# A Double Blind Placebo Controlled Trial of Donepezil Adjunctive Treatment to Risperidone for the Cognitive Impairment of Schizophrenia

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**Background:** *Despite the beneficial effects of atypical antipsychotics on cognition, these improvements will not return most schizophrenic patients to normative standards of cognitive functioning. Therefore, other treatments need to be considered. Subtle changes in cholinergic function in schizophrenic patients provide the rationale to test the effectiveness of cholinesterase inhibitors in treating cognitive impairment in schizophrenia.*

**Methods:** *Given this, a 12-week, double-blind, placebo-controlled trial of donepezil (5 mg and 10 mg) as adjunctive treatment to risperidone was conducted in a total of 36 schizophrenic patients.*

**Results:** *Neither the 5-mg nor 10-mg dose of donepezil produced significant improvements in any cognitive measure compared with placebo.*

**Conclusions:** *It is possible that nicotinic receptor desensitization produced by chronic tobacco use in these patients rendered their nicotinic receptors refractory to the effects of increased agonist activity produced by donepezil. An alternative treatment is the allosterically potentiating ligands, which enhance the activity of (sensitize) nicotinic receptors in the presence of acetylcholine.* Biol Psychiatry 2002;51:349–357 © *2002 Society of Biological Psychiatry*

**Key Words:** Schizophrenia, acetylcholine, cognitive, donepezil, clinical trial

## Introduction

On average, schizophrenic patients perform poorly in most domains of cognition (Saykin et al 1994). Therefore, the introduction of several new atypical antipsychotic medications over the last decade represents an advance in the treatment of schizophrenia given their reported superior effects on cognitive functioning compared with typical antipsychotics. To date, 24 published reports of 20 different studies indicate that clozapine, risperidone, olanzapine, quetiapine, ziprasidone, and aripiprazole have greater effects on cognitive functioning compared with treatment with typical antipsychotics (Harvey and Keefe 2001). While many of these studies report statistically significant effects, a statistically significant effect does not necessarily translate into a clinically meaningful effect. The weighted average of the improvement effects of atypical antipsychotics on cognitive functions determined by Harvey and Keefe (2001) demonstrate modest effects by atypicals (range = .13 – .39). When considering the severity of neuropsychological impairment in schizophrenic patients, these improvements will not return most patients to normative standards of cognitive functioning. For example, the weighted average improvement effect of atypical antipsychotics on secondary memory of .39 (Harvey and Keefe 2001) would, on average, only restore secondary memory to within one to two standard deviations of normative standards according to the severity of impairment observed by Saykin et al (1994). Therefore, other treatments need to be considered to address the continued problem of cognitive impairment in the face of atypical antipsychotic treatment.

While dopamine (DA) has been regarded as the key neurotransmitter involved in the pathogenesis of schizophrenic symptoms (Davis et al 1991), there are a number of studies implicating a role of cholinergic neurons in schizophrenia. Although the obvious pathology of the cholinergic system as seen in Alzheimer's disease (e.g., decreased cell density in the nucleus basalis of Meynert) is absent from the brains of schizophrenic patients (el-Mallack et al 1991), a correlation has been found at post mortem examination between decreases in brain choline acetyltransferase levels and the severity of ante mortem cognitive impairments (Haroutunian et al in press; Karson et al 1996). Therefore, subtle changes in cholinergic function may contribute to the cognitive impairment associated with schizophrenia.

Patients with schizophrenia have deficits in episodic memory, a cognitive ability dependent upon normal hippocampal function. Moreover, significant reductions in

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hippocampal volume and function of schizophrenic patients have been identified by structural (Nelson et al 1998) and functional imaging. At the receptor level, muscarinic receptors, important to hippocampal functions such as learning and memory (Levey et al 1995; McAlonan et al 1995), are reduced in the brains of schizophrenic patients (Crook et al 2000). Therefore, these changes may contribute to the memory impairments associated with schizophrenia. Indeed, the administration of the muscarinic antagonists scopolamine or atropine induces memory impairments in animal models and healthy humans (Blozovski et al 1977; Aigner et al 1986; Drachman 1977) similar to the memory impairments of schizophrenia. This drug-induced impairment is subsequently reversed by the administration of acetylcholinesterase inhibitors (Nielsen et al 1989; Wanibuchi et al 1994; Rupniak et al 1997).

