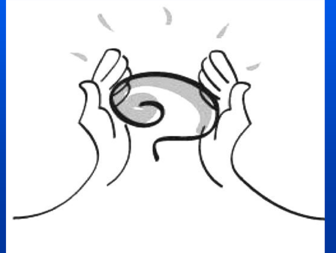
Integrative Therapy Postpones Cognitive Decline in Demented Depressed Patients: A Naturalistic 48 Months Follow-up Study



Valentin Bragin, MD, PhD[1], Marina Chemodanova, PhD, MEd[1], Ilya Bragin, MD[1], Narmina Dzhafarova, MD, DO[1], Irina Mescher, MD[1], Pavlo Chernyavskyy, BA[1], Gjumrakch Aliev, MD, PhD [2]

[1]Stress Relief and Memory Training Center, Brooklyn, New York, NY USA, [2] School of Health Science and Healthcare Administration, University of Atlanta, Atlanta, GA, USA

Contact e-mail: val11235@yahoo.com

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Introduction

Alzheimer's disease is characterized by multiple pathophysiological processes, including but not limited to, amyloid and tau deposition. Among the many pathophysiological processes implicated in the development of Alzheimer's, are cardiovascular pathology with subsequent changes in regional cerebral blood flow, small vessel disease (1, 2, 3), hypoperfusion (4), chronic hypoxia (5, 6), white matter lesions (7), nitrogen oxide and free radical accumulation, oxidative stress (8), and mitochondrial dysfunctions (9), all of which have been shown to be detrimental to energy metabolism. Specifically, these changes have a strong negative effect on protein synthesis, neuronal malfunctions, cognitive speed, gait, coordination and global cognition.

Based on the pathogenesis of AD, an integrative approach to the prevention and therapy has been developed and has gained significant attention in recent years (10, 11). However, in most clinical practices, patients with dementia (especially AD) are solely given medications (cholinesterase inhibitors or NMDA receptors antagonists), resulting in a transient cognitive improvement followed by a subsequent decline below baseline levels (12).

Recent studies have suggested that the combination of medications alongside non-pharmacological interventions could be more effective in treating AD than medication alone, and possibly this may be the most effective way of treating these patients in the future. In these studies, medication treatment was accompanied by one or two non-pharmacological intervention modalities, such as cognitive rehabilitation interventions (13, 14), vitamins or nutriceutical formulations (15) or physical exercise (16). There have been no comprehensive studies hitherto which have investigated the long-term effect of this integrative therapy model when multiple non-pharmacological treatment modalities are implemented simultaneously in real clinical settings.

The current presentation is a part of an ongoing, naturalistic, observational study of integrative treatment for severely, medically ill seniors with mild to moderate dementia and depression. So far, in our previous presentations, we have demonstrated the preservation of cognitive functioning relative to baseline levels in demented patients by 12, 24 and 36 months of treatment (17, 18).

The aim of this study is to investigate the effectiveness of this integrative treatment model for arresting cognitive decline in demented patients in an outpatient setting, over a length of 48 months.

Methods & Analysis

The study group consists of 156 geriatric patients (79 male, 77 female; mean age – 73.63) with an average education level of 12.71 years, who were diagnosed with mild to moderate dementia and depression, and have multiple medical problems (hypertension, coronary artery disease, hyperlipidemia, diabetes, arthritis and others). Their psychiatric diagnoses are probable Alzheimer Disease (AD), Vascular Dementia (VaD), mixed AD and VaD and Organic Mood Disorder with Depressed Mood.

The medications include antidepressants (sertraline, citalopram, escitalopram, or venlafaxine alone or in combination with bupropion), or cholinesterase inhibitors (donepezil, rivastigmine or galantamine alone or in combination with memantine). Over the period of this study, newer medications (escitalopram and memantine), vitamins (vitamin D, L-methylfolate) and supplements (Axona, alpha-lipolic acid and acethyl-L-carnitine) were added to the treatment regimen. Some of the patients at certain points in their treatment were given medications to manage insomnia (zolpidem, zaleplon, and eszopiclone), anxiety (lorazepam, oxazepam), neuropathic pain (gabapentin) and/or behavioral problems (risperidone, haloperidol, quetiapine).

Non-pharmacological interventions included vitamins (multivitamins, vitamin E, vitamin D, Folic acid or L-methylfolate), supplements (alpha-lipoic acid, acetyl-l-carnitine, omega-3 and coenzyme Q-10), diet recommendations and the Brain Activation Program™ (BAP)™ (19).

The optimal combinations of medications and non-pharmacological interventions were individually tailored to every patient based on his or her disease and medication profile, cognitive performance and physical abilities and limitations. These patients underwent yearly cognitive retesting to assess the progress of the treatment and to make necessary adjustments. This presentation is based on data collected from the charts of patients who had been in treatment for 48 months (45 patients) and less.

