ORIGINAL ARTICLE

Cognitive effects with rivastigmine augmentation of risperidone: A 12-month, randomized, double-blind, placebo-controlled study in schizophrenia

Pattath Narayanan Suresh Kumar, Seema P. Mohemmedali[1], P. K. Anish[2], Chittaranjan Andrade[3]
Department of Psychiatry, KMCT Medical College, Calicut, [2]Department of Psychiatry, Institute of Mental Health and Neurosciences, Calicut, Kerala, [1]Department of Pharmacology, Government Medical College, Manjeri, Malappuram, [3]Department of Psychopharmacology, National Institute of Mental Health and Neurosciences, Bengaluru, Karnataka, India

ABSTRACT

Objective: An important challenge in schizophrenia therapeutics is to develop an efficacious treatment for cognitive impairment. Acetylcholinesterase inhibitors, such as rivastigmine, have been studied for improving cognitive performance in these patients.
Materials and Methods: Rivastigmine (uptitrated to 6 mg/day) was given as an add-on therapy to risperidone-treated stable schizophrenia patients in a randomized, double-blind, placebo-controlled design. Of 67 patients who met eligibility criteria, 55 were recruited into the study. Twenty-eight were assigned to rivastigmine and 27 to placebo. These patients completed tests of attention, executive functioning, verbal skills, verbal and visuospatial working memory, and psychomotor speed on five occasions: at baseline, and at the end of the 1st, 3rd, 6th, and 12th months.
Results: The groups were similar in terms of sociodemographic profile and baseline clinical characteristics (Positive and Negative Syndrome Scale and Clinical Global Impression-Severity). Contrary to expectations, rivastigmine patients showed poorer outcomes on several cognitive measures. Rivastigmine patients experienced also more psychological as well as neurological side effects. Core psychopathology ratings, however, did not differ between rivastigmine and placebo groups.
Conclusions: Our study does not support the long-term use of rivastigmine as an augmentation agent in schizophrenia. Rivastigmine may be associated with higher incidence of psychological and neurological side effects in patients with schizophrenia.

Key words: Cholinesterase inhibitors, cognitive dysfunction, randomized controlled trial, rivastigmine, schizophrenia

INTRODUCTION

Cognitive impairments in schizophrenia, particularly those affecting memory, have long been reported as a major factor interfering with prognosis and social reintegration.[1] Atypical antipsychotic drugs have been found superior to neuroleptic drugs in their effects on cognitive functioning.[2] Nevertheless, treated patients do not return to normal levels of cognitive functioning.[3]

Some studies suggest an abnormal cholinergic system with decrease in the number of muscarinic and nicotinic receptors, implicating a role for cholinergic neurons in the

Address for correspondence: Dr. Pattath Narayanan Suresh Kumar,
KMCT Medical College, Calicut, Kerala, India.
E-mail: drpnsuresh@gmail.com

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cognitive dysfunction associated with schizophrenia.[4-6] A correlation has been found at postmortem examination between decrease in brain choline acetyltransferase levels and the severity of antemortem cognitive impairments in schizophrenia.[7] 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). It is reasonable to speculate that increasing cholinergic activity at muscarinic and nicotinic receptors may alleviate some of the cognitive impairments associated with schizophrenia.

Rivastigmine is classified as an intermediate-acting or pseudo-reversible agent due to its long inhibition of AChE (up to 10 hours) relative to tacrine and donepezil, both of which are classified as short-acting or reversible agents (binding to AChE and hydrolyzed within minutes).[8] In Alzheimer's disease, rivastigmine has been found to improve daily activities, cognitive functioning and psychopathology, with effects occurring as early as 12 weeks.[9] Recent trials with rivastigmine showed improved cognitive performance in schizophrenia patients.[10-13]

There are reports of robust increase in the activation of brain regions associated with spatial attention and visual processing with adjunctive rivastigmine treatment in schizophrenia.[14,15] Negative results also have been reported.[16,17] The inconsistent results may be due to differences in the samples studied, in relation to variables like tobacco use (associated with nicotinic tolerance). Other explanations include differences in the tools used to evaluate cognition as well as relative nonspecificity of usual neuropsychological measures in relation to cognitive processes.

This study sought to determine whether rivastigmine augmentation of risperidone in patients with schizophrenia would improve secondary memory and attention relative to placebo.

MATERIALS AND METHODS

Setting

Patients were recruited from outpatient department of the hospital after getting approval from the Institutional Ethics Committee.

