Benefits of cognitive-motor intervention in MCI and mild to moderate Alzheimer disease

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Abstract—*Objective:* To evaluate the efficacy of a cognitive-motor program in patients with early Alzheimer disease (AD) who are treated with a cholinesterase inhibitor (ChEI). *Methods:* Patients with mild cognitive impairment (MCI) (12), mild AD (48), and moderate AD (24) (Global Deterioration Scale stages 3, 4, and 5) were randomized to receive psychosocial support plus cognitive-motor intervention (experimental group) or psychosocial support alone (control group). Cognitive-motor intervention (CMI) consisted of a 1-year structured program of 103 sessions of cognitive exercises, plus social and psychomotor activities. The primary efficacy measure was the cognitive subscale of the AD Assessment Scale (ADAS-cog). Secondary efficacy measures were the Mini-Mental State Examination, the Functional Activities Questionnaire, and the Geriatric Depression Scale. Evaluations were conducted at 1, 3, 6, and 12 months by blinded evaluators. *Results:* Patients in the CMI group maintained cognitive status at month 6, whereas patients in the control group had significantly declined at that time. Cognitive response was higher in the patients with fewer years of formal education. In addition, more patients in the experimental group maintained or improved their affective status at month 12 (experimental group, 75%; control group, 47%; $p = 0.017$). *Conclusions:* A long-term CMI in ChEI-treated early Alzheimer disease patients produced additional mood and cognitive benefits.

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Recent evidence suggests that cognitive activity may delay the clinical onset of Alzheimer disease (AD).[1] Most stimulation programs for early AD patients target cognition because some neuronal plasticity and compensation capacity are believed to persist.[2,3] Some positive results have been observed in the stimulated areas, but the specificity of effects, the impact in non-stimulated domains, and long-term maintenance of benefits remain controversial. Most studies with an adequate control group only evaluate the stimulated functions, and there are few long-term reports.[4-9]

Cholinesterase inhibitors (ChEI) are of benefit in AD.[10,11] A combination of both pharmacologic and cognitive therapy improves cognition in elders with memory complains or dementia.[12,13] We performed a multicenter, randomized, single-blind, controlled, parallel-group trial of a non-pharmacologic intervention in ChEI-treated AD patients to investigate the long-term benefits of cognitive therapy on cognition, function, and mood.

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Methods. *Patients.* Patients were recruited from January 1999 to June 2001 from 12 neurologic, geriatric, or psychiatric clinics and 5 behavioral neurology units of the central and eastern metropolitan area of Madrid. Only community dwelling patients were included and they had to fulfill the following criteria: a clinical diagnosis of either mild cognitive impairment (MCI)[14] or probable AD,[15] a stage 3, 4, or 5 in the Global Deterioration Scale,[16] current use of a daily dose of 5 to 10 mg of donepezil or 6 to 12 mg of rivastigmine for more than 1 month, and patient's and caregiver's willingness and capability to receive a cognitive intervention. Exclusion criteria were illiteracy and any physical condition that could preclude regular attendance and full participation in the intervention program (e.g., a non-controlled systemic illness, relevant hearing and vision deficits, severe physical disability). Routine laboratory analyses and neuroimaging studies (CT or MRI) had been previously performed, and were consistent with an AD or MCI diagnosis. The intake of sedative and antidepressant med-

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ications was permitted in accordance with the patient's physician's prescribing practice.

Study design. The study physicians, who gave additional details about the study when requested, evaluated candidates. If inclusion criteria were fulfilled, patients and caregivers gave written informed consent. When patients or caregivers were reluctant to receive cognitive-motor intervention (CMI), they were not considered for randomization and they were excluded from the study. Once informed consent had been signed, the patient number was sent for randomization and the basal assessment was performed. Randomization was made by a member of the research team who had no contact with patients or caregivers, using a random number table.[17] During assessments, the study physicians informed patients and caregivers about the progression of the disease and offered medical advice when requested. All the study assessments were performed in a Senior Citizen Center (Centro Alonso Heredia), without any link to the therapy centers. Physician's and blind evaluator's assessments were run independently. The CMI was performed in two Maria Wolff, non-medical units for mildly demented outpatients. These units were located in the city center of Madrid. Study patients were treated in small groups, together with other patients not participating in the trial. Patients assigned to the CMI group had to pay a monthly fee of 10,000 pesetas (approximately $60 US dollars). The coordination of the study was run at one of the Maria Wolff day care centers where a social worker scheduled assessments and received any questions about the study. All schedules and questions were transmitted telephonically. A 24-hour telephone help-line was also implemented for the caregivers of both groups.

