Neurological Sciences (2018) 39:1021–1028
https://doi.org/10.1007/s10072-018-3316-3

ORIGINAL ARTICLE

Combining drug and music therapy in patients with moderate Alzheimer's disease: a randomized study

Anna Rita Giovagnoli[1] · Valentina Manfredi[1] · Letizia Schifano[1] · Chiara Paterlini[1] · Annalisa Parente[1] · Fabrizio Tagliavini[1]

Received: 21 November 2017 / Accepted: 8 March 2018 / Published online: 17 March 2018

Abstract

Alzheimer's disease (AD) can impair language, but active music therapy (AMT) and memantine (M) can improve communication. This study aimed to clarify whether adding AMT to M may improve language in comparison with drugs alone in patients with moderate AD on stable therapy with acetylcholinesterase inhibitors (AchEI). Forty-five AD patients treated with stable dose of AchEI were randomized to receive AMT plus M 20 mg/day or M 20 mg/day for 24 weeks. The Severe Impairment Battery-Language (SIB-l), SIB, Mini Mental State Examination, Neuropsychiatric Inventory (NPI), Lubben Social Network Scale, Activities of Daily Living, and Instrumental Activities of Daily Living scores at baseline and 12 and 24 weeks assessed language (primary variable) and overall cognitive, psycho-behavior, social, and functional aspects (secondary variables). The SIB-l showed a stabilization of the baseline condition in both groups, in the absence of between-group differences. The NPI depression and appetite scores significantly improved in the M-AMT group. Moreover, significantly less patients in the M-AMT group than those in the M group showed worsening of the NPI total score. Daily activities, social relationships, and overall cognitive performance did not deteriorate. In patients with moderate AD, AMT added to pharmacotherapy has no further benefits for language in comparison with pharmacotherapy alone. However, this integrated treatment can improve the psycho-behavioral profile.

Keywords Alzheimer's disease · Memantine · Cholinesterase inhibitors · Language · Behavioral and psychological symptoms in dementia

Introduction

Impaired verbal communication is a distressing manifestation of Alzheimer's disease (AD) [1]. Frequent language defects include anomia, altered comprehension, paraphasia, empty speech, decreased verbal fluency, and digression from the topic [2], impacting mood and quality of life (QoL) of patients and caregivers [3].

Cholinesterase inhibitors (AchEI) and memantine (M) (an uncompetitive *N*-methyl-D-aspartate receptor antagonist) are pharmacologic options [4]. M demonstrated safety and efficacy in monotherapy [5] or in combination with AchEI [6, 7] and, in a meta-analysis collecting 1826 patients with moderate or severe AD, it resulted more effective than placebo on global health, cognition, function, and behavior [8]. In patients with mild to moderate AD, treatment with AchEI and M resulted in significant but clinically marginal improvement of cognition, behavior, or functionality [9], while M alone did not relate to any

✉ Anna Rita Giovagnoli
annarita.giovagnoli@istituto–besta.it

Valentina Manfredi
valemanfre@gmail.com

Letizia Schifano
letizia.schifano@email.it

Chiara Paterlini
cpaterlini.psicologia@gmail.com

Annalisa Parente
annalisa.parente@istituto-besta.it

Fabrizio Tagliavini
tagliavini@istituto-besta.it

[1] Department of Diagnostics and Applied Technology, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy

significant changes [10]. AchEI and M are indicated in mild-to-moderate and moderate AD, respectively, but almost 50% of patients with mild AD have been receiving M [11]. In this regard, Schneider et al. [11] completed a meta-analysis of clinical trials, stating that there was scarce evidence for benefits of M in mild to moderate AD and posed indications to prospective trials of M either alone or in combination with AchEI in this condition.

Overall, treatment with AchEI and M resulted in small cognitive and functional improvements, but outcome assessment did not comprehend any measures of communication, social life, progression of disability, or caregiver burden.

In patients with severe AD, M improved language and communication [12], but there are no information concerning patients with less serious forms of AD.