Patients

All participants met the Diagnostic and Statistical Manual of Mental Disorders-4th Edition (DSM-IV) diagnostic criteria for schizophrenia, based on the structured clinical interview schedule for DSM-IV Text Revision.[18] Patients aged 18–55 years who had been receiving a stable dose of risperidone as their primary antipsychotic treatment for at least the past 4 weeks were eligible for recruitment. Patients also needed to demonstrate symptom stability for a minimum period of 4 weeks, defined as no more than 20% change on the Positive and Negative Syndrome Scale (PANSS).[19] Patients with substance abuse (with nicotine, amphetamines, ecstasy, phencyclidine, cocaine, tetrahydrocannabinol, or alcohol), in the previous 6 months, those with other Axis 1 or Axis 3 diagnoses, those at suicidal risk, those with medical diagnoses, and those receiving medications that could affect cognitive performance were excluded from the study. The following psychotropic medications were not allowed for the duration of the study: anticholinergics, sedating antihistamines, antidepressants, mood stabilizers, or a second antipsychotic. Benzodiazepine use was limited to lorazepam and was withheld for 24 hours before cognitive testing. All patients provided written informed consent for participation in the study.

Experimental design

This study was a randomized, double-blind, placebo-controlled trial (randomized controlled trial [RCT]). Patients were randomly assigned to one of the following two groups for 12 months – rivastigmine plus risperidone or risperidone plus placebo group. Rivastigmine, available as 1.5 mg and 3 mg capsules, was dosed at 1.5 mg/day twice daily in the 1st month, 3 mg/day twice daily in the 2nd month, 4.5 mg/day twice daily in the 3rd month, and 6 mg/day thereafter. Placebo was dosed similarly using identical, starch-filled capsules. Patients who did not tolerate a particular dose were allowed to drop by one level in dosing. Ongoing treatment with risperidone was continued unchanged unless the clinical status required dose adjustment; this was permitted, as required. Lorazepam up to 2 mg was allowed as the only rescue medication for anxiety, agitation, or insomnia.

Clinical assessments

Cognitive functioning was assessed with digit-span test – digit forward and digit backward.[20] Digit-span task is used to measure working memory. Logical memory was assessed with Wechsler Memory Scale.[21] The Rey–Osterrieth complex figure test was used to assess visuospatial memory.[22] The Kohs block design test was used to assess visuospatial problem-solving skills,[23] and scoring was calculated based on the time in seconds to complete the given task (within 30 s - 4, 31–60 s - 3, 61–90 s - 2, 91–120 s - 1, and more than 120 s - 0).

Psychopathology was rated using the PANSS[19] and social functioning using the Scarf Social Functioning Index (SSFI).[24] Global outcome was assessed using Clinical Global Impression-Severity and Improvement (CGI-I).[25] Tolerability was assessed using the Simpson Angus Scale[26] and Udvalg for Kliniske Undersogelser (UKU)[27] Side Effect Rating Scale. Clinically evident tardive dyskinesia, if present, was noted. These assessments were performed at baseline and at the end of the 3rd, 6th, 9th, and 12th months by the

same trained rater. Vital signs and body weight were also recorded during each study visit.

Statistical analysis

This study set out to recruit approximately thirty patients in each group. The sample size is adequate to identify a moderate effect size of 0.75. The primary outcome measure was change in attention score at the 52-week endpoint, as measured using the digit-span test. The intent-to-treat sample was defined as all patients who were randomized and who had at least one follow-up visit; last observation carried forward was used wherever data were missing.

Continuous variables were compared between groups using the independent sample *t*-test (with modified degrees of freedom, wherever variances were heterogeneous) or Mann–Whitney test (when distributions were not normal); categorical variables were compared using the Chi-square test or Fisher's exact test. Data were compared between groups and across time using two-way repeated measures analysis of variance. Two-sided hypotheses were tested, and alpha for statistical significance was set at $P = 0.05$, unless indicated otherwise.

RESULTS

A total of 67 patients were screened for the study; 12 were ineligible for various reasons (older age, a diagnosis of drug abuse, failure to meet the diagnosis, associated medical problems, or refusal to participate).

Out of 55 randomized patients, 48 completed the 12-month treatment. Four in the rivastigmine group and three in the placebo group dropped out during the course of this study but had completed baseline assessment. Details are shown in Figure 1. In the 1st and 2nd months, one patient from each group dropped out. In the 3rd month, two from rivastigmine and one from placebo group dropped out.

