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Cognitive effects of adjunctive 24-weeks Rivastigmine treatment to antipsychotics in schizophrenia: A randomized, placebo-controlled, double-blind investigation

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Abstract

Cognitive impairment has the greatest impact on illness outcome in schizophrenia. The most significant challenge in schizophrenia therapeutics, thus, is to develop an efficacious treatment for cognitive impairments. Acetylcholinesterase inhibitors, such as Physostigmine and Rivastigmine, are considered effective treatments for cognitive decline in Alzheimer's Disease, where the loss of cholinergic neurons is thought to be responsible for various cognitive deficits. The current study investigated the cognitive effects of Rivastigmine given as an add-on therapy to antipsychotic-treated schizophrenia patients in a placebo-controlled double-blind design. The study initially involved 40 patients, of which 21 patients (11 assigned to Rivastigmine and 10 assigned to placebo) agreed to continued participation, remained on the study drug, and underwent assessment of executive functioning, verbal skills, verbal and spatial working memory, attention and psychomotor speed on three occasions: (i) at baseline, and then (ii) after 12 weeks and (iii) 24 weeks of treatment with placebo or Rivastigmine. The results failed to reveal significant improvement on any cognitive measure with Rivastigmine treatment, compared with the placebo treatment. Some cognitive variables showed significant practice effects in both the placebo and Rivastigmine groups. No effects were noted in symptoms or side effects ratings. The beneficial cognitive effects of Rivastigmine seen in an open-label preliminary study are not substantiated by this study. Future studies should investigate the effects of other procholinergic drugs, such as Galantamine, which also act on the nicotine receptors and may produce stronger cognitive effects in schizophrenia.

Keywords: Schizophrenia; Cholinergics; Cognitive enhancement; Nicotine

1. Introduction

Cognitive impairment is an enduring feature of schizophrenia (review, Rund, 1998) which is often present at illness onset (Riley et al., 2000) and persists

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regardless of a change in patients' symptom state (Hughes et al., 2003). Following the observation that cognitive impairment is more strongly related to the functional outcome than the severity of positive or negative symptoms (Green, 1996; Velligan et al., 1997; Addington and Addington, 1999; Evans et al., 2003), cognition has become a prime treatment target in schizophrenia (Sharma and Harvey, 2000; Harvey et al., 2004).

The acetylcholinesterase inhibitors (AChE-Is), such as Donepezil, Tacrine, Rivastigmine and galantamine, are known to be effective in treating cognitive decline in Alzheimer's disease (AD; reviews Doody, 2003; Giacobini, 2003; Terry and Buccafusco, 2003; Harry and Zakzanis, 2005). Although schizophrenia is not associated primarily with a cholinergic pathology, the decreases in choline acetyltransferase (ChAT) levels at postmortem have been found to be associated with the severity of antemortem cognitive deficits in patients with schizophrenia (Powchik et al., 1998). These data taken together with other evidence showing cognitive facilitation with cholinergic stimulation in experimental animals (e.g. Mandel et al., 1989; Decker and McGaugh, 1991) suggest that patients with schizophrenia may benefit from procholinergic treatment (Friedman et al., 1999). Cognitive improvement with some atypical antipsychotics, such as Clozapine, has also been hypothesised to involve their ability to increase ACh (Shirazi-Southall et al., 2002). However, cognitive functioning in patients treated with atypical antipsychotics generally remains below normative standards so there is still a need for an alternative treatment (Lehman et al., 1995).

In recent years, several groups have investigated the effects of AChE-Is on cognitive functions in schizophrenia. Preliminary studies and case reports showed significant cognitive improvements with 4–12 weeks Donepezil treatment as add-on therapy in schizophrenia or schizoaffective disorder (Risch et al., 2001; MacEwan et al., 2001; Howard et al., 2002; Stryjer et al., 2002; Buchanan et al., 2003). There is preliminary functional magnetic resonance imaging (fMRI) evidence for its effects at the neural level in schizophrenia (Risch et al., 2001; Nahas et al., 2003). Two 12-weeks randomized, double-blind, placebo-controlled studies, however, failed to observe significant cognitive effects of Donepezil in this population (Friedman et al., 2002; Tugal et al., 2004).