Music therapy is a non-pharmacological intervention with theoretical and operational bases that applies the effects of sound, music, and sound-movement integration on cognition and behavior, stimulating interpersonal relations and non-verbal communication, as well as personal expressions, creativity, and emotions [13–15]. In patients with AD, active music therapy (AMT) involving sound and music playing resulted in improved coordination, attention, and memory [16]. Furthermore, AMT can facilitate communication [17] and improve language [18] and determine positive effects on emotions, mood, and social behavior [17, 19, 20] and QoL [16], and may enhance the effects of drugs for dementia [17]. Patients with mild to moderate AD undergoing AMT for 3 months showed a mild decline of initiative and episodic memory and a significant decrease of anxiety and depression [21]. In patients with chronic vascular encephalopathy, AMT may improve executive functions and mood [22]. To our knowledge, no randomized clinical studies have compared the effects of pharmacological treatment using M or AchEI and AMT on language in AD patients.

Given the positive influence for AMT on language and communication [17, 18] and that these effects were also documented with M [12], and AMT may also contribute to stabilize initiative in patients with not serious cognitive decline [22], the question has been risen whether the addition of AMT to a pharmacological treatment may give additional benefits compared to drug therapy alone in patients with moderate AD. The primary objective of this study was to determine the effect of an integrated approach on language in comparison to M added to stable AchEI treatment. Secondarily, we evaluated the influence of such an approach on global cognitive functioning, psycho-behavioral and social aspects, and daily activities. We hypothesized that, in comparison with pharmacotherapy alone, combining AMT and pharmacotherapy may contribute to stabilize language and improve psycho-behavioral aspects.

Method

Patients

Patients with probable AD were selected in one center according to the Diagnostic Statistical Manual of Mental Disorders IV TR [23] and NINCDS-ADRDA revised criteria [24]. Patients followed up at the hospital outpatient clinic for cognitive disturbances were contacted to participate to a prescreening evaluation and to receive information about the trial. Six to 8 months after the prescreening, consenting patients underwent the baseline assessment and were randomly assigned to a study group. At baseline, overall cognitive functioning (as expressed by the Mini Mental State Examination, MMSE) [25] indicated a moderate cognitive decline in all of the patients. The MMSE mean scores decreased from prescreening (mean ± SD: M-AMT group, 17.86 ± 5.53; M group, 17.48 ± 5.54) to baseline. The adjusted mean changes from prescreening to baseline in the M-AMT group (− 1.27, 95% CI − 2.31 to − 0.24, $p = 0.018$) did not significantly differ from those observed in the M group (− 1.24, 95% CI − 2.16 to − 0.32, $p = 0.011$). Eligible patients were on stable treatment with AchEI for at least 4 weeks and had impaired language [2]. Gate imbalance, extrapyramidal signs, seizures, neurovegetative failures, and severe psychiatric conditions (major depression, psychosis, bipolar disorders) preceding cognitive decline were exclusion criteria.

Interventions

M 20 mg/day was added to AchEI. AMT included twice weekly sessions, each lasting 40 min, conducted by a music therapist. A non-verbal approach and free sound-music interactions, using rhythmical and melodic instruments, were adopted. The sound-music interaction involved cognition and emotions, stimulating interpersonal adaptation. Each session began with musical improvisation inviting patients to choose an instrument and to play using a free technique. Patients contemporarily listened to other patients playing, freely searching an interplay. No music knowledge was required [13, 18]. The equipment included xylophones, glockenspiels, triangles, wind chimes, maracas, small woods, guiros, and ethnic percussions. The sessions were videotaped. The interventions lasted 24 weeks.

Randomization and blinding

The randomization was made using a computer-generated list of random numbers, assigning the patients to treatment with M or M plus AMT (M-AMT). Figure 1 shows the participant's flow through the study. The patients were evaluated blindly by a neuropsychologist at baseline and at weeks 12 and 24.