Cognitive-motor intervention. A comprehensive and uniform stimulation program was designed, with cognition as a primary target, according to the principles of compensation. Efforts were made to elicit the best individual performance within a flexible framework.[6,8] Patients were invited to attend a CMI group of 7 to 10 individuals, twice weekly, for 3.5 hours per session. Groups were created according to severity of dementia and personal affinities. A detailed description of the intervention can be found at the *Neurology* Web site at www.neurology.org. In brief, sessions included a welcome (10 minutes), reality orientation techniques (50 minutes), cognitive exercises (30 minutes), training of activities of daily living (ADL) (30 minutes), coffee break (30 minutes), psychomotor exercises or workshops (50 minutes), and conclusion (10 minutes). Cognitive exercises were designed to stimulate one specific cognitive function at each session (every month two sessions focused on memory, two sessions focused on attention, and one monthly session focused on language, visuospatial abilities, calculation, and frontal/executive functions). The ADL training was related to the particular cognitive function stimulated at each session (e.g., money handling was trained after calculation exercises). Every month a leitmotiv was used to reinforce structure and motivation (e.g., winter in January). To maintain quality of the therapy, the CMI program was written in a manual for the 103 sessions of the year.

Outcome measures. The standard 11-item cognitive subscale of the AD Assessment Scale (ADAS-cog) was the primary efficacy measure. This scale assesses memory, language, ideational praxis, and visuospatial ability.[18] Two equivalent validated Spanish versions were alternatively used.[19] A four-point effect in this scale is generally accepted as a clinically relevant benefit.

Secondary efficacy measures included the 30-item Mini-Mental State Examination (MMSE),[20] the 13-item Functional Activities Questionnaire (FAQ)[21] that measures instrumental ADL, and the 15-item Geriatric Depression Scale (GDS) (Shiekh and Yesavage, 1986).[22] These instruments have been translated and validated in Spanish groups of patients.[23,24] Basic ADL were measured with the Index of Independence in Activities of Daily Living[25] and caregiver burden was measured with a 22-item Spanish version of the Burden Interview.[26] All the above-mentioned outcome measures were blindly recorded at baseline and after 1, 3, 6, and 12 months by trained psychologists. The MMSE was not administered at month 1.

The study physicians recorded from the patient and the caregiver any potential adverse reaction to the cognitive therapy at every follow-up visit. In addition, satisfaction with therapy was measured with a five-point Likert-type scale. The physicians also recorded the number and type of drugs used for behavioral and psychological symptoms of dementia (BPSD) and relevant milestones such as death and institutionalization.

After the study was started, three post hoc efficacy measures were added in the 12-month assessment only: the 10-item Neuropsychiatric Inventory (NPI),[27] the Cornell Scale for Depression in Dementia,[28] and the AD-Related Quality of Life scale (ADRQL).[29] Only results related to cognition, instrumental ADL, mood, and behavior are presented in this article.

Responder definition. A definition of responder was stated prior to study initiation to further assess the effect of the intervention in different domains. Patients were defined as cognitive responders when they maintained or improved their ADAS-cog basal scores at the 12-month assessment. Functional responders were defined as patients who maintained or improved their FAQ basal scores at month 12. Mood responders were patients who maintained or improved their basal GDS scores at month 12.

