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Beneficial effects of an Integrated Psychostimulation Program in patients with Alzheimer's disease

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Abstract

Background—The existing pharmacological treatments for Alzheimer disease (AD) can only slow the progression of symptoms or delay admission to long-term care facilities. The beneficial effects of non-drug treatments are poorly studied.

Objective—To describe the effects of an Integrated Psychostimulation Program (IPP) in patients with mild-moderate AD treated with acetylcholinesterase inhibitors; and to identify factors related to greater benefit of the IPP.

Methods—206 patients (mean age= 75.9 years; MMSE= 19.6) were evaluated before starting the IPP and 3, 6, 9 and 12 months later. Measures included: Mini-Mental State Examination (MMSE), Cognitive Subscale of Alzheimer's Disease Assessment Scale (ADAS-Cog), Rapid Disability Rating Scale (RDRS-2) and Neuropsychiatric Inventory Questionnaire (NPI-Q).

Results—Patients remained cognitively stable (MMSE/ADAS-Cog) for more than 6 months and significantly worsened at 9-month and 12-month follow-ups, without clinically significant functional changes (RDRS-2) or psychiatric symptoms (NPI-Q). The mean annual change on MMSE and ADAS-Cog were 2.06 and 3.56 points, respectively, lower than the annual decline demonstrated previously in similar patients (2.4 and 4.5, respectively). 42.7% of patients

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Declaration of Conflicting Interests

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maintained or improved global cognitive scores between baseline and 12-month follow-up. The patients who maintained cognitive functions were older than those who did not (77.5 vs. 74.7 years).

Conclusions—The IPP may be an effective treatment to maintain cognition, functionality and psychiatric symptoms in AD patients pharmacologically treated, and older age seems to increase beneficial effects of IPP.

Keywords

Integral Psychostimulation Program; cognitive stimulation; Alzheimer's disease; cognition; functionality; non-pharmacological therapy; dementia

Introduction

Alzheimer's disease (AD) is the most common form of dementia and its prevalence has undergone an exponential increase in recent years. At the present time, there is no cure or biological prevention of AD, and existing pharmacological treatments can only slow the progression of symptoms [1,2] or delay admission to long-term care facilities [3,5].

An alternative approach to the treatment and management of the AD dementia is to use non-pharmacological interventions. We have previously demonstrated the efficacy of a 12-week cognitive stimulation program, in combination with pharmacological therapy, by improving and maintaining cognitive functions [6]. These kinds of programs can be viewed as methods to delay cognitive morbidity and allow the affected patient (and family) to have a better quality of life for longer, prior to progression to the most severe stages of dementia [7].

AD is a complex illness in which several genetic and environmental factors are involved. Recent studies have demonstrated that the apolipoprotein $\epsilon 4$ (APOE $\epsilon 4$) allele could be mainly involved in human susceptibility to AD [8,9], but not in the disease progression or AD drug effectiveness, which could depend on a completely different set of genetic and environmental factors [10].

Up to now, genes cannot be altered, but a combination of pharmacological and non-pharmacological treatments may improve quality of life, by extending mental status time, and/or delaying the progression to more severe dementia and death [11]. Thus, non-pharmacological therapies are emerging as a strategy potential treatment for people with dementia, focused on slowing or delaying the worsening of cognitive and functional abilities, and minimizing caregiver burden [12–14].

Non-pharmacological therapies can encompass a wide range of activities providing general stimulation for reasoning, concentration and memory, usually in a social setting [15]. Examples of the range of such therapies [16] include reminiscence, validation, physical exercise, reality orientation, music therapy [17] and computerized cognitive rehabilitation programs [18]. However, it is the combination of pharmacological and non-pharmacological treatments that likely produces the most beneficial results in AD patients, [12,17,19–27] potentially because the cognitive training [28–30] stimulates a neuroplastic response.

The present study will be focused on the Integrated Psychostimulation Program (IPP) (developed at *Fundació ACE*), designed to enhance, preserve, and promote the independence of the patient in their basic activities of daily living (ADLs) and thus, reduce caregiver burden. This IPP is based on three principles – cognitive neuroplasticity, neuropsychology and behavior modification techniques - [6,31–33], by integrating cognitive, motor and mood-related rehabilitation/stimulation techniques. This IPP has been used primarily for the management of patients with mild to moderate AD dementia; more than 1350 individuals have been able to use the program [34].