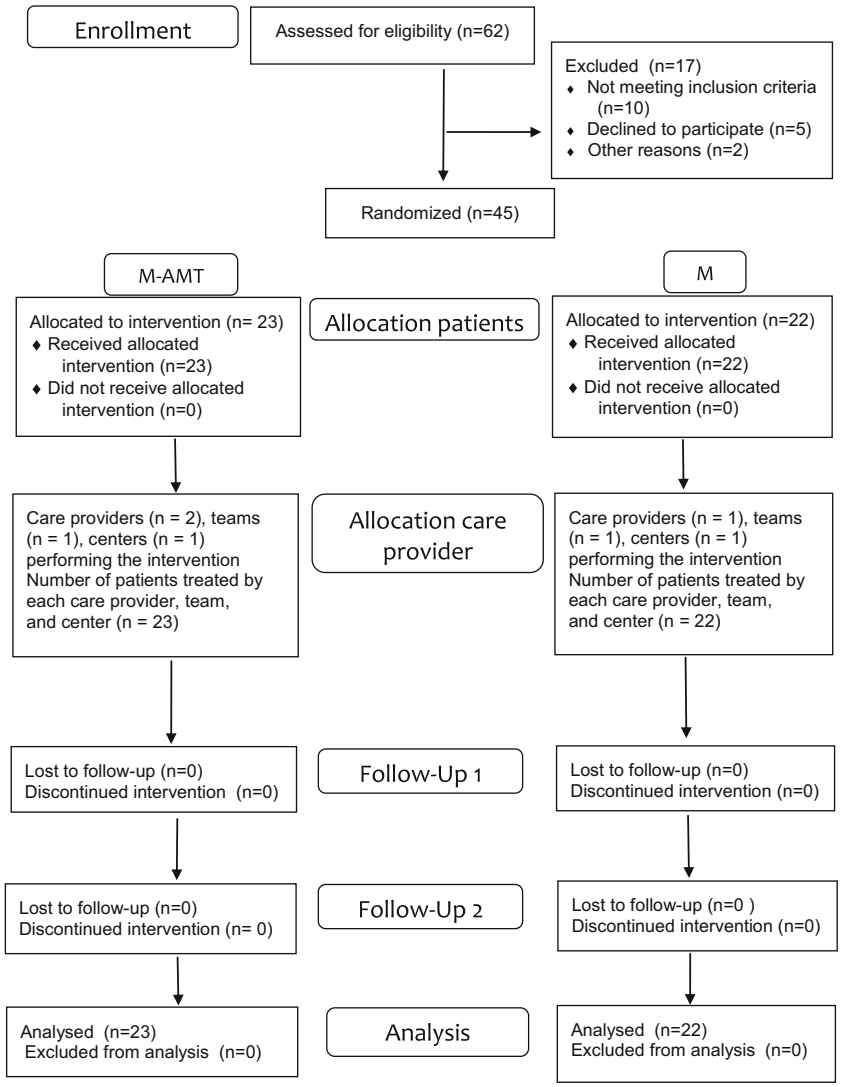

Fig. 1 CONSORT flow chart showing participants flow through the study

Outcome measures

The primary efficacy variable was the change from baseline to week 24 of the Severe Impairment Battery Language (SIB-l) subscale score [26]. The SIB-l, included in the Severe Impairment Battery (SIB) [27], includes 24 items evaluating naming, reading, writing, and repetition (maximum score 46, the higher the score, the better the language). The secondary efficacy endpoints were the SIB [27], Activities of Daily Living (ADL) [28] and Instrumental Activities of Daily Living (IADL) scales [29], Neuropsychiatric Inventory (NPI) [30], MMSE [25], and Lubben Social Network Scale (LSNS) scores [31] at 12 and 24 weeks. The SIB [27] is a 40-item, 100-point scale that assesses, in addition to language, social interactions, memory, orientation, attention, praxis, visual-spatial ability, and orientation, with lower scores indicating greater impairment. The ADL [28] measures independence in daily activities (bathing, dressing, toileting, transferring, eating, and the use of incontinence materials), with a score ranging from 0 (total independence) to 6 (total dependence). The IADL [29] assesses eating, dressing, sphincter control, house works, cooking, using telephone, using money, and outside movement, with scores ranging from 0 to 8 (complete independence). The NPI [30] assesses psychic and behavioral symptoms in individuals with dementia, using a caregiver's interview. It evaluates delusions, hallucinations, depressed mood, anxiety, agitation, euphoria, apathy, irritability, inhibition, aberrant motor behavior, nighttime behavior disturbances, and eating behavior changes, for which the frequency and severity are rated 1–3 (higher numbers indicate greater frequency or severity); a score for each symptom is computed by multiplying the frequency by the severity. The LSNS [31] evaluates the perceived social support received by family, friends, and neighbors. It is a self-report 10-item scale; each item is rated 0–5 (higher scores indicate better social support). The MMSE [25] is based on

questions testing five cognitive functions (orientation, registration, attention and calculation, recall, language), giving a 0–30 total score (the higher the score, the higher the cognitive level).

