Poster # P1-103

PRESERVATION OF COGNITIVE FUNCTIONING IN PATIENTS WITH MILD DEMENTIA AFTER TWO-YEAR COMBINED TREATMENT (Cholinesterase Inhibitors, Antidepressants and Non-Pharmacological Intervention): A Naturalistic Study

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INTRODUCTION

- In recent years, a new more active approach of dementia treatment has been published (4, 13).
  This presentation is part of an ongoing naturalistic study observing cognitive function changes in dementia patients. Our patients were treated with a combination of medications and non-pharmacological interventions.
- In previous presentations, we demonstrated preservation in cognitive function in medically ill people with mild to moderate dementia and depression after 6 and 12 months of integrative treatment (2, 3).
- The purpose of this study is to evaluate cognitive changes in the same group of patients which was followed up to a period of 24 months.

METHOD

- ***Subjects:***
  The study consisted of 68 patients (mean age = 76.1) including 37 males and 31 females with complaints of memory decline and depression. By January 2004, 27 patients had completed two years of treatment. The educational level ranged from 4 to 16 years. Their diagnoses were probable Alzheimer's Disease (AD), Vascular Dementia (VaD), or mixed AD and VaD (8).
  Exclusion criteria include patients with severe dementia (MMSE less than 15), psychosis, alcohol and substance abuse, severe neurological disorders, and recent major stresses (death in the family, surgery, etc).
- ***Design***:
  Patients were assessed by a battery of neuropsychological tests at the baseline, and after 6, 12 and 24 months of treatment. One of three antidepressants was used: Sertraline, Citalopram, Venlafaxine XR alone, or in combination with Bupropion XR and one of three cholinesterase inhibitors (Donepezil, Rivastigmine or Galantamine).
  The patients were taking their regular medications (for Hypertension, Cardiac problems, Diabetes, etc.), as well as Aspirin or Plavix, Multivitamins, Vitamin E, Folic acid, Alpha-Lipolic Acid, Omega-3 and Coenzyme Q-10. We encourage our patients to use stress management tools regularly, to maintain healthy diets, to modify their lifestyle, and to perform mild physical exercises.

Cognitive tests:

1. Mini-Mental State Examination (MMSE, a maximum score of 30). For attention assessment we used serial 7 (5).
2. Cognometer, a chronometrical test, is a computer program which is used to measure reaction time (RT) and attention (www.cognitivecare.com).
3. Neurobehavioral Cognitive Status Examination (Cognistat) is used along with MMSE to assess 10 cognitive domains: attention (digit span), orientation, language abilities, construction abilities, memory (four items), calculations, similarities and judgment (9).
4. Ruff 2&7 Selective Attention Test is designed to measure sustained and selective attention over a short period of time (2-4 minutes) on trials of a visual search and cancellation task (16).
5. The Intermediate Visual and Auditory Continuous Performance Test (IVA) is implemented for assessment of intermediate (about 25 minutes) sustained and selective attention. (17).
6. Word List Memory Learning Test (WLMLT) is used to assess verbal memory. Delayed recall of the word list is tested after a 5 minutes.
7. Ruff-Light Trail Learning test (RULIT) is designed to measure visual spatial learning and memory. Delayed recall is tested after 60 minutes.(15).
8. Word retrieval category tests (animals and letters).
9. Ruff Figural Fluency Test (RFFT) provides information regarding nonverbal capacity of the right frontal lobe to produce unique designs (14).
10. Wisconsin Card Sorting Test (WCST), computerized version, is used primarily to assess prefrontal cortical function, including working memory (shifting, abstraction, and responsiveness to feedback) (7).

Statistical Analysis:

Statistical analysis was done by using SPSS software and running the Wilcoxon Signed ranks Test (6, 18). In this presentation, tests of significance were one-tailed.

