Effects of galantamine on working memory and global functioning in patients with mild cognitive impairment: A double-blind placebo-controlled study

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Abstract

Mild cognitive impairment (MCI) causes memory impairment and executive function deficits in those with the condition. There is also some evidence that MCI patients are impaired in their daily functioning. Cholinesterase inhibitors have been widely used for patients with Alzheimer's disease (AD), with evidence of improving cognitive function. There is currently no established treatment for MCI, and cholinesterase inhibitors are beginning to be studied in these patients. Galantamine is a cholinesterase inhibitor that also has nicotinic receptor-modulating properties that has been successful in improving AD patients. This study examined the effects of galantamine in patients with MCI in areas of memory, executive functioning, and global functioning. There was a significant improvement in scores on the Functional Activities Questionnaire, which is a measure of global functioning. There were also improvements in the galantamine group on two of six measures in the Cambridge Automated Neuropsychiatric Test Assessment Battery and in immediate free recall on the California Verbal Learning Test.

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Key words: mild cognitive impairment, memory, galantamine, pharmacotherapy, cholinesterase inhibitors, nicotinic receptors

Introduction

Mild cognitive impairment (MCI) is a topic of great interest in current geriatric research as a possible risk factor for dementia of the Alzheimer's type.[1] While episodic memory deficiency is a primary characteristic of patients with MCI, there is evidence of other cognitive impairments, such as a decline in executive functioning and working memory.[2] There has been no approved treatment to ameliorate symptoms of MCI.

Cholinesterase inhibitors have been the most widely used treatment for Alzheimer's disease (AD),[3,4] and there is evidence that these compounds may slow its progression.[5,6] Little has been done to investigate the benefit of cholinesterase inhibitors in the treatment of MCI, but a connection between MCI and AD suggested by epidemiological data[7-10] and the characterization of MCI as a transitional state to AD[11,12] suggest that this might be promising.

At the time of this writing, there were many incomplete or ongoing MCI treatment studies (registered at *http://www.clinicaltrials.gov*). Only two reports of completed acetylcholinesterase inhibitor studies[13,14] were available for reference.

In one study, the effectiveness of donepezil in combination with vitamin E was examined in 769 MCI patients from the United States and Canada.[13] The donepezil group showed significant benefits on the Mini-Mental State

Table 1. Data analysis for CANTAB				
	Baseline galantamine (placebo)	**Visit 3 galantamine (placebo)**	**p**	**n**
DMS (delayed matching to sample)				
Mean number correct simultaneous	8.8 ± 2.17 (9.1 ± 9.9)	9.2 ± 1.30 (8.6 ± 1.35)	0.264	15
Mean number correct short delay	6.4 ± 2.97 (7.4 ± 1.07)	7.6 ± 1.95 (6.3 ± 2.21)	0.032*	15
Mean number correct medium delay	5.8 ± 2.95 (6.3 ± 1.06)	7.4 ± 2.30 (6.3 ± 1.77)	0.116	15
Mean number correct long delay	5.0 ± 1.58 (5.4 ± 1.71)	6.2 ± 0.84 (6.5 ± 2.64)	0.944	15
SOC (stockings of Cambridge)				
Mean number of problems solved in minimum required moves	5.2 ± 2.17 (7.0 ± 1.73)	4.6 ± 2.90 (7.7 ± 2.40)	0.311	14
PRM (pattern recognition memory)				
Mean latency to correct answer choice	2006 ± 461 (3364 ± 887)	2449 ± 807 (2239 ± 690)	0.001*	14
Mean total number correct	17.6 ± 3.58 (18.0 ± 2.70)	19.4 ± 3.51 (19.4 ± 3.51)	0.317	14
PAL (paired associates learning)				
Mean number of errors	30.2 ± 9.98 (34.3 ± 25.12)	30.6 ± 20.44 (41.8 ± 24.43)	0.521	14
Mean total trials completed	11.6 ± 1.82 (15.3 ± 5.83)	11.8 ± 4.60 (15.2 ± 3.90)	0.921	14
IED (intradimensional/extradimensional shift)				
Mean total errors	34.4 ± 18.77 (29.2 ± 17.06)	32.6 ± 28.52 (24.3 ± 10.09)	0.798	14
Mean pre-extradimensional shift errors	28.8 ± 15.74 (16.2 ± 10.89)	26.8 ± 31.78 (12.2 ± 7.55)	0.848	14
Mean extradimensional shift errors	3.2 ± 5.50 (7.7 ± 11.77)	4.2 ± 7.26 (8.0 ± 6.38)	0.922	14
SRM (spatial recognition memory)				
Mean total number correct	13.4 ± 1.34 (12.6 ± 2.92)	14.4 ± 2.88 (14.0 ± 2.00)	0.763	14
Mean latency to correct answer choice	2276 ± 752.5 (3137 ± 1363.9)	2425 ± 1288.1 (2457 ± 606.4)	0.259	14