A role for muscarinic receptors in the processes of attention has also been demonstrated. For example, impaired performance of rats on the five-choice serial reaction task is observed following basal forebrain lesions (Robbins et al 1989). Furthermore, both the systemic administration of physostigmine and the transplant of cholinergic embryonic cells into the brains of rats with basal forebrain lesions improve the visual attentional impairments (Muir et al 1992). In addition, continuous intraventricular injections of scopolamine during a continuous performance task impair the performance of monkeys (Callahan et al 1993).

Alterations in nicotinic cholinergic receptor function may also contribute to the cognitive impairment of schizophrenia. Nicotinic receptor stimulation can increase arousal, improve attention, and influence a number of cognitive functions. In addition, nicotinic receptor stimulation transiently normalizes sensory gating deficits (Adler et al 1993) and dysfunctional smooth eye pursuit movements (Klein and Anderson 1991) in schizophrenic patients. Sensory motor gating is a hippocampal phenomenon which manifests itself in the schizophrenic symptomatology as an inability to attend appropriately to sensory stimuli and, therefore, may impact greatly on cognitive performance.

Schizophrenic patients have been shown to have a reduced number of nicotinic receptors, especially in the hippocampus (Freedman et al 1995; Leonard et al 1996). Furthermore, pharmacological studies show that treatment with high affinity nicotinic receptor antagonists blocks habituation of auditory-evoked responses (Luntz-Leybman et al 1992). Moreover, nicotine self administration through cigarette smoking has been shown to diminish this impairment in schizophrenic patients (Adler et al 1993).

Given these data, it is reasonable to speculate that increasing cholinergic activity at muscarinic and nicotinic receptors may alleviate some of the cognitive impairment associated with schizophrenia. Treatment with a cholinesterase inhibitor is an effective means of stimulating nicotinic and muscarinic receptor activity, since inhibition of acetylcholinesterase increases the synaptic level of the natural agonist acetylcholine (ACh). Newer generation drugs such as donepezil have pharmacological and pharmacokinetic advantages over drugs such as tacrine that permit easier administration and reduce the adverse effect profile. Donepezil is a mixed inhibitor of acetylcholinesterase exhibiting primarily noncompetitive, but also some competitive, inhibition of this enzyme (Nochi et al 1995). Donepezil selectively inhibits acetylcholinesterase rather than butylcholinesterase, producing a more favorable side effect profile than Tacrine (Sugimoto et al 1992). Its long half life (70 hours) supports once-daily administration (Rogers et al 1998a). Given this, donepezil appeared to be the optimal choice of acetylcholinesterase inhibitor to use as an adjunct to antipsychotic treatment to target the cognitive impairment of schizophrenia. Donepezil has proven effective in treating the cognitive symptoms of patients with mild to moderate Alzheimer's disease (AD) (Rogers et al 1998b; 1998c), but to date has not been studied as a treatment of cognitive symptoms of schizophrenia. Therefore, we aimed to determine if donepezil added to the atypical antipsychotic risperidone in schizophrenic patients would improve secondary memory and attention compared with placebo.

