

ORIGINAL ARTICLE

Rivastigmine treatment as an add-on to antipsychotics in patients with schizophrenia and cognitive deficits

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Key words: Acetylcholinesterase inhibitors – Cognition – Rivastigmine – Schizophrenia

ABSTRACT

Objective: Although new atypical antipsychotic agents have been found to improve overall cognitive function in patients with schizophrenia (SZ), some aspects of memory, attention and executive functions still remain impaired. Acetylcholinesterase (AChE) inhibitors, such as rivastigmine, have been shown to improve cognition in other disorders, particularly Alzheimer's disease. Dysfunctions in cholinergic systems, especially in the prefrontal cortex, have been identified in SZ, suggesting that cholinesterase inhibitors may be effective in treating cognitive deficits in this disease.

Research design and methods: Using a randomized crossover design, we assessed SZ patients with stable symptoms and poor cognitive functioning. Fifty-eight patients with memory deficits, according to subjective complaints or based on clinicians' observations, were assessed with the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) and Subjective Scale to Investigate Cognition in Schizophrenia (SSTICS). Only 24 of these subjects met the inclusion criteria.

Twenty patients took part in the study (four dropped out). All subjects meeting the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) criteria for SZ were maintained on their current antipsychotic medication (18 atypicals and two typicals) and were randomly assigned to treatment with rivastigmine. Dosage was a function of tolerability, beginning at 3 mg/day and progressively increasing to 9 mg/day. Subjects were given the Cambridge Neuropsychological Test Automated Battery (CANTAB) at baseline and 3 and 6 months.

Results: The results revealed no significant improvement in any of the cognitive variables investigated following rivastigmine treatment and symptom severity scores remained unchanged over all recorded time periods.

Conclusion: Rivastigmine treatment did not appear to enhance cognition in SZ patients with important cognitive impairments. This finding needs to be interpreted with care and requires substantiation with larger sample size studies with patients treated with cognitive enhancer for longer periods.

Introduction

It has been suggested that cholinergic agonists, including acetylcholinesterase (AChE) inhibitors, such as rivastigmine, may slow down cognitive decline not only in Alzheimer's disease but also in other pathologies^{1,2}. In Alzheimer's disease, the effect of AChE inhibitors may slow down cognitive deficits in patients with mild to moderate deficits but does not improve deficits that already exist³. A recent systematic review showed that donepezil, rivastigmine and galantamine can delay cognitive impairment (evaluated with the Alzheimer's Disease Assessment Scale Cognitive Subscale [ADAS-Cog]) in patients with mild-to-moderate Alzheimer's disease, at least for 6 months⁴. Important future studies on AChE inhibitors in Alzheimer's disease would be to evaluate combination therapies or prevention with other agents, such as A-beta or estrogens³. Another study investigating the effects of rivastigmine on dementia associated with Parkinson's disease showed an improvement in attention and executive functions¹. Others authors also investigated the pharmacological treatment of cognitive impairment in dementia with Lewy bodies; AChE inhibitors were shown to be effective².

Some studies have also pointed to an abnormal cholinergic system in schizophrenia (SZ) as decreased numbers of muscarinic and nicotinic receptors^{5,6}. The presence of abnormal cholinergic function in patients with SZ provides a rationale for testing the effectiveness of cholinesterase inhibitors in treating the cognitive impairments often seen in SZ, such as memory and attention deficits^{7,8}. Such impairments are often observed at the onset of the illness and do not appear to be attributable to the antipsychotic treatment⁹.

The cognitive impairments that appear in the earliest phases of schizophrenia persist throughout its course¹⁰. Attention¹¹⁻¹³, memory^{14,15}, and executive function^{16,17} may be affected, usually moderately. Neurocognitive impairments are a major impediment to social and vocational rehabilitation¹⁸. In addition, patients with executive deficits have been found to be less functional in their daily living activities, assessed with specific tasks (choosing a menu, shopping the ingredients, cooking a meal)¹⁹. Thus, improvement in cognitive function in SZ patients should be considered in the search for new treatments.