More recently, a preliminary study has reported cognitive improvement with Rivastigmine in schizophrenia (Lenzi et al., 2003; $n=16$ of which 6 discontinued, significant memory and attention improvements evident at 2 and 3 months post-treatment in remaining 10 patients). Rivastigmine is classified as an intermediate-acting or pseudo-reversible agent due to its long inhibition of AChE (up to 10 h), compared to Tacrine and Donepezil which are classified as short-acting or reversible agents (binding to AChE hydrolysed within minutes) (Polinsky, 1998). In AD, it has been found to improve daily activities, cognitive functions and psychopathology, with effects occurring as early as 12 weeks post-treatment (reviews, Birks et al., 2000; Jann, 2000; Williams et al., 2003). We recently reported robust increases in activation in brain regions associated with spatial attention and visual processing but only small (and non-significant) improvements in measures of attention and working memory with 12-weeks adjunctive Rivastigmine treatment to antipsychotics in schizophrenia patients (Aasen et al., 2005; Kumari et al., 2006).

In this report we describe the cognitive effects of 12- and 24-weeks adjunctive Rivastigmine treatment to antipsychotics in stable schizophrenia patients. Given the pharmacological properties of this drug and previously described cognitive effects in AD, we expected to find cognitive improvement with Rivastigmine treatment, especially when assessed at 24-weeks post-treatment, relative to the placebo, in this study. We also examined the effect of Rivastigmine treatment on symptoms given the earlier reports showing a beneficial effect of Donepezil on psychotic symptoms (Stryjer et al., 2003) and depression (Risch et al., 2001) in patients with schizophrenia.

2. Methods

2.1. Subjects

Forty patients with a diagnosis of schizophrenia, diagnosed using the Structured Clinical Interview for DSM-IV (SCID; First et al., 1995), were recruited from a catchment area including inner and outer London hospital trusts and via referrals from community mental health teams.

A screening visit was arranged and a full explanation of the study prior to screening was provided if the patient appeared suitable for and interested in taking part. For inclusion, all patients were required to meet the following criteria: (i) aged between 18 and 60 years, (ii) receiving stable treatment with an atypical (Risperidone, Olanzapine, Quetiapine) antipsychotic and have stable psychotic symptoms (i.e. no change in medication/dose of current medication over last 6 weeks and unlikely to require change in antipsychotic medication), (iii) no adjunctive anticholinergic treatment required since initiation of the antipsychotic, (iv) negative urine screening for illicit drugs and negative pregnancy test for female patients, (v) cooperative, able to ingest oral medication and willing to undertake repeated cognitive testing, (vi) able to provide written informed consent, (vii) reading ability of not more than 40 errors on National Adult Reading Test (Nelson and Willison, 1991), and (viii) between 1 and 2 standard deviations (S.D.) below expected performance on the basis of age and education level on the California Vernal Learning Test (Delis et al., 1987). In addition, the following criteria were used to define unsuitable patients: (i) concurrent DSM-IV diagnosis, (ii) known hypersensitivity to cholinergic agents, (ii) current treatment with benzodiazepines or antidepressants (iii) history of neurodegenerative disorder in first degree relative (e.g. AD, Parkinson's disease, Huntingdon's disease, multiple sclerosis), (iv) medical conditions that preclude administration of Rivastigmine i.e. severe hepatic impairment, (v) history of DSM-IV substance dependence in the last year or substance abuse within last month, (vi) lifetime history of trauma resulting in loss of consciousness for 1 h or longer, (vii) participation in another investigational drug trial within 6 weeks prior to study entry, (viii) recent (within last 3 months) history of suicidal or violent acts, and (ix) current diagnosis of uncontrollable seizure disorder, active peptic ulceration, severe and unstable cardiovascular disease or/and acute severe unstable asthma.

Of 40 patients initially enrolled in the study, 18 patients (none due to side effects or adverse events) dropped out at some point during the course of this study. Of these, four patients dropped out while on single-blind placebo for 1 week prior to baseline cognitive assessment, two patients did not complete cognitive assessment at baseline and 12 patients were unwilling to continue with the study or study drug. One patient was excluded because of a relapse (soon after the baseline). The final sample thus consisted of 21 patients who remained in the study with continued consent and provided data on all three occasions of testing (see Study design). Of this final sample, 11 patients were allocated to receive Rivastigmine and 10 to receive placebo. Seventeen patients were regular cigarette smokers: 8 patients allocated to receive Rivastigmine and 9 patients to receive placebo. The final sample included parts of the sample (about 75%) described in one or the other of our two recent functional magnetic resonance imaging (fMRI) studies of Rivastigmine effects in schizophrenia (Aasen et al., 2005; Kumari et al., 2006; fMRI not carried out at 24 weeks in any patient). Demographic and clinical characteristics of patients are shown in Table 1.