## Methods and Materials

### *Subjects*

Subjects were recruited from both inpatient and outpatient departments at Mount Sinai Hospital, New York, NY; Pilgrim Psychiatric Center, Brentwood, NY; Bronx Veterans Hospital, Bronx, NY; and Montrose Veterans Hospital, Montrose, NY. All participants met DSM-IV diagnostic criteria for schizophrenia utilizing the Comprehensive Assessment of Symptoms and History (CASH) structured interview (Andreasen et al 1992). 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 4 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 1991). The minimum level of cognitive impairment required for participation was performance on learning trials 1–5 on the California Verbal Learning Test (CVLT) (Delis et al 1987) that was two or more standard deviations below normative standards. This CVLT cutoff was chosen because it is consistent with the average level of impairment of secondary memory observed in schizophrenic patients (Saykin et al 1994), and this type of adjunctive treatment would only be justified in patients with demonstrable cognitive impairment. 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. Benzodiazepine use was limited to medium- or short-acting preparations and was held for 24 hours before cognitive testing. All patients provided written informed consent in accordance with the procedures outlined by the local institutional review boards of all participating facilities before participation in the study.

### *Assessments*

The PANSS (Kay 1991) was used weekly to assess the severity of psychiatric symptoms, and the Extrapyramidal Symptom Rating Scale (ESRS) (Chouinard et al 1979) was used to assess the severity of extrapyramidal symptoms. The cognitive assessment battery included measures of attention, working memory, and executive function: Simple Spatial Working Memory Test (McGurk et al submitted), Continuous Performance Test (CPT)-computerized (Cornblatt et al 1989), Trail Making Tests Parts A & B (TMTA and B) (Spreen and Straus 1998), and Wisconsin Card Sorting Test (WCST) (Grant and Berg 1948). In addition, measures of serial verbal learning and delayed recall (Rey Auditory Verbal Learning Test [RAVLT]) (Spreen and Strauss 1998), selective attention Digit Span Distraction Test (DSPT) (Green et al 1997), and verbal productivity (Verbal Fluency) (Spreen and Strauss 1998) were used. The Simple Spatial Working Memory Test (SSWMT) was developed at the Diagnostic and Psychopathology Unit at University of California, Los Angeles (UCLA) (McGurk et al submitted). This test measures spatial working memory using a computerized delayed response paradigm. The dependent measure is the number of targets correctly identified at each delay. The Continuous Performance Tests (CPT) is a commonly used test of vigilance. In the identical pairs version of this test (CPT450), subjects are asked to press a computer response key whenever the same four-digit target stimulus appears twice in a row. The Trail Making Tests Part A & B are tests of visuo-motor speed and the ability to set shift. A computerized version of the WCST was used in this protocol (WCST-CV2, PAR Software Inc.). The WCST measures the ability to form abstract concepts, shift, and maintain the set. The RAVLT is a test of immediate memory span, new learning, susceptibility to interference, and delayed memory (Spreen and Strauss 1998). The test contains 15 target words (List A) which are read aloud in five separate learning trials, with each trial followed by a free-recall test and a 20-min delayed recall of List A. The dependent measures include indices of concentration measured by word span (trial 1 performance), cumulative practice-related learning (total learning across the five learning trials), and delayed recall savings (trial 5 performance minus delayed recall). The Digit Span Distraction Test is a commonly used test of memory span and distraction. There are two conditions in this test: distraction and nondistraction. Verbal fluency tests measure verbal productivity and the intactness of the lexical system. In this protocol, the category fluency test was administered.

### *Study Design*

Following baseline assessments, subjects entered a 12-week, double-blind, parallel-design treatment phase. Subjects were randomized in a 1:1 fashion to receive treatment with 5 mg of donepezil or placebo daily in addition to risperidone treatment for a 4-week period. Following this, the cognitive assessment battery was repeated. Subsequently, half of the group receiving donepezil had their dose increased to 10 mg per day, while the other half remained at the 5-mg daily dose. This treatment continued for another 8 weeks until a total of 12 weeks of treatment had been achieved, after which the cognitive assessment battery was repeated. Therefore, 50% of subjects received placebo and 25% received donepezil 5 mg daily for the entire 12 weeks, while 25% were to be treated with donepezil 10 mg daily for the last 8 weeks of the study.