MATRICES, a new US-funded program that brings together representatives of academia, industry and government, has been set up to investigate cognitive deficits in SZ²⁰. This program has identified the main obstacles that are likely to interfere with the development of pharmacological agents for treating cognitive problems in schizophrenia. These include a lack of a consensus as to how cognition in schizophrenia should

be measured, differing opinions as to the most promising pharmacological approaches, challenges in clinical trial design, concerns in the pharmaceutical industry regarding the US Food and Drug Administration's (FDA) approaches to drug approval for this indication and issues in developing a research infrastructure that can carry out clinical trials of promising drugs.

A number of studies have shown that various atypical antipsychotic medications result in cognitive benefits in schizophrenia patients^{21,22}. A meta-analysis conducted by Woodward *et al.*²³ revealed that atypicals are superior to typicals in improving overall cognitive function. In this study, estimate of effect size was calculated (ES = 0.24). Some improvements were noted in the speed of learning and processing with specific atypical antipsychotics. However, cognitive impairment still persists with atypical neuroleptics and provides a rationale to search for new agents to improve cognition.

Several hypotheses have been advanced concerning the neural systems involved in SZ. Alteration of cholinergic activity may play an important role in the cognitive impairments seen in this disease. Freedman *et al.*²⁴ showed that there is a lower density of nicotinic receptors in the hippocampus of SZ patients. Reduced numbers of muscarinic and nicotinic receptors may contribute to cognitive impairments²⁵. Karson *et al.*²⁶ demonstrated that there is a correlation between cognitive impairments and decreased brain choline acetyltransferase levels in SZ. These results suggest that the abnormality of cholinergic system is correlated with cognitive dysfunction in SZ²⁷.

Physostigmine showed a trend in improving visuospatial working memory ($p = 0.07$), but not serial verbal learning among patients with schizotypal personality disorder²⁸. A case study by MacEwan *et al.*²⁹ using donepezil as an add-on treatment (10mg per day for 12 weeks) to risperidone in patients with schizophrenia (paranoid type) showed an improvement in verbal fluency. Conversely, a report by Friedman *et al.*³⁰ failed to show any beneficial effect of donepezil add-on therapy (10mg per day for 12 weeks) on cognition in SZ patients ($n = 36$). The cognitive battery used evaluated, attention, memory and executive functions. The authors suggested that these unexpected results may be due to the effects of tobacco (nicotinic tolerance was not evaluated). In fact, chronic tobacco use produces desensitization of nicotinic receptors³¹. It is noteworthy that in SZ smokers, nicotine is associated with improved performance on visuospatial memory tasks³².

More recent studies have produced contradictory results regarding the efficiency of AChE inhibitors in SZ. As highlighted by MATRICES²⁰, many obstacles may interfere with the development of pharmacological

agents for treating cognitive problems in schizophrenia. Some reports suggest that the enhanced cholinergic activity triggered by AChE inhibitors improves cognitive function significantly in SZ³³⁻³⁵ but others have failed to find any significant improvement^{36,37}.

A meta-analysis of 10 studies conducted by our group investigated the effects of AChE inhibitors on memory in SZ³⁸. The results revealed a mild but significant improvement in short-term ($p = 0.07$) and long-term ($p = 0.01$) memory after treatment with cholinergic enhancers. However, additional analyses showed that these patients still performed worse than controls after treatment with cholinergic enhancers. The symptom progression was not affected as observed on the Positive and Negative Symptoms Scale (PANSS) curve which, remained stable through out the trial.

In this perspective, the current study was designed to assess the effects of rivastigmine as an add-on therapy to antipsychotic medication on cognitive function in SZ-spectrum patients who have moderate to severe cognitive impairment. We aimed to determine the extent to which this type of medication may enhance cognition in SZ, taking into account nicotine consumption.

Methods

Setting

This study was carried out at the Fernand-Seguin research center, which is part of Louis-Hippolyte Lafontaine Hospital. As two patients were recruited from Charles LeMoyne Hospital (by Dr J-P. Melun), the study was approved by the ethics committees of both hospitals.