The study procedures were approved by the ethics committee of the Institute of Psychiatry, London and Dartford and Gravesham Local Research Ethics Committee, Dartford. All patients provided written informed consent.

2.2. Study design

After screening had identified a suitable patient and provision of informed consent, patients were placed on a single-blind placebo for 1 week. After 1 week on placebo (baseline), all patients completed a comprehensive cognitive test battery (see Cognitive Assessments) and underwent clinical assessments, and then were randomized into the double-blind protocol so that, half of the sample received Rivastigmine and the remaining half received placebo for the next 24 weeks. Cognitive and clinical assessments were carried out again at 12 weeks and 24 weeks. The duration of this study was chosen on the basis of previously reported cognitive effects of Rivastigmine in patients with AD (Birks et al., 2000; Jann, 2000; Williams et al., 2003; Farlow et al., 2005) and schizophrenia (Lenzi et al., 2003).

2.3. Drug dose and administration

Patients assigned to the Rivastigmine group received 1.5 mg/bd dose for the first 2 weeks, 3 mg/bd over the next 2 weeks, 4.5 mg/bd dose for the next 2 weeks and then 6 mg/bd for the remaining period so

Table 1
Baseline demographic, clinical and cognitive data in patients classified by treatment [mean (S.D.)]

	Rivastigmine $n=11$	Placebo $n=10$	t	p
Demographics				
Age [range]	42.64 (8.89) [27–53]	46.80 (13.02) [28–65]	0.86	0.39
Age at illness onset	25.18 (6.00)	30.30 (9.63)	1.47	0.15
Education (years)	9.64 (2.98)	11.30 (0.95)	1.68	0.10
Premorbid IQ	94.72 (12.01)	98.80 (12.10)	0.77	0.44
Sex	9 male, 2 female	5 male, 5 female		
Clinical characteristics				
Illness duration	17.45 (8.58)	16.50 (12.57)	0.20	0.84
No. of previous episodes	4.36 (2.54)	4.20 (3.55)	0.12	0.90
Positive symptoms	10.54 (4.78)	9.80 (3.64)	0.39	0.69
Negative symptoms	11.27 (5.93)	13.80 (3.01)	1.21	0.24
General psychopathology	25.09 (9.61)	29.70 (5.81)	1.31	0.20
PANSS total	46.90 (19.63)	53.30 (9.88)	0.92	0.36
AIMS	0.28 (0.90)	0.60 (0.70)	0.92	0.37

PANSS: Positive and Negative Syndrome Scale.
AIMS: Abnormal Involuntary Movement Scale.

at the time of 12 weeks cognitive assessments all patients were on the maximum dose. The placebo group received identical appearing capsules containing ascorbic acid (100 mg).

The choice and scheduling of dosages selected was chosen on the basis of cognitive effects of Rivastigmine seen in studies of AD patients (Birks et al., 2000; Jann, 2000; Williams et al., 2003; Farlow et al., 2005).

2.4. Clinical assessments

Symptoms were rated within 4 days of cognitive testing using the Positive and Negative Syndrome scale (PANSS) (Kay et al., 1987) on all three occasions. Side effects were also assessed within 4 days of testing using the Abnormal Involuntary Movement Scale (AIMS) (Guy, 1976). Inter-rater reliability was carried out for PANSS at 6 monthly intervals by rating exemplar cases based on patient interviews on videotapes. The kappas were between 0.82 and 0.86.

