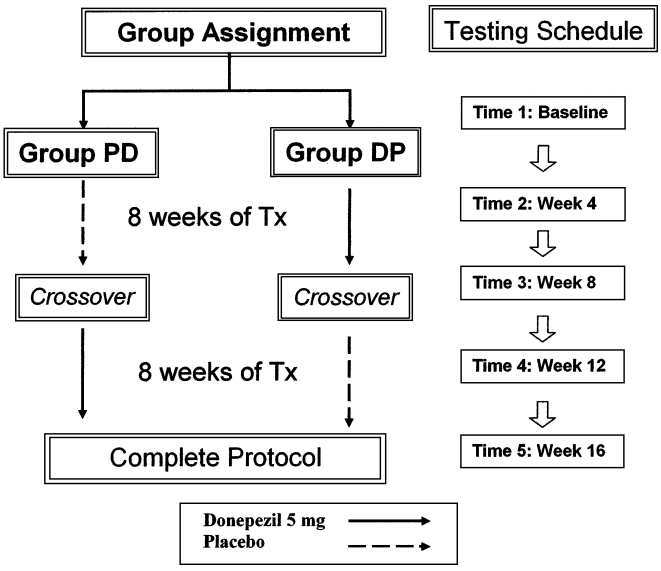

FIGURE 1. Study design including testing schedule. A 2-week ''washout'' period followed the initial 8-week assignment.

of donepezil in the realms of overall psychiatric symptoms, psychosis ratings, and a number of domains of cognitive processing.

Diagnostic and Clinical Ratings

Raters were trained in the use of the Structured Clinical Interview of DSM-IV[41] and the Positive and Negative Syndrome Scale (PANSS).[42] Interrater reliability for the PANSS was greater than 0.80. For inclusion in this study, subjects were required to have a diagnosis of schizophrenia with at least 1 negative symptom scale score of 4 points or more, or 4 points or more using the Cognitive Disorganization Scale of the PANSS. The PANSS was administered biweekly during the study to assess psychiatric symptoms closely during treatment and were averaged at 8-week intervals.

Medication Administration

After signing informed consent, screening, and baseline testing, subjects were randomly assigned to either donepezil or placebo for 8 weeks (identical single pills every morning). At week 8, all subjects entered a 2-week medication washout period and then subjects were crossed over to the alternate treatment for another 8 weeks of the other treatment (either placebo or donepezil). The blind was broken after the end of the trial and those subjects that improved on donepezil were identified to their treating psychiatrists, with this medicine being available for their treatment at the hospital (Fig. 1).

TABLE 1. PANSS Scores by Individual

Donepezil to Placebo			Placebo to Donepezil		
Baseline	**T2/T3**	**T4/T5**	**Baseline**	**T2/T3**	**T4/T5**
99	95.5	93	90	80.5	71.5
72	71	68.5	91	77	66.5
93	98	97.5	69	57	55
87	76.5	64.5	94	92	86.5
55	60.5	60	88	87	79
87	77.5	75	73	71.5	74
91	75.5	115.5	106	97	107.5
80	79	77.5	—	—	—

Neurocognitive Testing

The Rey Auditory Verbal Learning Test (RAVLT) and Trails A and B were administered to assess executive functioning and learning. Testing was administered biweekly during the study to measure symptom and cognitive changes during the study.

Data Analysis

The primary hypotheses tested were (1) subjects would tolerate the addition of donepezil to their medication regimen without untoward effects on their psychiatric status compared with patients taking placebo; (2) subjects receiving donepezil, compared with placebo, would show significant improvement in their psychosis ratings and general symptoms; and (3) subjects receiving donepezil would show enhanced cognitive functioning compared with those receiving placebo. Measures were examined using repeated-measures analysis of variance (ANOVA), with time and group (order of medication administration, placebo to donepezil [PD] vs. donepezil to placebo [DP]) as main factors, and the time-by-group interaction as a critical factor in the analysis. The cognitive test scores (RAVLT, Trails A and B) underwent the previous ANOVA analysis after log transformation and this resulted in their normal distribution (Wilks-Shapiro test) and therefore appropriate for parametric analysis. All other measures met criteria for normal distribution. The General Linear Model procedure of SAS adjusts for unequal number of subjects using the type IV sums of squares. This was used in all repeated-measures analyses. No adjustments for multiple comparisons were made, and 2-tailed testing was used in all statistical tests.