CANTAB, Cambridge Automated Neuropsychiatric Test Assessment Battery. The data were analyzed at baseline and visit three with 15 patients. Group means are presented for the two visits, and a p value is shown. * p values that are significant ($p \leq 0.05$).

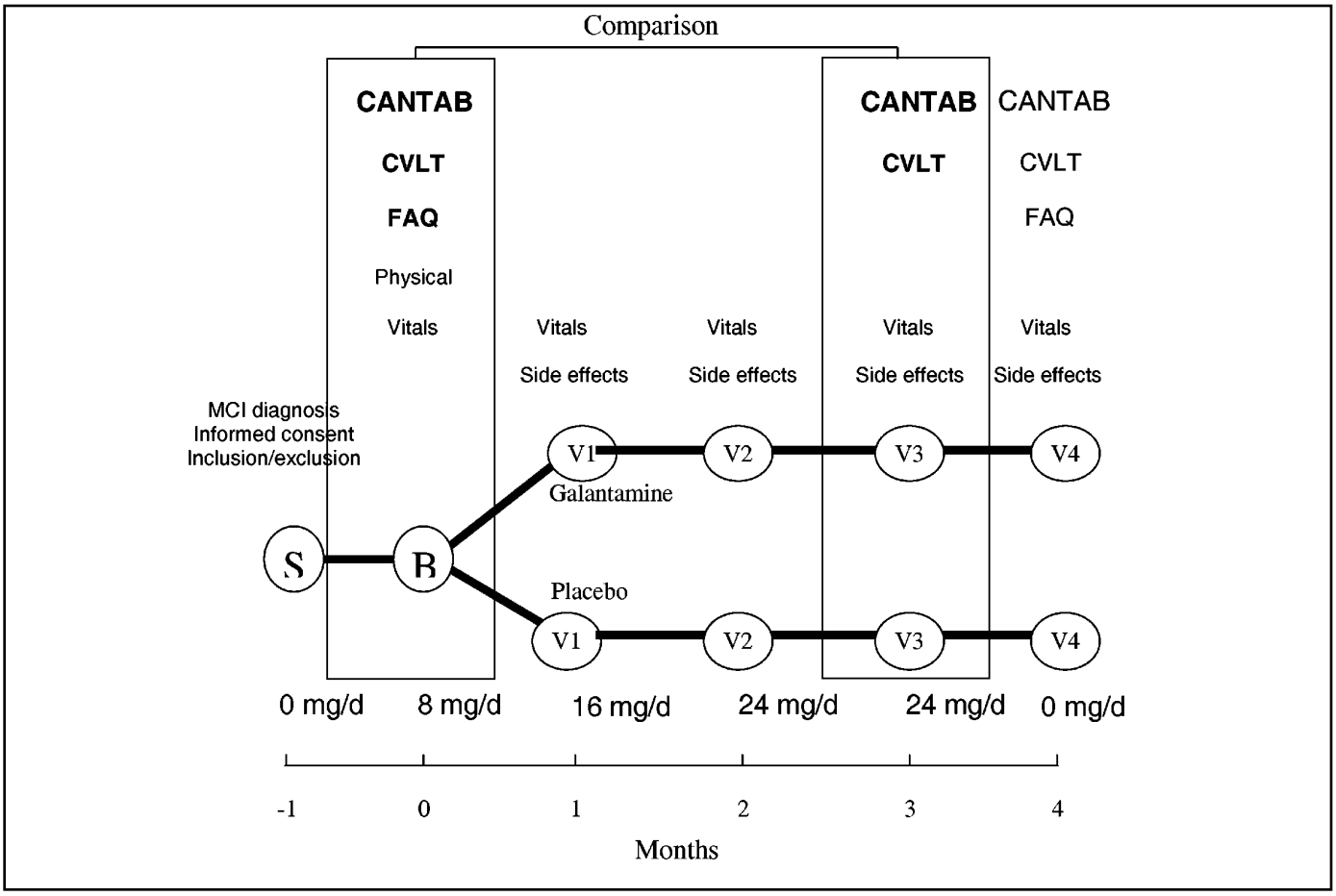

Figure 1. Experimental design. The study was 16 weeks long and consisted of four monthly visits. Treatment was initiated at 4 mg galantamine/placebo twice daily at the baseline visit. The dose was increased to 8 mg twice daily at visit one and to the therapeutic dose of 12 mg twice daily at visit two. Memory testing was administered at baseline, visit three, and visit four. The FAQ was administered at baseline and visit one, and vital signs and side effects were recorded at every visit. CANTAB, Cambridge Automated Neuropsychiatric Test Assessment Battery; CVLT, California Verbal Learning Test; FAQ, Functional Activities Questionnaire.

Examination (MMSE), the Clinical Dementia Rating scale, the Global Deterioration Scale, and the Alzheimer's Disease Assessment Scale-cognitive (ADAS-cog). By 24 months, however, significant differences between the groups were lost and did not recover by the end of the study at 36 months.[13] In another study, patients treated with donepezil reported "feeling sharper mentally" and improved on a modified ADAS-cog, the Symbol Digit Modalities Test, and the Digit Span Backwards, which suggests improved working memory capacity and executive control.[14] However, there was no improvement on the New York University Paragraph Test Delayed Recall, Boston Naming Task, Verbal Fluency test, Number Cancellation test, and Maze test.

Together, these studies suggest that the acetylcholinesterase inhibitor donepezil tends to improve global outcome measures, executive function, and working memory in MCI patients. Animal studies indicate that the mechanism of action of acetylcholinesterase inhibitors involves n-acetylcoline (nicotinic) receptors,[15] long considered a possible therapeutic target for both MCI and AD.[16-19] Among cholinesterase inhibitors, only galantamine can cause allosteric sensitization of nicotinic receptors[20] and has been shown to potentiate nicotinic acetylcholine agonist binding.[21-24] Although galantamine has already been shown to improve cognitive measures in patients with AD,[3,5,25,26] its effects in MCI patients have not been studied. The present study therefore investigated the possible benefit of galantamine in patients with MCI.

