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No effect of donepezil on neurocognition and social cognition in young persons with stable schizophrenia

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Introduction. Cognitive dysfunction is common in schizophrenia and linked with psychosocial dysfunction. We examined the possible effect of a 16-week trial of donepezil on cognition in young persons with stable schizophrenia.
Method. Twenty-six outpatients who met criteria for age, duration of illness, clinical stability, and medications were randomly assigned to 16-week treatment with donepezil or placebo using a double blind design. At beginning and conclusion of the trial, participants completed standardised computerised assessment of neurocognition and social cognition. Symptomatology and functioning were assessed using standard rating scales for negative and positive symptoms, depression and mania, and quality of life.
Results. No treatment effects were found on any cognitive functions or clinical symptoms in placebo or donepezil groups.
Conclusion. Similar to other studies using acetylcholinesterase inhibitors in more heterogeneous and symptomatic groups of patients with schizophrenia, donepezil does not appear to enhance cognitive abilities. Persistent cognitive impairment in schizophrenia with pervasive effects on psychosocial functioning and outcome, urge the search for agents that may offer improvement.

INTRODUCTION

In schizophrenia, neurocognitive dysfunction is present at first onset of illness and shows a similar profile compared to persons with chronic schizophrenia (Bilder et al., 1991; Gold, Arndt, Nopoulos, O'Leary, & Andreasen, 1999; Hoff et al., 1999; Kurtz, 2005; Saykin et al., 1994). Cognitive dysfunction may improve with first (Braff & Saccuzzo, 1982) and second generation antipsychotics (Harvey & Keefe, 2001), however,

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significant dysfunction may remain despite adequate antipsychotic treatment (Censits, Ragland, Gur, & Gur, 1997; Purdon et al., 2001). Similar to neurocognition, social cognition is impaired at first onset of psychosis (Edwards, Pattison, Jackson, & Wales, 2001) and may not improve with stabilisation of symptoms (Herbener, Hill, Marvin, & Sweeney, 2005). Attempts to improve cognition by modulation of serotonergic (Friedman et al., 2005; Sumiyoshi et al., 2001), noradrenergic (Friedman et al., 2001), and NMDA (Evins, Fitzgerald, Wine, Rosselli, & Goff, 2000) pathways have shown variable results. Such findings may have been limited by nonspecific effects of medications and, possibly, patient characteristics. In persons with schizophrenia, neurocognition and social cognition, independent of psychosis, show considerable association with functional outcome and prognosis (Bowie, Reichenberg, Patterson, Heaton, & Harvey, 2006; Green, 1996).

For persons with Alzheimer disease, which is characterised by progressive cognitive dysfunction, especially memory, treatment with acetylcholinesterase inhibitors has been shown to improve cognition and slow cognitive decline. Over the past decade, several therapeutic agents have become available and, based on efficacy and favorable side effect profile, donepezil has become widely used. In mild to moderate Alzheimer disease, 12-week (Rogers, Doody, Mohs, & Friedhoff, 1998) and 24-week (Rogers, Farlow, Doody, Mohs, & Friedhoff, 1998) placebo controlled trials with donepezil reported improved cognition and functioning with few side effects.

In schizophrenia, cholinergic dysfunction, involving both muscarinic and nicotinic receptors, may underlie abnormal brain processing (Adler, Hoffer, Wiser, & Freedman, 1993; Klein & Andersen, 1991) and cognitive impairment (Furey, Pietrini, Alexander, Schapiro, & Horwitz, 2000; Hasselmo & Bower, 1993). Recent efforts have examined donepezil as an adjunctive treatment of cognitive dysfunction, positive and negative symptoms (Buchanan, Summerfelt, Tek, & Gold, 2003; Stryjer et al., 2004), mood symptoms (Risch et al., 2005), and tardive dyskinesia (Tammenmaa, Sailas, McGrath, Soares-Weiser, & Wahlbeck, 2004). Several open-label trials reported beneficial effects of donepezil on cognition (Buchanan et al., 2003; Howard, Thornton, Altman, & Honer, 2002; MacEwan, Ehmann, Khanbhai, & Wrixon, 2001; Stryjer et al., 2003), but placebo-controlled trials generally failed to find such an effect (Freudenreich et al., 2005; Friedman et al., 2002; Mazeh, Zemishlani, Barak, Mirecki, & Paleacu, 2006; Stryjer et al., 2004; Tugal, Yazici, Anil Yagcioglu, & Gogus, 2004). A single trial in institutionalised persons with schizophrenia treated with olanzapine found improvements in psychotic symptoms and verbal learning (Erickson et al., 2005). The diverse results may have been influenced by acute psychotic symptoms and hospitalisation status (Erickson et al., 2005; Mazeh et al., 2006), wide age range (Erickson et al., 2005; Freudenreich et al., 2005) and older age (Mazeh et al., 2006), and treatment with first generation

(Tugal et al., 2004), combination with second generation antipsychotics (Freudenreich et al., 2005) or clozapine (Stryjer et al., 2003), which may not share the same effect on cognition as more recent antipsychotics.