This work builds on our previous study [6] which showed that the IPP helped to maintain cognitive functions in combination with acetylcholinesterase inhibitors (AChEIs), relative to medication alone. While non-pharmacological treatment of dementia is often presented in one-hour workshops, two or three times a week, our IPP provides a more extensive program covering eight hours daily, five days a week. Therefore, the purpose of the present report is to highlight the effects of the IPP intervention in patients with mild to moderate AD treated with stable doses of AChEIs, and to identify the factors that affect the likelihood that a patient will benefit from the program.

Methods

The study was approved by the *Fundació ACE* Research Ethics Committee and all caregivers of patients signed an informed consent for their data to become part of a database for future research.

Subjects

The data from this observational study were drawn from the individuals who attended the day care center *Alzheimer Educational Centre* of *Fundació ACE* during 1 year and for at least 3 months between January 2006 and November 2011.

This center includes a day care facility and a geriatric day hospital. The day care center provides services to a total of 80 individuals, 30 of whom are supported by the *Institut Català d'Assistència i Serveis Socials* of the Department of Welfare and Families of the *Generalitat de Catalunya*. The day hospital provides services to a total of 75 patients, and 52 of the available positions are financed by the *Servei Català de la Salut*.

Of the total of 407 patients attending the center during the study period, there were 206 patients eligible for the study. The inclusion criteria were: a diagnosis of Probable or Possible AD according to the *National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association* (NINCDS-ADRDA) criteria; [35] mild to moderate severity of dementia, with a Clinical Dementia Rating (CDR) [36] staging of 1 to 2 and a Global Deterioration Scale (GDS) [37] staging of 4 to 5; taking a stable dose of AChEIs and/or memantine for at least 3 months prior to the first IPP session; not institutionalized; and having a responsible caregiver who could accompany them to the center.

Subjects were not included in the study if they were illiterate, were suffering from major depression or other DSM-IV Axis-I psychiatric disorders (except for dementia), had sensory loss, were not treated with AChEIs or memantine or had not been assessed at least of the 3-month follow-up visit.

Treatment procedure

All selected subjects received a combination of non-pharmacological and pharmacological therapy. Participants started the IPP between January 2006 and November 2011 and they had at least 3-month follow-up during the study period. The pharmacological treatment consisted of the administration of stabilized daily doses of AChEIs and/or memantine for at least 3 months before the first IPP session. They could change their medications during the 12 months of IPP, but none of them initiated any antipsychotic medication during the study period.

Integrated Psychostimulation Program

The IPP is composed of cognitive training strategies adapted to the dementia patient, and it is used to improve functioning in specific domains for the purpose of delaying the clinical progression of AD [6]. The IPP assumes that even the mild/moderately dementia patient is capable of neuroplastic response and will respond to targeted therapies.

The techniques used in the IPP are varied and include: cognitive stimulation [38], active and passive gymnastics, music therapy and relaxation and occupational activities to maintain ADLs. The program makes partial use of several therapies such as validation, reminiscence or remotivation in order to facilitate the socialization and participation by the patients in the group activities. Because the set of strategies and interventions target both the patient and their primary caregiver, it takes a holistic approach for care and management [6,31].

The patients participated in the IPP daily, Monday to Friday, from 10 a.m. to 6 p.m., in the different workshops. While some of the patients completed the “full” IPP schedule, others attended only during the morning (10:00 – 14:00), and others attended only three days per week in the morning. These differences were due to the differences between public and private payment systems. The daily activities of IPP are detailed in table 1.

In cognitive psychostimulation workshop, the main activities were addressed to cognitive functions, such as memory, language, orientation, praxis, recognition, reasoning and calculation. The psychoexpression workshop was focused in the personal and spatial orientation, motor coordination, controlled exercise, relaxation and body language. In the occupational workshop, entertainment was enhanced by participation in board games, their occupational choice tasks and creative activities.

The activities were distributed depending on the emotional and cognitive stage of each subject; the patients were grouped according to their dementia stage. Maintenance daily living activities, both instrumental and basic, are always present in the individualized intervention programs.

The IPP is an amusing and dynamic program designed as a daily routine which includes breaks between different activities. They work cognition, functionality and emotions through a variety of activities adapted to their needs.

Cognitive, Functional, and Psychiatric Outcomes

A neuropsychological screening battery was administered by the same rater to all patients at baseline (one week before the first IPP session) and at 3, 6, 9, and 12-month follow-ups. The battery included the MMSE [39] and the Cognitive Subscale of Alzheimer's Disease Assessment Scale (ADAS-Cog) [40].