Methods

Patient population

Of 35 consecutive outpatients with memory problems,

Table 2. Data analysis for CANTAB					
	Baseline galantamine (placebo)	**Visit 3 galantamine (placebo)**	**Visit 4 galantamine (placebo)**	**p**	**n**
DMS (delayed matching to sample)					
Mean number correct simultaneous	8.75 ± 2.50 (9.10 ± 0.99)	9.2 ± 1.30 (8.1 ± 1.35)	8.6 ± 2.61 (9.0 ± 1.73)	0.095	12
Mean number correct short delay	6.4 ± 2.97 (7.3 ± 1.11)	7.6 ± 1.95 (5.9 ± 2.54)	7.6 ± 2.07 (7.0 ± 2.24)	0.070	12
Mean number correct medium delay	5.8 ± 2.95 (6.1 ± 1.21)	7.4 ± 2.30 (5.7 ± 1.70)	8.2 ± 2.17 (7.4 ± 2.23)	0.235	12
Mean number correct long delay	5.0 ± 1.58 (5.0 ± 1.73)	6.2 ± 0.84 (6.4 ± 2.23)	7.0 ± 1.41 (5.6 ± 2.38)	0.246	12
SOC (stockings of Cambridge)					
Mean number of problems solved in minimum required moves	6.0 ± 1.41 (7.5 ± 1.05)	5.5 ± 2.38 (8.2 ± 2.71)	8.3 ± 1.89 (7.0 ± 1.41)	0.023*	10
PRM (pattern recognition memory)					
Mean latency to correct answer choice	2006 ± 461 (3114 ± 790)	2449 ± 807 (1963 ± 362)	2219 ± 802 (2071 ± 608)	0.001*	11
Mean total number correct	17.6 ± 3.58 (17.8 ± 2.40)	19.4 ± 3.51 (18.5 ± 1.76)	18.2 ± 4.27 (17.8 ± 1.47)	0.813	11
PAL (paired associates learning)					
Mean number of errors	30.2 ± 9.98 (29.7 ± 22.51)	30.6 ± 20.44 (46.0 ± 21.95)	37.2 ± 26.27 (32.7 ± 18.50)	0.222	11
Mean total trials completed	11.6 ± 1.82 (14.2 ± 5.27)	11.8 ± 4.60 (16.3 ± 3.50)	12.4 ± 4.67 (12.8 ± 4.71)	0.301	11
IED (intradimensional/extradimensional shift)					
Mean total errors	34.4 ± 18.77 (27.5 ± 10.97)	32.6 ± 28.52 (25.5 ± 11.20)	30.8 ± 11.92 (23.8 ± 11.92)	1.00	11
Mean pre-extradimensional shift errors	28.8 ± 15.74 (17.7 ± 12.23)	26.8 ± 31.78 (12.5 ± 7.82)	23.2 ± 16.53 (8.2 ± 3.66)	0.915	11
Mean extradimensional shift errors	3.2 ± 5.50 (7.5 ± 13.35)	4.2 ± 7.26 (8.0 ± 6.20)	7.0 ± 10.58 (14.2 ± 10.96)	0.901	11
SRM (spatial recognition memory)					
Mean total number correct	13.4 ± 1.34 (12.2 ± 3.25)	14.4 ± 2.88 (13.3 ± 2.07)	12.8 ± 1.92 (14.5 ± 1.38)	0.096	11
Mean latency to correct answer choice	2276 ± 752 (2782 ± 1080)	2425 ± 1288 (2382 ± 475)	2350 ± 1146 (1769 ± 304)	0.191	11
CANTAB, Cambridge Automated Neuropsychiatric Test Assessment Battery. The data were analyzed at baseline, visit 3, and visit 4 with 10 patients. Group means are presented for the three visits and a p value is shown; * p values are significant (≤ 0.05).					