### *Analyses*

Baseline comparisons between groups were performed using *t* tests for continuous variables and chi square for categorical variables. The comparative efficacy of donepezil to placebo was examined in the fully evaluable population and the intent to treat (ITT). The fully evaluable population was defined as all patients who completed 12 weeks of double-blind treatment without significant protocol violations. The intent to treat analysis included all subjects who completed baseline assessments, received at least one dose of study drug, and provided a minimum of one post-baseline data point. Comparative efficacy was analyzed with analysis of variance (ANOVA) to examine the interaction between treatment (placebo, donepezil 5 mg, donepezil 10 mg) over time (baseline, week 4, week 12) on cognitive performance. The primary outcome measures included total words learned and delayed recall after 20 min on the RAVLT and signal detection index (d-prime) from the CPT. The alpha significance for these tests was set to a level of .05.

## Results

Thirty-six subjects entered the study and 36 were randomized to study drug (18 placebo, 18 donepezil). Ten subjects were randomized to receive 5 mg/day of donepezil for the entire 12 weeks, while 8 patients had their dose of donepezil increased to 10 mg per day for the last 8 weeks of the study. Thirty-four subjects completed the entire protocol. Two subjects in the donepezil 10 mg group terminated early from the study shortly after the dose increase due to increased agitation and uncooperativeness with study procedures, but both were able to complete midpoint (week 4) cognitive assessments. No other significant adverse effects occurred following randomization.

Demographic data and baseline symptom and cognitive data are shown in Table 1. The mean age of evaluable

patients in the placebo versus donepezil group was 48.8 ± 11.1 and 50.3 ± 10.1 years; mean duration of illness was 25.9 ± 13.9 and 26.9 ± 9.6; and the mean daily dose of risperidone was 6.4 mg and 5.9 mg, respectively. The donepezil group did not differ significantly at baseline on any demographic, clinical, or cognitive variables. Finally, it is important to note that at baseline, both groups performed almost 3½ standard deviations below normative standards on total learning trials from the CVLT, indicating severe levels of cognitive impairment for this study sample.

Since the ITT analyses and analyses of the fully evaluable population were essentially the same, further discussion of these results will report the more conservative ITT analyses. Comparison of the change in total word list learning from the RAVLT from baseline to week 12 using last observation carried forward revealed no significant improvement with either the donepezil 5 mg or 10 mg dose compared with placebo (5.2 ± 7.7 vs. 6.5 ± 8.8 vs. 7.4 ± 12, F = .37, df = 102, $p$ = .69) (Figure 1). Furthermore, there were no significantly greater improvements with either the 5 mg or 10 mg dose of donepezil compared with placebo on the delayed recall from the RAVLT (1.3 ± 2.3 vs. 1.5 ± 2.6 vs. 1.6 ± 4.4, F = .46, df = 31, $p$ = .5) (Figure 2) and on the signal detection index from the CPT (.13 ± .64 vs. .42 ± .57 vs. .03 ± .46, F = .57, df = 22, $p$ = .46) (Figure 3). Since it is possible that this trial was underpowered to detect smaller effects, effect sizes were calculated for each measure and are shown in Table 2. Effect sizes on total word list learning and delayed recall from the RAVLT were similar for donepezil and placebo treatment (Table 2). To detect significant differences between placebo and donepezil, 10 mg treatment conditions on total learning and delayed recall at an $\alpha < .05$ and with .80 power samples sizes of 1509 and 12,504, respectively, would be required; however, a significant difference in change on the CPT signal detection between placebo and the 10-mg donepezil treatment condition would be detected with a sample size of 14 in each group.