2.5. Cognitive assessments

The cognitive battery (see Table 2) included measures of executive functioning, verbal skills, verbal and spatial working memory, attention and psychomotor speed. The battery was administered to all patients on all three occasions in the same fixed

Table 2
Details of the cognitive battery

Cognitive domain	Tests
Premorbid functioning[a]	National Adult Reading Test: premorbid IQ (NART, Nelson and Willison, 1991).
Verbal learning and memory[a]	California Verbal Learning Test: total learning trials 1–5 (CVLT, Delis et al., 1987).
Executive functioning	Wisconsin Card Sorting Test: total errors, preservative errors and categories completed (WCST, Heaton, 1993);
	Trail Making Test: time trails B (Morris, 1995).
Verbal skills	Verbal Fluency: category and phonological fluency (Benton et al., 1983).
	Wechsler Adult Intelligence Scale: letter number scaled score (WAIS-III, Wechsler, 1997).
Verbal working memory	Digit symbol scaled score (WAIS-III, Wechsler, 1997).
Spatial working memory	Dot Test (Keefe et al., 1995).
Attention	Continuous Performance Test: signal detection index, d′ (CPT, Cornblatt and Keilp, 1994).
Psychomotor processing	Trail Making Test: time trails A (Morris, 1995).
	Finger Tapping Test: total score (Halstead, 1947).

[a] Administered only at screening.

order. Patients were allowed to take breaks as needed in order to obtain maximal performance at all times. The assessment took between 1 1/2 and 2 h to complete. Tests were administered and scored by trained psychologists who were blind to patients' group affiliations and were not involved in patients' treatment plan in any way.

2.6. General procedure

Patients were told that the aim of the study was to investigate the cognitive effects of Rivastigmine. They were requested to abstain from alcohol for at least 24 h prior to their scheduled cognitive testing.

2.7. Data analysis

The patients in the Rivastigmine and placebo groups were compared on demographic, clinical (Table 1) and cognitive variables (Table 3) obtained at baseline using independent sample *t*-tests. Those who dropped out but had completed baseline assessment were compared using independent sample *t*-tests with the entire sample remaining in the study.

The effects of Rivastigmine on positive symptoms, negative symptoms, general psychopathology score, total PANSS scores, and the scores on the AIMS were analyzed (separately) by 2 (Treatment: Rivastigmine, placebo) × 3 (Time: baseline, 12 weeks, 24 weeks) analysis of variance (ANOVA).

All cognitive variables were first examined for their distribution properties, i.e. to ensure normality. The cognitive effects of Rivastigmine over time were then evaluated by Treatment × Time ANOVA, performed separately for each variable, with Time as a within-subjects factor and Treatment as a between-subjects factor, followed by post-hoc mean comparisons wherever appropriate. All cognitive effects were then re-evaluated using ANOVA performed separately on change scores computed for each variable (12

Table 3
Baseline cognitive data in patients classified by treatment [mean (S.D.)]

	Rivastigmine $n=11$	Placebo $n=10$	t	p
CVLT	32.18 (9.11)	28.70 (11.09)	0.78	0.44
Executive functioing				
WCST Total Errors	57.91 (25.19)	60.78 (25.60)	0.24	0.80
WCST Preservative Errors	35.20 (17.46)	32.78 (19.93)	0.29	0.77
WCST Completed Categories	3.09 (2.07)	2.40 (2.12)	0.75	0.45
Trail Making Test B	110.36 (61.87)	149.00 (79.14)	1.25	0.22
Verbal skills				
Verbal Fluency Category	34.91 (12.32)	32.50 (8.46)	0.51	0.61
Verbal Fluency Phonological	26.45 (11.33)	28.20 (11.11)	0.35	0.72
Verbal working memory				
WAIS-III Letter Number	6.91 (3.18)	7.50 (3.81)	0.38	0.70
WAIS-III Digit Span	8.64 (3.78)	8.60 (2.07)	0.02	0.97
Spatial working memory				
Dot Test score	1.10 (0.99)	1.78 (1.38)	1.30	0.20
Attention				
CPT d′	0.88 (0.46)	0.68 (0.36)	1.22	0.28
Psychomotor speed				
Trail Making Test A	42.55 (12.31)	58.80 (22.99)	2.04	0.06
Finger Tapping	85.56 (20.56)	62.16 (19.48)	2.67	0.01

CVLT: California Verbal Learning Test.
WCST: Wisconsin Card Sorting Test.
WAIS: Wechsler Adult Intelligence Scale.
CPT: Continuous Performance Test.

