Journal of Alzheimer's Disease 58 (2017) 109–121
DOI 10.3233/JAD-160792
IOS Press

Do Hearing Aids Influence Behavioral and Psychological Symptoms of Dementia and Quality of Life in Hearing Impaired Alzheimer's Disease Patients and Their Caregivers?

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Abstract.
Background: It has been suggested that age-related hearing loss (ARHL) and Alzheimer's disease (AD) are commonly associated.
Objective: The Alzheimer Disease, Presbycusis and Hearing Aids (ADPHA) clinical trial assessed the influence of hearing aids (HAs) on patients affected by ARHL and AD, as judged by behavioral symptoms and functional abilities, as well as patient and caregiver quality of life (QoL).
Methods: A multicenter double-blind randomized placebo-controlled trial, with a semi-crossover procedure over 12 months, was conducted from 2006 to 2012. For the first 6 months, the active group was treated with active HAs and the placebo group with inactive HAs. For the last 6 months, HAs in the placebo group were activated. Assessment was conducted at baseline, 6 months, and 12 months. We performed intergroup and intragroup comparisons. Behavioral symptoms were assessed by neuropsychiatric inventory (NPI), functional abilities by instrumental activities of daily living, and QoL by Zarit, Alzheimer's disease related quality of life, and simplified Duke scales.
Results: Fifty-one patients were included and randomized: 22 in active group (mean NPI 17.6; mean age 83 ± 6.2) and 26 in placebo group (mean NPI 25.8; mean age 82.3 ± 7.2) were fitted with HAs. At 6-month follow-up, all scores worsened without significant difference between the two groups. In placebo group, activation of HAs had no effect on the change of these scores.
Conclusion: These findings do not provide evidence of improvement in behavioral symptoms, functional status, or QoL of hearing impaired AD patients and their caregivers after 6 months of HA use. However, we cannot exclude that HAs may have a positive effect in patients aged less than 75 years.

Keywords: Age-related hearing loss, Alzheimer's disease, behavioral symptoms, hearing aids

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INTRODUCTION

Alzheimer's disease (AD) is a common neurodegenerative disorder and is therefore an important public health issue. There are currently 44.3 million people who are affected by dementia worldwide and it is expected that this prevalence will reach 135.5 million by 2050 [1]. Over the course of the disease, there are many social and family consequences, which are mostly due to behavioral and psychological symptoms of dementia (BPSD). These symptoms that often determine the evolution of patients are frequent, affecting more than 80% of patients and include apathy, depression, anxiety, agitation, irritability, aberrant physical behaviors, delusion, eating disorders, sleep disorders, disinhibition, hallucinations, and euphoria [2]. Disruptive behavioral symptoms such as agitation and aberrant physical behavior are some of the most prevalent BPSD and have the highest impact on caregivers and institutional care settings [3]. These neuropsychiatric symptoms are associated with many adverse outcomes such as medication misuse, excess healthcare use, increased healthcare costs, decreased quality of life (QoL) for patients and their caregivers, and earlier institutionalization [4–6]. They are therefore an important therapeutic target; however, the limited efficiency of pharmacological agents that can partially stabilize the symptoms but have no disease-modifying effects, and their many adverse effects, incites further research, in particular into non-pharmacological solutions [2, 7, 8].

Age-related hearing loss (ARHL), also known as presbycusis, is a common condition affecting aging individuals. It is estimated that about two-thirds of persons aged 70 years or older exhibit hearing problems. Deficits in both peripheral hearing and central auditory processing can contribute to ARHL [9]. This disorder is known to directly affect an individual's ability to communicate and to interact with his/her environment. Behavioral and psychological symptoms such as depression, anxiety, paranoia, and reduced social activities due to hearing impairment are identified, and improved hearing ability is reported to be effective on communication function and interaction among those without dementia [10–12].

Accordingly, several studies assessing the combined impact of both peripheral auditory function and central auditory processing deficits have shown an association with incident AD and psychological symptoms of dementia [9]. With regards to the cognitive aspect of AD, Lin et al. have also found that the hearing-impaired population is at higher risk of accelerated cognitive decline [13]. Moreover, Amieva et al. have recently demonstrated that hearing aid (HA) use attenuates such decline and may have a protective effect [14]. However, it has been suggested that while elderly individuals without any abnormal cognitive dysfunction are routinely assessed and treated for hearing loss (HL), age- and hearing level-matched demented individuals are not [15]. This could reflect the assumption that such patients would not be good candidates for HAs, with a high risk of poor compliance, yet studies have found that demented patients have no difficulties with audiometric testing [16] or with the use of amplification [17, 18]. There is, however, a lack of interventional studies investigating the fitting of HAs to people suffering from BPSD. The few that have been carried out [17, 18] did not use adequate methodology (monaural hearing aid, no control group) and their conclusions as to the potential benefit of intervention differed. Thus, it seemed important to conduct a rigorous interventional study to investigate potential benefits in terms of psychological symptoms, of auditory rehabilitation of elderly patients suffering both ARHL and AD.

We hypothesized that subjects receiving active HAs would show less behavioral symptoms by reconnecting with their acoustic environment. We also hypothesized that loss of functional abilities would be reduced and the QoL of patients and their caregivers would be improved. Indeed, neuropsychiatric symptoms have been shown to be a leading cause of stress and overload for caregivers and increase rates of functional limitation for demented patients [3].