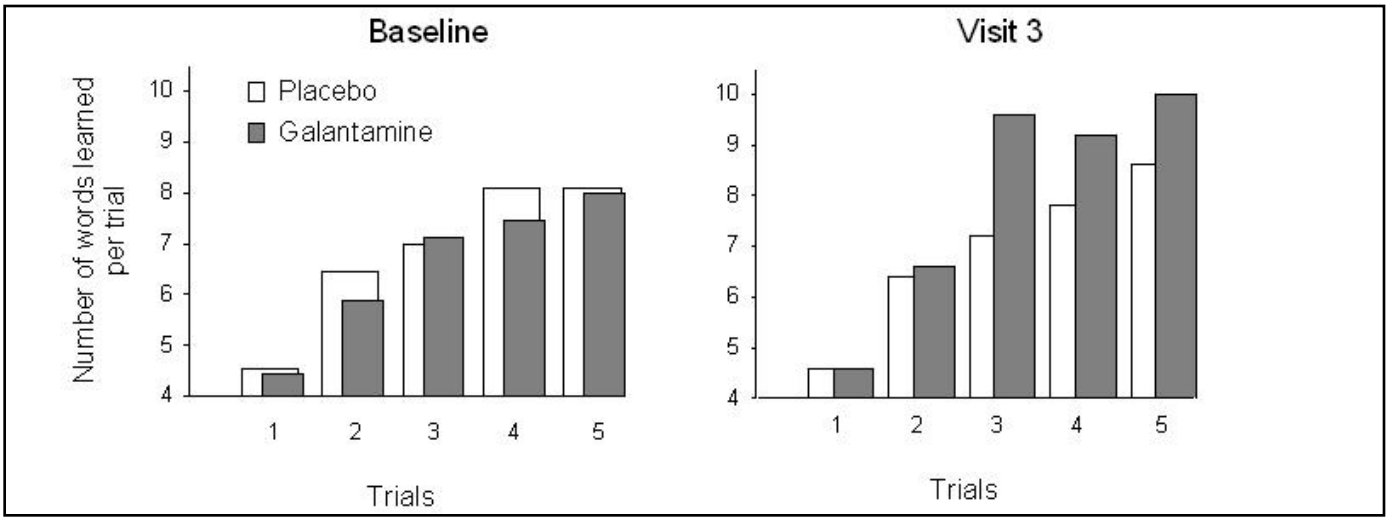

Figure 2. California Verbal Learning Test Immediate Free Recall. The mean number of words remembered per group is plotted separately for each trial, for the five trials (baseline and visit three). It is evident that the galantamine group exceeded the placebo group's highest number of words recalled in all five trials by the third trial in visit three. The normal learning curve of the galantamine group has been accelerated.

19 men aged 51 to 87 years (mean, 71 years; standard deviation, 9.31 years) met Petersen criteria[27] for MCI and enrolled in the study. The Petersen criteria were as follows: 1) memory complaints, 2) normal or close to normal activities of daily living, 3) normal general cognitive functioning, 4) abnormal memory for age, and 5) no dementia. Study participants were free from any physical or mental conditions that could account for impaired memory, in good enough health to participate in an experimental drug study, living independently, were not taking any cognition enhancers, and had an MMSE score of ≥ 26. Of the 19 participants, eight were assigned to galantamine and 11 to placebo groups. Of the nine patients who dropped out of the study, one no longer met criteria from screening to baseline; for the eight others, four were from the galantamine group, and four were on placebo. Reasons for the dropouts in the galantamine group were that one patient was noncompliant, one patient experienced a "hangover feeling" after two doses, one had headaches, and one withdrew consent. In the placebo group, two patients withdrew consent, one patient was diagnosed with lymphoma, and one patient was noncompliant.

Study design

This was a single-center, double-blind, randomized, placebo-controlled, dose-escalation study that was 16 weeks long and consisted of four monthly visits. The study design is shown in Figure 1. Patients received galantamine or placebo initiated at the baseline visit at a dose of 4 mg twice daily. The dose was increased to 8 mg twice daily after one month and to 12 mg twice daily after two months, remaining at that level for the rest of the study. Cognitive testing was administered at the baseline visit, visit three, and visit four. The Functional Activities Questionnaire (FAQ) was given at baseline and at visit four. Vital signs and information about side effects were recorded at each visit.

Outcome measures

The primary outcome measure was the Cambridge Automated Neuropsychiatric Test Assessment Battery (CANTAB, Cambridge Cognition, Ltd, Cambridge, UK). This nonverbal, computerized test uses a touch-sensitive screen to assess different cognitive domains such as executive functioning/working memory, recognition memory, and association learning. The CANTAB battery included six subtests:

1. The delayed matching to sample test (DMS) required participants to choose the one patterned shape out of four shapes that matched the earlier presented shape. Patients had to match the shapes presented simultaneously (the patterned shape and four choices all remained on the screen until the selection was made) or with a delay of 0, four, or 12 seconds (short, medium, or long delays), and the number of correct matches was recorded.