Sample size and statistical analyses. A sample size of 172 patients (86 in each treatment arm) was estimated to detect a four-point mean difference in ADAS-cog with a SD of 10.26 as in the Spanish validation study,[19] for a type I error = 0.05, an 80% power, and a 20% estimated attrition rate.

The primary sample for evaluation of efficacy was a modified intent-to-treat (MITT) sample defined as all randomized patients who provided at least one post-baseline efficacy assessment and, if they belonged to the experimental group, attended at least one session. An observed-cases (OC) analysis at each visit was first carried out, followed by a 12-month last observation carried forward (LOCF) analysis where there were missing values. Changes from baseline in continuous variables were compared in the experimental and control groups using analysis of covariance (ANCOVA) with baseline scores, age, sex, and education as covariates. Changes from baseline and differences between the two study groups were further investigated with Wilcoxon test and *t*-test at the four follow-up assessments. Differences in number of responders were analyzed with the χ^2 test at month 12. Post hoc efficacy measures were compared with the *t*-test. To assess a possible dose effect, a subanalysis was performed including in the treatment arm only patients who attended the sessions until the 12-month assessment. All statistical tests were two sided, and p values < 0.05 were considered significant. To avoid an increase in type II error, multiple comparison adjustment was not performed.[30] Statistical analyses were performed using SPSS version 10.0 software (SPSS, Chicago, IL).

Results. *Disposition of patients.* Fifty-four percent of the patients who were informed about the study in the clinical recruiting units contacted the study secretary. Main reasons for not contacting were patient lack of willingness to participate and logistic problems on the part of the caregiver. Most patients (67%) who contacted the study secretary were finally screened. At the end of the inclusion period, 84 patients were enrolled (49% of the initial enrollment target) (figure 1). Reasons for exclusion after screening were illiteracy (2 cases), patient rejection of CMI (2 cases), systemic illnesses (2 cases), advanced AD (2 cases), cerebrovascular disease (1 case), advanced AD and cerebrovascular disease (1 case), caregiver rejection of randomization (1 case), and not stated (2 cases). One of the recruiting units enrolled 35 patients (42%). These patients were similar to the rest of the sample (data not shown). One patient could not start CMI because a multiple myeloma was diagnosed immediately after randomization; three additional patients rejected enrollment in the cognitive-motor therapy sessions and were excluded from the MITT population. Most patients could be evaluated at 12-month assessment (final population); at that time, 30 of them were still attending therapy sessions (68% of those who were randomized to this treatment arm) (see figure 1).

Baseline characteristics. Demographic and clinical variables of the randomized samples are shown in table 1. No significant differences were observed between the two study groups at baseline. One patient in the treatment

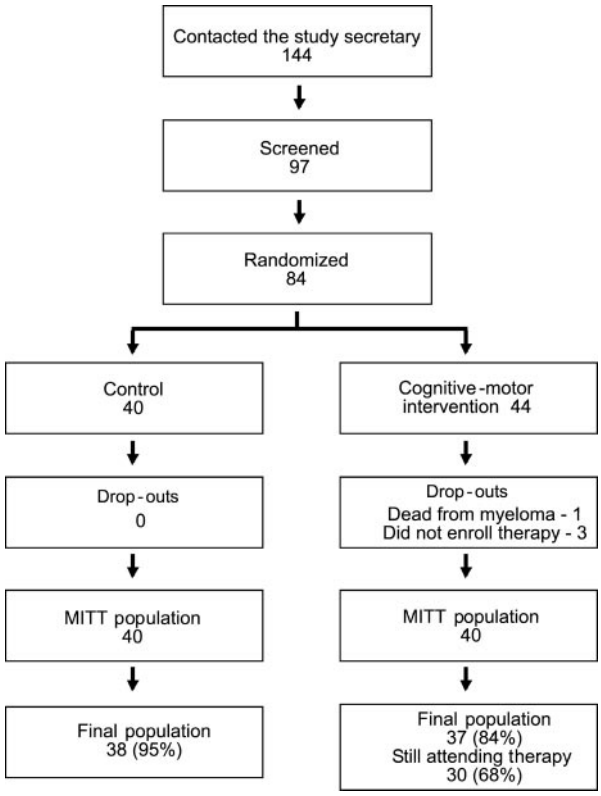

Figure 1. Disposition of patients. MITT = modified intent-to-treat.

group had a small subcortical lacunar infarct, which was not deemed as contributing to dementia.