The aim of this study was to assess the efficacy of fitting binaural HAs to patients with ARHL and AD, as judged by neuropsychiatric symptoms, abilities for Instrumental Activities of Daily Living (IADL), and QoL of participants and their caregivers. Compliance and adverse effects with HAs were also investigated.

MATERIALS AND METHODS

This multicenter, randomized, double blind, controlled trial versus placebo, included patients affected by AD and ARHL in order to evaluate the efficacy of fitting HAs on cognitive abilities (with the Alzheimer's disease assessment scale-cognitive subscale, ADAS-COG, as the primary endpoint, reported in the companion paper by Nguyen et al. [19]) and neuropsychiatric symptoms (secondary endpoint, addressed in this paper). Ethics committee

approval was obtained prior to the study (reference A06–162).

Inclusion and exclusion criteria

Subjects were community-dwelling volunteers with memory complaints, recruited from three memory consultations. Prior written informed consent was obtained from subjects, support person, or family.

First, biological tests, cerebral magnetic resonance imaging (MRI) and neuropsychological tests were conducted for diagnosis and to exclude another cause of dementia. Participants were included in the study if they met the following criteria: probable diagnosis of AD according to the Diagnostic and Statistical Manual of Mental Disorders IV (DSM IV) [20] and the National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) [21], aged $\geq$65 years, Mini-Mental State Examination (MMSE) [22] score between 10 and 28, bilateral sensorineural HL appropriate for the range of amplification provided by the HAs (i.e., between 21 and 80 dB HL), not to have benefited from HAs for the last 2 years, to tolerate wearing HAs for at least one hour a day, living with an informal motivated caregiver (partner, child, friend, paramedical personnel). It is important to note that in France, clinical practice at the time of the trial were not to systematically treat patients with AD with antidementia drugs. Thus, even participants without pharmacological treatment had been diagnosed as probable AD patients.

HL was assessed by pure tone audiometry, preceded by a bilateral otoscopy. Tested frequencies were between 250 and 8000 Hz, at one-octave intervals. Vocal audiometry was not applied due to practical constraints related to the type of patients studied, who suffered from AD, with possible comprehension difficulties related to their cognitive disorders that did not ensure a complete audiological evaluation. A tympanometry was also performed to assess middle-ear function. Participants were excluded if they met the following criteria: non-AD dementia as evidenced by medical history, clinical elements, biological and/or medical imaging data (for instance vasculitis, vitamin B12 or B9 deficiency, ionic or glycemic control dysfunction, hypothyroidism, extrapyramidal syndrome, Creutzfeldt-Jakob Disease, Lewy body dementia, purely vascular or frontotemporal dementia); recent introduction of cognitive-behavioral treatment, prior to the study (less than 6 months for cholinergic inhibitors and memantine or less than 2 months for psychotropic medication), and/or recent change in dosage for one of these treatments (less than 2 months for cholinergic inhibitors and memantine, less than 1 month for psychotropic medication); to break or to lose HAs twice or more during the study.

Intervention

After inclusion, patients were randomized to two groups: one group of patients was fitted with active HAs (active HAs group), and the other with placebo HAs (placebo HAs group). We used a semi-crossover procedure over 12 months. At 6 months, we realized an inter-group comparison of all the scores. After activation of the HAs of the placebo HAs group at 6 months, we realized an intra-group comparison in this group of all the scores between 12 and 6 months, thus making it possible to measure the effect of activating HAs among the placebo group (Fig. 1).

Binaural HAs were used, supplied in part by Phonak© France. The HAs used were SAVIA™ or VALEO™ models, manufactured by Phonak©.

Control condition

The placebo HAs were produced from active models by using standard sound tubes and open canal fitting, with a minimal sound amplification (gain of 30 dB on average) to compensate for the occlusion effect. Theses HAs consumed energy and needed battery replacement like active HAs.

Randomization and blinding

Enrolled subjects were randomized just before fitting of binaural HAs. Only the hearing aid specialist knew the randomization group of each subject. Double blinding was ensured by the impossibility of distinguishing active from placebo HAs. Furthermore, assessment of the effect of HAs on experimental variables was conducted by a clinical research associate (CRA) and not by the hearing aid specialist.

Each participant was assigned to a group according to chronological order of inclusion, pre-established in a randomization list. It was effective at the signature of the informed consent by patient, caregiver, and investigator.