RESULTS

- MMSE had increased to 26.40 (6 months, $p < 0.05$) and 27.5 (24 months, $p>0.05$). Reaction time (Cognometer) decreased from 587.48 ms (milliseconds) to 383.74 ms by the end of two years (34.68%, $p<0.007$).
- Attention domain
  Four cognitive tests (10 parameters) were used to assess attention domain (Table 1). None of the parameters gave any indication of decline in function and 7 out of 10 parameters showed significant improvement by 24 months of treatment. There was consistent improvement during the 24 months in the Cognistat Attention Scale (to 85.26%, compared to baseline, $p<0.001$). On the 2 & 7 Selection Attention Test a significant increase in detection and controlled search speed ($p<0.02$) with no decrease in accuracy were observed. On IVA there was an increase in performance in both the audio and visual components, by 14% ($p < 0.03$) and 24% ($p<0.01$), respectively.
- Memory domain
  Four cognitive tests (11 parameters) were used to assess memory domain function (table 1). None of the parameters gave any indication of decline in function and 9 out of 11 parameters showed significant improvement by 24 months of treatment.
  The memory scale on the Cognistat had a tendency to increase during the first 6 months ($p>0.05$), and significantly increased by the end of the 24 months by 59.9% ($p<0.001>$).
  The naming scale on the Cognistat showed the same changes: tendency to increase after 6 months ($p>0.05$) and significantly increase after 24 months of treatment by 15.7% ($p<0.012$). The construction scale on the Cognistat significantly increased at the end of the first 6 months by 19.5% ($p<0.0024$) and remained at this level by 24 months (24.1%, $p<0.033$).
  Working memory (WCST), the number of complete categories, did not change in the first 6 months, but improved by the end of 24 months by 90.91% ($p<0.014$).
  On the WLMLT we found gradual improvement for the 5 minute recall, up 17.6 % ($p < 0.01$) after 6 months and continued at the same level by 24 months.