Data analysis

Previously published data of patients with moderate to severe AD [12] were taken into consideration to determine baseline SIB-l total score, but preliminary assessment of patients did not support such a comparison. In particular, the MMSE scores indicating moderate cognitive impairment did not match to moderate to comparable impairment on the SIB. Therefore, the sample size was determined according to an observational design of a naturalistic condition, prospecting 20 patients in each group.

Statistical analyses were performed using SAS software (SAS Inc., Cary, NC) and all statistical tests were two-sided. All subjects who received at least one dose of M were included in the data analysis (intention-to-treat population). Descriptive statistics for demographic and other baseline characteristics, efficacy, and safety variables was expressed as mean ± SD for continuous variables and as frequency and percentage for categorical variables. The paired *t* test was used to assess the changes from baseline to 12 and 24 weeks. An ANCOVA model including the baseline values as covariate was used in the comparisons between groups. Unpaired *t* test was also used in the comparisons between groups of subscales scores. A χ^2 test compared between groups the rates of patients with worsening in NPI total score from baseline to week 24.

Results

Patient's disposition and baseline characteristics

Forty-five patients (31 females; mean age 73.2) were randomly assigned to the M-AMT ($n = 23$) or M group ($n = 22$). One patient in each group did not perform the post-baseline visits and was not evaluable for assessment of treatment effects. Table 1 shows the demographic and other characteristics of patients at the baseline and week 12 and week 24 visits. The comparisons between groups did not show statistically significant differences for all examined parameters, except in mean NPI total score ($p < 0.001$), which was significantly higher in the M group than in the M-AMT group.

Effects of the treatments

Table 2 shows the results of SIB total score and subscales in the two groups at baseline and 12- and 24-week follow-ups. The mean SIB-l score significantly decreased from baseline to week 24 in the M-AMT group (adjusted mean change − 4.70; 95% CI − 8.16 to − 1.23), compared to a small decrease in the M group (adjusted mean change − 2.46; 95% CI − 6.01 to 1.09), with no between-group differences. Both groups showed no relevant decreases from baseline to week 12.

In the M-AMT group, the SIB total (adjusted mean change − 10.65; 95% CI − 17.50 to − 3.80) and memory scores (adjusted mean change − 2.40; 95% CI − 3.88 to − 0.93) decreased significantly from baseline to week 24. In the M group, the SIB social interactions score decreased significantly from baseline to week 24 (adjusted mean change − 0.46; 95% CI − 1.09 to 0.17), compared to a small decrease in the M-AMT group (adjusted mean change − 0.15; 95% CI − 0.76 to 0.46).

ANCOVA showed no significant between-group differences and the baseline value was a significant predictor of results at 24 weeks for the SIB total [$F(1) = 10.61$, $p = 0.002$] and SIB-l scores [$F(1) = 8.28$, $p = 0.006$].

Table 3 shows the ADL, IADL, and LSNS scores. The ADL score significantly decreased from baseline to week 24 in the M-AMT group ($p = 0.039$). The IADL score significantly decreased from baseline to week 24 in the M-AMT ($p = 0.005$) and M group ($p = 0.001$). At week 24, the adjusted mean changes from baseline of the ADL score were − 0.61 (95% CI − 1.07 to 0.15) in the M-AMT group and − 0.27 (95% CI − 0.74 to 0.20) in the M group, while the corresponding values for IADL in the two groups were − 1.05 (95% CI − 1.75 to − 0.34) and − 1.48 (95% CI − 2.20 to − 0.75), respectively. No significant between-group differences were found for ADL and IADL in the ANCOVA model. The baseline value of ADL resulted in a significant predictor of values at week 24 [$F(1) = 9.11$, $p = 0.004$]. The baseline IADL value also predicted the IADL score at week 24 [$F(1) = 81.25$, $p < 0.001$].