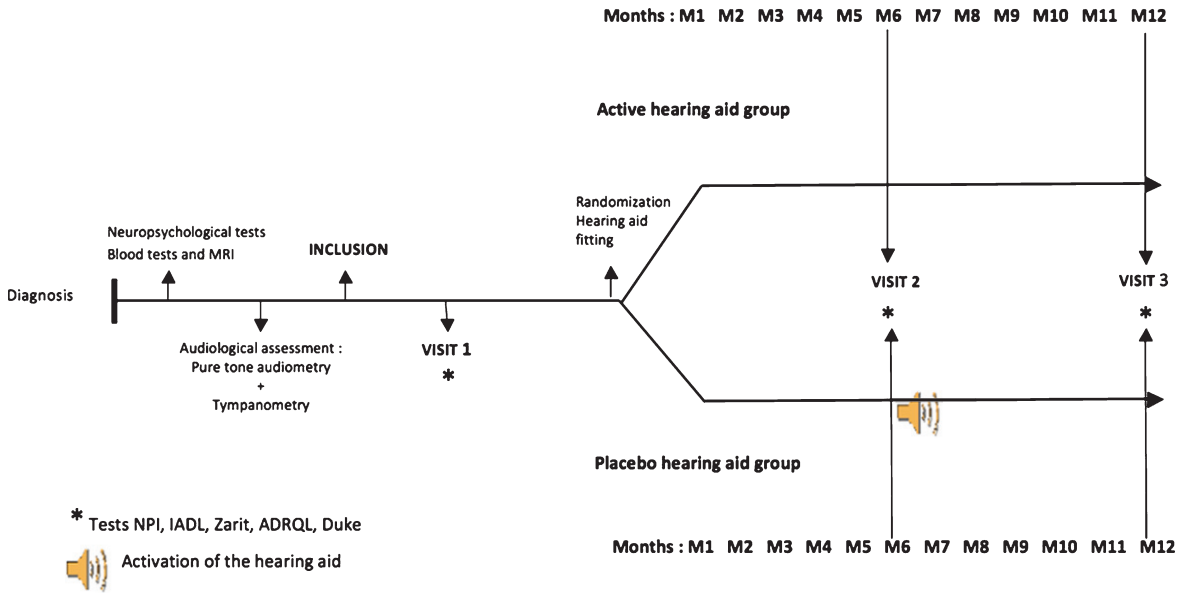

Fig. 1. Chronological diagram of the study. Patients were included in the study after they were diagnosed as probable Alzheimer's disease patients and after hearing loss was assessed by pure tone audiometry. Then, patients were randomized to two groups: one group of patients was fitted with active HAs (active HAs group), and the other with placebo HAs (placebo HAs group). Data were collected at 3 moments: baseline (Visit 1), the 6-month (Visit 2) and the 12-month (Visit 3) follow-up visits for both groups. A semi-crossover procedure was used over 12 months. At 6 months, an inter-group comparison of all the scores was realized. After activation of the HAs of the placebo HAs group at 6 months, an intra-group comparison in this group of all the scores was realized between 12 and 6 months, thus making it possible to measure the effect of activating HAs among the placebo group.

Assessment

Data were collected from the caregiver by a CRA at baseline (Visit 1), at 6 months (Visit 2), and at 12 months (Visit 3). Neuropsychiatric symptoms were assessed by the neuropsychiatric inventory (NPI) [23], functional status was assessed by IADL [24], patient and caregiver QoL were assessed by Zarit [25], and Alzheimer Disease Related Quality of Life (ADRQL) [26] scales and with a simplified version of the Duke health profile, centered on patient and caregiver social interactions [27, 28].

Compliance with treatment was assessed using monthly self-administered patient or caregiver questionnaires that collected daily duration and weekly frequency of HA wearing. From these data, a composite score of HA wearing compliance was computed (daily duration multiplied by weekly frequency of HA wearing), scored out of a total of 100 points, as described in the Supplementary Table 1. From that score, four compliance subgroups were defined: bad: [0–9], moderate: [9–70], good: [70–100], and very good: [100].

Every serious or mild adverse effect was notified. Adverse effect was defined by all events linked or not to HAs that could lead to death, pathological condition with risk of death, hospitalization, prolongation of hospitalization, disability or temporary or permanent disability, any other event does not meet the qualifications listed above, but can be regarded as potentially serious including some laboratory abnormalities or clinically relevant event in the judgment of the investigator. A CRA reported every adverse effect at the 1-week, 3-month, 6-month, 9-month, and 12-month follow-up visits.

Analyses

Analyses were performed by the hospital clinical investigation unit (*Pôle information médicale et evaluation recherche,* IMER, of the *Hospices Civils de Lyon*, HCL). Calculation of sample size was based on the primary study endpoint, the ADAS-COG that focuses on cognitive benefit of auditory rehabilitation, addressed in the companion paper reported by Nguyen et al. [19]. We hypothesized that after 6 months, intervention would have beneficial effects in 60% of subjects of the active hearing aid group and 5% of subjects of the placebo hearing aid group. A sample size of 12 subjects in each group was

estimated to provide 90% power to detect a benefit in terms of reducing or slowing down cognitive decline and behavioral symptoms, with 5% of alpha risk. Taking into account potential loss to follow-up, the number of subjects to be included was 15 in each group, and therefore a total of 30.

All parameters collected were analyzed using descriptive statistics. Comparability of the two groups was tested with Student *t*-test (or Mann-Whitney test in case of non-normal distribution) for continuous variables, and with chi-square test (or Fisher's exact test, if chi-square test's conditions were unfulfilled) for qualitative variables. Intergroup comparisons were performed at 6 months. Score differences between 6 months and inclusion were calculated for each patient and mean differences (delta) were compared between the two groups using the Student *t*-test (or Mann-Whitney test in case of non-normal distribution).

For the active HAs group, we performed intra-group comparison between scores at inclusion, at 6 months, and at 12 months, using a mixed model for repeated measures. For the placebo HAs group, after activation of the HAs at 6 months, we performed intra-group comparison between scores at 12 months and those at 6 months, using the paired Student's *t*-test (or Wilcoxon signed-rank test for matched samples in case of non-normal distribution).