Table 4
Results of the analyses of variance on the cognitive variables obtained at baseline, 12 weeks and 24 weeks

	Time			Treatment			Time × Treatment		
	F *df*=2,38	*p*	Effect size (pta^2)	*F df*=1,19	*p*	Effect size (pta^2)	*F df*=2,38	*p*	Effect size (pta^2)
Clinical variables									
PANSS: Positive Symptoms	2.34	0.11	0.11	0.03	0.88	0.00	0.25	0.78	0.01
PANSS: Negative Symptoms	0.69	0.51	0.04	1.41	0.25	0.07	0.98	0.40	0.05
PANSS: General Psychopathology	2.80	0.09	0.13	2.10	0.16	0.10	0.55	0.58	0.03
PANSS Total	1.88	0.17	0.09	1.10	0.31	0.06	0.60	0.55	0.03
AIMS	2.24	0.12	0.11	0.02	0.88	0.00	1.79	0.20	0.09
Neurocognitive variables									
Executive functioning									
WCST Total Errors	5.34	0.009*	0.44	1.44	0.25	0.07	2.05	0.14	0.10
WCST Preservative Errors	5.56	0.04*	0.17	0.09	0.77	0.01	1.15	0.33	0.06
WCST Completed Categories	1.34	0.18	0.09	2.42	0.14	0.11	1.34	0.27	0.07
Trail Making Test B	0.47	0.63	0.01	1.40	0.25	0.07	0.90	0.41	0.04
Verbal skills									
Verbal Fluency Category	0.27	0.77	0.01	0.83	0.38	0.04	0.69	0.51	0.03
Verbal Fluency Phonological	0.17	0.84	0.01	0.10	0.75	0.01	0.08	0.92	0.01
Verbal Working Memory									
WAIS-III Letter Number	0.54	0.59	0.03	0.03	0.86	0.00	0.30	0.75	0.02
WAIS-III Digit Span	1.77	0.18	0.09	0.01	0.98	0.00	1.92	0.16	0.09
Spatial working memory									
Dot test score	0.98	0.38	0.05	12.44	0.00	0.40	0.29	0.75	0.02
Attention									
CPT d′	1.23	0.30	0.06	0.04	0.85	0.01	2.98	0.07	0.13
Psychomotor Speed									
Trails A	0.19	0.83	0.01	6.81	0.02	0.26	0.18	0.84	0.01
Finger Tapping	0.59	0.56	0.03	8.84	0.01	0.32	0.90	0.41	0.05

PANSS: Positive and Negative Syndrome Scale.
AIMS: Abnormal Involuntary Movement Scale.
WCST: Wisconsin Card Sorting Test.
WAIS: Wechsler Adult Intelligence Scale.
CPT: Continuous Performance Test.
* Indicates significant practice effects.

weeks data minus baseline data, 24 weeks data minus baseline data). Effects sizes, where reported (see Tables 4 and 5), are partial eta squared (i.e. the proportion of variance associated with a factor). No subject had missing data for any cognitive variable for the baseline assessment. All patients had undergone all three assessments and tested on the entire battery. Three subjects had missing data on the continuous performance test and one patient had missing data on the Wisconsin Card Sorting test (WCST) for 24 weeks assessments. For these cases, missing values were replaced with the values observed for the 12 weeks (last observation carried forward). These missing data had resulted from equipment failure. Finally, data were analysed with and without the missing data (replaced with the values obtained for the last assessment) and found to produce the same pattern of effects. The results for the analyses with missing data are thus not reported any further.

All analyses were performed by SPSS windows (version 11). Alpha level for testing significance of effects was $p=0.05$ unless indicated otherwise.

3. Results

As shown in Tables 1 and 3, no demographic, clinical or cognitive variables differentiated the Rivastigmine

Table 5
Results of the analyses of variance on change scores (12 weeks and 24 weeks scores subtracted from the baseline scores)