Baseline data and clinical changes

Demographic and clinical details are presented in Table 1. The two groups were similar at baseline. The mean dose

Table 1: Characteristics of the two groups

	Rivastigmine (*n*=28)	Placebo (*n*=27)
Age years, (SD)	42.8 (12.10)	37.3 (8.8)
Sex (*n*)		
Male	15	12
Female	13	15
Married (*n*)	15	8
Employed (*n*)	18	10
Education, years, (SD)	6.8 (3.4)	7.6 (3.5)
Illness duration, months (SD)	14.5 (9.2)	12.2 (5.5)
Treatment duration, months (SD)	12.6 (9.2)	9.1 (4.8)
Family history of psychiatric illness (*n*)	7	8
Medical illness (*n*)	1	1

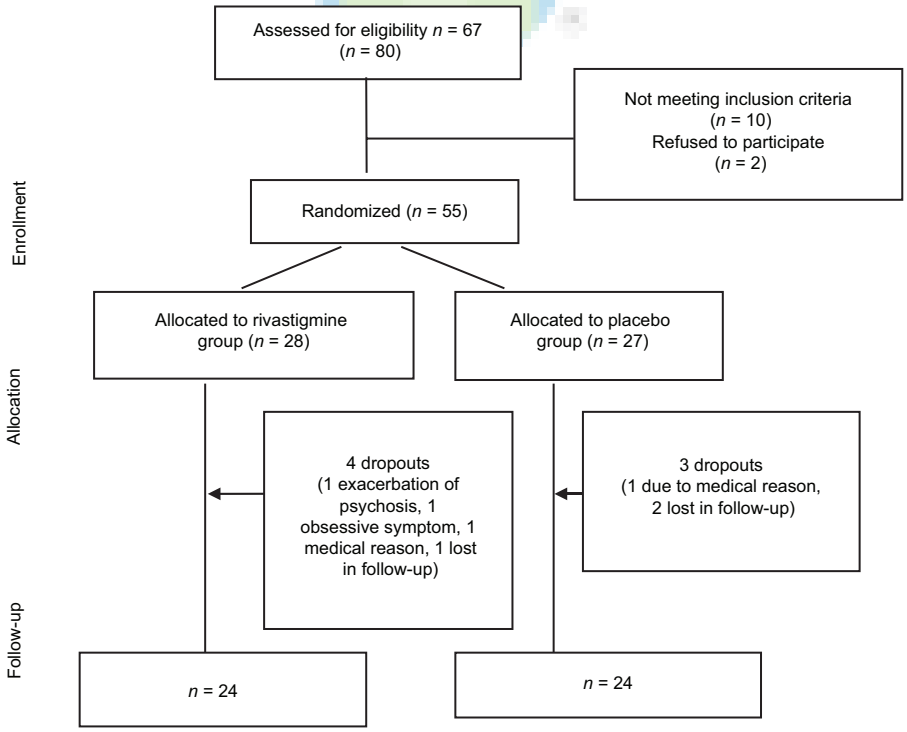

Figure 1: Consort diagram

of risperidone (4–5 mg/day) was comparable in the two groups [Table 2]. However, subjects in the rivastigmine group were more likely to use rescue lorazepam.

Both groups improved significantly across time on the PANSS and the CGI-I; there was significant improvement in PANSS total score and negative symptoms in rivastigmine group. However, improvement on SSFI was poorer with rivastigmine and improvement on CGI-I was greater with rivastigmine [Table 3].

Table 2: Mean dose of risperidone and lorazepam

	Rivastigmine (*n*=28)	Placebo (*n*=27)
Mean risperidone dose		
Baseline	4.8 (2.4)	4.6 (2.0)
1 month	4.6 (2.5)	4.7 (2.1)
3 months	4.5 (2.7)	4.4 (2.1)
6 months	4.2 (2.8)	4.4 (2.0)
12 months	4.1 (2.7)	4.4 (2.0)
Mean lorazepam dose		
Baseline	0.3 (0.7)	0.2 (0.5)
1 month	0.3 (0.7)	0.1 (0.4)
3 months*	0.4 (0.8)	0.1 (0.4)*
6 months*	0.4 (0.7)	0*
12 months*	0.4 (0.7)	0*

Table 3: Comparison of scores of Positive and Negative Syndrome Scale, Scarf Social Function Index Scale, and Clinical Global Impression-I at baseline, 1st, 3rd, 6th, and 12th months

