Group and individual cognitive therapies in Alzheimer’s disease: the ETNA3 randomized trial

Hélène Amieva,1,2 Philippe H. Robert,3 Anne-Sophie Grandoulier,4 Céline Meillon,2 Jocelyne De Rotrou,5 Sandrine Andrieu,6,7 Claudine Berr,8,9 Béatrice Desgranges,10 Bruno Dubois,11 Chantal Girtanner,12 Marie-Eve Joël,13 Benoit Lavallart,14 Fati Nourhashemi,6,7 Florence Pasquier,15 Muriel Rainfray,2 Jacques Touchon,8,9 Geneviève Chêne1,4 and Jean-François Dartigues1,2

1 INSERM, U897-Epidemiology-Biostatistics, University of Bordeaux, F-33076, Bordeaux, France
2 CHU Bordeaux, Memory Center of Bordeaux (Centre Mémoire de Ressources et de Recherche), France
3 CHU Nice, Memory Center of Nice (Centre Mémoire de Ressources et de Recherche), France
4 CHU Bordeaux, Pôle de Santé Publique, USMR and CIC-EC 7, F-33000, Bordeaux, France
5 AP-HP, Hôpital Broca, Service de Gerontologie, F-75013, Paris, France
6 INSERM, UMR1027, University of Toulouse III, F-31000, Toulouse, France
7 CHU Toulouse, Department of epidemiology and public health, F-31000, Toulouse, France
8 INSERM, UMR 1061, University of Montpellier, F-33400 Montpellier, France
9 CHU Montpellier, Memory Center of Montpellier (Centre Mémoire de Ressources et de Recherche), Department of Neurology, F-33400 Montpellier, France
10 INSERM, U1077, Université de Caen Basse-Normandie, Ecole Pratique des Hautes Etudes, CHU de Caen, France
11 INSERM UMR S975, Hôpital de la Salpêtrière, F-75651 Paris cedex 13, France
12 CHU de Saint-Étienne, Hôpital Charité, Service de gérontologie clinique, France
13 University of Paris-Dauphine, Laboratoire d’Economie et de Gestion des Organisations de Santé (LEDu-LEGOS), Paris, France
14 Direction Générale de la Santé, Paris, France
15 CHU Lille, Memory Center of Lille (Centre Mémoire de Ressources et de Recherche), France

ABSTRACT

Background: Although non-drug interventions are widely used in patients with Alzheimer’s disease, few large scale randomized trials involving a long-term intervention and several cognitive-oriented approaches have been carried out. ETNA3 trial compares the effect of cognitive training, reminiscence therapy, and an individualized cognitive rehabilitation program in Alzheimer’s disease to usual care.

Methods: This is a multicenter (40 French clinical sites) randomized, parallel-group trial, with a two-year follow-up comparing groups receiving standardized programs of cognitive training (group sessions), reminiscence therapy (group sessions), individualized cognitive rehabilitation program (individual sessions), and usual care (reference group). Six hundred fifty-three outpatients with Alzheimer’s disease were recruited. The primary efficacy outcome was the rate of survival without moderately severe to severe dementia at two years. Secondary outcomes were cognitive impairment, functional disability, behavioral disturbance, apathy, quality of life, depression, caregiver’s burden, and resource utilization.

Results: No impact on the primary efficacy measure was evidenced. For the two group interventions (i.e. cognitive training and reminiscence), none of the secondary outcomes differed from usual care. The larger effect was seen with individualized cognitive rehabilitation in which significantly lower functional disability and a six-month delay in institutionalization at two years were evidenced.

Conclusions: These findings challenge current management practices of Alzheimer’s patients. While cognitive-oriented group therapies have gained popularity, this trial does not show improvement for the patients. The individualized cognitive rehabilitation intervention provided clinically significant results. Individual interventions should be considered to delay institutionalization in Alzheimer’s disease.

Key words: non-drug therapies, Alzheimer, dementia, cognitive training, reminiscence, individualized cognitive rehabilitation

Introduction

The repeated failures of pharmacological clinical trials to cure or even slow down Alzheimer’s disease...
have raised interest for alternative non-drug interventions, in particular cognition-oriented therapies. Among them, cognitive training and reminiscence therapy are very popular. Cognitive training is the first established non-drug intervention that focused on improvement of cognition in dementia (Breuil et al., 1994). This approach generally consists of a structured practice on a set of standard tasks designed to involve various cognitive functions such as memory, attention, or language. Reminiscence therapy is probably the second most common non-drug therapy for patients with dementia. Even though it has been initially designed to improve mood, self-esteem and quality of life, it also involves a cognitive rationale. Indeed, with people with dementia often able to recall events from their youth or childhood, but not from earlier on the same day, reminiscence therapy, historically linked to Butler’s work on “life review process” (Butler, 1963), offers the opportunity to tap into the apparently preserved store of remote memories. Both cognitive training and reminiscence therapies are typically conducted in groups of patients to enhance social functioning. Although less frequently applied given its higher cost, cognitive rehabilitation, developed mainly through work with younger brain-injured people, is increasingly discussed in relation to dementia. Cognitive rehabilitation relies on an individualized approach where personally relevant goals are identified, and the therapist works with the patient and his/her caregiver to devise strategies to address these goals. The emphasis is put on improving performance in everyday life situations, rather than on cognitive performance per se, building on the person’s strengths and developing ways of compensating for impairment (Clare and Woods 2004).