Safety and compliance. One patient had major psychological distress during the first therapy session. He refused to continue attending therapy and rejected the 1-month follow-up assessment. At the 3-month follow-up visit, either the caregiver or the study physician observed no residual effects. No other adverse events were recorded. Ten patients had abandoned cognitive-motor therapy by the 12-month assessment. Reasons for discontinuation were lack of willingness to continue participation on the part of the patient (7 cases), difficulty in taking the patient to the center (2 cases), and change of residence (1 case). Therapists believed that dropouts were due to discordance between patient and group cognitive level, quality of social interactions, or both. Patients who were still attending sessions at the 12-month assessment reported being very satisfied (37.9%), satisfied (48.3%), or indifferent (13.8%) about therapy. Corresponding figures for caregivers were 57.1%, 39.3%, and 3.6%.

Efficacy. Changes in ADAS-cog, MMSE, FAQ, and GDS scores are presented in figures 2 and 3. There was an improvement in ADAS-cog in the experimental group at month 1 ($Z = -1.95$, $p = 0.05$). Patients in the experimental group maintained cognitive status at month 6, whereas patients in the control group had declined at that time ($Z = -0.07$, $p = 0.95$ for experimental group vs $Z = -2.14$, $p = 0.03$ for control group in the ADAS-cog; $Z = -0.74$, $p = 0.46$ for experimental group vs $Z = -2.58$, $p = 0.01$ in the MMSE) (see figure 2). An effect of education on the cognitive response was detected in the ANCOVA analyses ($F = 6.40$, $p = 0.01$ in the ADAS-cog at month 6; $F = 3.92$, $p = 0.05$ in the ADAS-cog at month 12). Subsequent analyses revealed that this education effect was restricted to the experimental group, appeared at month 6, persisted at month 12, and was independent of age, sex, and basal performance ($F = 10.17$, $p = 0.003$ in the ADAS-cog at month 6; $F = 11.14$, $p = 0.002$ in the ADAS-cog at month 12; and $F = 4.37$, $p = 0.05$ in the MMSE at month 12). Patients with a lower educational attainment showed a higher cognitive response. In the functional domain, there was a tendency toward less deterioration in the experimental group, but it was not significant (see figure 2). As for depressive symptoms, patients from the control group tended to show an increase in their GDS scores at the conclusion of the study, whereas those who attended cognitive therapy tended to improve their scores at the final observation point. Differences between groups were significant at 12-month assessment ($t = -1.99$, $p = 0.05$) (see figure 3). The frequency of responders in the different domains is presented in figure 4. The highest difference in responder rate between the two study groups was observed in the affective domain and reached significance ($\chi^2 = 6.25$, $p = 0.02$). When LOCF analyses were performed, results did not change (only OC analyses are mentioned in the text). When only the patients who did not stop attending therapy sessions were analyzed, all the results remained essentially the same (data not shown).

The results in the post hoc efficacy measures confirmed a response in the realms of mood and behavior (see table 2). When the different domains of the NPI were analyzed, main differences were detected in agitation and irritability ($p < 0.005$). Comparisons in the ADRQL showed better relation with others and less behavior disturbances in the experimental group patients (see table 2).

Treatment benefits in behavior and affective areas could not be attributed to pharmacologic treatments. Actually, the experimental group had 25% less BPSD medications than the control group at the 1-year follow-up visit (data not shown). Since differences in the Burden Interview were not detected, treatment benefits could not be attributed to a respite effect on the caregiver either (data not shown).