Given some evidence from the literature suggesting a possible effect of cholinomimetic treatment on schizophrenic symptomatology (Edelstein et al 1981) and on extrapyramidal symptoms (Caroff et al 2001), exploratory analyses were performed to examine the effects of donepezil on these symptom domains. Change in PANSS positive (F = 1.74, df = 101, $p$ = .18) and negative symptoms (F = .38, df = 100, $p$ = .68) did not differ

Table 1. Baseline Demographic, Clinical, and Cognitive Data for Subjects

| | Mean (SD) | | | |
|---|---|---|---|---|
| | Placebo ($n$ = 18) | Donepezil ($n$ = 18) | $t$ | $p$ |
| Age | 48.8 (11.1) | 50.3 (10.1) | .41 | .69 |
| Education | 11.9 (1.3) | 12.1 (1.6) | .24 | .82 |
| Illness duration (years) | 25.9 (13.9) | 26.9 (9.6) | .24 | .82 |
| Daily risperidone dose | 6.4 | 5.9 | | |
| WRAT-R reading score | 57.9 (13.5) | 58.6 (11.1) | .16 | .87 |
| CVLT total learning $t$ score | 16.2 (10.7) | 17.9 (10.9) | .48 | .63 |
| PANSS positive scale score | 16.8 | 16.6 | .13 | .54 |
| PANSS negative scale score | 19.4 | 20.8 | .58 | .91 |
| | | | $\chi^2$ | $p$ |
| Ethnicity | | | | |
| White | 65% | 55% | .31 | .58 |
| Black | 29% | 45% | | |
| Hispanic | 5% | 0% | | |
| Gender | | | | |
| % male | 89% | 89% | 0 | 1 |
| % female | 11% | 11% | | |

WRAT-R, Wide Range Achievement Test-Revised; CVLT, California Verbal Learning Test; PANSS, Positive and Negative Syndrome Scale.

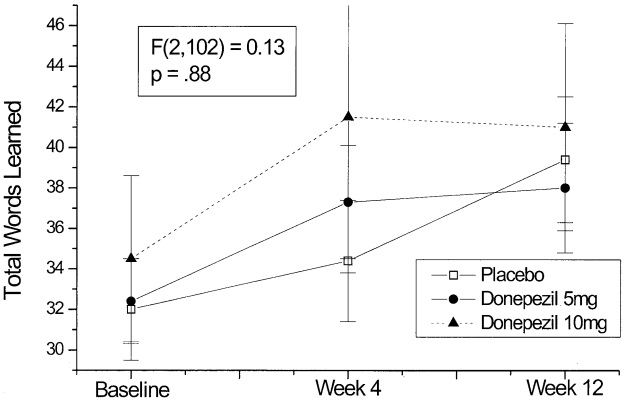


Figure 1. Effect of donepezil on serial verbal learning performance from the Rey Auditory Verbal Learning Test (RAVLT). Error bars represent standard error of the mean.

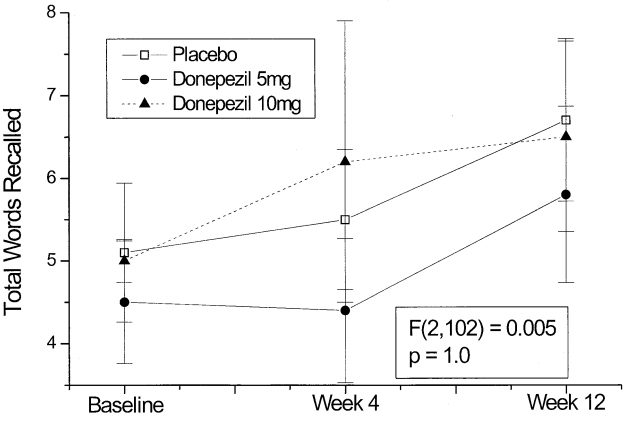


Figure 2. Effect of donepezil on delayed recall performance from the Rey Auditory Verbal Learning Test (RAVLT). Error bars represent standard error of the mean.