Cognitive variables	Time			Treatment			Time × Treatment		
	F df = 1,19	*p*	Effect size (pta^2)	*F df* = 1,19	*p*	Effect size (pta^2)	*F df* = 1,19	*p*	Effect size (pta^2)
Executive functioning									
WCST Total Errors	1.79	0.20	0.09	1.44	0.24	0.07	2.80	0.11	0.13
WCST Preservative Errors	1.59	0.22	0.08	0.82	0.38	0.04	1.44	0.24	0.07
WCST: Completed Categories	1.50	0.24	0.07	1.14	0.30	0.06	1.55	0.23	0.08
Trail Making Test B	0.02	0.88	0.00	1.19	0.29	0.06	1.19	0.29	0.06
Verbal skills									
Verbal Fluency Category	0.15	0.70	0.01	0.23	0.64	0.01	1.54	0.23	0.07
Verbal Fluency Phonological	0.01	0.94	0.00	0.06	0.80	0.00	0.11	0.75	0.01
Verbal working memory									
WAIS-III Letter Number	0.02	0.88	0.00	0.16	0.69	0.01	1.38	0.60	0.03
WAIS-III Digit Span	0.26	0.62	0.01	0.00	1.00	0.00	3.38	0.08	0.15
Spatial working memory									
Dot test score	0.92	0.35	0.05	0.12	0.73	0.01	0.82	0.36	0.04
Attention									
CPT d′	1.14	0.30	0.06	1.44	0.24	0.07	4.22	0.06	0.18
Psychomotor speed									
Trails A	0.01	0.91	0.00	0.23	0.64	0.01	0.05	0.82	0.00
Finger Tapping	1.67	0.21	0.08	0.12	0.73	0.01	2.34	0.14	0.11

WCST: Wisconsin Card Sorting Test.
WAIS: Wechsler Adult Intelligence Scale.
CPT: Continuous Performance Test.

and placebo groups except the total finger tapping score. Male/female ratio, however, was slightly different between the two groups due to disproportional drop out of men from the placebo group. Twelve patients who dropped out at some point during the course of this study but had completed baseline assessment were not significantly different on any cognitive variables from those who remained in the study.

Rivastigmine treatment did not produce a significant change in symptoms or side effects (see Table 4).

Cognitive data for the Rivastigmine and placebo groups at baseline, 12 weeks and 24 weeks are displayed in Fig. 1. The results of the ANOVAs (with observed effect sizes) on cognitive variables are presented in Tables 4 and 5. As can be seen in Tables 4 and 5, cognitive variables failed to show significant effects of Rivastigmine treatment in our sample. Of all the cognitive variables assessed in this study, practice (Time) effects were noted for the total error as well as preservative errors on the WSCT.

4. Discussion

The present study was designed to assess the effects of 24-weeks Rivastigmine treatment on measures of executive functioning, verbal skills, verbal and spatial working memory, attention and psychomotor speed in patients with schizophrenia using a rigorous double-blinded parallel-group design.

Our data failed to support the hypothesis of enhanced cognitive performance with adjunctive 24-weeks Rivastigmine treatment to antipsychotics in schizophrenia. Our findings do not substantiate the positive results reported by preliminary studies and case reports (Risch et al., 2001; MacEwan et al., 2001; Howard et al., 2002; Stryjer et al., 2002; Buchanan et al., 2003); they appear more in line with two other randomized, double-blind, placebo-controlled studies which failed to find significant cognitive effects of cholinergic facilitation with Donepezil in schizophrenia (Friedman et al., 2002; Tugal et al., 2004). The lack of significant change with