Discussion. We measured the effects of an extended and comprehensive cognitive and motor stimulation program in ChEI-treated MCI and mild to moderate AD patients who attended group sessions twice weekly during 1 year. A transitory cognitive stabilization and a long-term mood benefit were demonstrated in the experimental group. In addition, the post hoc measurements suggested a possible effect in behavior and quality of life. The size of the cognitive effect was slightly lower than that observed in the ChEI trials.[31] In contrast, the behavioral benefits seemed higher, reaching the usual standards for clinical relevance.[32] In light of these findings, ChEI and our CMI could be regarded as complementary therapies in the management of AD.

A comprehensive stimulation program in AD patients is hypothesized to enhance neuroplasticity processes, reduce cognitive loss, and help the patient to stretch functional independence through better cognitive performance.[2,3,8] However, our more remarkable effects were observed in the areas of mood

Table 1 *Baseline demographic and clinical characteristics of the two study groups*

Characteristic	Treatment, n = 44	Control, n = 40	*p* Value
Age, y	75.30 ± 1.05 (58–87)	73.35 ± 1.05 (54–84)	0.193
% Female	54.55	65.00	0.378
Education, %*			0.293
None/incomplete	18.18	32.50	
Basic	61.36	47.50	
Superior	20.45	20.00	
Number of chronic illnesses†	1.05 ± 0.16 (0–4)	1.26 ± 0.17 (0–4)	0.364
Number of medications‡	3.11 ± 0.21 (1–6)	3.28 ± 0.31 (1–9)	0.662
Number of medications for BPSD	0.45 ± 0.10 (0–2)	0.55 ± 0.10 (0–2)	0.504
ChEI, time since effective dose§			0.135
% Donepezil 5 mg, mo	31.8%, 8.68 ± 1.86 (1–24)	27.5%, 8.27 ± 2.15 (1–19)	0.888
% Donepezil 10 mg, mo	25%, 10.55 ± 1.88 (2–24)	45%, 9.47 ± 1.78 (1–27)	0.695
% Rivastigmine 6–12 mg, mo	43.2%, 4.53 ± 1.07 (1–16)	27.5%, 4.59 ± 0.91 (1–12)	0.967
Evolution, y	3.4 ± 0.4 (0.75–16)	3.0 ± 0.2 (0.5–7)	0.438
Global Deterioration Scale stage, %			0.564
3	18.2	10.0	
4	54.5	60.0	
5	27.3	30.0	
MMSE scores at the stage levels			
3	17.3 ± 1.3 (13–24)	21.8 ± 3.0 (16–29)	0.200
4	18.5 ± 0.9 (11–25)	17.6 ± 1.3 (4–28)	0.570
5	14.9 ± 1.8 (2–24)	15.5 ± 1.6 (4–26)	0.954
ADAS-cog	24.7 ± 1.5 (11–64)	25.8 ± 1.6 (12–56)	0.629
FAQ	15.3 ± 1.1 (3–30)	14.1 ± 1.1 (2–28)	0.422
GDS	3.0 ± 0.3 (0–10)	3.4 ± 0.4 (0–11)	0.396

Values are expressed as mean ± SE (range) unless otherwise indicated.

* None/incomplete: literate, but less than 6 years of formal education; basic: 6 to 10 years of formal education; superior: more than 10 years of formal education.
† Neurologic and psychiatric diseases are not included.
‡ ChEI and BPSD medications are included.
§ An effective dose is defined as 5 to 10 mg of donepezil or 6 to 12 mg of rivastigmine.

BPSD = behavioral and psychological symptoms of dementia; ChEI = cholinesterase inhibitors; MMSE = Mini-Mental State Examination; ADAS-cog = cognitive subscale of the Alzheimer's Disease Assessment Scale; FAQ = Functional Activities Questionnaire; GDS = Geriatric Depression Scale.

and behavior. These are also relevant outcomes, since behavioral disturbances are thought to influence caregiver burden and institutionalization[33] as well as being associated with patient and caregiver distress. Increase in social attention and interaction has been noted to improve mood and behavior in demented elderly.[34] Moreover, important mood benefits have been reported in stimulation programs predominantly aimed at cognition.[35,36] Therefore, mood and behavior gains could be a nonspecific benefit from every therapeutic effort in AD, possibly resulting from physical activity and socialization. On the other hand, more specific benefits have been obtained as a consequence of some particular cognitive and functional tasks (e.g., orientation, ADL training, verbal learning).[37-39] Our positive results in mood, behavior, and quality of life could be reasonably attributed to the non-cognitive part of the therapeutic program. Within this non-cognitive part, we believe that psychomotor exercises exerted a particularly strong effect.