Table 1. Performance on cognitive tests after 6, 12, and 24 months of treatment

Test	Baseline (0) Mean	N	6 Months (6) Mean	N	p 6-0	12 Months (12) Mean	N	p 12-0	24 Months (24) Mean	N	p 24-0
General											
MMSE	**25.54**	67	**26.6**	55	*0.038*	**26.94**	53	*0.001*	**27.51**	27	*ns*
Cognometer Reaction time	**587.48**	50	**485.68**	40	*0.031*	**477.71**	38	*0.010*	**383.74**	19	*0.003*
Attention Domain											
Cognometer Attention	**22.74**	49	**28.62**	39	*0.003*	**30.65**	35	*0.003*	**32.47**	19	*0.003*
Cognistat Attention	**3.91**	68	**5.46**	55	*0.001*	**6.04**	53	*0.001*	**7.26**	27	*0.001*
Cognistat Repetition	**10.03**	68	**11.26**	55	*0.003*	**11.15**	53	*0.001*	**11.85**	27	*0.001*
Cognistat Calculation	**3.46**	68	**3.56**	55	*ns*	**3.64**	53	*0.022*	**3.74**	27	*ns*
2&7 Auto Detection Speed	**127.59**	37	**150.94**	33	*0.024*	**95.81**	33	*ns*	**109.33**	21	*0.006*
2&7 Auto Detection Accuracy	**90.03**	37	**89.04**	33	*ns*	**91.04**	33	*ns*	**94.94**	21	*ns*
2&7 Controlled Search Speed	**112.38**	37	**133.61**	33	*0.012*	**87.36**	33	*ns*	**98**	21	*0.006*
2&7 Controlled Search Accuracy	**88.72**	37	**88.62**	33	*ns*	**88.53**	33	*ns*	**91.46**	21	*ns*
IVA Performance Audio	**101.10**	58	**104.69**	50	*ns*	**105.31**	42	*ns*	**115.19**	21	*0.031*
IVA Performance Visual	**92.55**	58	**91.63**	50	*ns*	**94.48**	42	*ns*	**114.76**	21	*0.011*
Memory Domain											
Cognistat Naming	**6.5**	68	**6.89**	55	*0.028*	**7.63**	53	*0.001*	**7.52**	27	*0.012*
Cognistat Construction	**3.19**	68	**3.82**	55	*0.032*	**3.79**	53	*0.001*	**3.96**	27	*0.033*
Cognistat Memory	**6.16**	68	**7.07**	55	*ns*	**8.09**	53	*0.001*	**9.85**	27	*0.000*
WCST Catergories Complete	**2.42**	38	**2.76**	29	*ns*	**3.63**	24	*ns*	**4.62**	13	*0.014*
WLMLT 5 minute recall	**4.2**	40	**4.94**	31	*0.008*	**4.77**	31	*0.043*	**5.05**	20	*0.019*
RULIT Total Correct	**101.415**	41	**97.56**	34	*ns*	**95.08**	26	*ns*	**110.5**	16	*0.017*
RULIT Total Step Error	**43.51**	41	**39.71**	34	*0.034*	**40.54**	26	*ns*	**31.88**	16	*0.020*
RULIT immediate memory correct	**9.88**	41	**9.53**	34	*ns*	**8.73**	26	*0.003*	**10.56**	16	*ns*
RULIIT immediate memory errors	**6.34**	41	**6.77**	34	*ns*	**8.04**	26	*0.010*	**7.38**	16	*ns*
RULIT delayed memory correct	**10.68**	41	**11.59**	34	*0.020*	**11.36**	26	*ns*	**12.69**	16	*0.006*
RULIT delayed memory errors	**5.42**	41	**4.71**	34	*ns*	**4.52**	26	*ns*	**3**	16	*0.010*
Frontal Lobe Domain											
Cognistat Comprehension	**5.65**	68	**5.8**	55	*ns*	**5.77**	53	*ns*	**6**	27	*0.012*
Cognistat Similarities	**6.02**	68	**7.15**	55	*0.001*	**7.23**	53	*0.001*	**7.63**	27	*0.000*
Cognistat Judgment	**5.09**	68	**5.23**	55	*0.005*	**5.59**	53	*0.004*	**5.7**	27	*ns*
Word Fluency Letter	**7.96**	48	**9.91**	54	*0.002*	**9.82**	49	*0.000*	**11.33**	27	*0.001*
Word Fluency Animals	**10.94**	67	**12.37**	54	*0.011*	**12.52**	49	*0.007*	**14.85**	27	*0.001*
RFFT Unique Designs	**43.73**	64	**48.846**	52	*0.006*	**46.67**	52	*ns*	**52.12**	25	*0.006*
RFFT Perservative Errors	**12.172**	64	**12.75**	52	*ns*	**10.923**	52	*0.043*	**7.16**	25	*0.023*
RFFT Error Ratio	**0.3**	64	**0.33**	52	*0.010*	**0.26**	52	*0.005*	**0.14**	25	*0.005*
WCST Total Correct	**71.58**	38	**76.69**	29	*0.099*	**76.83**	24	*ns*	**73.77**	13	*ns*
WCST Total Errors	**51.92**	38	**46.04**	29	*0.038*	**39.38**	24	*0.027*	**29.92**	13	*0.011*
WCST Perserverative Responses	**35.11**	38	**28.9**	29	*0.027*	**23.83**	24	*0.014*	**15.69**	13	*0.004*
WCST Perserverative Errors	**30.03**	38	**25.55**	29	*0.040*	**21.08**	24	*0.017*	**14.54**	13	*0.003*
WCST Non-perseverative Errors	**21.9**	38	**20.48**	29	*ns*	**18.29**	24	*ns*	**15.85**	13	*ns*
WCST Conceptual Responses	**52.32**	38	**60.931**	29	*0.034*	**64.54**	24	*0.005*	**66.54**	13	*0.016*
WCST Trials to complete	**47**	38	**41.41**	29	*ns*	**29.46**	24	*ns*	**20.69**	13	*ns*

ns - not significant at p<.05

* - Not Significant

On the visual-spatial memory test (RULIT), by the end of 24 months, the one-hour delayed recall showed an improvement in delayed memory correct recall (18.8%, $p<0.006$) and a significant decrease in delayed memory errors (44.7 %, $p<0.001$). In the immediate recall visual memory there was no change throughout the whole observation period.

- Executive Function Domain
  Four cognitive tests (15 parameters) were used to assess executive domain function. None of the parameters gave any indication of decline in function and 12 out of the 15 parameters showed improvement by 24 months of treatment (Table 1).
  On the Cognistat, performance of comprehension, similarities and judgment increased by 6.2% ($p<0.012$), 6.7% ($p<0.001$), 12% ($p > 0.05$), respectively.
  On the Word Fluency Test the capacity to produce words increased categorically for animals by 42.3 % ($P < 0.001$) and for letters by 35.7 %, ($P < 0.001$).
  Unique design (RFFT) was significantly increased by the end of two years by 19.19 % ($p<0.06$), and at the same time, perseverative errors was decreased by 41.2 % ($p<0.023$).
  On the WCST, total correct responses did not change and conceptual level responses increased by the end of 24 months. At the same time, the number of total errors, perseverative errors, and perseverative responses decreased.