Subjects

The study examined 20 patients (five women and 15 men) assigned to one of two groups (groups 1 or 2). The mean age of the patients was 28.85 ± 7.92 years. Nineteen patients fulfilled the diagnostic criteria of the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) diagnosis of SZ and one patient in group 2 presented with schizoaffective disorder (APA)³⁹. Fourteen patients reported smoking cigarettes on a daily basis (three women and 11 men, age 27.5 ± 6.1 years) and six were non-smokers (two women and four men, age: 32.5 ± 10.3 years). The clinical characteristics of the two groups are reported in Table 1.

All patients had been on stable antipsychotic medication for at least 2 months prior to the commencement of the study and medication dosage

was kept unchanged for the duration of the study. Four patients included in the study received anticholinergic medication during the study. Eighteen patients were under atypical antipsychotics (nine olanzapine, four clozapine, three quetiapine and two risperidone), one was receiving zuclopenthixol (male, 50 year old) and one was receiving chlorpromazine (male, 37 year old). The mean doses and chlorpromazine equivalence for each group were calculated and presented in Table 1⁴⁰.

Eligibility

Patients aged 18 to 50 years participated in the study. The inclusion criteria were a score < 75 on the immediate or delayed memory indices of the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS). This battery has been previously validated with schizophrenia patients⁴¹. This criterion was established based on the scores of healthy subjects (range = 90.8 to 102.9 on the memory index). It takes about 30 minutes to complete the test. Patients with current substance abuse (amphetamines, Ecstasy, PCP, cocaine, THC or alcohol), other Axis 1 or 3 diagnoses, or pronounced suicidal potential were excluded.

Recruitment

A total of 58 patients were assessed with the RBANS and the Subjective Scale to Investigate Cognition in Schizophrenia (SSTICS) upon referral by psychiatrists, based on subjective complaints of memory deficits or on doctors' observations. Thirty-five patients were eliminated for various reasons (older age, a diagnosis of drug abuse, failure to meet the diagnosis for SZ spectrum, or possible pregnancy). Ten patients scored higher than the allowed RBANS score in the inclusion criteria and 13 patients refused to participate. All participants received a full explanation of the study before they gave informed written consent.

Twenty-four patients were thus recruited and only twenty completed the study. Four patients dropped out of the study after a few weeks into the trial while they were receiving rivastigmine. Of these four patients, one developed disorganized thought, another was hospitalized due to pronounced suicidal tendencies and two refused to continue the trial without giving any specific reason.

Clinical assessments

All patients were assessed with classical psychiatric assessments, in addition to the PANSS. These assessments were performed at baseline, 3 and 6 months into the study by the same trained rater⁴².

Table 1. Characteristics of the two groups at baseline

	Group 1		Group 2	
N	9		11	
Age, years (SD)	32.67 (8.65)		25.73 (5.95)	
Sex, <i>n</i>				
Female	3		2	
Male	6		9	
Disease duration, years (SD)	8.77 (7.79)		4.25 (5.28)	
RBANS (SD)	71.11 (8.45)		67.64 (10.96)	
PANSS total (SD)	74.00 (0.71)		75.00 (5.66)	
SSTICS (SD)	39.00 (23.79)		32.38 (12.35)	
Fagerström (SD)	3.77 (3.90)		4.78 (3.15)	
Smokers	5		9	
	<i>n</i>	Mean dose, mg	<i>n</i>	Mean dose, mg
Olanzapine	4	13.75	5	16.50
Risperidone	0	–	2	3.25
Quetiapine	2	450.00	1	600.00
Clozapine	2	600.00	2	400.00
Chlorpromazine	0	–	1	50.00
Zuclopenthixol*	1	15.00	0	–
Chlorpromazine (equiv.)	9	490.00	11	402.30

*From the thioxanthene class, characterized with a high affinity for dopamine D₁, D₂, α_1 -adrenergic and serotonin 5-HT₂ receptors and a low affinity for histamine H₁, muscarinic, cholinergic and α_2 -adrenergic receptors
 PANSS = Positive and Negative Symptoms Scale; RBANS = Repeatable Battery for the Assessment of Neuropsychological Status; SSTICS = Subjective Scale to Investigate Cognition in Schizophrenia