	Rivastigmine (*n*=28)	Placebo (*n*=27)	*t/F/Z*	*P*
PANSS total score				
Baseline	43.1 (12.2)	43.2 (8.1)	*t*=0.0	0.99
1 month	39.1 (8.6)	41.8 (8.4)	*F*=1.1	0.31
3 months	37.2 (9.2)	39.6 (6.9)		0.08
6 months	36.9 (8.2)	39.9 (6.3)	*F*=1.1	0.38
12 months	36.1 (6.4)	38.6 (6.2)	*F*=8.9	0.00
PANSS positive score				
Baseline	9.4 (3.6)	9.2 (2.4)	*t*=0.3	0.80
1 month	8.5 (2.4)	8.6 (2.5)	*F*=0.2	0.67
3 months	8.1 (2.4)	7.9 (1.1)	Axt pillai	0.05
6 months	8.5 (2.9)	7.8 (1.2)	*F*=0.4	0.61
12 months	8.0 (2.0)	7.8 (0)	*F*=4.4	0.004
PANSS negative score				
Baseline	12.3 (5.3)	12.6 (5.6)	*t*=0.2	0.82
1 month	11.5 (5.1)	12.6 (5.6)	*F*=1.2	0.27
3 months	10.1 (3.6)	11.8 (5.3)	*F*=1.1	0.14
6 months	9.8 (3.4)	11.8 (4.8)	*F*=2.0	0.10
12 months	9.8 (3.2)	11.3 (4.6)	*F*=4.8	0.00
Scarf Social Function Index				
Baseline	42.2 (8.1)	40.4 (7.3)	*t*=0.9	0.38
1 month	40.4 (7.6)	41.9 (7.6)	*F*=6.4	0.014
3 months	37.5 (7.8)	45.6 (7.9)	*F*=0.2	0.63
6 months	36.6 (7.6)	46.7 (7.9)	*F*=21.7	0.00
12 months	39.0 (9.1)	46.6 (10.3)	*F*=0.8	0.55
CGI-I				
1 month	2.9 (1.0)	2.7 (0.9)	*t*=0.9	0.38
3 months	2.5 (1.3)	2.3 (0.9)	*F*=0.1	0.71
6 months	2.2 (1.2)	2.3 (1.0)	*F*=1.0	0.39
12 months	2.2 (1.2)	2.2 (1.0)	*F*=6.7	0.00

PANSS – Positive and Negative Syndrome Scale; CGI-I – Clinical Global Impression-Improvement

Cognitive effects of rivastigmine

The results for digit forward, digit backward, and logical memory are shown in Tables 3 and 4. On all the three measures, performances at various time points were actually better in the placebo group than in the rivastigmine group. Performance on the complex figure task also showed greater improvement in the placebo group [Table 5]. There

Table 4: Comparison of scores of digit-span and logical memory test at baseline, 1, 3, 6, and 12 months

	Rivastigmine (*n*=28)	Placebo (*n*=27)	*t/F/Z*	*P*
Digit forward				
Baseline	3.9 (1.4)	3.8 (0.8)	*t*=0.4	0.72
1 month	3.8 (1.5)	4.3 (1.1)	*F*=3.9	0.06
3 months	3.7 (1.2)	4.6 (1.0)	*F*=0.4	0.33
6 months	3.7 (1.4)	4.7 (1.0)	*F*=6.2	0.00***
12 months	3.9 (1.0)	4.3 (1.2)	*F*=1.7	0.16
Digit backward				
Baseline	2.8 (1.4)	2.5 (1.4)	*t*=0.9	0.37
1 month	2.9 (1.5)	2.8 (1.5)	*F*=0.2	0.63
3 months	2.5 (1.4)	3.0 (1.3)	*F*=0.6	0.23
6 months	2.6 (1.4)	3.0 (1.2)	*F*=3.8	0.11
12 months	2.6 (1.5)	2.9 (1.6)	*F*=0.6	0.65
Logical memory-immediate recall				
Baseline	2.9 (2.6)	2.8 (3.1)	*Z*=1.0	0.33
1 month	3.4 (4.1)	4.3 (4.4)	*Z*=1.1	0.29
3 months	3.2 (3.5)	6.1 (4.9)	*Z*=2.8	<0.01**
6 months	3.5 (3.7)	7.0 (4.9)	*Z*=3.0	<0.00**
12 months	3.8 (3.5)	5.8 (4.7)	*Z*=1.5	0.14
Logical memory-delayed recall				
Baseline	3.2 (3.4)	1.8 (2.6)	*Z*=2.7	0.01**
1 month	2.9 (4.0)	3.1 (3.5)	*Z*=0.4	0.69
3 months	2.6 (3.4)	4.2 (3.6)	*Z*=2.6	<0.01
6 months	2.9 (3.9)	4.7 (3.4)	*Z*=2.9	<0.00**
12 months	3.5 (4.2)	4.5 (3.4)	*Z*=1.8	0.07