The efficacy of cognition-oriented interventions has often been discussed but rarely demonstrated. Two Cochrane reviews examining cognitive training have been published. The first one (Clare et al., 2003) including six randomized controlled trials (RCTs) could not evidence any benefit on cognition, activities of daily living, or quality of life. The second and third ones provided limited evidence for cognitive training and both concluded for the urgent need of well-designed studies to draw definitive conclusions (Woods et al., 2012a; Bahar-Fuchs et al., 2013).

Two Cochrane studies have also been published for reminiscence therapy. The first one (Spector et al., 2000) yielded to inconclusive results while the second one (Woods et al., 2005) on four RCTs reported significant results in cognition, mood, general behavioral function, caregivers strain, and staff knowledge of patients. However, recently, the REMCARE trial (Woods et al., 2012b), a quite large multicenter RCT in 488 participants provided challenging results showing no differences between the intervention and control conditions on self-reported quality of life or autobiographical memory, activities of daily living, mood, and service use and costs. Unexpectedly, caregivers of participants allocated to the reminiscence intervention reported a significant increase in anxiety at the ten-month end-point.

Regarding individualized cognitive rehabilitation, most of the reports are issued from single case experimental designs showing that individuals with early-stage dementia can to some extent, learn or re-learn important and personally-relevant information, maintain this learning over time, and apply it in the everyday context (Camp et al., 2000; Anderson et al., 2001; Clare et al., 2001; 2002) and that they can develop compensatory strategies using for instance memory aids (Clare et al., 2000). To date, no large RCT on individualized cognitive rehabilitation has been conducted.

Therefore, RCTs aiming to reliably assessing the impact of cognitive interventions are too scarce. Those existing report limited or negative impact. No large scale interventional study involving a comprehensive approach of both patients and caregivers, a long-term treatment, and several cognitive-oriented approaches has been carried out to date. We report the results of the ETNA3 study, a large RCT funded by the French Ministry of Health comparing the effect of cognitive training, reminiscence therapy, and an individualized cognitive rehabilitation program to usual care in Alzheimer’s disease.

**Methods**

**Study design**

ETNA3 is a multicenter, stratified (by clinical site), parallel-group trial, with balanced randomization (1:1:1:1), enrolling patients with Alzheimer’s disease followed at 3, 6, 12, 18, and 24 months after the initiation of the non-drug therapy. The study complied with the declaration of Helsinki regarding investigation in humans and was approved by the ethics committee of Bordeaux Hospital.

**Study population**

Between April 2008 and December 2009, 655 patients diagnosed with Alzheimer’s disease according to criteria of the NINCDS-ADRDA (McKhann et al., 1984) were enrolled in 40 centers across France. Two patients were excluded: one for misdiagnosis and another one who withdrew consent. Enrollment was restricted to patients...
aged 50 years and over, in the mild to moderate stage of the disease as established by Mini-Mental State Examination (Folstein et al., 1975) (MMSE) (i.e. 16 to 26) and Global Deterioration Scale (Reisberg et al., 1988) (GDS) score (i.e. 2 to 5), non-institutionalized and with an identified family caregiver. Clinical sites were Memory centers or geriatric day-care units involving a multidisciplinary medical team with neurologists, geriatricians, or psychiatrists and psychologists trained for cognitive and behavioral care.

Randomization and masking
The list of randomization was prepared by a statistician using permuted blocks, stratified by site. Each clinical site proposed two of the three interventions in addition to the usual care strategy. Interventions were randomly assigned in order to have an equal number across the four groups. Block size was randomly assigned to 10 or 11 with a ratio 2:4:4 or 3:4:4 (usual care: 1st intervention: 2nd intervention). Following completion of baseline assessments and consent, participants were randomized through an independent and remote telephone randomization service provided by the clinical trial unit. Participants and clinical staff were aware of the trial arm to which the study participants were allocated but all assessment interviews were done by physicians and psychologists blinded to allocation status.

Interventions
Each therapy program was developed according to current scientific data, standardized by a leader known to have scientific and clinical expertise in the field (JDR, PHR, HA) and ultimately validated by the working group of the ETNA3 trial, a multidisciplinary group of neurologists, geriatricians, psychiatrists, psychologists, biostatisticians, and researchers. To guarantee homogeneity in the way interventions were applied, a standardized procedure was followed: the therapists were psychologists with at least three years of experience in the field of dementia. All therapists received a three-day training session where the therapy programs were thoroughly presented. A manual detailing the guidelines of each intervention was provided. The therapists were informed that, in case of any question regarding a particular aspect of the program, the experts who designed the programs could be consulted. A phone number was given to them for this purpose. Once the patients were included in a clinical site, a Psychologist-Clinical Research Assistant from the coordinating center visited in situ the therapists to ensure that interventions were applied in accordance with the protocol. Each intervention program consisted of weekly sessions (duration: 1 h 30 min) during the first three months and maintenance sessions held every six weeks for the next 21 months.