In the M-AMT group, the LSNS total score decreased from baseline to weeks 12 and 24, while the Relatives and Neighbors scores, but not the Friends score, decreased at week 24. In the M group, all scores decreased except for an increase of the Relatives score. However, no significant changes within-group or between-group differences were observed. ANCOVA showed that the baseline LSNS total score was a significant predictor of results at 24 weeks [$F(1) = 6.21$, $p = 0.017$].

The NPI total, Depression (mean change ± SD − 1.77 ± 3.78; $p = 0.039$), and Appetite disorders scores (mean change ± SD − 1.68 ± 2.82; $p = 0.011$) decreased significantly in the M-AMT group at week 12. The mean change in NPI total score from baseline to week 24 was advantageous for the M-AMT group (− 0.55 ± 20.64) but not for the M group (6.29 ± 17.78). The between-group difference in mean changes from baseline of the NPI total score was not significant ($p = 0.253$). However, the rates of worsened/no worsened patients at week 24 differed significantly ($p = 0.048$) due to a lower rate of worsened patients in the M-AMT group (7 patients, 31.8%) than in the M group (13 patients, 61.9%). Between-group comparisons showed a significant difference for depression at week 24 due to a decrease from baseline in the M-AMT group and an increase in the M group (mean ± SD difference between groups, − 2.87 ± 1.25; 95% CI −

Table 1 Demographic and clinical characteristics and scale scores at baseline and 12- and 24-week follow-ups (mean ± SD)