RESULTS

Demographics

The subjects' mean age was 43 years (SD, 5.2 years); 12 were African-American, 3 were white; and 11 were male and 4 were female. Schizophrenia subtypes were paranoid (n = 5), undifferentiated (n = 5), and 5 had a diagnosis of schizoaffective disorder. Eleven subjects were on atypical antipsychotics during the study (clozapine [n = 4], olanzapine [n = 4], risperidone [n = 1], and quetiapine [n = 2]), 3 subjects were on a combination of typical and atypical antipsychotics (haloperidol + quetiapine [n = 1] chlorpromazine + olanzapine [n = 1], fluphenazine + clozapine [n = 1]). Concomitant medications were as follows: lithium, n = 3; valproic acid, n = 5; gabapentin, n = 4; carbamazepine, n = 1; fluvoxamine, n = 2; fluoxetine, n = 1; bupropion, n = 1; sertraline, n = 1; venlafaxine, n = 1; clonazepam, n = 1; lorazepam, n = 3; and buspirone, n = 1. Medications available to subjects as needed included, choral hydrate, n = 6; fluphenazine, n = 4; hydroxyzine, n = 2; diphenhydramine, n = 1; lorazepam, n = 2; and haloperidol, n = 2.

Tolerability

Fifteen of the 24 enrolled subjects completed the protocol. Of those who were discontinued from the protocol, 5 were unable to tolerate the baseline testing, 2 withdrew, 1 was discharged from the hospital prior to completion of the protocol, and 1 was discontinued by the treating psychiatrist for reasons other than adverse reaction to donepezil (during placebo phase and prior to receiving donepezil). None of the subjects were terminated due to adverse events. For 3 patients there was a noted increase in "energy" and activity, as noted by ward staff, although this did not require discontinuation or change of their medications. Despite concerns over symptom exacerbation, the results strongly support the tolerability of donepezil at a dose of 5 mg/day even for severely ill patients recruited in this study.

Psychotic Symptoms

Of the subjects completing the protocol, 7 were assigned to the PD group and 8 were assigned to the DP group, making for a well-balanced group in terms of order of administration. There was no overall group effect, but there was a significant effect of time for the total PANSS ratings (repeated-measures ANOVA, $P < 0.02$), as depicted in Figure 2. The mean PANSS scores for both groups combined were 85 points at baseline, 79.7 points at T2/T3 ($\bar{x}$ = weeks 4 and 8), and 79.4 points at T4/T5 ($\bar{x}$ = weeks 12 and 16).

There was a strong trend for a time-by-group interaction for the total PANSS scores (Fig. 2). This was due to the different pattern of change over time for those receiving placebo, then donepezil (gradual improvement over time) compared with those receiving donepezil, then placebo (initial improvement, then worsening with placebo at the end of the trial). For the PD group, the average PANSS scores were 87.3 points at baseline, 80.3 points at T2/T3, and 77.1 points at T4/T5 (where T2/T3 is the average of time 2 and time 3 and T4/T5 is the average of time 4 and time 5). For the DP group, the average PANSS scores were 83 points at baseline, 79.2 points at T1/T2, and 81.4 points at T4/T5. Examining placebo versus donepezil on the PANSS, the overall mean scores among subjects were 83 points at baseline, 89.3 points at T2/T3, and 81.4 points at T4/T5 (Table 2).

TABLE 2. Measures Used to Assess Cognition and Psychiatric Symptoms

Measure	Purpose
PANSS	Measures the positive and negative symptoms of schizophrenia. Items are scored on an interval scale with lower numbers indicative of less symptoms and higher numbers representing more severe symptoms.
RAVLT	This is a verbal learning and recall task that requires participants to use short-term memory. Subjects are presented a series of words and are then asked, after a distraction task, to recall the words from the list.
Trails A	Processing speed is tested by asking participants to draw lines that connect numbers in a sequence.
Trails B	Executive functioning is tested by asking participants to draw lines from numbers to letters in a specific sequence.