2. In the paired associates learning test (PAL), patients were shown up to eight locations of different patterned shapes, which were then hidden

behind a box. The patient had to choose which pattern was behind which of the boxes, and the number of correct choices was recorded.

3. The pattern recognition memory test (PRM) required participants to choose between a pattern they had already seen and a novel pattern, and the number of correct matches was recorded.

4. In the spatial recognition memory test (SRM), patients were presented with a white square that moved in sequence to five different places on the screen, and then a series of five pairs of squares, in which one of each pair was in a place previously seen. The number of correctly identified locations was recorded.

5. The intradimensional/extradimensional shift test (IED) measured the participants' ability to attend to the specific attributes of compound stimuli and to shift that attention when required. Two color-filled shapes were presented and, through forced choice, the participants learned which was the "correct" one. As the test progressed, the rule of what was "correct" was changed by the computer, and the previously "incorrect" stimulus was now "correct." Patients had to learn this new rule and begin choosing the "correct" shape again. A second object was then introduced as overlapping with the previously shown shapes (one object per shape), serving as a distracter, and the rules continued to shift back and forth; the participants were required to realize that the second object was a distracter and then ignore it. After a few more rule changes in the colored shapes (intradimensional shift), the second object (distracter) became the dictator of the rule (extradimensional shift). The patient then had to figure out that the rule was no longer dependent on the color-filled shapes, but on the second object, and then figure out which of the second objects was "correct." The total number of correct choices was recorded.

6. The stockings of Cambridge test (SOC) required that the patients arrange three colored balls, as modeled by the computer, in the least number of moves possible. The number of problems that were solved in the minimum number of moves possible was recorded.

The secondary outcome measure was the California Verbal Learning Test (CVLT, The Psychological Corporation, San Antonio, TX). The CVLT consists of recall and recognition of word lists through free recall, cued recall by category, yes/no recognition, and forced choice.

To test the subject's global functioning, we used the FAQ.[28] The FAQ measures the amount of dependence on a caregiver/spouse in performing certain daily activities on a scale of 0 to 3, with 0 being completely dependent and 3 being completely independent, through responses to a questionnaire. The FAQ is reportedly 90 percent sensitive and specific for the identification of global functioning deficits in dementia.[29]

Data analysis

CANTAB measures were analyzed using repeated-measure analysis of variance (ANOVA) and post-hoc analyses using paired t-tests. Data were analyzed first with scores from baseline and visit three with 15 patients (Table 1), and then calculated with scores from baseline, visit three, and visit four (Table 2), with N ranging from 10 to 12. CVLT data were analyzed by collapsing data from the five trials of immediate free recall to obtain a mean number of words remembered per trial. These were compared using repeated-measure ANOVA. To avoid false positives owing to multiple comparisons, Bonferroni correction was used where appropriate. FAQ scores were analyzed using a two-sided t-test for independent samples. Only the 10 patients who completed the study were included for the FAQ analysis, as the FAQ was administered at the first and last visits (first month and fourth month).

Results

Primary cognitive measure

On the CANTAB there were significant results on two of the six subtests, DMS (Table 1) and SOC (Table 2). There was a significant difference between the groups on the short delay of the DMS by visit three ($p = 0.032$), although only marginally significant by visit four ($p = 0.070$), and also on the number of problems solved in the minimum required moves on the SOC ($p = 0.023$) by visit four. Post-hoc analyses showed that the differences were contributed to by an improvement in the galantamine group, and, to a lesser extent, a worsening of the placebo group. Data for the IED, PAL, and SRM measures did not differ significantly between the two groups. The PRM data showed one highly significant measure ($p = 0.001$) between the groups of the mean latency time in choosing the correct answer at visit three and still at visit four, with post-hoc analyses revealing that the significance was caused by a shortening of the latency to correct answer choice in the placebo group, and, to a much

lesser extent, a lengthening in the latency to the correct answer choice in the galantamine group.