Cognitive response was higher in patients with a low educational attainment. Influence of education on responsiveness to nonpharmacologic interventions in AD patients has barely been investigated. We only found a former study where the relationship between cognitive response and education was analyzed.[8] In this study, an inverse correlation was also found. These findings are somehow counterintuitive and not easy to interpret. A possible explanation could be provided within the framework of the cognitive reserve paradigm. Within this paradigm, education and other activities are proposed to increase

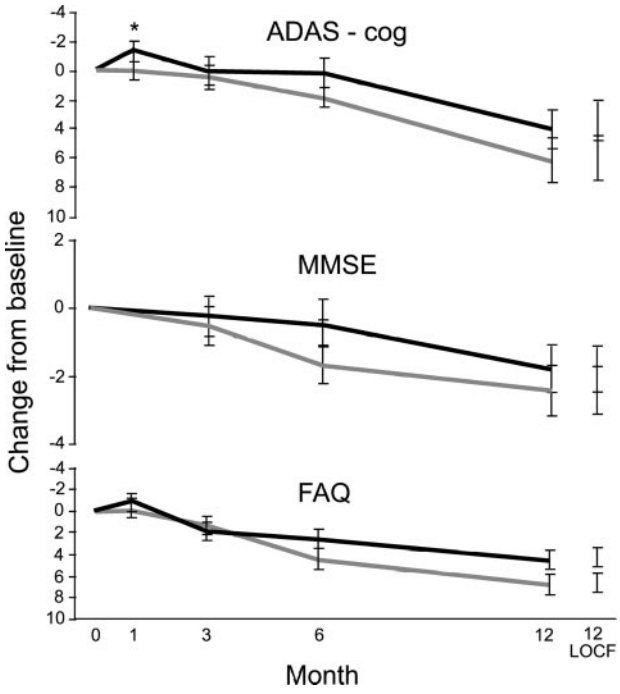

*Figure 2. Mean (± SE) change from baseline score by treatment group. Downward slope means deterioration. *p = 0.05 vs basal performance. ADAS-cog = cognitive subscale of the AD Assessment Scale; MMSE = Mini-Mental State Examination; FAQ = Functional Activities Questionnaire; GDS = Geriatric Depression Scale; LOCF = last observation carried forward. Black line = experimental group; gray line = control group.*

cognitive reserve and coping with AD. Therefore, given a similar level of clinical severity, AD pathology would be more advanced in the highly educated patients, rendering them in an inferior learning potential situation.[40]

The conditions of this study were very close to those of current AD care. The program was systematically offered to the patients attending mainly non AD-specialized medical clinics, and the inclusion criteria were not restrictive. In addition, patients were not compelled to be enrolled in the study or to attend the therapy sessions once started. Apart from patient reluctance, main reasons for non-participation

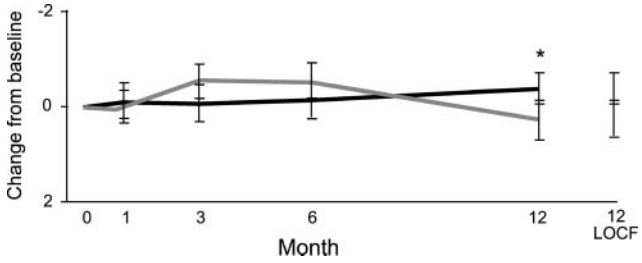

*Figure 3. Geriatric Depression Scale. Mean (± SE) change from baseline by treatment group. Downward slope indicates more depressive symptoms. *p = 0.05 Between experimental and control groups. LOCF = last observation carried forward. Black line = experimental group; gray line = control group.*