The Rapid Disability Rating Scale (RDRS-2) [41], to evaluate functional status, and the Neuropsychiatric Inventory Questionnaire (NPI-Q) [42], to assess neuropsychiatric symptoms, were administered to caregivers at baseline and at the 6 and 12-month visits.

The time between assessments of patients is shorter for cognitive (we only need patients) than for functional (where we need family opinion) assessment because we adjust the activities of the program to their cognitive impairment. It is difficult for the family to attend Fundació ACE so often. Thus, we had caregivers' interviews each 6-month follow-ups.

Statistical analysis

All statistical analyses were performed using SPSS (version 20.0; SPSS Inc., Chicago, Ill). General descriptive statistics were calculated. To determine if participants who discontinued the IPP differed from those who completed the study, their age, gender, education, and MMSE and ADAS-Cog scores were compared at the baseline visit by t-test or chi-square tests. These scores were also compared between APOE $\epsilon 4$ carriers and non-carriers.

A Mixed Model Analysis was carried out in order to be able to evaluate changes in cognitive, functional and psychiatric scores, and excuse participants with a missing value in some of the follow-up assessments. The main factor of the analysis was time and the adjusting factors were age, gender, years of education and GDS. Time effect and the rest of the factors included in the analysis were considered as fixed factors. Subject effect was considered a random effect. The same set of analyses was repeated excluding subjects younger than 65 years.

Differences between baseline and 12-month follow-up for the MMSE and ADAS-Cog scores, subjects were classified into the following two groups: 1) Responders (R): Subjects whose scores on global cognition (MMSE and ADAS-Cog, separately) did not change or improved between baseline and 12-month follow-up; 2) Non-responders (NR): Subjects whose scores on MMSE/ADAS-Cog worsened between baseline and 12-month follow-ups.

Demographical, comorbidities, genetic and clinical variables (age, gender, education, APOE $\epsilon 4$ genotyping, GDS) were compared between R and NR groups (as classified by changes on MMSE and ADAS-Cog scores, separately). Significance level was set at $P < .05$.

Results

Of 407 patients, data from 206 patients (150 women, 56 men) with mild ($n=112$, 54.2%) to moderate ($n=94$, 45.8%) AD was entered for the analyses. 201 patients were excluded because they discontinued the IPP before 3-month follow-up, they had severe dementia or they did not fulfill any of the other inclusion. The mean of time that participants spent in the IPP program was of 10.2 ($SD= 3.43$) months. The mean age of participants was 75.88 ($SD= 8.97$; range: 54–93). Only 8 patients were younger than 65. With regard to their educational level, 41.2% were literate with less than elementary school (that is, from 1 to 6 years of formal education), 43.2% of subjects had Elementary or High School education (from 7 to 11 years of formal education) and 15.6% had a Bachelor's degree or higher (from 12 years of formal education). Means and standard errors (SE) of the cognitive, functional, and psychiatric measures at baseline and at 3, 6, 9 and 12-month follow-ups are detailed in Table 1.

The comparison of the sub-samples with and without all the follow-ups available showed that those participants who completed the whole study were significantly younger than those without all the follow-ups ($t= 3.67$, $p< .001$). However, the two groups were statistically comparable in gender (Chi Square= .77, $p= .379$), years of education ($t= 1.61$, $p= .110$), and basal MMSE ($t= 1.21$, $p= .228$) and ADAS-Cog ($t= .75$, $p= .457$) scores.

With regard to MMSE, the Mixed Model analysis showed a statistically significant time effect ($F= 23.66$, $p< .001$). *Post-hoc* comparisons indicated that the main statistically significant differences were found at 9 and 12-month follow-ups. The MMSE mean score worsened .98 units (CI 95% .28 – 1.68) between baseline and 9-month follow-up, and 2.06 units (CI 95% 1.32 – 2.81) between baseline and 12-month follow-up. *Post-hoc* comparisons between baseline and 3 and 6-month follow-ups showed no statistically significant differences.

With regard to ADAS-Cog, the Mixed Model analysis showed a statistically significant time effect ($F(4, 276, 55)= 16.72$, $p< .001$). Paralleling the differences found in the MMSE, at 9-month and 12-month follow-ups, ADAS-Cog performances were lower than at baseline ($p= .003$ and $p< .003$, respectively). The mean difference between the baseline and 9-month assessments was 1.55 units (CI 95% .35 – 2.75), and between baseline and 12-month was 3.56 units (CI 95% 2.08 – 5.04). Comparisons between scores at baseline and 3-month and 6-month follow-ups were not statistically significant.