The cognitive training therapy consisted of a structured program of a set of standard tasks designed to involve various cognitive functions such as memory, attention, language, or executive function. Each task involved two levels of difficulty to suit the patients’ level of ability. For each session, a set of standard tasks was designed to tap on a particular activity of daily life (e.g. calculation exercises and money counting to train domestic finances handling). Groups involved five to eight patients. Separate sessions were arranged in parallel with the caregivers. During these sessions, information upon disease, symptoms, progression, and treatment were delivered by psychologists and medical staff. As for the patients, the caregivers support groups sessions were held once a week during the first three months and every six weeks afterwards.

Each session of reminiscence therapy focused on a different personal theme (e.g. schooldays, birthday, wedding, working life, holidays . . . ). The groups involved five to eight patients. Caregivers were encouraged to contribute with materials (e.g. pictures . . . ) brought from home. As for the cognitive training therapy, the caregivers support groups sessions were held once a week during the first three months and every six weeks afterwards.

The individualized cognitive rehabilitation therapy consisted of a made-to-measure program conducted through individual sessions. The first two sessions were exclusively dedicated to select meaningful activities (activities of daily living or leisure activities) with the person suffering from dementia and his/her caregiver. The activities to be trained had to be selected according to personally relevant goals for the patients. The psychologist had to adapt the program according to patients’ cognitive abilities in order to anticipate and avoid as much as possible failures. When appropriate, the psychologist could rely on “errorless learning procedure” to train a particular activity. At each session, the psychologist had to value the relevance of pursuing the selected activity and if appropriate could change the trained activity at any time during the program. During the first three months, the caregiver received a weekly telephone contact where he/she could express a particular difficulty or ask any question. Afterwards, telephone contacts were held every six weeks.

Finally in the reference group, the patients received usual medical care excluding non-drug therapy. Caregivers were offered the opportunity to
participate in caregivers support groups sessions. The aim and calendar of sessions arranged for caregivers of patients allocated to the control condition was similar to that of caregivers of patients allocated to cognitive training and reminiscence arms.

**Efficacy outcomes**

The primary outcome was the rate of patients alive and without moderately severe to severe dementia at two years. Moderately severe to severe dementia was measured according to current guidelines (Vellas et al., 2005) (MMSE lower than 15 or stages 5 to 6 of the GDS). The secondary outcomes measured at 3 and 24 months included: institutionalization, cognitive deterioration (ADAS-cog) (Rosen et al., 1984), behavioral symptoms (Neuropsychiatric Inventory; NPI) (Cummings et al., 1994), functional abilities (Disability Assessment for Dementia; DAD (Gélinas et al., 1999) and Grille d’Autonomie Gérontologique-Groupes Iso-Ressources, a standardized scale providing an indicator of dependency used in French legislation; AGGIR), apathy (Apathy Inventory; AI) (Robert et al., 2002), depressive symptoms (Montgomery-Asberg Depression Rating Scale; MADRS) (Montgomery and Asberg, 1979), quality of life (Quality of Life - Alzheimer’s Disease scale; QoL-AD) (Logsdon et al., 1999), caregiver’s burden (Zarit Burden Interview) (Zarit et al., 1986), and resource utilization (RUD Lite) (Wimo and Winblad, 2003). Each measure was calculated in each group and compared to that observed in the reference group at 3 and 24 months.

**Sample size**

The main hypothesis was a higher survival without moderately severe to severe dementia at two years for patients undergoing non-drug interventions compared to patients receiving the usual medical care estimated at 70% according to REAL.FR study, a clinical cohort study involving similar patients from French memory centers (Vellas, 2003). An effect size at 15% was considered to be a significant benefit. With a type-I error (Cronbach’s $\alpha$) adjusted to 0.0182 (to preserve an overall risk of 0.05) and 85% power to demonstrate a 15% difference in survival without moderately severe to severe dementia at two years between each intervention tested and the reference group, we planned to include 178 patients per arm.

**Statistical analysis**

Categorical variables were described in terms of numbers, proportions, and confidence intervals (95%) by the exact binomial method. Continuous variables were described in terms of mean, standard deviation, median, interquartile range (IQR), and range. All outcome analyses were done first according to intention-to-treat principle replacing missing data by the most pejorative value (hereinafter referred to as “Missing Equal Failure” [MEF] analysis) and secondly on available data. Comparisons to the reference strategy were performed with Cronbach’s $\alpha = 0.0182$ in order to take into account the multiplicity of tests. Logistic regressions were used for the analysis of primary end-point. Non-parametric tests (Kruskal–Wallis test), Cox models, or logistic regression models were used for the analysis of secondary end-points as appropriate. All comparisons were adjusted for the clinical site, except when a non-parametric test was used and for analyses on available data. Analyses were performed with the use of SAS® software (version no. 9.2).