Cognitive assessment

The Cambridge Neuropsychological Test Automated Battery (CANTAB) was administered to all patients by someone well trained to administer this battery. This battery has been standardized on large populations, including patients with SZ, and can be used repeatedly with the same subject^{43–46}. Because all tests in the battery are nonverbal, CANTAB evaluates cognitive performance independently of language and culture. The tasks used were: (1) Paired Associates Learning (PAL) for the assessment of long term memory (LTM); (2) Reaction Time (RTI) for processing speed; (3) Rapid Visual Processing (RVP) for sustained attention; (4) Stockings of Cambridge (SOC) for executive function; and (5) Spatial Working Memory (SWM) for working memory. Subjective complaints of cognitive deficit were evaluated using the SSTICS^{47,48}.

Nicotine questionnaire

The Fagerström questionnaire, a reliable questionnaire on tobacco smoking habits, was administered to each

patient before and after 3 months of treatment with rivastigmine⁴⁹. The maximum score on this questionnaire is 11 and the lowest score is 0; a score greater than 6 represents nicotine dependence.

Titration and administration of rivastigmine

Rivastigmine was administered as a function of patients' tolerance. Patients began rivastigmine treatment at a dose of 1.5 mg twice daily during the first month. This dose was raised to 3 mg twice daily during the second month and then to 4.5 mg twice daily during the third month. The dose was taken with a full meal in the morning and evening.

Tolerability

During rivastigmine treatment, patients were closely followed on a weekly basis by nurses. At each visit, parameters were checked including vital signs (weight and blood pressure). In addition, blood samples were taken before and after rivastigmine treatment (urea, creatine, total bilirubin, triglycerides, creatinine kinase

[CK], aspartate aminotransferase [AST], alanine aminotransferase [ALT], phosphate alkaline and cholesterol levels).

Experimental design

This study was a randomized crossover trial. All patients were assessed at baseline (T1). Patients were randomly assigned to one of two groups for 3 months – rivastigmine plus antipsychotics (group 1) or antipsychotics alone (group 2). At the end of 3 months (T2), all patients were evaluated a second time with the same cognitive tests used at baseline. For the next 3 months, the patients in group 1 discontinued rivastigmine while the patients in group 2 received rivastigmine. At the end of this additional 3 months (T3), the cognitive performance of patients in both groups was evaluated for the third time (T3) (see Table 2).

Statistical analysis

Random assignment was used to avoid any confound between the two groups. Baseline differences in cognitive functioning (CANTAB) and clinical symptoms (PANSS) were assessed using *t*-tests for independent groups. The statistical relationships between SSTICS, RBANS and PANSS were also conducted at baseline.

All CANTAB cognitive variables were assessed separately using a Latin square design. The same analyses were performed with the PANSS measures (negative, positive, general and total scale scores).

Results

Baseline

Despite the random assignment, we found significant age differences between the two groups of patients. The Student *t*-test revealed that patients in group 1 were significantly older than those in group 2 ($p = 0.05$). There was no other difference between the two groups in the duration of illness, CANTAB or PANSS measures at baseline. In addition, there was no significant difference between the two groups with regard to antipsychotic medication, chlorpromazine equivalent or nicotinic dependence. Duration of illness data was missing for two patients in group 2.

There was a significant positive correlation between the RVP (CANTAB) and the PANSS at baseline, suggesting that sustained attention is correlated with positive and general symptoms, and patients with more positive symptoms made more errors ($p = 0.03$). Also, patients who scored high on the Fagerström questionnaire (categorized as smokers) performed better on the total RBANS scale and had more negative symptoms ($p < 0.05$) than patients with lower scores. Seven patients showed nicotine dependence in scoring higher than 6 on the Fagerström questionnaire.