Secondary cognitive measure

There was a significant improvement in the galantamine-treated group in their performance on the CVLT immediate free recall ($p = 0.05$). No other measures showed statistically significant differences.

Global function measure

The galantamine-treated group significantly improved ($p = 0.0293$) on the FAQ scores.

Discussion

The participants of this study were diagnosed as having MCI, memory complaints, and mild impairment in global functioning. On the primary outcome measure of cognition, the CANTAB, there were significant differences between the groups in the DMS and SOC subtests. The differences between the groups faded to only marginal significance by the third measurement point, however, while significance was not seen in the SOC until the third measurement point. Reasons for these differences are unclear; however, a longer exposure to the drug (by visit four, the patients had been on the optimal therapeutic dose for two months, as opposed to one month at visit three) could have contributed to improvements at the final measurement point. Improvements that were there at the second measurement point and diminished by the final measurement point were consistent with the effects of other studies, which diminished over time. There was also a different number of patients in the baseline for analysis at visit three (15 patients) and visit four (10 to 12 patients). These temporary improvements are not inconsistent with the existing results of trials in MCI patients using donepezil.[13]

There was evidence of improvement in tasks that measured different areas of executive functioning. Those subsections that were improved, the DMS and SOC, used the executive functions such as working memory and planning behavior, whereas the tests that did not show significant improvement for the galantamine-treated group (PAL, SRM) required patients to rely on association and visuospatial memory. The IED is dependent on some aspects of executive functioning such as following directions and attention shifts, and relies on some memory of rules and history of correct/incorrect responses.

There was a peculiar finding in the PAL subtest data, namely, an increase in the latency to the correct answer choice for the galantamine group and a decrease for the placebo group. This may mean that there were treatment-related changes in thinking time. The importance of this finding is unclear, because findings of increased thinking time can be equivocal as to whether they mark an improvement in attention or concentration, a decline in functioning, or an increase in confusion. There is a possibility that this effect was caused by the nicotinic receptor-modulating properties of galantamine, creating an increase in attention or focus, thus increasing thinking time. However, the significant decrease in latency for the placebo group is not explained by this speculation.

There were significant improvements in the galantamine-treated group on the immediate free recall task of the CVLT. This task also reflects improved performance in working memory. These results resemble the results of Salloway[14] in MCI patients, in which the patients did not have significant improvements in primary memory measures, but did so in secondary measures of cognitive function.

It was apparent that the measures chosen were sensitive enough to detect changes in the general executive functioning and working memory of the MCI patients. Other measures assessing other types of memory that were more independent from executive functioning did not change significantly, leaving the possibility for measurement error in the sensitivity to these functions. The FAQ questionnaire was very sensitive at picking up differences in general functioning improvement in the MCI patients. Instruments for assessing global impairment of MCI patients have not been established yet; based on our results, the FAQ should be examined further as a possible measure for use in future studies.

The implications of these results are similar to what has been seen in other research in MCI patients: there are mild improvements, primarily in the areas of executive functioning, working memory, and global daily functioning, and these effects are significant, but fleeting. In such a short study, it is unknown whether or not the improvements seen would have disappeared over time as they did with donepezil/vitamin E,[13] although the effects of the DMS subtest were already losing significance by the end of the four-month study.

One significant problem with this study was its sample size. With few patients to start, there was considerable attrition from one measurement point to the next. Future research of galantamine in larger groups of MCI patients and of longer duration could shed more light into the nature of memory impairment and nicotinic receptor role in MCI.

Acknowledgment

This study was supported by an investigator-initiated research grant from Janssen Pharmaceutica to Andrius Baskys, MD, PhD.

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