We could not realize repeated measures models on both groups because activation of the HAs was not the same between inclusion and 12 months for placebo group. Also we tested the evolution of the scores only for active HAs group using mixed models for repeated measures (repeated measures ANOVAs were not adapted because no fixed factor could be considered). In each group, Spearman correlation between scores differences and MMSE score at inclusion were performed: scores difference at 6 months were calculated from inclusion for both groups; Scores differences at 12 months were calculated from inclusion for active HAs group and from 6 months for placebo HAs group.

Analyses were conducted on an intention-to-treat basis, using Statistical Analysis System (SAS version 9.2, Cary, NC, USA).

RESULTS

Between 2006 and 2012, a total of 51 patients were included and randomized, of whom 48 were fitted with HAs: 22 received active HAs, and 26 placebo HAs for the first six months. From month 6 to 12, all patients had active HAs. Data were available for 38 patients at 6 months and 34 patients at 12 months (Fig. 2). Deviations from protocol occurred. At inclusion, 4 patients did not respect the MMSE score inclusion criterion that should have been between 10 and 28 : 2 had MMSE score of 9 (one discontinued prematurely), 1 patient had MMSE score of 29, and 1 patient had missing MMSE score (with consent withdrawal before the beginning of the intervention). However, these 4 patients were retained for the analysis.

There was no significant difference at baseline between the two groups with regards to demographic characteristics, education level, audiometric characteristics, medication use, behavioral symptoms, and functional status or caregiver burden. Patients were at a mild to moderate stage of AD, and at a moderate stage of HL (Table 1). Bilateral hearing thresholds included extreme values ranging from 30.5 to 69 dB HL for active HAs group and from 31.5 to 65.5 dB HL for placebo HAs group. MMSE score distribution at inclusion among active HAs group and placebo HAs group is presented in Supplementary Figure 1.

Outcome measures

There was no significant difference between groups at 6-months follow-up for NPI, IADL, Zarit, ADAS-COG, and Duke scores. At 12 months, a significant difference in ADRQL score was found in favor of active HAs group, compared to placebo HAs group (Table 2).

The results of an intra-group analysis of active HAs group, comparing the data between baseline, 6 months, and 12 months are presented in Supplementary Table 2. No change was found, irrespective of the outcome variable, except for IADL score, for which a statistically significant decrease over time was found ($p < 0.0001$). Six months after activating their HAs (12-month follow-up), there was a trend toward worse scores among those of the placebo group and there was a significant worsening for Duke score (Table 3).

There was no significant difference between groups in favor of active HAs when the mean change of individual scores (delta scores) over the first 6 months of follow-up were compared, both among the total population and stratified according to the level of compliance (Table 4). There was a significant improvement of ADRQL in case of good compliance with active HAs ($p = 0.02$) for active HAs group.