Additionally, both the MMSE and ADAS-Cog subtests were further separately analysed. As detailed in supplementary table 1, for the ADAS-Cog subtests, scores on the commands, orientation, verbal recognition memory, language and ideational praxis had significantly worsened ($p< .005$) from baseline compared to the 12-month follow-up. However, from baseline to 9-month follow-up only verbal recognition memory significantly worsened ($p< .005$).

From the MMSE subtests, the MMSE-orientation was analysed to measure the change in reality orientation. The main effect (time) was statistically significant ($F(4, 300, 52)= 12.29$, $p< .001$). Bonferroni's comparisons showed statistically significant differences between

baseline and 9-month and 12-month follow-ups. The mean difference between baseline and 9-month follow-up scores was $-.38$ units (CI 95% $-.78 - .02$), and from baseline to 12-month follow-up the mean difference was $-.66$ units (CI 95% $-1.09 - -.24$). Post-hoc comparisons between baseline and 3-month and 6-month follow-ups showed no significant differences.

Concerning functionality, RDRS-2 showed a statistically significant time effect ($F(4, 280, 41) = 34.80, p < .001$). All *post-hoc* comparisons were statistically significant (all comparisons $p < .016$). Between baseline and the 12-month follow-up there was a mean difference of 2.62 units (CI 95% $-3.56 - -1.67$).

However, no statistically significant psychiatric changes were found between baseline and the 12-month study period. Neither the NPI-stress nor the NPI-severity showed significant time effects ($p = .750$ and $p = .537$, respectively).

After excluding the 8 patients younger than 65, all the results detailed above remained unchanged.

The 42.7 % ($n = 88$) of participants were into the group of R and the 57.3 % ($n = 118$) were NR, as measured by MMSE; and taking the ADAS-Cog scores, the 36.9 % ($n = 76$) were R and the 63.1 % ($n = 130$) were NR. Concerning demographical, genetic and clinical data, the only variable that significantly differed between R and NR was the age.

The R patients (as measured by the MMSE) were significantly older (mean = 77.49 , SD = $.93$) than the NR patients (mean = 74.68 , SD = $.82$) ($p = .026$). With regard to comorbidities, although no statistically significant differences were found between R and NR groups (as measured by MMSE or ADAS-Cog), the NR tended to have more comorbidities than the R (as detailed in Supplementary Table 2).

With regard to genetics, we did not find statistically significant differences between APOE $\epsilon 4$ carriers and non-carriers on age, gender, years of education, or basal MMSE and ADAS-Cog. Changes on MMSE and ADAS-Cog were also analyzed in the subsample of APOE $\epsilon 4$ carriers. The cognitive, functional or psychiatric changes were not significantly related to APOE $\epsilon 4$ carrier status. That is, the interaction between APOE $\epsilon 4 \times$ time was not statistically significant on the ADAS-Cog ($F = .99, p = .417$), MMSE ($F = 1.71, p = .152$), MMSE-orientation ($F = 1.18, p = .324$), RDRS-2 ($F = .511, p = .602$), NPI-stress ($F = .246, p = .782$), NPI-severity ($F = .056, p = .946$) or CDR sum of boxes ($F = .573, p = .566$).

DISCUSSION

The results of the present study have shown that an integrated psychostimulation program, the IPP, could benefit cognition, psychiatric symptoms and functionality on ADLs in patients with mild to moderate AD treated with stable doses of AChEIs. Patients in the IPP tended to maintain stable levels of global cognitive functioning (as measured by MMSE and ADAS-Cog) for at least 6 months relative to their own baseline. A significant worsening of function was found between baseline and the 9- and 12-month follow-up visits. These declines, however, were somewhat lower than would be expected by the average

progression of treated AD. Our patients had a stability of psychiatric symptoms assessed by the NPI-Q, while other studies observed a worsening of depressive symptoms in this kind of patients [43].

The degree of engagement of our participants was very high. They did kindly participate in all the assessments made throughout their stay in the center. Any participant refused to be assessed, we only excluded participants who did not meet the inclusion criteria.

To this end, in the present study the mean yearly change on MMSE and ADAS-Cog were 2.06 and 3.56 points, respectively, lower than the yearly decline demonstrated previously in similar patients (2.4 and 4.5, respectively) [44]. This finding replicates and extends the knowledge about the beneficial effects of combined pharmacological and non-pharmacological treatments in daily function among AD patients [12,17,19–27,45].