**Results**

Of the 653 patient, 170 were randomized in the cognitive training group, 172 in the reminiscence group, 157 in the individualized cognitive rehabilitation group, and 154 in the control group (Figure 1). Five hundred eighty-six (89.7%) were followed-up at the three-month visit and 472 (72.3%) at 24 months.

Table 1 shows participants’ baseline characteristics. Mean age was 78.7, 389 (59.6%) were women and 321 (49.1%) had a diploma higher than primary level certificate. Mean MMSE was 21.6 and most patients rated 3 (34.5%) or 4 (46.4%) on the GDS scale. A majority (88.2%) were being prescribed anti-dementia drugs.

Tables 2 and 3 present the efficacy outcome scores at 3 and 24 months by trial arm. Using the MEF analysis (Table 2) or available data analysis (Table 3), none of the interventions showed superiority to the usual care reference group for the primary outcome, i.e. survival without moderately severe to severe dementia. In the cognitive training or reminiscence therapy groups, none of the secondary efficacy outcomes differed significantly from that measured in the usual care group. The patients who received the individualized cognitive rehabilitation therapy exhibited a lower functional decline at 24 months as measured by the two scales assessing functional abilities: DAD scale (available data analysis, $p = 0.01$) and AGGIR scale (available data analysis, $p = 0.007$; MEF analysis, $p = 0.02$). There was also a trend in favor of this intervention for the NPI score both on the available data ($p = 0.03$) and MEF analysis ($p = 0.08$) at 24 months. The score on the Burden Zarit scale rated by
caregivers at three months was lower than that of the caregivers involved in the control group (available data, \( p = 0.01 \); MEF analysis, \( p = 0.05 \)). There was still a statistical trend on the available data analysis (\( p = 0.05 \)) at 24 months. Social-medical costs related to disease management were compared in the available data only. Although not significant at \( p = 0.0182 \), a statistical trend of lower costs (a difference of approximately 600 euros per month with the control group) in the individualized cognitive rehabilitation therapy group compared to the control group (\( p = 0.08 \)) can be seen. At 24 months, the rate of institutionalized patients was lower in the individualized cognitive rehabilitation therapy group than in the control group (27.3% vs. 19.1% respectively in the MEF analysis). Figure 2 displays the Kaplan–Meier curves of institutionalization. As may be seen, the probability of being non-institutionalized was higher in the individualized cognitive rehabilitation therapy group than in the other groups, at any time of follow-up. In addition, Cox regression model showed a significant difference in the delay of institutionalization (MEF analysis, \( p = 0.01 \)). Compared to the control group, patients having received individualized cognitive rehabilitation entered institution about six months later.

**Discussion**

Three main conclusions may be drawn. First, none of the three non-drug interventions applied during a 24-month period delayed the progression to the severe stages of Alzheimer’s disease. Second, cognitive training and reminiscence therapy had no impact on secondary efficacy outcomes as compared to usual care. Therefore, even though we cannot rule out the possibility that cognitive training or reminiscence have impact on other clinical measures than that considered in this study, our findings do not provide support for the effectiveness of these two interventions on cognition, functional abilities in daily life.
## Table 1. Baseline characteristics. ETNA3 study