	M-AMT group ($n = 23$)			M group ($n = 22$)		
	Baseline	12 weeks	24 weeks	Baseline	12 weeks	24 weeks
Age	74.3 ± 5.7			72.0 ± 7.3		
Sex, *n* (%)						
Males	7 (30.4%)			7 (31.8%)		
Females	16 (69.6%)			15 (68.2%)		
Education (years)	8.43 ± 3.92			8.50 ± 4.73		
MMSE total score	16.59 ± 4.01	17.5 ± 6.38	15.82 ± 8.04	16.24 ± 4.10	17.14 ± 6.89	15.43 ± 7.18
SIB score						
Total	84.09 ± 15.02	83.18 ± 19.44	74.00 ± 31.36	81.57 ± 20.24	81.10 ± 23.87	75.38 ± 28.98
Social interactions	5.55 ± 1.06	5.73 ± 1.08	5.41 ± 1.44	5.62 ± 0.81	5.57 ± 1.12	5.14 ± 1.62
Memory	10.55 ± 2.03	10.00 ± 3.78	8.14 ± 4.83	10.19 ± 3.74	10.05 ± 3.56	9.24 ± 4.12
Orientation	4.36 ± 1.53	4.50 ± 1.63	4.05 ± 1.81	4.52 ± 1.29	4.52 ± 1.54	4.29 ± 1.79
Language	39.68 ± 7.96	38.86 ± 9.44	35.36 15.55	37.67 ± 10.67	37.05 ± 11.75	34.81 ± 14.83
Attention	5.18 ± 1.01	5.41 ± 0.96	4.50 ± 2.11	5.05 ± 1.20	4.81 ± 1.63	4.62 ± 1.53
Praxis	5.68 ± 2.12	5.86 ± 2.78	5.50 ± 3.14	6.05 ± 2.22	6.24 ± 2.66	5.86 ± 2.80
Visual-spatial ability	7.50 ± 1.26	7.23 ± 1.44	6.05 ± 2.66	7.38 ± 1.86	7.10 ± 1.97	6.62 ± 2.50
Construction	3.68 ± 0.72	3.73 ± 0.93	3.23 ± 1.51	3.24 ± 1.18	3.48 ± 1.25	2.95 ± 1.40
Name orientation	1.91 ± 0.29	1.86 ± 0.35	1.77 ± 0.61	1.86 ± 0.48	1.86 ± 0.35	1.86 ± 0.48
ADL total score	5.50 ± 0.80	5.23 ± 1.07	4.91 ± 1.41	5.57 ± 1.17	5.48 ± 0.98	5.29 ± 0.84
IADL total score	4.23 ± 2.43	3.55 ± 2.77	3.23 ± 2.98	5.24 ± 2.61	4.81 ± 2.82	3.71 ± 2.67
LSNS score						
Total	25.23 ± 14.73	21.82 ± 13.89	20.14 ± 8.11	32.05 ± 17.54	31.43 ± 16.46	28.72 ± 15.62
Relatives	14.50 ± 5.14	13.45 ± 6.50	12.36 ± 5.14	14.09 ± 7.27	16.52 ± 6.19	14.43 ± 6.75
Neighbors	6.64 ± 6.15	4.86 ± 5.34	4.14 ± 4.09	7.71 ± 7.77	6.14 ± 6.71	5.76 ± 7.61
Friends	4.09 ± 6.64	3.50 ± 5.45	4.18 ± 5.63	10.14 ± 9.02	8.76 ± 9.76	8.38 ± 8.27
NPI score						
Total	21.41 ± 12.07*	18.41 ± 15.82	21.05 ± 20.58	8.24 ± 9.54	10.65 ± 13.27	14.52 ± 16.90
Delirium	0.14 ± 0.47	0.91 ± 2.43	0.59 ± 1.87	0.67 ± 2.06	1.38 ± 4.49	0.43 ± 1.96
Hallucinations	0.86 ± 2.15	1.0 ± 2.53	1.41 ± 2.58	0.29 ± 1.31	1.38 ± 4.49	0.43 ± 1.96
Stirring	1.95 ± 2.98	2.09 ± 2.39	1.41 ± 2.82	0.52 ± 1.17	0.10 ± 0.44	0.38 ± 0.97
Depression	3.50 ± 3.67	1.73 ± 3.13	1.86 ± 2.82	1.19 ± 2.96	0.71 ± 2.12	1.90 ± 3.48
Anxiety	3.14 ± 3.82	2.36 ± 3.67	2.41 ± 3.58	1.24 ± 1.92	1.48 ± 2.38	1.71 ± 2.49
Euphoria	0.41 ± 1.05	0.36 ± 1.71	0.95 ± 2.40	0.00 ± 0.00	0.0 ± 0.00	0.76 ± 2.72
Apathy	2.95 ± 4.24	2.95 ± 4.37	4.27 ± 4.56	2.10 ± 3.29	2.10 ± 3.28	2.19 ± 3.36
Disinhibition	1.18 ± 2.46	1.32 ± 3.11	1.09 ± 3.01	0.14 ± 0.48	0.14 ± 0.48	1.0 ± 3.19
Irritability	1.82 ± 2.63	1.36 ± 2.26	1.41 ± 2.59	0.48 ± 1.75	0.48 ± 1.75	0.52 ± 1.83
Motor activity	1.27 ± 3.18	2.0 ± 4.11	2.27 ± 4.11	0.29 ± 1.31	0.29 ± 1.31	1.57 ± 3.38
Sleep	1.59 ± 2.70	1.55 ± 3.55	1.55 ± 2.72	0.38 ± 1.75	0.38 ± 1.75	0.81 ± 2.16
Appetite disorders	2.59 ± 3.71	0.91 ± 2.81	1.64 ± 3.18	0.95 ± 2.80	0.95 ± 2.80	0.81 ± 2.18

AMT active music therapy, *MMSE* Mini Mental State Examination, *SIB* Severe Impairment Battery, *ADL* Activities of Daily Living, *IADL* Instrumental Activities of Daily Living, *LSNS* Lubben Social Network Scale, *NPI* Neuropsychiatric Inventory

*$p < 0.001$ between groups; NS between groups in the other comparisons

5.40 to − 0.35; $p = 0.027$ in the unpaired t test). ANCOVA showed that the baseline NPI total score was a significant predictor of results at 24 weeks [$F(1) = 4.48$, $p = 0.04$].