While cognition impacts persons with schizophrenia irrespective of stage of illness, cognitive improvement may be most beneficial in younger people with short duration of illness and stable clinical symptoms. Improved cognition may eventually translate into functional progress involving socialisation, work, or school. To examine this possibility, we carefully selected a group of young to middle-aged persons with stable schizophrenia, based on age, duration of illness, clinical stability, and potentially confounding medications, and examined possible beneficial effects of a 16-week trial of donepezil on neurocognition and social cognition.

METHODS

Participants

Twenty-six outpatients (18 men, 8 women) were enrolled, who met DSM-IV criteria for schizophrenia ($n = 24$) or schizoaffective disorder ($n = 2$). There were 12 smokers and 14 nonsmokers. To limit possible confounding demographic and clinical effects on cognition, participants were between 18 and 40 years' old and illness duration was less than 10 years. Patients were clinically stable defined as: (1) living independently or with family, (2) no hospitalisations within the last 6 months, (3) no increase of antipsychotic medication within 3 months, and (4) Brief Psychiatric Rating Scale (BPRS) score of ≤ 35. All participants were treated with second-generation antipsychotics at standard daily dosages (olanzapine equivalents = 16.5 mg, $SD \pm 9.5$mg) (Kohler et al., 2003). To minimise possible adverse medication effects on cognition, participants were not treated with clozapine or anticholinergics. In addition, participants were not treated with anti-depressants, mood stabilisers, or benzodiazepines. All patients provided written consent to participate as mandated by the IRB at our institution.

Procedure

At baseline, patients completed standardised computerised neurocognitive assessment (Gur et al., 2001) that included selected tests of abstraction, attention, verbal and spatial memory, and spatial abilities. Assessment of social cognition included tests for emotion discrimination (Kohler, Bilker, Hagendoorn, Gur, & Gur, 2000) and differentiation (Silver, Shlomo, Turner, & Gur, 2002). Symptomatology and functioning were assessed at baseline and conclusion of trial, using standard rating scales for negative and

positive symptoms (Andreasen, 1984a, 1984b), depression (Hamilton, 1960), mania (Young, Biggs, Ziegler, & Meyer, 1978), general psychiatric symptoms, and quality of life (Heinrichs, Hanlon, & Carpenter, 1984).

Patients were randomly assigned to receive either donepezil or a placebo using a double blind design. Participants took one capsule for 4 weeks, then two capsules for 12 weeks. Donepezil dose was 5 mg per capsule. 22 patients completed the treatment trial, 11 (7 men, 4 women, mean age 31.73 years $\pm$ 8.04) in the donepezil group and 11 (9 men, 2 women, mean age 30.01 years ± 6.24) in the placebo group. Four subjects, two on donepezil and two on placebo, dropped out of the trial between Weeks 2 and 12. Reasons included stopping the medication for no specific reason ($n = 2$), agitation, and dizziness. At the conclusion of the trial, each patient completed the computerised battery a second time.

Data analysis

Test scores for neurocognition and social cognition were standardised (z-scores; mean = 0, standard deviation = 1), based on performance of all healthy participants in our database ($n = 144$, M:F = 75:69, average age = 31.10 years ± 13.15). The two cognitive batteries were combined into global summary outcomes by averaging each participant's z-scores on tests assessing the same functional domain (Censits et al., 1997; Saykin et al., 1991). Z-scores were compared between the treated and placebo groups at baseline and at follow-up using the Wilcoxon rank sum test. Linear regression analyses were used to compare changes over time in the z-scores by treatment group, adjusting for baseline z-scores. We also ran sensitivity analyses using median regression, which makes no distributional assumptions on the outcome, and found no substantive differences were found. Effect size measures (Cohen's d) were calculated to compare changes in neurocognition and social cognition by treatment group. Binary demographic measures (e.g., gender) were compared between the two treatment groups using the Pearson chi-square test or Fisher's exact test when cell counts were sparse. Continuous demographic measures were compared using the Wilcoxon rank sum test since some of the distributions were right-skewed. All analyses were performed using SAS Version 9.1 (SAS, 2004).