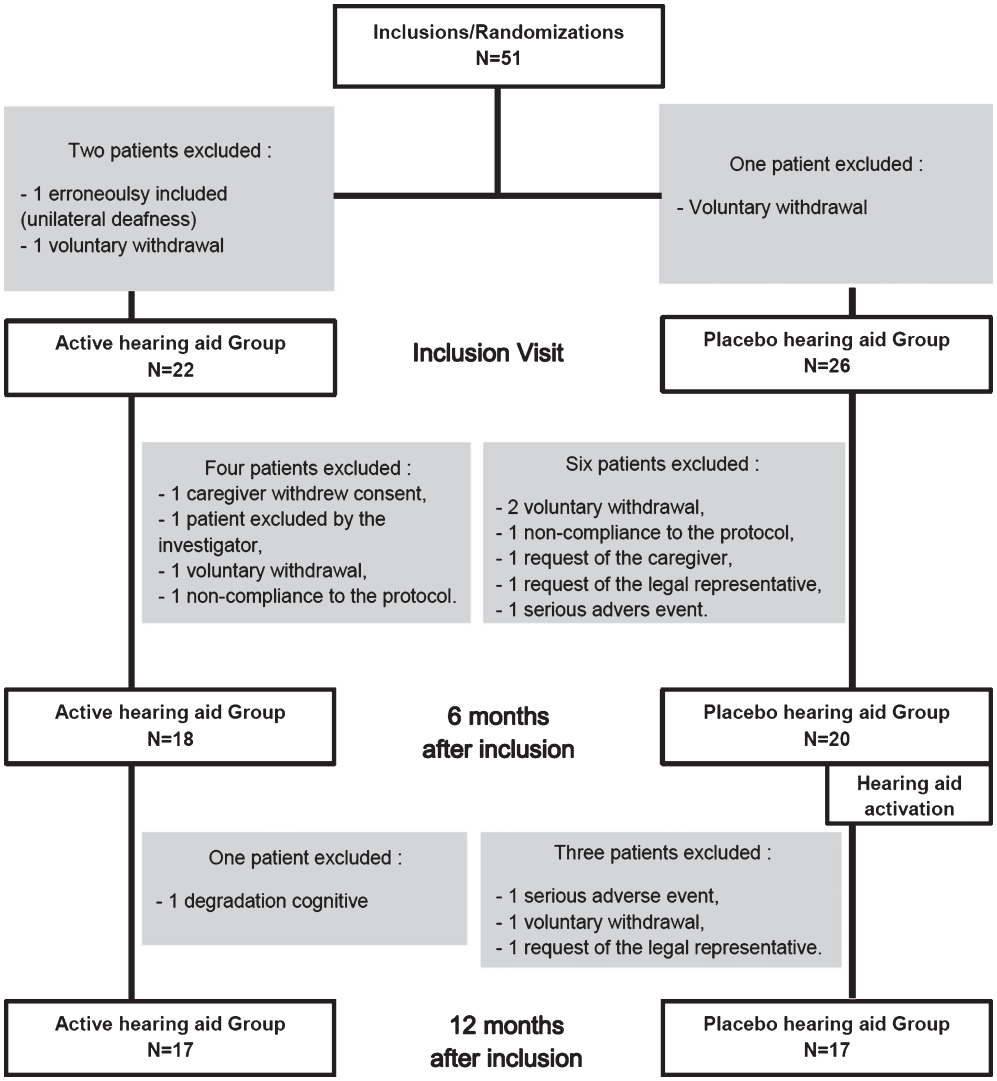

Fig. 2. Trial participant flow diagram.

Delta scores of NPI sub-scores over the first 6 months of follow-up in the two groups were also studied and these results are presented in Supplementary Table 3.

No correlation between the MMSE scores at baseline and the change in outcome variable scores from baseline (delta) at 6 and 12 months was observed, for both experimental groups (Supplementary Table 4).

Compliance and adverse effects

Compliance with treatment was acceptable to allow interpretation of the results [19]. There was no report of any adverse effect related to the study and the use of the HAs [19].

DISCUSSION

This study found that hearing aids for older people with hearing impairment and AD did not provide any benefit in terms of neuropsychiatric symptoms or activities of daily living, nor in the QoL of patients or their caregivers. However, the findings suggest a potential beneficial effect of HAs use on QoL particularly in case of good compliance with HAs. Some results are significant (delta ADRQL and Delta Duke score for patients; delta NPI/irritability-emotional lability for bad and moderate compliance), but in isolation, and without clear clinical relevance. Correlational analyses showed that changes in behavioral,

Table 1
Baseline characteristics of patients

	Active HAs group N = 22 (%)	Placebo HAs group N = 26 (%)	*p*
Age (years)	83 ± 6.2	82.3 ± 7.2	0.7
Sex, female, *n* (%)	14 (63.6)	15 (57.7)	0.7
Education level, *n* (%)			1.0#
<School certificate	3 (14.3)	3 (12.5)	
School certificate	8 (38.1)	10 (41.7)	
High school diploma	5 (23.8)	6 (25.0)	
University studies	5 (23.8)	5 (20.8)	
Medication use, *n* (%)	N = 19	N = 20	
Cholinergic inhibitors	15 (79.0)	20 (80.0)	1.0#
Memantine	4 (21.1)	5 (20.0)	1.0#
Cholinergic inhibitors+Memantine	3(15.8)	4 (16.0)	1.0#
Antidepressants	11 (57.9)	15 (60.0)	0.9
Benzodiazepines	7 (36.8)	9 (39.0)	0.9
Antipsychotics	2 (10.5)	0 (0.0)	0.2#
Bilateral hearing thresholds, dBHL	50.6 ± 11.4	47.2 ± 9.6	0.3
MMSE (/30)	N = 21	N = 26	
	19.8 ± 3.6	19.3 ± 5.2	0.7
NPI (/144)	N = 21	N = 26	
	17.5 ± 12.3	25.8 ± 15.1	0.1#
IADL (/8)	N = 21	N = 26	
	4.7 ± 2.1	4.0 ± 2.5	0.2
Zarit (/88)	N = 19	N = 25	
	19.6 ± 10.6	26.0 ± 14.4	0.1#
ADRQL (/544.76)	N = 22	N = 26	
	457.4 ± 112.4	450.4 ± 81.2	0.3#
Duke-patient (/8)	N = 21	N = 26	
	4.5 ± 2.0	3.7 ± 1.4	0.1#
Duke-caregiver (/8)	N = 21	N = 26	
	4.6 ± 2.3	3.9 ± 2.0	0.3

Values are mean ± SD unless otherwise noted. #Indicates the outcomes variables assumed to have a non-normal distribution and which were tested with Mann-Whitney test for continuous variables and $\chi 2$ test or Fisher test for categorical variables. Otherwise variables were assumed to have a normal distribution and were tested with Student *t*-test. ADRQL, Alzheimer Disease Related Quality of Life; HAs, hearing aids; MMSE, Mini-Mental State Examination; NPI, Neuropsychiatric Inventory; IADL, Instrumental Activities of Daily Living.

functional, and QoL scores were independent of baseline MMSE scores at 6- and 12-months follow-up, irrespective of the experimental group. These findings are not in favor of the assumption that the lack of HA benefit could have been related to heterogeneity in stage of AD in the study groups.