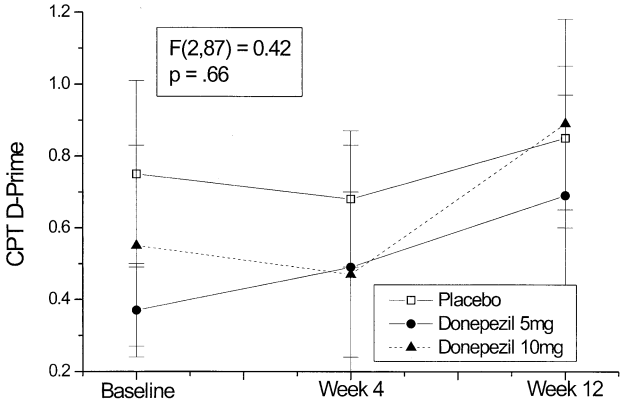


Figure 3. Effect of donepezil on signal detection index from the Continuous Performance Test (CPT). Error bars represent standard error of the mean.

between either donepezil 5 mg or 10 mg and placebo treatment conditions. Moreover, ESRS ratings of change in parkinsonism (F = .51, df = 101, $p$ = .6) and dyskinesia severity (F = .01, df = 101, $p$ = .99) also did not differ significantly between either donepezil dose and placebo treatment. No other significant differences were seen in any other outcome measure (summarized in Table 2).

## Discussion

The primary efficacy hypothesis for donepezil as adjunctive treatment to risperidone for cognitive impairment in schizophrenia was not supported by the data from this study. Indeed, the change in performance on measures of serial verbal learning, delayed recall, and vigilance associated with donepezil treatment was not significantly different from placebo. Nonetheless, there appeared to be an increasing effect on vigilance (measured by the CPT) with an increasing dose of donepezil (Table 2). Power calculations provide some rationale for future studies with the 10 mg dose of donepezil using a larger sample size; however, a possible effect on this one particular cognitive measure has questionable implications for overall functional outcome.

While two patients left the study shortly after an increase to 10 mg of donepezil because of increased agitation and uncooperativeness, it is unclear if this is an important signal given the lack of statistically significant changes for the whole group on these items from the PANSS. There are no prior reports of schizophrenic patients receiving this dose of donepezil, and Alzheimer's patients have, in contrast, demonstrated a transient improvement in behavioral dysregulation with 10 mg of donepezil (Weiner et al 2000). Finally, comparison of the donepezil treatment groups and placebo failed to produce any significant differences on any of the other cognitive, symptom, or movement disorder measures.

In contrast, donepezil was shown to improve cognition and increase activation of the prefrontal cortex and basal ganglia on functional magnetic resonance imaging in a single patient with schizoaffective disorder (Risch et al 2001); however, the Risch et al study (2001) reported on a single case, whereas the study reported here evaluated a much larger sample size. In addition, the subject in the Risch et al study (2001) did not experience the same level of severity of impairment as our subjects given that this subject performed in the average range at baseline for

Table 2. Comparison of Change Scores from Baseline to Week 12 and Effect Sizes of Symptom, Movement Disorder, and Cognitive Assessments

| | Mean Change Score | | | Effect Size | | | | |
|---|---|---|---|---|---|---|---|---|
| Change Score Item | Placebo ($n$ = 18) | Donepezil 5 mg ($n$ = 10) | Donepezil 10 mg ($n$ = 8) | Placebo ($n$ = 18) | Donepezil 5 mg ($n$ = 10) | Donepezil 10 mg ($n$ = 8) | F | $p$ |
| PANSS positive total score | −.89 | −1.67 | .40 | .14 | .28 | .06 | .51 | .61 |
| PANSS negative total score | 1.0 | .09 | −1.60 | .15 | .01 | .22 | .64 | .53 |
| ESRS total Parkinsonism score | −.41 | 2.67 | −.17 | .07 | .42 | .02 | .84 | .44 |
| ESRS total dyskinesia score | −.71 | .58 | −.17 | .38 | .08 | .02 | .31 | .74 |
| RAVLT total learning trials 1–5 | 7.39 | 5.17 | 6.5 | .71 | .70 | .65 | .16 | .85 |
| RAVLT delayed recall | 1.61 | 1.25 | 1.5 | .45 | .48 | 2.08 | .04 | .96 |
| Spatial working memory 15 sec delay | .29 | −.36 | 2.17 | .06 | .06 | .35 | 1.5 | .24 |
| CPT d-prime | .03 | .13 | .42 | .03 | .33 | .70 | .14 | .87 |
| Trail making part A (sec) | −2.0 | 17.58 | .80 | .16 | .24 | .05 | .93 | .40 |
| Trail making part B (sec) | −11.12 | −20.08 | −2.40 | .21 | .20 | .03 | .23 | .80 |
| Verbal fluency | 1.06 | −1.67 | −1.67 | .17 | .42 | .52 | .35 | .71 |
| Digit span distraction (non-distraction) | 1.39 | −2.27 | −1.00 | .16 | .47 | .35 | 1.85 | .17 |
| Digit span distraction (distraction) | .56 | −2.91 | −1.67 | .08 | .43 | .30 | 1.99 | .15 |
| Wisconsin card sort (total categories) | −.18 | −.08 | −.17 | .09 | .04 | .06 | .02 | .98 |