Cognitive Tests & Statistics

Results from four tests from our neuropsychological battery are presented in this poster.

1. The Folstein Mini Mental Status Exam (MMSE) with a maximum score of 30. For attention assessment, serial 7's calculation was used (20). Patient history of mood disorders, trauma, stroke and family history of similar symptoms, which may have contributed to the patient's decline, was assessed. Exclusion criteria for this presentation includes patients with severe dementia (MMSE less than 15) and severe depression, any evidence of psychosis or history of alcohol or substance abuse, severe neurological disorders, and recent major stresses (death in the family, surgery, etc.).

2. Clock Drawing Task (CDT).
3. Verbal Fluency Tasks (VTF) – categories included animals and letters.
4. Neurobehavioral Cognitive Status Examination (Cognistat), which is used along with MMSE to assess different cognitive domains: orientation, attention (digit span), language abilities (comprehension, repetition, naming), construction abilities, word memory (four items), calculations, similarities, and judgment (21).

Data analyses were carried out with SPSS for Windows, version 16.0 (SPSS Inc., Chicago, Ill.) utilizing descriptive and non-parametric statistical analysis (Wilcoxon signed-rank test) (22). All statistical analyses two-tailed with a p value of <.05 were considered statistically significant.

Results

All participants exhibited depression and memory problems. The length of depression and memory loss before the treatment was 39 months and 37 months retrospectively. Most of the cohort suffered from anxiety and insomnia (83.3%, 82.0%, respectively). A significant number of patients had hypertension (85.3 %), dyslipidemia (71.8%) and coronary artery disease (58.3 %). Nearly half of the cohort (71 patients, 45.5%) underwent imaging studies (mainly MRI). A normal brain MRI was found in 18 patients (25.3%). The rest of the patients (54, 74.7%) had cortical atrophy, lacunar infarcts, dilated ventricles and white matter microvascular changes, either alone or in combination with each other.

Descriptive statistics are shown in Table 1.

Table 1. Cognitive test results

Test	Baseline			12 Months				24 Months				36 Months				48 Months			
	N	Mean	SD	N	Mean	SD	P 1-0*	N	Mean	SD	P 2-0**	N	Mean	SD	P 3-0***	N	Mean	SD	P 4-0****
MMSE	156	25.74	3.96	124	26.35	3.53	0.015	81	26.93	2.99	0.004	68	26.56	3.39	0.013	45	26.84	3.30	0.217
CDT (Clock Drawing Task)	153	2.65	1.30	122	3.01	1.16	0.002	80	3.33	0.98	0.001	67	3.31	1.56	0.001	44	3.16	1.10	0.046
WFT (Animals)	148	10.22	4.45	123	11.30	4.88	0.028	81	11.74	4.54	0.031	68	11.75	5.20	0.005	42	11.29	4.01	0.277
WFT (Letters)	133	8.35	4.08	120	9.58	4.16	0.001	81	9.85	4.36	0.004	68	9.81	4.67	0.004	42	10.07	4.25	0.440
Cognistat																			
Orientation	156	11.01	1.64	119	11.37	1.58	0.005	81	11.64	0.88	0.006	60	11.60	0.99	0.019	35	11.86	0.36	0.022
Attention	156	5.68	2.57	119	6.63	1.99	0.001	81	7.16	1.62	0.001	60	7.28	1.42	0.001	35	7.14	1.68	0.010
Comprehension	156	5.76	0.63	119	5.86	0.59	0.043	81	5.93	0.41	0.035	60	5.97	0.26	0.023	35	5.97	0.17	0.096
Repetition	156	10.90	2.23	119	11.31	1.60	0.022	81	11.63	1.02	0.001	60	11.73	0.80	0.002	35	11.46	1.42	0.020
Naming	156	6.90	1.76	119	7.31	1.37	0.028	81	7.52	1.22	0.007	60	7.32	1.38	0.316	35	7.77	0.91	0.093
Construction	156	3.21	1.89	119	3.73	1.89	0.001	81	3.99	1.65	0.001	60	3.83	1.95	0.041	35	4.37	1.83	0.023
Memory	155	7.01	3.46	119	8.08	3.29	0.021	81	8.69	2.96	0.001	60	8.37	2.99	0.002	35	8.69	3.43	0.057
Calculation	156	3.53	1.03	119	3.73	0.84	0.006	81	3.72	0.78	0.375	60	3.78	0.56	0.116	35	3.86	0.43	0.262
Similarities	156	6.53	1.91	119	7.15	1.47	0.001	81	7.22	1.42	0.006	60	7.03	1.68	0.059	35	7.49	1.12	0.099
Judgement	156	5.16	1.40	119	5.57	0.88	0.001	81	5.73	0.85	0.005	60	5.68	1.02	0.013	35	5.91	0.37	0.057

* - P Value between baseline and 12 months
** - P Value between baseline and 24 months
*** - P Value between baseline and 36 months
***** - P Value between baseline and 48 months

No tests at any point of cognitive assessment during the treatment period showed significant decline.