Results from previous studies focusing on fitting HAs to patients suffering from neuropsychiatric symptoms are inconsistent. Among them, Palmer et al. [17] recruited 8 patients (mean age: 79.6 years, mean MMSE: 13.6, mean hearing thresholds: 40 dB) in a multicenter trial, and compared behavioral symptoms exhibited prior to, and following monaural HA fitting over 4–5 months of follow-up. They found significant reduction in at least one of four problem behaviors identified by caregivers as being the most frequent and important (searching, negative statements, repeating questions, acts restless, hallucinations). In another multicenter trial, Allen et al. [18] evaluated 31 subjects (mean age: 84 years, mean MMSE 18, mean hearing thresholds: 59 dB) who they followed for 6 months. Compliance was low (56% daily wearing by the end of the study) and they found no impact of HA fitting on neuropsychiatric symptoms or caregiver burden. These inconsistent results are probably due to divergent methodologies, with the use of monaural HA, and the absence of control group in these two studies. According to the literature [29], the present study is the first to employ rigorous methodology (multicenter, double-blind, controlled, randomized trial) evaluating the efficacy of fitting binaural HAs to people suffering from both hearing disability and AD, and to provide reliable results, despite implementation difficulties concerning assessment and follow-up of neuropsychiatric symptoms in this population.

Many similarities have been noted when comparing ARHL and dementia. Particularly, some

Table 2
Mean NPI, IADL, Zarit, ADRQL, and Duke scores at 6- and 12-months follow-up

	Active HAs group	Placebo HAs group	*p*
NPI (/144)			
6 months	N = 18	N = 18	
	23.6 ± 22.6	26.1 ± 14.7	0.3#
12 months	N = 15	N = 17	
	20.1 ± 20.0	34.4 ± 27.8	0.1#
IADL (/8)			
6 months	N = 18	N = 18	
	3.2 ± 2.0	3.0 ± 2.3	0.6
12 months	N = 17	N = 17	
	3.0 ± 1.9	2.7 ± 2.5	0.3#
Zarit (/88)			
6 months	N = 14	N = 18	
	22.4 ± 14.7	26.3 ± 15.2	0.5
12 months	N = 15	N = 16	
	20.3 ± 12.3	25.7 ± 13.5	0.3#
ADRQL (/544.76)			
6 months	N = 18	N = 18	
	452.0 ± 88.4	446.4 ± 45.8	0.2#
12 months	N = 17	N = 17	
	474.5 ± 56.3	431.3 ± 69.5	0.0496#
Duke-patient (/8)			
6 months	N = 18	N = 20	
	3.9 ± 2.3	4.8 ± 1.9	0.3#
12 months	N = 17	N = 17	
	3.9 ± 2.0	3.7 ± 1.8	0.6#
Duke-caregiver (/8)			
6 months	N = 18	N = 20	
	4.6 ± 1.8	4.3 ± 1.8	0.6
12 months	N = 17	N = 17	
	4.6 ± 2.5	4.1 ± 1.5	0.5

Values are mean ± SD unless otherwise noted. Significant differences in bold. #Indicates the outcomes variables assumed to have a non-normal distribution and which were tested with Mann-Whitney test, otherwise variables were assumed to have a normal distribution and were tested with Student *t*-test. ADRQL, Alzheimer Disease Related Quality of Life; HAs, hearing aids; NPI, Neuropsychiatric Inventory; IADL, Instrumental Activities of Daily Living.

Table 3
Mean NPI, IADL, Zarit, ADRQL, and Duke scores of Placebo HAs group at 6- and 12-months follow-up

	6 months	12 months	*p*
NPI (/144)	N = 16	N = 16	
	24.8 ± 15.0	30.2 ± 22.4	0.5#
IADL (/8)	N = 16	N = 16	
	3.3 ± 2.4	2.8 ± 2.5	0.3#
Zarit (/88)	N = 15	N = 15	
	24.7 ± 15.0	25.1 ± 13.8	0.8
ADRQL (/544.76)	N = 16	N = 16	
	445.4 ± 43.6	440.9 ± 59.0	1.0#
Duke patient (/8)	N = 17	N = 17	
	4.9 ± 1.7	3.7 ± 1.8	**0.02**#
Duke caregiver (/8)	N = 17	N = 17	
	4.5 ± 1.8	4.1 ± 1.5	0.3

Values are mean ± SD unless otherwise noted. Significant differences in bold. #Indicates the outcomes variables assumed to have a non-normal distribution and which were tested with Wilcoxon test, otherwise variables were assumed to have a normal distribution and were tested with Student *t*-test. ADRQL, Alzheimer Disease Related Quality of Life; NPI, Neuropsychiatric Inventory; IADL, Instrumental Activities of Daily Living.

psychological symptoms are common, such as depression, anxiety, paranoia, and reduced social activities [11]. Mulrow et al. reported the success of improved hearing ability on depression and communication, as well as social and emotional functions in people exempt from dementia [10]. Mosnier et al. [30] conducted a prospective study about the effect of hearing rehabilitation on cognitive function among 94 patients aged 65 to 85 years old (average age at implantation 72 years) and postlingually deafened. They suggest that by improving hearing for verbal communication, cochlear implantation decreases the cognitive load and may have a positive effect on attention, concentration, and executive function. Thus, another hypothesis linking ARHL and cognitive disorders may refer to an increase in "cognitive load" for understanding speech, as a compensation for deterioration of peripheral auditory inputs [19, 31].

Even if the mechanisms are not clearly established, epidemiological and neuropathological evidence suggests that social isolation and loneliness, resulting from communication impairments caused by HL, could lead to AD [9]. Thus, enhancing the communication ability of the patients by use of hearing devices, could reduce the perceived disability in older individuals, and caregiver burden [9]. Therefore, some explanations could be proposed for the lack of benefits provided by HAs in the present study.