<table>
<thead>
<tr>
<th>CHARACTERISTICS</th>
<th>USUAL CARE GROUP (N = 154)</th>
<th>COGNITIVE TRAINING GROUP (N = 170)</th>
<th>REMINISCENCE THERAPY GROUP (N = 172)</th>
<th>INDIVIDUALIZED COGNITIVE REHABILITATION THERAPY GROUP (N = 157)</th>
<th>TOTAL (N = 653)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age at inclusion</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean(SD)</td>
<td>78.7(6.5)</td>
<td>78.5(7.2)</td>
<td>78.8(6.9)</td>
<td>78.9(6.2)</td>
<td>78.7(6.7)</td>
</tr>
<tr>
<td>Median(IQR)</td>
<td>80.0(75.0–83.0)</td>
<td>79.0(75.0–84.0)</td>
<td>80.0(76.0–84.0)</td>
<td>79.5(75.0–83.0)</td>
<td>80.0(75.0–84.0)</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>63 (40.9%)</td>
<td>69 (40.6%)</td>
<td>61 (35.5%)</td>
<td>64 (40.8%)</td>
<td>257 (39.4%)</td>
</tr>
<tr>
<td>Women</td>
<td>90 (58.4%)</td>
<td>99 (58.2%)</td>
<td>108 (62.8%)</td>
<td>92 (58.6%)</td>
<td>389 (59.6%)</td>
</tr>
<tr>
<td><strong>Education</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary school diploma</td>
<td>51 (33.1%)</td>
<td>59 (34.7%)</td>
<td>58 (33.7%)</td>
<td>56 (35.7%)</td>
<td>224 (34.3%)</td>
</tr>
<tr>
<td>Secondary school</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No diploma</td>
<td>24 (15.6%)</td>
<td>17 (10.0%)</td>
<td>28 (16.3%)</td>
<td>27 (17.2%)</td>
<td>96 (14.7%)</td>
</tr>
<tr>
<td><strong>Anti-dementia drugs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IaCHe, Memantine</td>
<td>133 (86.4%)</td>
<td>152 (89.4%)</td>
<td>155 (90.1%)</td>
<td>136 (86.6%)</td>
<td>576 (88.2%)</td>
</tr>
<tr>
<td><strong>MNA score</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean(SD)</td>
<td>13.2 (1.6)</td>
<td>13.2 (1.5)</td>
<td>13.5 (1.6)</td>
<td>13.1 (1.7)</td>
<td>13.2 (1.6)</td>
</tr>
<tr>
<td>Median(IQR)</td>
<td>13.5 (12.5–14.0)</td>
<td>13.5 (12.5–14.0)</td>
<td>13.5 (12.5–14.5)</td>
<td>13.5 (12.5–14.0)</td>
<td>13.5 (12.5–14.0)</td>
</tr>
<tr>
<td><strong>MMSE score</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean(SD)</td>
<td>21.6 (3.3)</td>
<td>21.5 (3.2)</td>
<td>21.1 (3.1)</td>
<td>21.6 (3.0)</td>
<td>21.5 (3.1)</td>
</tr>
<tr>
<td>Median(IQR)</td>
<td>22.0 (19.0–24.0)</td>
<td>22.0 (19.0–24.0)</td>
<td>21.0 (19.0–23.0)</td>
<td>22.0 (19.0–24.0)</td>
<td>22.0 (19.0–24.0)</td>
</tr>
<tr>
<td><strong>GDS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage 2</td>
<td>1 (0.7%)</td>
<td>0 (0.0%)</td>
<td>1 (0.6%)</td>
<td>0 (0.0%)</td>
<td>2 (0.3%)</td>
</tr>
<tr>
<td>Stage 3</td>
<td>50 (32.5%)</td>
<td>57 (33.5%)</td>
<td>59 (34.3%)</td>
<td>59 (37.6%)</td>
<td>225 (34.5%)</td>
</tr>
<tr>
<td>Stage 4</td>
<td>76 (49.4%)</td>
<td>75 (44.1%)</td>
<td>80 (46.5%)</td>
<td>72 (45.9%)</td>
<td>303 (46.4%)</td>
</tr>
<tr>
<td>Stage 5</td>
<td>24 (15.6%)</td>
<td>35 (20.6%)</td>
<td>29 (16.9%)</td>
<td>24 (15.3%)</td>
<td>112 (17.2%)</td>
</tr>
<tr>
<td>Stage 6</td>
<td>2 (1.3%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>2 (0.3%)</td>
</tr>
<tr>
<td><strong>DAD score</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean(SD)</td>
<td>26.6 (8.8)</td>
<td>26.5 (8.1)</td>
<td>27.1 (8.6)</td>
<td>27.4 (8.1)</td>
<td>26.9 (8.4)</td>
</tr>
<tr>
<td>Median(IQR)</td>
<td>27.0 (21.0–33.0)</td>
<td>27.0 (20.0–33.0)</td>
<td>28.0 (22.0–34.0)</td>
<td>28.0 (23.0–34.0)</td>
<td>28.0 (21.0–34.0)</td>
</tr>
<tr>
<td><strong>NPI (total score)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean(SD)</td>
<td>17.5 (15.2)</td>
<td>16.3 (12.6)</td>
<td>15.8 (12.9)</td>
<td>16.0 (16.1)</td>
<td>16.4 (14.2)</td>
</tr>
<tr>
<td>Median(IQR)</td>
<td>13.0 (5.0–26.5)</td>
<td>14.0 (7.0–22.0)</td>
<td>12.0 (6.0–21.0)</td>
<td>11.0 (5.0–20.0)</td>
<td>13.0 (6.0–23.0)</td>
</tr>
<tr>
<td><strong>Zarit score</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean(SD)</td>
<td>23.1 (14.9)</td>
<td>20.5 (13.7)</td>
<td>22.2 (14.9)</td>
<td>18.6 (14.0)</td>
<td>21.1 (14.5)</td>
</tr>
<tr>
<td>Median(IQR)</td>
<td>21.0 (11.0–34.0)</td>
<td>18.0 (10.0–30.0)</td>
<td>19.0 (11.0–29.0)</td>
<td>16.0 (7.0–27.0)</td>
<td>18.0 (9.0–30.0)</td>
</tr>
</tbody>
</table>
Table 2. Results of assessments in the three therapy groups during follow-up (3 and 24 months). Missing equals failure analysis (linear or logistic regression models). ETNA3 study