The MMSE total score slightly decreased from baseline to week 24 in both groups. The adjusted mean changes from baseline to week 24 in the M-AMT (− 0.77, 95% CI − 3.01 to 1.46, $p = 0.48$) did not differ significantly from those observed in the M group (− 0.81, 95% CI − 2.34 to 0.72, $p = 0.28$). ANCOVA showed no relationships between the baseline and 24-week MMSE scores.

Table 2 Adjusted mean changes of the SIB scores from baseline (95% CI)

		M-AMT group ($n = 22$)	M group ($n = 21$)
SIB Total score	Week 12	− 1.03 (− 5.06 to 2.30)	− 0.78 (− 4.90 to 3.35)
	Week 24	− 10.65 (− 17.50 to − 3.80)	− 5.61 (− 12.62 to 1.41)
SIB Social interactions	Week 12	0.17 (− 0.24 to 0.57)	− 0.03 (− 0.45 to 0.38)
	Week 24	− 0.15 (− 0.76 to 0.46)	− 0.46 (− 1.09 to 0.17)
SIB Memory	Week 12	− 0.51 (− 1.66 to 0.63)	− 0.17 (− 1.34 to 1.00)
	Week 24	− 2.40 (− 3.88 to − 0.93)	− 0.96 (− 2.47 to 0.55)
SIB Orientation	Week 12	0.11 (− 0.42 to 0.65)	0.02 (− 0.52 to 0.57)
	Week 24	− 0.32 (− 0.86 to 0.21)	− 0.23 (− 0.78 to 0.32)
SIB Language	Week 12	− 0.87 (− 2.62 to 0.88)	− 0.57 (− 2.36 to 1.22)
	Week 24	− 4.70 (− 8.16 to − 1.23)**	− 2.46 (− 6.01 to 1.09)*
SIB Attention	Week 12	0.26 (− 0.26 to 0.78)	− 0.27 (− 0.80 to 0.26)
	Week 24	− 0.67 (− 1.39 to 0.05)	− 0.45 (− 1.18 to 0.29)
SIB Praxis	Week 12	0.18 (− 0.57 to 0.96)	0.20 (− 0.57 to 0.96)
	Week 24	− 0.20 (− 1.20 to 0.80)	− 0.17 (− 1.19 to 0.85)
SIB Visual-spatial ability	Week 12	− 1.47 (− 2.24 to − 0.70)	− 0.75 (− 1.54 to 0.04)
	Week 24	− 0.26 (− 0.76 to 0.24)	− 0.30 (− 0.81 to 0.21)
SIB Construction	Week 12	0.17 (− 0.28 to 0.62)	0.11 (− 0.35 to 0.57)
	Week 24	− 0.42 (− 0.95 to 0.12)	− 0.33 (− 0.88 to 0.23)
SIB Name orientation	Week 12	− 0.03 (− 0.17 to 0.11)	− 0.02 (− 0.16 to 0.13)
	Week 24	− 0.14 (− 0.31 to 0.04)	− 0.00 (− 0.18 to 0.18)

AMT active music therapy; *SIB* Severe Impairment Battery

*$p < 0.05$, **$p < 0.01$ vs. baseline

Classification of evidence

This study provides Class II evidence that, in patients with moderate probable AD on stable therapy with AchEI, combined treatment with AMT and M was associated with improvement in depressive symptoms and stabilized psychiatric health status compared to M monotherapy.

Safety

Eight adverse events (AEs) were reported in 5 patients (21.8%) in the M-AMT group and 17 AEs were reported in 11 patients (50.0%) in the M group. The most common AEs were somnolence (six patients in the M group), insomnia (two patients in the M-AMT group, one in the M group), and

Table 3 Adjusted mean changes of ADL, IADL, and LSNS scores from baseline (95% CI)