An important point is that AD-related pathology has been observed in the ascending auditory pathways [32] with some specific histopathological lesions of central auditory nuclei, required for higher-order auditory processing [33] and higher-order cortical areas, involved in language processing [34]. Common pathological process or shared etiological pathways linking ARHL with cognitive disorders may have a central role; the use of HA alone could be not enough and should be associated with other interventions [9].

In addition, pure tone audiometry does not adequately reflect central auditory processing, contrary to vocal audiometry or dichotic tests which, according to some authors, could be predictive factors of dementia [35, 36]. However, pure tone audiometry was chosen because its reliability seems to be preserved in patients with mild to moderate stages of AD [37], which is not the case for vocal audiometry [9].

Table 4
Delta NPI, IADL, Zarit, ADRQL, and Duke scores between 6 months of follow-up and inclusion among the total population and according to compliance

		Delta NPI		
		Active Has	Placebo Has	*p*
All sub-groups	N	18	18	
	Mean	5.6 ± 15.7	–0.4 ± 11.5	0.2#
Bad-Moderate	n	4	7	
	mean	19.8 ± 27.0	1.3 ± 8.2	0.3
Good-Very good	n	14	11	
	mean	1.6 ± 8.7	–1.6 ± 13.5	0.5
Comparison (bad-moderate) versus (good-very good)	*p*-value	0.3	0.6	
		Delta IADL		
		Active Has	Placebo HAs	*p*
All sub-groups	N	18	18	
	Mean	–1.5 ± 1.3	–0.7 ± 1.2	0.1#
Bad-Moderate	n	4	7	
	mean	–1.5 ± 1.3	–0.7 ± 1.0	0.3#
Good-Very good	n	14	11	
	mean	–1.5 ± 1.4	–0.7 ± 1.4	0.2
Comparison (bad-moderate) versus (good-very good)	*p*-value	1	0.9#	
		Delta Zarit		
		Active HAs	Placebo Has	*p*
All sub-groups	n	14	18	
	Mean	3.8 ± 9.4	–0.1 ± 8.7	0.4#
Bad-Moderate	n	3	7	
	mean	6.7 ± 2.5	1.0 ± 10.7	0.4
Good-Very good	n	11	11	
	mean	3.0 ± 10.5	–0.7 ± 7.6	0.9#
Comparison (bad-moderate) versus (good-very good)	*p*-value	0.2#	0.7	
		Delta ADRQL		
		Active HAs	Placebo HAs	*p*
All sub-groups	N	18	18	
	Mean	–22.2 ± 75.0	–16.0 ± 40.9	0.6#
Bad-Moderate	N	4	7	
	Mean	–104.1 ± 80.2	–14.1 ± 36.9	**0.03**
Good-Very good	n	14	11	
	mean	1.2 ± 56.8	–17.3 ± 45.0	0.2#
Comparison (bad-moderate) versus (good-very good)	*p*-value	**0.02**#	0.9	
		Delta Duke-patient		
		Active HAs	Placebo Has	*p*
All sub-groups	n	18	20	
	Mean	–0.4 ± 1.5	1.1 ± 1.8	**0.02**#
Bad-Moderate	n	4	8	
	mean	–1 ± 1.2	0.1 ± 1.9	**0.3**#
Good-Very good	n	14	12	
	mean	–0.2 ± 1.6	1.7 ± 1.4	0.01#
Comparison (bad-moderate) versus (good-very good)	*p*-value	0.4#	0.05#	
		Delta Duke-caregiver		
Variables		Active HAs	Placebo Has	*p*
All sub-groups	n	18	20	
	Mean	0.0 ± 2.0	0.5 ± 1.6	0.4
Bad-Moderate	n	4	8	
	Mean	0.5 ± 1.0	0.6 ± 1.6	0.9#
Good-Very good	n	14	12	
	mean	–0.1 ± 2.2	0.3 ± 1.7	0.5
Comparison (bad-moderate) versus (good-very good)	*p*-value	0.4#	0.7	

Values are mean ± SD unless otherwise noted. Significant differences in bold. #Indicates the quantitative variables assumed to have a non-normal distribution and which were tested with Mann-Whitney test, otherwise variables were assumed to have a normal distribution and were tested with Student *t*-test. ADRQL, Alzheimer Disease Related Quality of Life; HAs, hearing aids; NPI, Neuropsychiatric Inventory; IADL, Instrumental Activities of Daily Living. Δ ADRQL > 0: increase of quality of life. Δ Duke > 0: increase of social interactions. Δ NPI > 0: increase of behavioral disorders. Δ IADL > 0: increase of instrumental abilities. Δ Zarit > 0: increase of caregiver burden.

Moreover, hearing thresholds were moderately elevated for included patients, and even if these levels were appropriate for the range of amplification provided, it is widely accepted that HAs must be fitted as soon as possible [38]. Indeed, neural plasticity may be insufficient to benefit from auditory rehabilitation, even at a moderate stage of AD, as suggested by Pichora-Fuller et al., and may be more effective at the prodromal phase of AD [39]. Blamey et al. also found that age at cochlear implantation of deaf adult patients over 70 years was a negative predictor of cochlear implantation success with presumably less plastic capacities [40]. Therefore, prevention of behavioral symptoms would be easier to address, rather than intervening on patients already affected by neuropsychiatric symptoms, as were the patients of the present study [41]. Since our study sample was rather old—on average, 10 years older than in Mosnier et al. [30], patients could have shown very poor or even no plastic abilities, preventing any benefit of HA use. Thus, even if neither MMSE ($R = -0.23456$, $p = 0.1125$) nor ADAS-COG ($R = 0.15280$, $p = 0.3052$) scores were linked with age, one could question whether a positive effect of HAs could have been observed in a sample aged less than 75 years.