The MMSE score was above the baseline for the whole period of treatment (Figure 1). Performance on the CDT increased by 13.6% at 12 months and remained above baseline (25.2%, p<0.046), by the end of the observation period (Figure 2). The VFT (animals) score increased by 10.5% at 12 months and remained at this level by the end of the 48 month period. The VFT (letters) score increased by 14.8% at 12 months and demonstrated further increase by the 48th month of treatment (20.1%, p>0.05) (Figure 3).

Figure 1. Mini Mental Status Exam

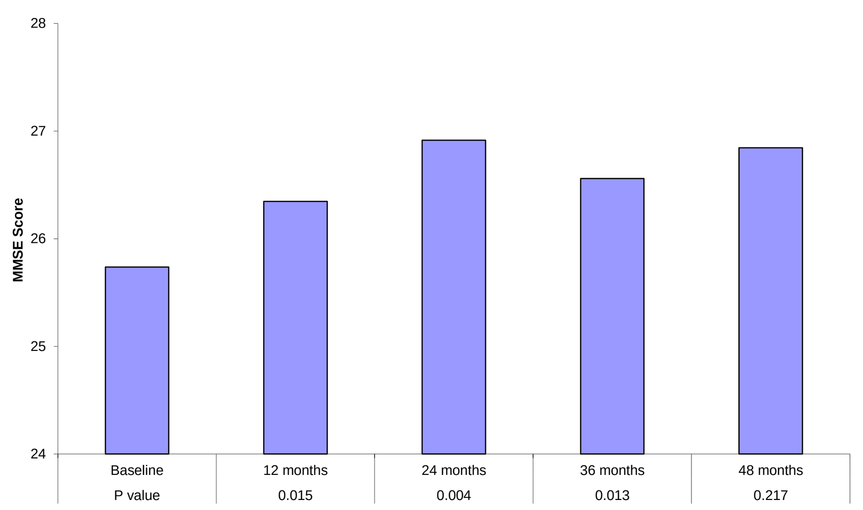


Figure 2. Clock Drawing Task

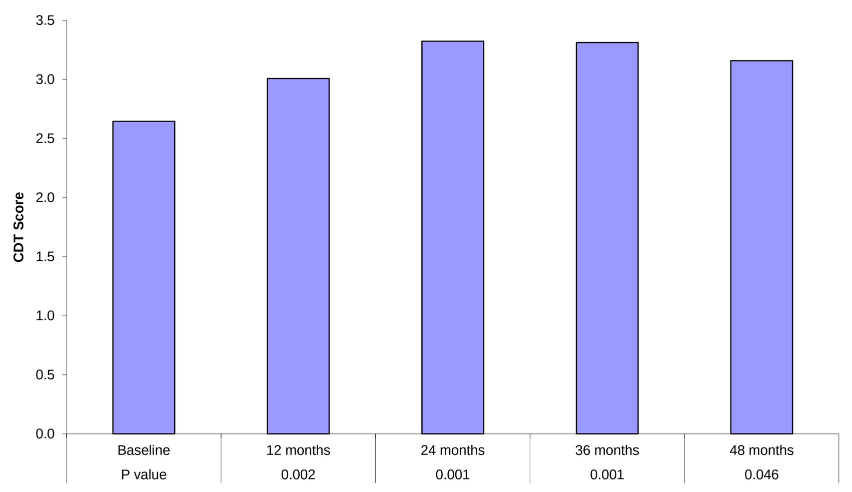
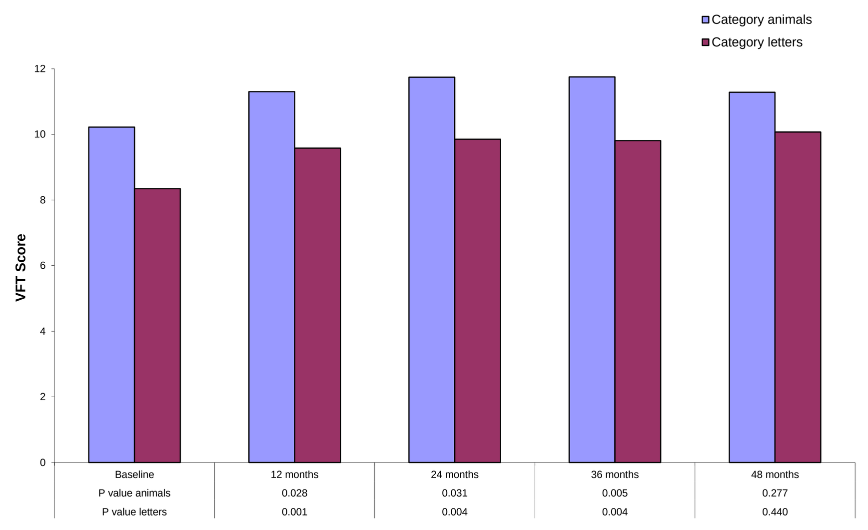