Neurocognitive Testing

RAVLT

The overall mean score on the RAVLT (Fig. 3) was 20 points at baseline, 25 points at T2/T3, and 27 points at T4/T5 for the groups combined (PD and DP together). For the PD

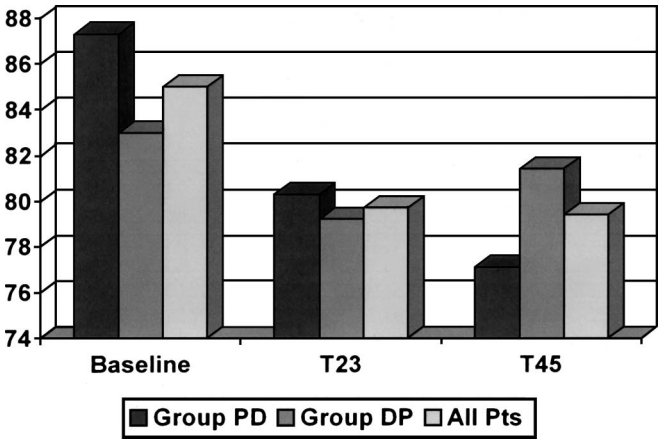

FIGURE 2. Total Positive and Negative Syndrome Scale (PANSS) scores by Group and Time. Means for baseline. Time 2/3 testing, and time 4/5 testing are shown for patients receiving placebo first (Group PD) and those receiving donepezil first (Group DP). As seen in all patients, a significant overall Time effect is shown. The pattern of change over time differed for the PD and DP group suggesting greater improvement during the donepezil treatment period compared to placebo period. This resulted in a strong trend for a Group by Time interaction (repeated measures ANOVA, $P < .10$ two tailed).

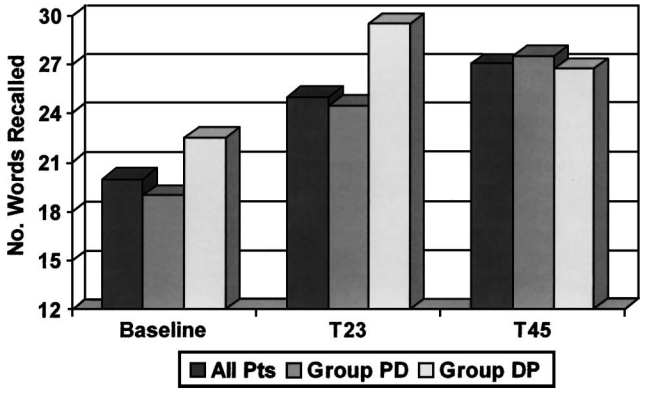

FIGURE 3. Total number of words recalled on the Rey Verbal Learning Test (VAVLT) by Time and Group. Means for baseline. Time 2/3 testing, and time 4/5 testing are shown for all patients, patients receiving placebo first (Group PD) and those receiving donepezil first (Group DP). A significant overall Time effect is shown across groups, with greater overall word recall over time ($P < .01$). However the pattern of change over time differed for the PD and DP groups, suggesting greater improvement during the donepezil treatment period compared to placebo period. This resulted in a significant Group by Time Interaction (repeated measures ANOVA, $P < .02$ two tailed).

group (placebo to donepezil), the average RAVLT scores were 19 points at baseline, with improvement to 25 points at T2/T3, and continued improvement to 28 points at T4/T5. Conversely, for the DP group (donepezil to placebo), the average RAVLT scores were 23 points at baseline, with a marked increase to 30 points at T1/T2, and a modest reduction to 27 points at T4/T5. This resulted in a significant time effect across groups ($P < 0.01$), as seen with the PANSS scores, no overall group effect, but a significant group-by-time effect period the differing pattern for the groups during the study period (group by time, $P < 0.02$).

Trails A

The mean average score for both groups on Trails A was 54 seconds at baseline, 55 seconds at T2/T3, and 44 seconds at T4/T5. The PD group had poorer scores initially: 64 seconds at baseline, 57 seconds at T2/T3, and 51 seconds at T4/T5, which was consistent with concurrent higher PANSS scores. The DP group scores were 43 seconds at baseline, 47 seconds at T2/T3, and 37 seconds at T4/T5. For both groups, there was little evidence for the superiority of donepezil over placebo.