PANSS, Positive and Negative Syndrome Scale; ESRS, Extrapyramidal Symptom Rating Scale; RAVLT, Ray Auditory Verbal Learning Test; CPT, Continuous Performance Tests.

most cognitive areas assessed. Although improvement was noted in several cognitive domains during active treatment, improvement continued in many of these domains, even during placebo treatment. Therefore, the improvement in cognitive test performance may have been a practice effect instead of a drug effect.

The negative results of our study may be related to the baseline characteristics of our subjects and/or the method of cholinergic enhancement chosen. Baseline levels of cognitive impairment were quite severe in these patients as baseline performance on the CVLT was, on average, almost 3 ½ standard deviations below age- and education-matched normative standards. Indeed, this level of impairment is more severe than the reported average of memory deficits from previous studies of the neuropsychological profile of schizophrenic patients (Aleman et al 1999). Perhaps, neuronal changes associated with the severe impairment observed in these patients makes them unresponsive to treatment with a cholinesterase inhibitor, raising the possibility that schizophrenic patients with less severe impairments may have responded; however, no improvement in serial verbal learning performance and nonsignificant changes on a spatial working memory test were observed in schizotypal patients after IV infusion of physostigmine (Kirrane et al 2001). Schizotypal personality disorder is a disorder of the schizophrenia spectrum, similar to schizophrenia in its biology and neuropsychological impairments (though much less severe than the patients from our study) (Siever et al 1993). Given this, the results of the Kirrane et al study (2001) support the conclusion of our study that cholinesterase inhibitor treatment is ineffective for the cognitive impairment of schizophrenia.

The decision to test a cholinesterase inhibitor as a potential cognitive enhancer in schizophrenic patients was based on the assumption that reduced cholinergic activity contributed to the cognitive impairment of schizophrenia; however, the results of this study compel us to reformulate this hypothesis. Perhaps the nonspecific increase in acetylcholine activity at nicotinic and muscarinic receptors produced by cholinesterase inhibitor treatment does not specifically address the cholinergic alterations in schizophrenia, which contribute to its cognitive impairment. Indeed, cholinesterase inhibitors have proven effective in Alzheimer's disease, a disease with a well-established cortical cholinergic deficit; however, compared with AD patients, cortical cholinergic activity is not significantly diminished in schizophrenic patients (Haroutunian et al in press; Haroutunian et al 1994).

While animal and human studies have indicated that direct muscarinic receptor activation reduces psychotic symptoms (Bynmaster et al 1999; Bodick et al 1997), there is no such evidence that it would improve cognitive impairments in schizophrenia. Conversely, there is evidence supporting a possible direct role of nicotinic receptors in the cognitive impairment of schizophrenia. Nicotinic agonists have been shown to improve working memory and attention in schizophrenic patients (Levin and Rezvani 2000; Levin et al 1996). More specifically, schizophrenic patients have a reduced number of the $\alpha_7$ subtype of nicotinic receptors in the hippocampus (Freedman et al 1995; Adler et al 1998) and there is substantial data indicating genetic linkage to the region containing the $\alpha_7$ nicotinic receptor (Freedman et al 1997; Riley et al 2000). Moreover, nicotine self administration by schizophrenic patients reverses sensory gating and eye tracking deficits which has been attributed to defects in the $\alpha_7$ nicotinic receptor (Adler et al 1993; Freedman et al 1997; Olney et al 1998).