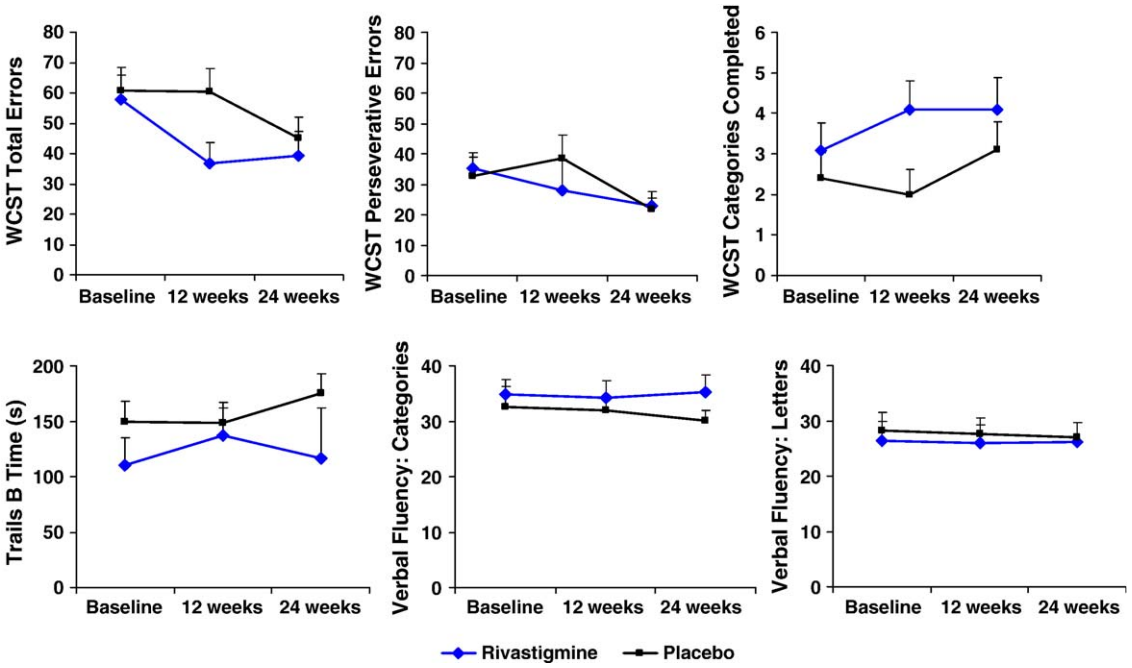

Fig. 1. Mean neurocognitive data for the Rivastigmine and placebo groups at baseline, 12 weeks and 24 weeks. (Error bars display +1 standard error of the mean; WCST: Wisconsin Card Sorting Test; WAIS: Wechsler Adult Intelligence Scale; CPT: Continuous Performance Test).

Rivastigmine on the WCST, however, might be due to the marked practice effect also seen in the placebo group and, if so, this would suggest that the WCST may not be very useful in future studies of this kind. Practice effect, however, does not explain the lack of significant improvement on other cognitive measures.

The maximum dose (i.e. 12 mg/daily) we used in the present study is known to be effective for cognitive symptoms in AD and all our patients had been on this dose for at least 12 weeks prior to their testing on the 3rd occasion. It can be argued that a higher (than 12 mg) dose would enhance cognitive functions in schizophrenia patients, and it should be possible to achieve this since we did not observe noticeable gastrointestinal side effects with Rivastigmine treatment, perhaps because all patients were also taking antipsychotics which act as antiemetics due to their dopamine blocking actions (Arnt and Skarsfeldt, 1998). However, even in AD patients, cholinergic facilitation is generally effective in slowing or preventing further cognitive decline rather than producing a noticeable cognitive enhancement. Although non-adherence to the medication can be considered a possible reason for our negative results, it is very unlikely given that our patients wanted to participate in the study without any financial incentive, were not taken off medication and were well known to the treating clinicians. Admittedly our sample was small and unable to detect effects of small magnitude. This limitation, however, does not eliminate the suggestion that cholinergic facilitation with Rivastigmine at doses known to be effective for cognitive symptoms in AD may not produce clinically meaningful cognitive improvement (assuming that cognitive improvements with medium-to-large effect sizes would be clinically meaningful) in schizophrenia patients treated with atypical antipsychotics.

It is possible that the outcome of our study, as also discussed in our recent report on the neural correlates of Rivastigmine effects in schizophrenia (Kumari et al., 2006), was to some extent affected by the smoking status of our patients. We had excluded patients who needed anticholinergic therapy (see Methods) as this would interact with cholinergic augmentation and is known to impair cognitive and information processing functions in both normal (Kumari et al., 2001; Zachariah et al., 2002) and schizophrenic populations (Strauss et al., 1990; Ettinger et al., 2003; Kumari et

al., 2003). We however did not exclude smokers in order to study a representative population since most schizophrenia patients smoke (Hughes et al., 1986). It has been suggested that cigarette smoking desensitises nicotine receptors in patients with schizophrenia who do not show the normal up-regulation following chronic nicotine use (review, Kumari and Postma, 2005). This might have prevented the AChE-I reaching its full potential for cognitive enhancement in smoking schizophrenia patients.

In conclusion, the present study, although limited by a small sample size, does not provide convincing data for the hypothesis that AChE-Is can produce meaningful and clinically relevant cognitive enhancement when added to atypical antipsychotics in patients with schizophrenia. It would be advisable for future studies to investigate potential cognitive enhancement in schizophrenia and related populations with allosterically potentiating ligands (Friedman, 2004), such as Galantamine (Maelicke et al., 2001), which inhibit cholinesterase and, at the same time, augment nicotinic receptor sensitivity in the presence of ACh by binding to the nicotinic receptor (Schrattenholz et al., 1996).

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