<table>
<thead>
<tr>
<th>OUTCOMES</th>
<th>3 MONTHS</th>
<th>24 MONTHS</th>
<th>3 MONTHS</th>
<th>24 MONTHS</th>
<th>3 MONTHS</th>
<th>24 MONTHS</th>
<th>3 MONTHS</th>
<th>24 MONTHS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>USUAL CARE</td>
<td>COGNITIVE TRAINING</td>
<td>REMINISCENCE THERAPY</td>
<td>INDIVIDUALIZED COGNITIVE REHABILITATION THERAPY</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td></td>
<td>n(%)</td>
<td>n(%)</td>
<td>n(%)</td>
<td>n(%)</td>
<td>n(%)</td>
<td>n(%)</td>
<td>n(%)</td>
<td>n(%)</td>
</tr>
<tr>
<td>Rate of patients alive and without moderately severe to severe dementia</td>
<td>130 (84.4%)</td>
<td>74 (48.1%)</td>
<td>139 (81.8%)</td>
<td>0.2000</td>
<td>81 (47.7%)</td>
<td>0.7694</td>
<td>140 (81.4%)</td>
<td>0.8219</td>
</tr>
<tr>
<td>Survival rate</td>
<td>141 (91.6%)</td>
<td>109 (70.8%)</td>
<td>151 (88.8%)</td>
<td>0.0209</td>
<td>124 (72.9%)</td>
<td>0.9440</td>
<td>150 (87.2%)</td>
<td>0.1404</td>
</tr>
<tr>
<td>ADAS-Cog score, Mean(SD)</td>
<td>19.84 (11.5)</td>
<td>38.25 (24.5)</td>
<td>21.26 (12.9)</td>
<td>0.5041</td>
<td>39.96 (24.8)</td>
<td>0.7060</td>
<td>21.02 (13.2)</td>
<td>0.8357</td>
</tr>
<tr>
<td>DAD score, Mean(SD)</td>
<td>26.94 (9.6)</td>
<td>25.38 (13.4)</td>
<td>27.54 (9.2)</td>
<td>0.6201</td>
<td>24.74 (13.4)</td>
<td>0.6695</td>
<td>28.17 (9.6)</td>
<td>0.2103</td>
</tr>
<tr>
<td>AGGIR score, Mean(SD)</td>
<td>6.63 (7.5)</td>
<td>15.21 (11.5)</td>
<td>7.00 (7.9)</td>
<td>0.6675</td>
<td>15.14 (11.2)</td>
<td>0.9923</td>
<td>7.10 (8.7)</td>
<td>0.4895</td>
</tr>
<tr>
<td>NPI score, Mean(SD)</td>
<td>23.29 (28.4)</td>
<td>39.31 (32.3)</td>
<td>25.34 (28.8)</td>
<td>0.2224</td>
<td>41.52 (32.1)</td>
<td>0.5313</td>
<td>27.02 (31.0)</td>
<td>0.3533</td>
</tr>
<tr>
<td>MADRS score, Mean(SD)</td>
<td>8.82 (9.1)</td>
<td>18.51 (17.1)</td>
<td>10.65 (9.9)</td>
<td>0.0590</td>
<td>20.21 (17.2)</td>
<td>0.3127</td>
<td>10.47 (10.6)</td>
<td>0.3456</td>
</tr>
<tr>
<td>QoLAD score (weighted score), Mean(SD)</td>
<td>33.28 (7.7)</td>
<td>28.83 (9.5)</td>
<td>31.99 (8.0)</td>
<td>0.2161</td>
<td>27.39 (9.2)</td>
<td>0.1304</td>
<td>32.34 (8.8)</td>
<td>0.5792</td>
</tr>
<tr>
<td>Apathy inventory (caregiver version), Mean(SD)</td>
<td>10.40 (11.8)</td>
<td>18.44 (14.4)</td>
<td>10.26 (11.7)</td>
<td>0.9703</td>
<td>20.39 (13.8)</td>
<td>0.2148</td>
<td>11.80 (13.1)</td>
<td>0.6888</td>
</tr>
<tr>
<td>Zarit Burden interview score, Mean(SD)</td>
<td>30.05 (25.6)</td>
<td>41.05 (28.7)</td>
<td>30.31 (25.9)</td>
<td>0.8795</td>
<td>41.81 (28.2)</td>
<td>0.7046</td>
<td>31.65 (27.5)</td>
<td>0.6973</td>
</tr>
<tr>
<td>Institutionalization</td>
<td>–</td>
<td>42(27.3%)</td>
<td>–</td>
<td>–</td>
<td>54 (31.8%)</td>
<td>–</td>
<td>–</td>
<td>40 (23.3%)</td>
</tr>
</tbody>
</table>

https://doi.org/10.1017/S1041610215001830
Table 3. Results of assessments in the three therapy groups during follow-up (3 and 24 months). Analysis on available data (linear or logistic regression models). ETNA3 study