Table 5: Comparison of scores of Rey-Osterrieth Complex Figure Test at baseline, 1, 3, 6, and 12 months

	Rivastigmine (*n*=28)	Placebo (*n*=27)	*t/F/Z*	*P*
Rey-Osterrieth Complex Figure-immediate recall				
Baseline	18.6 (10.9)	14.5 (9.3)	*t*=1.5	0.14
1 month	19.3 (11.3)	17.4 (9.8)	*F*=0.1	0.75
3 months	18.4 (10.6)	19.9 (9.5)		0.45
6 months	20.0 (11.1)	20.5 (9.9)	*F*=10.2	0.00***
12 months	20.6 (12.1)	20.1 (10.1)	*F*=15.5	0.00***
Rey-Osterrieth Complex Figure-delayed recall				
Baseline	7.9 (6.6)	4.7 (4.8)	*Z*=1.8	0.07
1 month	7.8 (6.3)	7.4 (6.3)	*Z*=0.2	0.81
3 months	7.6 (5.7)	9.2 (6.3)	*Z*=0.7	0.45
6 months	8.3 (6.1)	9.5 (6.7)	*Z*=0.7	0.48
12 months	11.3 (10.2)	9.9 (7.3)	*Z*=0.1	0.92

were no significant differences between groups in the Koh's task [Table 6].

Tolerability of rivastigmine

The UKU scale [Table 7] showed that subjects in the rivastigmine group experienced more psychological side effects (tiredness and increased sleep) at months 3 and 6 and more neurological side effects (rigidity, tremor, and hypokinesia) at all assessment points. However, comparison of Simpson Angus Score did not show any difference in the neurological side effects [Table 8]. Tardive dyskinesia was higher in the rivastigmine group, but this reflected a baseline effect rather than a treatment effect [Table 9].

DISCUSSION

This 52-week RCT of rivastigmine (12 mg/day) augmentation of risperidone in stable patients with schizophrenia found no cognitive advantage resulting from rivastigmine treatment; in fact, patients actually showed poorer performances on digit-span, logical (verbal) memory, and visuospatial memory tasks. Other studies have also failed to find significant cognitive benefits with rivastigmine augmentation in schizophrenia.[16,17] Contrary to previous reports,[11,28] rivastigmine was also associated with more psychological and neurological adverse effects including tardive dyskinesia.[28] However, rivastigmine improved the core psychopathology outcomes as measured by total PANSS score, negative score, and CGI-I score. Similar findings have been reported in other studies.[16]

Lenzi *et al*.[11] observed cognitive improvement after treatment with rivastigmine (12 mg per day for 12 months) in patients with schizophrenia. In that study, the patients had mild impairment of cognition at baseline. Hussain *et al*.[10] also reported improvements in attention, memory, and problem-solving with improved social and vocational functioning in a small group of seven patients receiving rivastigmine. Recent functional magnetic resonance imaging study revealed that rivastigmine treatment in schizophrenia increased cerebellar activity and influenced attentional processes.[14]

Other AChE inhibitors also needed to be focused in future studies. Unlike Sharma *et al*.,[17] who did not find a beneficial cognitive effect with rivastigmine, Schubert *et al*.[29] reported improvement in cognition (i.e., attention and memory) with galantamine treatment in schizophrenia patients.

Nonadherence to the medication cannot be considered a possible reason for our negative results, as the drug compliance was fairly good. There was no worsening of clinical symptoms in both the groups. In addition, in the rivastigmine group, drug-related adverse effects were more than the control group.