Cognitive data

Statistical analyses performed with the Latin square design did not reveal any change after rivastigmine treatment on any of the CANTAB variables (all

Table 2. *Experimental design*

	Group 1			Group 2		
	T1 baseline	T2 3 months	T3 6 months	T1 baseline	T2 3 months	T3 6 months
Treatment						
Rivastigmine		×			×	×
Eligibility						
RBANS	×			×		
Experimental measures						
CANTAB	×	×	×	×	×	×
SSTICS	×	×	×	×	×	×
Nicotinic tolerance	×	×	×	×	×	×
Safety, tolerability						
PANSS	×	×	×	×	×	×
Blood sampling	×	×			×	×
Vital signs	×	×			×	×

CANTAB = Cambridge Neuropsychological Test Automated Battery; PANSS = Positive and Negative Symptoms Scale; RBANS = Repeatable Battery for the Assessment of Neuropsychological Status; SSTICS = Subjective Scale to Investigate Cognition in Schizophrenia

p -values > 0.05) Table 3 shows several variables of each task analyzed. Nor was there any change on the SSTICS after rivastigmine treatment ($p = 0.42$).

Clinical data

Clinical symptoms remained unchanged following rivastigmine treatment in patients, as assessed with PANSS (positive, negative, general and global symptoms) (see Table 3). Effectively, we have not observed any difference in cognitive enhancement outcomes between add-on rivastigmine treatment and placebo.

Tolerability

As mentioned above, two patients were removed from the study because of worsening SZ symptoms. The most frequent side effects reported by patients ($n = 5$) during the study were nausea and vomiting, which disappeared almost entirely after the instruction to take the medication with a meal was emphasized to patients. Follow up for compliance with medication and doses was performed once weekly by nurses.

One patient reported weight loss and three others mentioned more vivid dreams. Ninety-five percent of the patients were compliant with the medication protocol with an exception of one patient that had side effects with a dose of 3 mg BID.

Some slight anomalies were found in blood samples during rivastigmine treatment. Three patients showed transitional CK augmentation with normal troponins (one of these patients also had a familial history of cholecystitis). Two of these patients were on olanzapine and the other on clozapine. The patient with familial history of cholecystitis was on clozapine. An increase in cholesterol and triglycerides was detected in two patients.

Discussion

This randomized crossover study investigated the effect of rivastigmine, an AChE inhibitor, concomitant to antipsychotic medication on cognitive function in patients with SZ. The results did not reveal any effect of this medication on cognitive functioning as assessed with neurocognitive tasks (CANTAB) or on clinical symptoms. Our main concern was that the well-known relationship between rivastigmine and increased cholinergic activity might increase patients' positive symptoms. But our results did not show any worsening of either positive or negative symptoms.

Table 3. Latin square analysis on cognitive variables (CANTAB) and clinical symptoms (PANSS) for rivastigmine effects

	<i>F</i>	<i>p</i> -value
Reaction time		
Movement time	0.26	0.62
Reaction time	0.64	0.56
Paired associates learning		
Stage completed	0.06	0.79
Total trials	1.16	0.29
Total errors	0.56	0.53
Stockings of Cambridge		
Initial think time	0.002	0.92
Subsequent time	0.070	0.85
Rapid visual processing		
Total hits	3.17	0.08
Total misses	2.55	0.12
Spatial working memory		
Total errors	0.24	0.63
Strategy	0.78	0.61
PANSS		
Positive symptoms	0.17	0.69
Negative symptoms	0.80	0.62
General symptoms	0.26	0.62
Total score	0.76	0.78

PANSS = Positive and Negative Symptoms Scale

In the study by Friedman *et al.*³⁰ there was no change in cognitive function after use of donepezil therapy as an adjunctive treatment to risperidone in SZ patients. The dose in two conditions was 5 mg and 10 mg per day for 12 weeks. The authors suggested that this was probably due to a selection confound, as their selected patients had a z -score of -3.5 on the California Verbal Learning Test (CVLT). Thus, the patients in their study had severe cognitive deficits, especially in memory. On the other hand, Lenzi *et al.*³⁵ observed cognitive improvement after only 1 month of treatment with rivastigmine (12 mg per day for 12 months) in patients with SZ. In that study, the patients presented mild cognitive impairment at baseline.

The effects of this type of inhibitor may be parallel to what is found in Alzheimer's disease, where the effect of AChE inhibitors may slow down cognitive deteriorations but will not improve any deficits that already exist³. In the present study, it is possible that the cognitive deficits exhibited by subjects were too severe for any beneficial effect of rivastigmine to be observed. In summary, these data suggest that AChE inhibitors in

SZ would serve more effectively as a preventive therapy than for the treatment of schizophrenia patients with severe cognitive deficits.