RESULTS

At baseline, placebo and donepezil groups showed similar neurocognitive performance, which ranged between $z = 0.37$ and $z = -1.84$, when compared to the healthy comparison sample (Table 1). The two groups also showed similar emotion discrimination and differentiation performance,

TABLE 1
Neurocognition

	Donepezil group (±SD)		*Placebo group (±SD)*		*Difference in change*	
	Before	*After*	*Before*	*After*	*Effect size*	*p-value*
Abstraction	−0.37 (1.46)	−0.22 (0.96)	−1.22 (1.51)	−0.46 (1.38)	−0.567	0.225
Attention	0.37 (0.31)	0.40 (0.25)	−0.17 (0.65)	−0.46 (1.40)	0.477	0.721
Verbal memory	−0.34 (0.93)	−0.85 (1.26)	−1.84 (1.94)	−2.36 (2.22)	0.018	0.820
Spatial memory	−0.64 (0.83)	−0.34 (0.87)	−1.28 (0.82)	−0.91 (1.08)	−0.098	0.974
Spatial abilities	−0.70 (1.05)	−0.89 (1.20)	−1.02 (1.44)	−1.13 (1.86)	−0.098	0.581

Values presented in average z-scores. z-scores are in comparison to performance by healthy control sample.

which ranged between $z = -0.73$ and $z = -1.70$ (Table 2). Clinical ratings at baseline revealed no differences between treatment groups in positive and negative symptoms of schizophrenia, general psychiatric symptoms, depressive and manic symptoms, and quality of life measurements.

At trial completion, placebo and donepezil groups showed similar neurocognitive performance, which ranged between $z = 0.40$ and $z = -2.36$. The groups also showed similar emotion discrimination and differentiation performance, which ranged between $z = -0.29$ and $z = -1.62$. Similarly, changes in neurocognition and social cognition between baseline and completion of trial and their calculated effect sizes did not differ between placebo and donepezil groups.

Clinical ratings at trial completion and changes between baseline and trial completion revealed no difference between groups.

CONCLUSIONS

This study examined the possible beneficial effect of donepezil, a widely used acetylcholinesterase inhibitor, on measures of neurocognition and social cognition in a small group of persons with schizophrenia, who were selected according to strict criteria regarding age, duration of illness, clinical stability, and concomitant medications. Our findings in patients who may benefit most from improved cognition is in line with negative results in studies involving more heterogeneous and symptomatic groups. Limitations of our study revolve around small group sizes, which could have lacked statistical power to detect differences. However, effect sizes were in the low to moderate range and indicate that a lack of benefit of donepezil may have been found in larger samples. In addition, patients were not limited to a specific second generation antipsychotic and their clinical stability was the result of naturalistic treatment.

TABLE 2
Social cognition

	Donepezil group (±SD)		*Placebo group (±SD)*		*Difference in change*	
	Before	*After*	*Before*	*After*	*Effect size*	*p-value*
Emotion discrimination	−0.87 (1.33)	−0.82 (1.21)	−1.08 (1.68)	−0.91 (1.42)	−0.152	0.726
Happy differentiation	−1.51 (1.33)	−1.62 (1.50)	−1.65 (0.86)	−1.46 (1.36)	−0.220	0.621
Sad differentiation	−1.61 (1.77)	−1.19 (1.80)	−1.65 (1.66)	−1.61 (1.73)	0.364	0.410

Values presented in average z-scores. z-scores are in comparison to performance by healthy control sample.

Positive or psychotic symptoms can respond well to antipsychotics. However, cognitive impairment and negative symptoms are reflections of a mesocortical hypodopaminergic state (Davis, Kahn, Ko, & Davidson, 1991) showing limited or modest response to antipsychotics (Arango, Buchanan, Kirkpatrick, & Carpenter, 2004; Keefe, Silva, Perkins, & Lieberman, 1999; Moller, 2003) or behavioural interventions (Hogarty et al., 2004; Kurtz, Moberg, Gur, & Gur, 2004). While other acetylcholinesterase inhibitors have not been studied to the extent of donepezil, trials using galantamine (Noren, Bjorner, Sonesson, & Eriksson, 2006) and rivastigmine (Sharma, Reed, Aasen, & Kumari, 2006) also failed to offer support for cognitive enhancement via cholinergic modulation in schizophrenia. Our small negative study will be available for future meta-analyses of donepezil in schizophrenia (Ferreri, Agbokou, & Gauthier, 2006).

Persistent cognitive impairment and negative symptoms in schizophrenia with pervasive effects on psychosocial functioning and outcome, urge the search for agents that may offer improvement. More selective modulation of related systems, involving dopamine (Arango et al., 2004; Sevy et al., 2005; Szeszko, Bilder, Dunlop, Walder, & Lieberman, 1999), NMDA (Millan, 2005), serotonin (Mitchell & Neumaier, 2005), and noradrenergic (Friedman, Stewart, & Gorman, 2004) pathways may ameliorate such deficits and their effects.

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