There were no significant changes in the NPI-stress and NPI-severity scales over time, and this may have been due to the quality of care provided by the clinical center. Although the RDRS's score showed a statistically significant worsening on functionality on activities of daily living, these changes were not clinically significant. Moreover, in a previous study [46], the IPP did not produce clinical changes on functionality. More than 40% of our patients with mild to moderate AD benefitted from the IPP treatment, as measured by MMSE and ADAS-Cog [17]. Although the responders were older than the non-responders, there were no other demographic, medical or genetic differences between the groups. However, we did not have a measure of brain structure or function, and thus the biological underpinnings of the response to IPP are not clear. However, our data could be relevant to the issue of cognitive reserve. Stern and colleagues proposed that “the neural implementation of cognitive reserve might take two forms: neural reserve and neural compensation. Neural reserve is the idea that cognitive reserve could be associated with differences between individuals in the resilience of pre-existing cognitive networks, and neural compensation is the idea that some individuals might be better than others at using compensatory mechanisms”[47]. Given that levels of education, which might be a surrogate for neural reserve, did not differ between the responders and non-responders, this leads us to the hypothesis that the IPP which included in its cognitive stimulation the Smartbrain program [18] may be having an effect on neural compensation. Specifically, they may be encouraging either behavioral or neural flexibility that would help the patient use compensatory neural mechanisms.

This research has some limitations, primarily because it was a descriptive study and not a clinical trial. Thus, the patients were not randomized to a condition, and there was not a control group. In a controlled study, the control group would be advisable, but in our case, it would be difficult to manage because, in this ecological context, it would be complicate to justify to the families, because there would be some patients who will not benefit from the center's activities. Nevertheless, these patients maintained their cognitive function from baseline to 6-month follow-up likely due to a non-pharmacological treatment that did not involve large economic costs.

Another limitation was that patients were not subjected to the same treatment duration. Due to the observational nature of the present study, it could not be controlled.

There are few studies using the same methodology of treatment. The IPP is the non-pharmacological treatment program more complete and extensive administered to this type of patients. For this reason, it is difficult to compare our results with the results described in previous studies.

The IPP offers the patient a range of cognitive stimulation techniques, exercises to maintain daily activities, as well as a balanced emotional state. Future studies should include indicators of brain functional response using techniques such as functional magnetic resonance imaging, as well as detailed analyses of structural and functional connectivity. In conjunction with the inclusion of a “usual treatment” control condition, this would provide critical information about the nature and extent of neural plasticity in MCI and AD, and how this can enhance traditional pharmacotherapy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Distribution of the day’s activities in the IPP

10:00–11:00	Welcome and breakfast.
11:00–12:30	Cognitive stimulation Workshop
12:30–13:00	Maintenance of Activities of Daily Living
13:00–14:00	Psychoexpression - Movement
14:00–15:30	Food
15:30–16:15	Maintenance of Activities of Daily Living
16:15–17:30	Occupational Therapy Workshop
17:30–18:00	Farewell
Additionally, physical therapy sessions (in small groups from 12:30 to 13:15, from 13:15 to 14:00 or from 15:45 to 16:30, and individual sessions for people with special needs).	

Table 1

Cognitive, functional and psychiatric scores at baseline and follow-up visits.

	Baseline	3-month follow-up	6-month follow-up	9-month follow-up	12-month follow-up
	Mean (SE)	Mean (SE)	Mean (SE)	Mean (SE)	Mean (SE)
	n= 206	n= 206	n= 171	n= 155	n= 147
MMSE total	19.60 (.33)	19.66 (.30)	19.19 (.31)	18.63 (.34) *	17.54 (.35) *
ADAS-Cog total	25.63 (.59)	25.48 (.58)	26.03 (.62)	27.18 (.60) *	29.19 (.67) *
MMSE-orientation	5.93 (.15)	6.16 (.14)	6.04 (.17)	5.55 (.15)	5.27 (.16) *
RDRS-2 total	28.18 (.32)	-	29.59 (.37) *	-	30.80 (.48) *
NPI-Q distress	6.87 (.55)	-	6.62 (.56)	-	6.43 (.58)
NPI-Q severity	4.10 (.25)	-	3.94 (.28)	-	4.31 (.34)

MMSE: Mini-Mental State Examination;

ADAS-Cog: Cognitive Subscale of Alzheimer's Disease Assessment Scale;

RDRS-2: Rapid Disability Rating Scale;

NPI-Q: Neuropsychiatric Inventory Questionnaire;

SE: standard error.

* p< .05