<table>
<thead>
<tr>
<th>OUTCOMES</th>
<th>USUAL CARE</th>
<th>COGNITIVE TRAINING</th>
<th>REMINISCENCE THERAPY</th>
<th>INDIVIDUALIZED COGNITIVE REHABILITATION THERAPY</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3 MONTHS</td>
<td>24 MONTHS</td>
<td>3 MONTHS</td>
<td>24 MONTHS</td>
</tr>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>n(%)</td>
<td>Mean (SD)</td>
<td>n(%)</td>
</tr>
<tr>
<td>Rate of patients alive and without moderately severe to severe dementia</td>
<td>130 (92.8%)</td>
<td>74 (66.1%)</td>
<td>139 (93.3%)</td>
<td>81 (66.0%)</td>
</tr>
<tr>
<td>Moderately severe to severe dementia rate</td>
<td>10 (7.1%)</td>
<td>28 (27.5%)</td>
<td>151 (100.0%)</td>
<td>–</td>
</tr>
<tr>
<td>Survival rate</td>
<td>141 (100.0%)</td>
<td>109 (91.6%)</td>
<td>124 (94.7%)</td>
<td>–</td>
</tr>
<tr>
<td>ADAS-Cog score, Mean(SD)</td>
<td>17.00 (7.4)</td>
<td>21.59 (10.2)</td>
<td>22.71 (12.3)</td>
<td>0.8036</td>
</tr>
<tr>
<td>DAD score, Mean(SD)</td>
<td>25.31 (9.0)</td>
<td>18.56 (10.8)</td>
<td>18.38 (10.7)</td>
<td>0.9386</td>
</tr>
<tr>
<td>AGHIR score, Mean(SD)</td>
<td>4.69 (4.5)</td>
<td>8.52 (6.8)</td>
<td>8.76 (6.6)</td>
<td>0.7260</td>
</tr>
<tr>
<td>NPI score, Mean(SD)</td>
<td>15.2 (16.3)</td>
<td>20.28 (16.3)</td>
<td>22.81 (18.3)</td>
<td>0.4121</td>
</tr>
<tr>
<td>MADRS, Mean(SD)</td>
<td>6.51 (5.6)</td>
<td>7.87 (7.6)</td>
<td>8.33 (7.5)</td>
<td>0.5216</td>
</tr>
<tr>
<td>QoLAD score (weighted score), Mean(SD)</td>
<td>35.43 (4.6)</td>
<td>34.84 (4.7)</td>
<td>33.91 (4.4)</td>
<td>0.1622</td>
</tr>
<tr>
<td>Apathy inventory (caregiver version), Mean (SD)</td>
<td>7.40 (8.4)</td>
<td>10.96 (10.3)</td>
<td>13.32 (10.7)</td>
<td>0.0718</td>
</tr>
<tr>
<td>Zarit Burden interview score, Mean(SD)</td>
<td>23.33 (17.2)</td>
<td>23.87 (15.6)</td>
<td>24.49 (14.8)</td>
<td>0.5820</td>
</tr>
<tr>
<td>RUD-Lite (socio-medical costs for one month), Mean (SD)</td>
<td>2259.3 (3078.3)</td>
<td>3323.1 (4021.0)</td>
<td>3578.5 (4023.0)</td>
<td>0.4982</td>
</tr>
<tr>
<td>Institutionalization</td>
<td>–</td>
<td>35 (22.7%)</td>
<td>–</td>
<td>41 (24.1%)</td>
</tr>
</tbody>
</table>

Primary outcomes:
- Rate of patients alive and without moderately severe to severe dementia

Secondary outcomes:
- Survival rate
- ADAS-Cog score, Mean(SD)
- DAD score, Mean(SD)
- AGHIR score, Mean(SD)
- NPI score, Mean(SD)
- MADRS, Mean(SD)
- QoLAD score (weighted score), Mean(SD)
- Apathy inventory (caregiver version), Mean (SD)
- Zarit Burden interview score, Mean(SD)
- RUD-Lite (socio-medical costs for one month), Mean (SD)

Institutionalization – 35 (22.7%) – – 41 (24.1%) – – 27 (15.7%) – – 23 (14.7%)
activities, behavioral disturbance, quality of life, depression, or caregiver’s burden. Third, the
greater clinical improvement was seen with the
individualized cognitive rehabilitation intervention.
The patients showed lower functional decline at
the 24-month visit than the other groups, as
reflected by the two scales assessing functional
abilities. Marginal favorable effects on behavioral
disturbance, caregivers’ burden and resource
utilization were also observed. In addition, a
significant impact on rates of institutionalization
was found. With impaired functional abilities
(Heyman et al., 1997; Hebert et al., 2001; Wattmo
et al., 2011; Gaugler et al., 2003), psycho-behavioral
disorders (Heyman et al., 1997; Hebert et al., 2001;
Yaffe et al., 2002; Gaugler et al., 2003; Wattmo
et al., 2011), and caregivers’ burden (Hebert et al.,
2001; Gaugler et al., 2003) being major predictors
of institutionalization, the joint effects observed in
these three critical dimensions of the disease may
explain the delayed institutionalization of patients
who received individualized cognitive rehabilitation
intervention of approximately six months.