DISCUSSION

- Three years ago, we developed and implemented a protocol specifically designed for treatment of these types of demented, depressed, medically ill people with MMSE range (15 – 26). People tolerated this treatment well, and by 6 months depression in mostly cases was resolved. At baseline, presented data showed that patient's cognitive deficit was across all three cognitive domains. Concomitant depression has an additional impact on cognition (1, 10, 12).
- After two years of treatment utilizing this protocol, performance in all the cognitive domains was preserved and even became better in certain parameters. The most interesting data found in improvement in the frontal lobe functions by 24 months of treatment. These findings are crucial for normal functioning as well as for the delay of nursing home placement (11).

CONCLUSIONS

These findings contribute to growing body of research into the integrative treatment in mild to moderate dementia with depression and support the need for future study.

References:

1. *Alexopoulos GS: Frontal Dysfunction in Geriatric Depression, AAGP 15th Annual Meeting, Am J Geriatr Psychiatry 2002; 10:2 Supplement 1: 11*
2. *Bragin V, Dzharfarova N, Bragin I, Perelmuter O: Assessment of different cognitive domains in dementia patients after six-month treatment. Poster at the 8th International Conference on Alzheimer's Disease and Related Disorders, Stockholm, Sweden, 2002; July 20-25 (973).*
3. *Bragin V, Chemodanova M, Dzhafarova N, Reznik D, Shereshevsky G: One-Year Combined (Cholinesterase Inhibitors and Antidepressants) Treatment and Non-Pharmacological Intervention of Patients with Mild to Moderate Dementia: Assessment of Cognitive Function Changes, Eleventh Congress of the International Psychogeriatric Association, Poster Presentation Chicago August 2003: 299*
4. *Clare L.: Cognitive rehabilitation in early-stage Alzheimer's Disease. Poster at the 8th International Conference on Alzheimer's Disease and Related Disorders, Stockholm, Sweden, 2002; July 20-25 (15).*
5. *Folstein MF, Folstein SE, McHugh PR: "Mini-Mental State": a practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975; 12: 189-198*
6. *Glass GV, Hopkins KD: Statistical Methods in Education and Psychology, Third Edition, 1996*
7. *Heaton RK, Chelune GJ, Tailey JL, Kay GG, Curtiss G: Wisconsin Card Sorting Test Manual. Odessa, Fla, Psychological Assessment Resources, 1993*
8. *Kalaria RN, Ballard C: Overlap between pathology of Alzheimer Disease and Vascular Dementia, Alzheimer Dis Assoc Disord 1999; 13(suppl3):S115-123*
9. *Kiernan RJ, Mueller J, Langston W: Cognistat (Neurobehavioral Cognitive Status Examination), Odessa, Fla. Psychological Assessment Resources, 2002*
10. *Kiosses DN, Klimstra S, Murphy C, Alexopoulos GS: Executive Dysfunction and Disability in Elderly Patients With Major Depression, Am J Geriatr Psychiatry 2001; 9:3:269-274*
11. *McAvay G. J., Bruce M L., Meyers B.S.: Combined effects of major depression and mild cognitive impairment associated with functional disability in elderly medical home care patients. AAGP 16th Annual Meeting, Honolulu Hawaii 2003; 80-81.*
12. *Moretti, R, Torre P, Antonello R M, Cazzato G, Bava A. : Depression and Alzheimer's disease: Symptom or comorbidity? American Journal of Alzheimer's Disease and Other Dementias. 2002; 17:6 pg 338-344.*
13. *Michael D B: A multifaceted approach to cognitive decline in patients with Alzheimer's disease, First Annual Dementia Congress, Poster Presentation Chicago Sept 2002 : 150*
14. *Ruff RF: Ruff Figural Fluency Test (RFFT), Odessa, Fla. Psychological Assessment Resources, 2002*
15. *Ruff RM, Allen CC: Ruff-Light Trail Learning Test (RULIT), Odessa, Fla., Psychological Assessment Resources 2002*
16. *Ruff RM, Allen CC: Ruff 2 & 7 Selective Attention Test, Odessa, Fla., Psychological Assessment Resources 2002*
17. *Sandford JA, Turner A: Intermediate Visual and Auditory Continuous Performance Test (IVA), Richmond, VA Manual 1995*
18. *SPSS Inc.: SPSS Base 10.0 Applications Guide, Chicago, IL 1999*

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