A meta-analysis investigating the effectiveness of AChE inhibitors in SZ in eight studies revealed a weak but significant improvement in short term memory and LTM³⁸. One interesting factor to consider in future efforts is the effect of the different AChE inhibitors used. As in our study, Sharma *et al.*⁵⁰ did not find a beneficial cognitive effect with rivastigmine, but Schubert *et al.*⁵¹ reported improvement in cognition (i.e. attention and memory) with galantamine treatment in schizophrenia patients. As proposed by MATRICS, the heterogeneity of the results may be partially explained by the problems concerning the tools and methodology used to investigate cognitive deficits. It is probable that certain tests to detect improvements in cognitive deficits in SZ are more sensitive than others.

It is possible that the lower dosage used in our study may have contributed to rivastigmine's lack of impact on cognitive function. Rivastigmine was administered at doses ranging from 1.5 mg to 4.5 mg twice daily (the last month of the trial 4.5 mg, BID). This was done to avoid nausea, the main side effect reported with this medication. In Alzheimer's disease, rivastigmine is usually administered at a higher dosage of 6 mg twice daily. It is also important to remember that 16 of the patients in this study were cigarette smokers, and this subgroup showed better performance on the RBANS initially. Cholinergic receptors in smokers are desensitized by nicotine and this may reduce the effect of AChE inhibitor treatment. Moreover, cognitive improvements associated with nicotine in smokers are probable and may mask the effect of rivastigmine in these patients. However, there is no drug interaction with rivastigmine, contrary to the possible drug interaction between tobacco products (such as nicotine) and donepezil or galantamine. In any case, the effects of these drugs on improving cognitive function and eventual social adaptation can be questioned. If any effect is reported, it is of little magnitude, and some studies, including ours, have failed to find any change over time in both cognitive and clinical symptoms.

The main limitation in our trial is that the sample might be too small to detect a relatively little effect size. Moreover, the treatment duration (3 months) on rivastigmine may be too short and the doses may be too low, so that no significant effect could be obtained. This seems to be true even in studies conducted to detect an effect in elderly patients with dementia. Finally, our sample was heterogeneous regarding the basic antipsychotic medication. Chew *et al.*⁵² reported that atypical antipsychotics clozapine, olanzapine and quetiapine have significant affinity for the muscarinic receptor and showed dose-dependant increases of

anticholinergic activity. However, in our study, the patients were equivalent in the two groups for these three medications and dosage (see Table 1). Sixteen of the twenty-one patients were on these medications, and this could partially explain why no changes were observed after rivastigmine treatment. Also, one possible difficulty concerns the fact that patients were randomly assigned to groups. As a result, the patients in group 1 were significantly older than those in group 2.

A recent functional magnetic resonance imaging (fMRI) study revealed that rivastigmine treatment in SZ increased cerebellar activity and influenced attentional processes⁵³. Recent psychopharmacological and fMRI studies tend to show that many neurotransmitters are involved in cognitive functions in SZ. Future research on cognitive enhancers in SZ is necessary, especially using physiological approaches such as fMRI and electrophysiology.

Conclusion

In conclusion, rivastigmine treatment did not appear effective in ameliorating cognitive deficits in SZ patients with important cognitive impairments. One must be careful in making any firm conclusions based on our current data, and our recommendation is that a larger sample should be treated with a cognitive enhancer over a longer time before any definitive conclusion can be drawn.

Acknowledgment

Declaration of interest: This research was supported by an Investigator Initiative Trial proposed to Novartis Canada and by the Université de Montréal Eli Lilly Canada Chair in Schizophrenia Research held by Emmanuel Stip, MD. We would like to thank Pierre Lalonde, MD, Ait Lahcen Bentaleb, MD, PhD, Robert Elie, MD, and Georgina Zahirney, MD for their help in recruitment; the nurses Carole Feltrin and Mylène Marchand for their invaluable support with the patients; and Adham Mancini-Marie, MD for his valuable comments and advice on this paper.

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Paper CMRO-3690_3, *Accepted for publication*: 14 December 2006

Published Online: 09 February 2007

doi:10.1185/030079906X167372