Figure 3. Verbal Fluency Tasks



Cognistat (Orientation, Comprehension, Repetition, Calculation, Similarities and Judgment) was above baseline for the whole duration of treatment (3.3 – 7.7%). Performance on Cognistat (Attention) increased by 25.8% (p<0.01) at 48 months of the treatment. Cognistat (Naming) increased by 12.7% (p>0.05) at 48 months of the treatment. Cognistat (Construction) increased by 36.4% (p<0.02) by the end of the 48 months. Cognistat (Memory) increased by 23.8% (p>0.05) at 48 months.

Discussion

The preservation of cognitive functions in demented patients including AD has become feasible based on intensive basic and clinical research over the last two decades (23). Basic research has expanded our understanding of AD pathophysiology and brought up new conceptualizations about the irreversible and partially reversible changes in AD, thereby allowing us to develop new interventions based on our changed conceptualizations.

Studies in rodents have shown that mental exercise enhances cerebrovasculature (24), reduces brain beta-amyloid deposition (25), induces neurogenesis (26), and synaptogenesis, and increases hippocampal synaptic reactivity (25). An adaptation to hypobaric intermittent hypoxia in rats with experimental AD ameliorated oxidative stress and blocked A-β induced memory decline (27). The combination of acetyl-L-carnitine and lipoic (ALCAR+LA) improves learning abilities in aging beagles (28). An antioxidant enriched diet partially reversed mitochondria dysfunctions in aging canines (29).

The results of this body of animal research are the foundation for the clinical implementation of these integrative treatment models for elderly humans: a combination of medication therapy and non-pharmacological modalities (diet, physical exercises and cognitive training). A combined treatment model for AD is in its earliest stage of development. There are still a large number of unanswered questions about adequate and safe physical and cognitive activities for fragile, sensory deprived, medically ill demented/depressed patients, who are not good candidates for an aerobic workout regimen.

A recent report by Chan A et al (15), showed an improvement in multiple domains of the neuropsychiatric inventory and maintenance of activities of daily living (ADL) in people with early stage AD, who were taking donepezil and a vitamin/nutriceutical formulation for 12 months. Another report by Bottino C et al (13) indicates a positive treatment effect on MMSE and the backward digit span as a result of combined therapy (cognitive rehabilitation and rivastigmine) in AD patients for 5 months. A study by Rozzini L et al (14) demonstrated an improvement in memory, abstract reasoning and depression scores in 12 months of combined therapy (cognitive rehabilitation and cholinesterase inhibitors). Reguena C et al (30) used a combination therapy model (medication and cognitive training) and showed an improvement in cognitive functions by the end of 12 months of therapy. However, by the end of 24 months of treatment, this effect diminished. Chapman SB et al (31) showed slowing rate of verbal and functional decline in AD patients, after 8 weeks of cognitive-communication stimulation and donepezil treatment. Erkroth-Bucher M and Siberski J (32) reported an improvement on the Dementia Rating Scale in mild AD patients after 6 weeks of cognitive training. Some of these patients were taking medications at the same time. Recently, it was demonstrated that meditation, chanting and finger movements (33), and cognitive training (34), increase brain blood flow.

We did not find data related to the results of integrative (combined) treatment in which all non-pharmacological modalities were used simultaneously in the office and, especially, with further continuation at home. Since 2000 we have been developing a "real life," integrative treatment model based on pharmacological and non-pharmacological interventions. The working hypothesis of our study is that preservation of cognitive functions in demented, depressed, medically ill people may be possible with implementation of our treatment program. The length of preservation has been investigated. A comparison with similar studies could not be done due to the lack of literature of any study with a similar objective, except our previous 24 and 36 months studies (17, 18).

In our work, by 48 months the performance on all tasks was above baseline. A more robust response from the presented tests for this cohort of patients was demonstrated on VFT (p<0.465), CDT (p>0.05), Cognistat (attention, p<0.01, naming, p>0.05, construction, p<0.023, and memory, p>0.05).

These findings suggest that an integrative treatment with medications, vitamins, supplements, cognitive training and multiple sensory stimulations shows promise in preserving cognitive functions in severely medically ill demented, depressed seniors. The results of this presentation based on an integrative therapy approach in AD should encourage further studies to investigate the possibility of both improving the quality of life of AD victims and delaying nursing home placement.

Conclusion

Our integrative treatment model for depressed, demented patients has been effective in delaying cognitive decline for 48 months of therapy. Going forward, prospective studies with combined therapy for "real life" patients with AD are necessary.

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