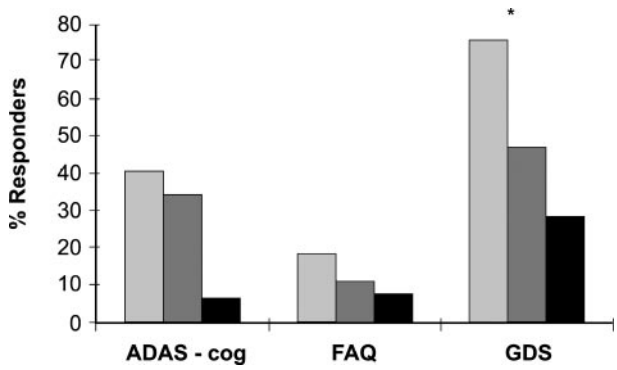

*Figure 4. Responder rate by treatment group (observed cases). *p = 0.02 Between experimental and control groups. ADAS-cog = cognitive subscale of the AD Assessment Scale; FAQ = Functional Activities Questionnaire; GDS = Geriatric Depression Scale. Light gray = experimental group; dark gray = control group; black = experimental group minus control group.*

were logistical. In this context, both participation and fidelity to the stimulation program were high but the obtained benefits did not depend on patient compliance with sessions. These results reinforce the need for treating incipient, mild and moderate AD from a holistic perspective of dementia management, where the patient's will and psychosocial characteristics should be respected.[41]

This study has limitations. First, verbal acceptance of a small payment was a prerequisite for being randomized. In addition, caregivers were informed that, if needed, they had to afford transportation to the therapy sites. For these reasons, our results are only generalizable to patients with adequate financial resources or sufficient social support. Second, the small sample size reduced the statistical power and precluded a more rigorous statistical analysis with control of multiple comparisons. There-

Table 2 *Post hoc efficacy measures after 1 year of follow-up*

Measure	Treatment, n = 38	Control, n = 37	*p* Value
CSDD	6.03 ± 0.74	7.68 ± 0.82	0.140
NPI	15.21 ± 2.16	26.51 ± 3.49	0.008
ADRQL			
Relation with others	67.49 ± 1.64	58.50 ± 2.63	0.005
Self-identity	57.48 ± 2.80	46.62 ± 3.26	0.071
Behavior disturbances	63.66 ± 2.99	54.90 ± 3.26	0.051
Leisure activities	52.64 ± 3.43	46.42 ± 4.79	0.295
Usual environment behavior	53.73 ± 2.83	48.73 ± 2.71	0.198

Values are expressed as mean ± SE. Lower scores mean less disturbances in the CSDD and NPI; higher scores mean higher quality of life in the ADRQL.

CSDD = Cornell Scale for Depression in Dementia; NPI = Neuropsychiatric Inventory; ADRQL = Alzheimer's Disease-Related Quality of Life.

fore, the results should be regarded as provisional, awaiting confirmation, and as a starting point for further research. Third, some conclusions are partly supported by post hoc measures that were not included at the initial visit, although basal comparability can be reasonably inferred in light of collateral behavior and mood-related data (see table 1). Fourth, although an effort was made to keep the evaluators blind to the study design, some of the outcomes were obtained from caregivers, who knew whether the patient was attending therapy. This circumstance should not influence the ADAS-cog and GDS scores, which were obtained without the presence of the caregiver. Fifth, the study was not designed to assess the particular effect of different cognitive intervention techniques. Rather, a global stimulation program was given, precluding definitive conclusions about which part of the therapy was responsible of the observed benefits. Studies aimed to assess the efficacy of more restricted nonpharmacologic interventions are warranted. Mood, behavior, and caregiver-perceived quality of life seem to emerge as priority domains for the evaluation of nonpharmacologic interventions in AD patients. Finally, the scope of potential benefits should be extended to other relevant areas such as institutionalization and economics.

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