These results are consistent with those reported
by a previous study which involved an individualized
approach close to that conducted in the present
study (Graff et al., 2006). The intervention focused
on meaningful activities patients and caregivers
wanted to improve and consisted of training patients
and caregivers in the use of aids to compensate for
cognitive difficulties. The results showed improved
patients’ daily functioning and reduced caregivers’
burden. However, this study was a monocentric trial
on 135 patients only, with an intervention limited
to five weeks.

The ETNA3 study has several strengths. It
relies on the largest sample (653 patients) with
the longest follow-up (two years) to date in the
evaluation of non-drug interventions in dementia.
The study population is broadly representative
of Alzheimer’s disease patients followed-up in
memory centers and daycare centers. The non-
drug therapies relied on semi-structured cognitive-
oriented programs administered to patients and
caregivers in a multicenter trial with centralized
training and monitoring of adherence to the
protocol. The assignment of the therapies was
randomized per clinical site and per patient and
all efficacy outcomes were blindly assessed. The
proportion of drop-outs was limited.

Some limitations must be also underlined. In
particular, the sample size was slightly lower than
that initially targeted which could have contributed
to weaken the statistical power of the study. The
sample size per condition was too limited to conduct
sub-groups analysis in order to identify responders.
In addition, the number of sessions attended by the patients was not systematically collected. Finally, regarding the benefits of the individualized cognitive rehabilitation program evidenced in our study, it is difficult to determine whether such benefits are due to the individual format of intervention or the content of intervention itself. The amount of therapist attention received is much greater in a one-on-one intervention than in a group intervention which could be a key point of individualized cognitive rehabilitation programs.

In conclusion, these findings challenge current management practices of Alzheimer’s disease patients. While cognitive-oriented group interventions have become very popular, our trial did not evidence improved outcomes in the patients. On the contrary, the individualized cognitive rehabilitation therapy provided modest but clinically significant improvement; in particular, lower functional disability and delayed institutionalization. Therefore, this latter intervention should be considered to delay institutionalization of patients with mild to moderate Alzheimer’s disease.

Conflict of interest

None.

Description of authors’ roles

Pr Amieva, Pr Chêne and Pr Dartigues have full access to all the data in the study and take the responsibility for integrity of the data and the accuracy of the data analysis.

Study concept and design: Amieva, Robert, De Rotrou, Andrieu, Berr, Desgranges, Dubois, Girtanner, Joel, Lavallart, Nourashemi, Pasquier, Rainfray, Touchon, Chêne, Dartigues

Analysis and interpretation of data: Amieva, Chêne, Dartigues, Robert

Drafting the manuscript: Amieva

Critical revisions of the manuscript: Robert, Grandoulier, Meillon, De Rotrou, Andrieu, Berr, Desgranges, Dubois, Girtanner, Joel, Lavallart, Nourashemi, Pasquier, Rainfray, Touchon, Chêne, Dartigues

Statistical analysis: Grandoulier, Chêne

Technical and material support: Meillon

Obtained funding: Amieva, Dartigues

Acknowledgments

Funding sources: This study was supported by the French Ministry of Health, Caisse Nationale d’Assurance des Travailleurs Salariés (CNAMTS), Programme Hospitalier de Recherche Clinique (PHRC), Caisse Nationale de Solidarité pour l’Autonomie (CNSA), Fondation Mederic Alzheimer. This work has received no funding from NIH, Welcome Trust, or Howard Hughes Medical Institute.

Role of the sponsors: The sponsors had no role in the study.

Clinical investigators: We thank the following clinical investigators for their help in data collection: Marie-Françoise AHSOUNE, Valéry ANTOINE, Eric ASSEMAT, Frédéric BLANC, François BONNEVAY, Déborah CHEVALIER, Thierry DANTOINE, Jean-François DARTIGUES, François DE LA FOURNIERE, Vincent DE LA SAYETTE, Frédéric DELMAZO, Agnès DEVENDEVILLE, Alain DYAN, Chantal GIRTANNER, Pierre HAOND, Sandrine HARSTON, Claude JEANDEL, Pierre JOUANNY, Jean-Paul LEMBELEMBE, Frédérique LOUIS, Marie-Dominique LUSSIER, Véronique MAILLAND, Bernard-François MICHEL, Jean-Marc MICHEL, Olivier MOREAUD, Claudine NEDELEC-CICERI, Fatemeh NOURHASHEMI, Marie-Pierre PANCRAZI, Brigitte PERRAULT, Maîtê RABUS, Anne-Sophie RIGAUD, Alain SAGNIER, Marie SARAZIN, Géraldine SOULE, François TIBERGHIEEN, Jacques TOUCHON, Martine VERCELLETTO, Lisette VOLPE-GILLOT, Luc VOGT.

Supplementary data

Available as supplementary material attached to the electronic version of this paper at www.journals.cambridge.org/10.1017/S1041610215001830.

References


N. A. Stigsdotter (eds.), *Cognitive Rehabilitation in Old Age*. Oxford: Oxford University Press.