		M-AMT group ($n = 22$)	M group ($n = 21$)
ADL	Week 12	− 0.27 ± 0.77	− 0.10 ± 0.89
	Week 24	− 0.59 ± 1.26	− 0.29 ± 1.06
IADL	Week 12	− 0.68 ± 1.84	− 0.43 ± 1.17
	Week 24	− 1.00 ± 1.48*	− 1.62 ± 1.75**
LSNS Total	Week 12	− 4.22 ± 12.23	− 2.05 ± 17.98
	Week 24	− 4.55 ± 12.49	− 3.38 ± 20.15
LSNS Relatives	Week 12	− 1.05 ± 5.32	2.43 ± 6.31
	Week 24	− 2.14 ± 6.09	0.33 ± 6.93
LSNS Neighbors	Week 12	− 1.77 ± 4.75	− 1.57 ± 7.08
	Week 24	− 2.50 ± 5.93	− 1.95 ± 9.26
LSNS Friends	Week 12	− 0.59 ± 4.88	− 1.38 ± 9.22
	Week 24	− 0.09 ± 5.57	− 1.76 ± 10.61

AMT active music therapy, *ADL* Activities of Daily Living, *IADL* Instrumental Activities of Daily Living, *LSNS* Lubben Social Network Scale.

* p=0.005, **p=0.001 vs baseline

depression (two patients in the M group). No other AEs were reported in more than one patient in either group.

Discussion

We investigated the effects of M plus AMT on verbal communication and, secondarily, on daily living, psycho-behavioral aspects, social relations, and global cognitive functioning in patients with moderate AD on stable treatment with AchEI.

The baseline SIB-l mean score of the two groups of intervention indicated a mild to moderate language impairment and hence a small probability of detecting differences between baseline and follow-up. Indeed, the probability of achieving a clinically relevant language improvement related to the SIB-l baseline score, with lower scores corresponding to greater improvements [12]. As further confirmation of the importance of the extent of baseline impairment, ANCOVA showed that the baseline SIB total and language scores predicted the results at 24 weeks. Significant effects of the baseline values were also observed for ADL, LSNS, and NPI.

The primary variable (SIB-l) and other SIB scores showed an overall stabilization over time of the baseline condition up to the end of the 12-week treatment phase.

The NPI total and subscale scores revealed significant benefits in the M-AMT group for Depression and Appetite disorders after 12 weeks of treatment, and a significant between-group difference for Depression at week 24, due to an improvement from baseline in the M-AMT group and a worsening in the M group. The rates of worsened/no worsened patients at week 24 also showed a significant difference in favor of the M-AMT group. In both groups, the other secondary variables (ADL, IADL, LSNS, MMSE) showed no substantial deterioration from baseline to week 24.

Worth noting, M-AMT was associated with improved psychiatric symptoms compared to drug therapy alone. Moreover, there was an advantage on the social interactions SIB subscale in the M-AMT group compared to the M group. This extends previous findings concerning a positive influence for AMT on mood and behavior [19, 32–34]. The activations of the emotions and memory circuits may explain the psycho-behavioral effects of AMT in dementia [35].

According to the cognitive reserve model, the variability in the clinical manifestation of a neuropathology reflects individuals' ability to use cognitive strategies [36]. Cognitive reserve can be continuously modified by experience even when the brain is already affected by pathology [36]. Education and personal experience can enhance cognitive reserve, contrasting the clinical AD manifestations [37, 38]. The capacity of the baseline SIB total, SIB-l, ADL, LSNS, and NPI scores to predict the results at week 24 suggests that cognitive reserve may enhance the effects of the treatment [39]. This extends the spectrum of non-pharmacological treatment, which may be comprehended in a wider range of palliative care for chronic neurological disorders [40].

The small sample size, mild language impairment, and high variance of baseline data may have compromised the possibility of observing between-group differences in the outcome variables.

To conclude, in patients with moderate AD, an association of AMT added to pharmacotherapy has no further benefits for language and verbal communication in comparison with pharmacotherapy alone. However, this integrated approach can improve the psycho-behavioral profile.

Acknowledgements The authors thank the patients and their caregivers for collaboration.

Funding information This study was supported by the Italian Ministry of Health through a Current Research project "Non-pharmacological therapies for cognitive disturbances" to A.R.G., and it was sponsored in part by Lundbeck (Valby, Denmark) through a non-profit research project to A.R.G. A salary of a neuropsychologist was supported by an Italian Ministry of Health's grant.

Compliance with ethical standards

The study was in compliance with the Declaration of Helsinki principles and was approved by the Institutional Review Boards and Ethical Committee, and all patients involved gave their written informed consent.

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