Trails B

There was no baseline difference between groups, in contrast to the PANSS and Trails A data. The mean time to complete the test for both groups on Trails B was 136 seconds at baseline, 131 seconds at T2/T3, and 115 seconds at T4/T5. The mean completion time for the PD group was 135 seconds at baseline, 152 seconds at T2/T3, and 131 seconds at T4/T5. The DP group mean times were 137 seconds at baseline, 111 seconds at T2/T3, and 99 seconds at T4/T5. Overall, there was a modest trend toward improvement over time ($P = 0.09$, 2-tailed), but there was no significant group difference that favored donepezil.

DISCUSSION

This study examined the treatment efficacy of adjunctive donepezil therapy for the treatment of psychiatric symptoms and cognitive dysfunction in schizophrenic patients. Despite the small sample size and the use of a low dosage of donepezil, findings were consistent with previous studies showing donepezil to have a beneficial effect in reducing psychiatric symptoms and enhancing cognitive functioning. In addition, the improvement of cognitive dysfunction seen in this study appeared more rapidly than those seen in Alzheimer disease,[32,36] which may suggest a distinct effect of donepezil in patients with schizophrenia compared with those with dementia. Although the use of donepezil in Alzheimer disease is believed to improve symptoms by slowing the cognitive decline associated with this neurodegenerative disorder, donepezil may have a direct effect in improving cognitive abilities.

In the current study there was a trend for PANSS improvement on donepezil and a modestly significant finding of improvement in cognition as revealed on the RAVLT. A possible explanation of this phenomenon is the emerging evidence suggesting a neural substrate linking deregulation of mesolimbic dopaminergic transmission. Some have suggested a connection of D2 dopaminergic superiority c-mediated accumbens transmission regulating cortical acetylcholine release and a decrement in the number and/or function of striatal cholinergic interneurons in patients with schizophrenia.[43,44]

Current research indicates that the severity and persistence of negative symptoms and neurocognitive deficits are highly correlated with long-term prognosis in schizophrenia.[2–5] Although blockage of D2 receptors remains the primary pharmacologic approach for the treatment of schizophrenia, current research suggests that treatments that affect other neurotransmitters may promote cognitive improvement. The current study provides support for the usage of donepezil for cognitive enhancement in schizophrenia, particularly in the area of verbal memory. With neurocognitive deficits being the most intractable symptom of schizophrenia, even modest improvements in this area may have a profound influence on overall functioning and psychiatric stabilization. The specific improvement in verbal memory is notably due to its link with level of skill acquisition in occupational and social rehabilitation.[3]

Given the vital role that acetylcholine plays in basic brain functioning and, in particular, on cognition, it is possible that further research will demonstrate that acetylcholine augmentation leads to improvement in social and vocational skills in individuals with acetylcholine deficits. Current research suggests that there is a compelling link between cognition in schizophrenia and acetylcholine deficiency.[45] Although impaired cognition and negative symptoms are likely the result of multiple factors and are indicative of a fundamental disruption of cortical processes, this study adds to the growing body of research that implies that acetylcholine augmentation is useful in the treatment of impaired cognition in schizophrenia.

The limitations of this study include the relatively small sample size and the fact that all subjects were current inpatients in a state psychiatric hospital, which suggests that the sample constituted individuals with a severe form of schizophrenia, with some or all within the treatment-refractory subgroup of the disease. The dosage of donepezil was lower than previous studies for both patients with schizophrenia and dementia. This resulted in an extremely favorable side effect profile and low attrition rate due to side effects, but may have limited the effectiveness of the medication compared with a higher and commonly used dose (10 mg/day). Additionally, improvements on PANSS and RAVLT were modest, and further studies are needed to ascertain whether improvements would continue with prolonged administration of donepezil. Further studies with larger sample sizes and the inclusion of outpatients are warranted to explore further the usefulness of acetylcholine augmentation in schizophrenia. Moreover, these studies will help reconcile the contradicting results that investigators have arrived at using donepezil as an adjunctive treatment of schizophrenia.

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