Table 6: Comparison of Kohs Block design test total score at baseline, 1, 3, 6, and 12 months

	Rivastigmine (*n*=28)	Placebo (*n*=27)	MWZ	*P*
Baseline	4.2 (3.2)	3.4 (3.0)	0.9	0.35
1 month	5.4 (3.3)	5.3 (3.7)	0.4	0.66
3 months	5.5 (4.2)	5.2 (3.5)	0.1	0.96
6 months	5.2 (3.7)	5.9 (3.7)	0.8	0.44
12 months	6.6 (5.7)	5.8 (4.1)	0.0	0.99

Table 7: Comparison of adverse events in the Udvalg for Kliniske Undersogelser scale at baseline, 1, 3, 6, and 12 months

	UKU scale		*Z*	*P*
	Rivastigmine (*n*=28)	Placebo (*n*=27)		
Psychological				
Baseline	4.6 (3.2)	3.6 (3.1)	1.5	0.14
1 month	4.4 (3.3)	3.3 (2.8)	1.5	0.14
3 months	3.9 (2.8)	1.8 (2.6)	3.3	0.00**
6 months	2.9 (2.9)	1.7 (2.5)	2.0	0.05
12 months	2.6 (2.8)	1.8 (2.6)	1.6	0.12
Neurological				
Baseline	1.4 (1.6)	0.5 (1.4)	3.0	0.00**
1 month	1.3 (1.6)	0.4 (1.3)	3.1	0.00
3 months	1.0 (1.3)	0.4 (1.2)	2.5	0.02
6 months	0.9 (1.0)	0.4 (1.3)	2.9	0.00**
12 months	0.6 (0.9)	0.3 (1.2)	2.3	<0.03*
Autonomic				
Baseline	0.9 (1.3)	0.9 (1.5)	0.5	0.63
1 month	0.8 (1.1)	0.6 (1.2)	1.1	0.26
3 months	0.6 (1.0)	0.4 (0.8)	0.9	0.35
6 months	0.4 (0.6)	0.3 (0.6)	0.5	0.60
12 months	0.4 (0.7)	0.3 (0.8)	0.3	0.74

UKU – Udvalg for Kliniske Undersogelser

Table 8: Comparison of adverse events in the Simpson Angus Scale at baseline, 1, 3, 6, and 12 months

	Rivastigmine (*n*=28)	Placebo (*n*=27)	*Z*	*P*
SAS				
Baseline	2.4 (3.4)	0.8 (1.7)	2.1	0.04
1 month	2.0 (3.2)	0.9 (1.8)	1.8	0.07
3 months	1.5 (2.8)	0.6 (1.7)	1.6	0.12
6 months	1.4 (2.7)	0.5 (1.7)	1.8	0.07
12 months	1.4 (2.7)	0.4 (1.6)	2.2	0.03

SAS – Simpson Angus Scale

Table 9: Comparison of tardive dyskinesia at baseline, 1, 3, 6, and 12 months

	Rivastigmine (*n*=28)	Placebo (*n*=27)	*Z* (χ^2)	*P*
Tardive dyskinesia present (*n*)				
Baseline	9	3	3.6	0.06
1 month	8	4	1.5	0.22
3 months	8	2	3.8	0.08
6 months	10	3	4.6	0.03
12 months	9	2	5.3	0.02

Strengths

This study had several strengths. The sample was homogeneous for the nature and dose of the antipsychotic

used in the study; therefore, confounds related to drug and dose were eliminated. Smokers were excluded from this study, and so smoking-related confounds related to nicotinic receptor stimulation were eliminated.[28]

Limitations

This study had some limitations. We did not preselect patients for baseline cognitive impairment. It is possible that rivastigmine may have helped patients who did have baseline disturbances in cognitive domains. However, we consider this possibility unlikely because patients actually deteriorated in the rivastigmine group. The 1-day withholding of lorazepam before cognitive assessment may have produced a state of relative withdrawal that may have compromised cognitive outcomes more in rivastigmine patients than in placebo patients because lorazepam use was greater in the rivastigmine group. Whereas this is a definite possibility, to have continued the lorazepam would have risked the known cognitive deficits related to benzodiazepine use. We believe that lorazepam was unlikely to have been a significant confound because very few patients used the drug (six patients).

CONCLUSIONS

The present study does not support the use of rivastigmine (12 mg/day) augmentation of risperidone as a strategy to improve cognitive functioning in stable patients with schizophrenia who have not been preselected with regard to baseline cognitive performance. We do not rule out the possibility that other cholinesterase inhibitors, with additional mechanisms of action (e.g., galantamine), may hold promise in this regard.

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Conflicts of interest

There are no conflicts of interest.

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