Yamada et al. explain that people with hearing impairment may find their environment unfamiliar and frightening, and may have less ability to know how to apprehend it [3]. Probably an adaptation time is required to acclimatize to auditory rehabilitation before speech is correctly perceived, especially with patients suffering from dementia who are very sensitive to changes of environment. This adaptation time could explain a paradoxical worsening of neuropsychiatric symptoms [38]. However, in the active HA group, the absence of significant improvement in behavioral and quality of life scores, even after one year, would not suggest that the follow-up of this trial may be too short to observe beneficial effect of HA use. Mosnier et al. found that rehabilitation of hearing communication through cochlear implantation significantly improved speech perception and cognitive abilities and above all, positively influenced their social activity, signs of depression, and QoL at 12 months post-implantation [30]. Similarly, comparing the two groups at 12 months, we can note a significant difference of ADRQL score in favor of those who benefited from active HAs since the beginning of the study compared to those who had their HAs activated at 6 months of follow-up, but this positive result must be balanced because it was isolated compared to others scores also reflecting QoL (Zarit and Duke scales) that were negative. The significant deterioration of IADL score over this same one-year period shows that HA use cannot prevent functional degradation in AD patients with HL in our study.

Thus, in light of these results, we could hypothesize that patients with mild cognitive impairment could represent a more adequate target population for such interventions. In early AD, lesions of the central auditory pathway that could limit the benefits of acoustic amplification are uncommonly observed [9], neural plasticity may be sufficient to benefit from auditory rehabilitation with patients who more readily engage areas of the brain so that adjustment to complex new HAs is facilitated [39]. In addition, and as suggested by Panza et al. [29], HA alone could be insufficient to properly manage ARHL, and interventions should also incorporate counseling, environmental accommodations, and rehabilitative hearing training, which should be easier to implement in patients at the early stages of AD. Moreover, several studies have demonstrated that neuropsychiatric symptoms can be found at MCI stage with approximately one-third of patients suffering from apathy, nearly 45% from depressive symptoms, and from 10 to 45% feeling anxiety [42, 43]. These symptoms could represent an increased risk for conversion to dementia; from 2.6-fold increased risk for depression, to a 7-fold increased risk for apathy [43]. As these symptoms are improved by HAs in people without dementia [10], we could therefore expect that early-stage AD patients with higher cognitive abilities might achieve the same improvement in order to limit the evolution towards dementia.

CONCLUSION

The present clinical trial did not find that fitting binaural HAs to elderly patients with hearing impairment and AD improved neuropsychiatric symptoms, activities of daily living, or QoL for patients and their caregivers. These findings contribute to a better knowledge of the benefits and limitations of auditory rehabilitation in such patients, and it may be suggested that a potential reason for the lack of efficacy was disease stage. In this perspective, we cannot rule out that HAs may have benefited younger patients.

ACKNOWLEDGMENTS

The authors thank all the care professionals having taken part in this project: S. Ait-Abderrahim (Lyon

Sud hospital), E. Andre-Fouet (Lyon Croix-Rousse hospital), F. Bertin-Hugault (Lyon Charpennes geriatric hospital), C. Chabe (Lyon Sud hospital), F. Delphin (Lyon Sud hospital), C. Dubreuil (Lyon Sud hospital), P. Falgon (Hospices Civils de Lyon, IMER center), M.O. Favre (Lyon Sud hospital), A. Fernandez (Lyon Sud hospital), G. Kalfoun (Amplifon©), Z. Makaroff (Lyon Charpennes geriatric hospital), C. Maurice (Hospices Civils de Lyon, IMER center), H. Mollion (Lyon Pierre Wertheimer neurological hospital), C. Revillon (Amplifon©), C. Rivière (Lyon Fourvière hospital), A. Vighetto (Lyon Pierre Wertheimer neurological hospital). They also thank subjects who agreed to participate in the study and their caregivers. The authors acknowledge Mr. Christian Canepa and Phonak© France for the provision of hearing aids free of charge, Amplifon-CCA© France for their logistical support, and Dr. Philip Robinson (DRCI, Hospices Civils de Lyon) for help in manuscript preparation.

The ADPHA clinical trial was hosted by the Hospices Civils de Lyon (HCL: 2006.414/7). This study was funded by a grant of the French Ministry of Health (Clinical Research Hospital Program 2005 – National Call for Projects, PHRC 2005 – APN) and by a grant of the Fondation Médéric Alzheimer (Paris, France).

Funding bodies had no role in the study design and the collection, analysis or interpretation of the data, writing the manuscript, or the decision to submit it for publication.

Authors' disclosures available online (http://j-alz.com/manuscript-disclosures/16-0792r2).

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CLINICAL TRIAL REGISTRATION

This trial is registered with ClinicalTrials.gov under the identifier NCT00488007 ("Clinical Trial on Alzheimer Disease Presbycusis and Hearing Aids").

SUPPLEMENTARY MATERIAL

The supplementary material is available in the electronic version of this article: http://dx.doi.org/10.3233/JAD-160792.

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