During chronic tobacco use, nicotinic receptors accumulate in deep states of desensitization (Fenster et al 1999; Benwell et al 1995; Reitsletter et al 1999). Moreover, schizophrenic patients who smoke demonstrate a blunted response of the nicotinic receptor upregulation seen in healthy smokers in the hippocampus, cortex, and caudate (Breese et al 2000). Chronic desensitization may uncouple regulatory mechanism important for proper nicotinic receptor functioning and promote incorrect recycling of receptors. Desensitized nicotinic receptor channels are closed and refractory to agonist activation. The $\alpha_7$ receptor shows very rapid desensitization, which is relevant to the current discussion given that $\alpha_7$ containing nicotinic receptors mediate the predominant nicotinic current in hippocampal neurons (Frazier et al 1998; Zarei et al 1999) and is involved in the attentional and cognitive deficits associated with schizophrenia (e.g., sensory gating deficits). Since 78% of the subjects in our study were smokers and we did not control for cigarette smoking, it is difficult to understand the interaction between smoking and donepezil treatment; however, given that the vast majority of schizophrenics are regular smokers (Hughes et al 1986), this would not be practical.

An alternative to a pure cholinesterase inhibitor such as donepezil should be considered given that desensitized nicotinic receptors in schizophrenic patients may be unresponsive to increased ACh activity produced by cholinesterase inhibitors. Even direct-acting nicotinic agonists may cause desensitization rather than increased activation of nicotinic receptors (Maelicke et al 1996); however, nicotinic cholinergic therapy may still be feasible with the class of compounds referred to as allosterically potentiating ligands (APLs) (Maelicke et al 2001). Allosterically potentiating ligands interact with the nicotinic receptor at binding sites separate from that for ACh and nicotinic agonists and act specifically to enhance the activity (sensitize) nicotinic receptors in the presence of ACh

(Maelicke et al 2001). Two examples of APLs are physostigmine and galantamine (Schrattenholz et al 1996; Maelicke et al 1995), which act as both cholinesterase inhibitor and nicotinic receptor modulator. This modulation produces more effect from ACh in addition to the increase in synaptic ACh. Moreover, APLs such as galantamine seem to produce a greater allosteric sensitization of the $\alpha_7$ compared with the $\alpha_7\beta_2$ subtype of nicotinic receptor, which may be particularly beneficial in the treatment of cognitive impairment in schizophrenia.

Since $\alpha_7$ nicotinic receptors are located not only on cholinergic terminals, but also on the terminals of noncholinergic neurons (Alkondon et al 1996), the $\alpha_7$ nicotinic receptors enhances ACh release as well as the release of glutamate, serotonin, and other neurotransmitters (Alkondon et al 1996). Therefore, the nicotinic modulating action of APLs will lead to release of these other neurotransmitters throughout the brain. The possibility that deficiencies of such neurotransmitters would be restored by APLs and could lead to improvement in cognitive functions modulated not only by ACh, but also by these other neurotransmitters, is a provocative possibility that warrants further investigation; however, enthusiasm for the application of APLs to schizophrenia should be tempered by previous experience with the APL physostigmine, which did not improve schizophrenic symptoms (Davis et al 1978; Modestin et al 1973). Furthermore, if one is looking to treat the cognitive impairments of schizophrenia, it might be better to focus on treatments which directly address deficits in neurotransmitters found at autopsy (e.g., DA, NE, 5 HT) (Powchik et al 1998; Bridge et al 1985).

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