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The Effect of the Association between Donepezil and Choline Alphoscerate on Behavioral Disturbances in Alzheimer's Disease: Interim Results of the ASCOMALVA Trial

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Abstract.
Background: Behavioral and psychological symptoms of dementia (BPSD) are a group of psychological reactions, psychiatric symptoms, and behaviors commonly found in Alzheimer's disease (AD). Four clusters of BPSD have been described: mood disorders (depression, anxiety, and apathy), psychotic symptoms (delusions and hallucinations), aberrant motor behaviors (pacing, wandering, and other purposeless behaviors), and inappropriate behaviors (agitation, disinhibition, and euphoria). Most of them are attributed to acetylcholine deficiency.
Objective: To evaluate if a higher amount of acetylcholine obtained by associating donepezil and choline alphoscerate might have a favorable effect on BPSD.
Methods: BPSD were measured at baseline and after 24 months in 113 mild/moderate AD patients, included in the double-blind randomized trial ASCOMALVA, by the Neuropsychiatric Inventory (NPI). Two matched groups were compared: group A treated with donepezil (10 mg/day) plus choline alphoscerate (1200 mg/day), and group B treated with donepezil (10 mg/day) plus placebo.
Results: Data of NPI revealed a significant decrease of BPSD severity and distress of the caregiver in patients of group A compared with group B. Mood disorders (depression, anxiety and apathy) were significantly decreased in subjects treated with donepezil and choline alphoscerate, while their severity and frequency was increased in the other group.
Conclusions: Patients treated with donepezil plus choline alphoscerate showed a lower level of behavioral disturbances than subjects treated with donepezil only, suggesting that the association can have beneficial effects.

Keywords: Alzheimer's disease, behavioral and psychological symptoms of dementia, choline alphoscerate, donepezil, neuropsychiatric symptoms

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INTRODUCTION

Behavioral and psychological symptoms of dementia (BPSD) are a group of psychological reactions, psychiatric symptoms, and behaviors often

occurring in dementia patients [1, 2]. BPSD prevalence is of about 30% in the subjects living in the general community [3, 4] and rises to 80% in those living in nursing facilities [5]. Up to 90% of Alzheimer's disease (AD) patients have at least one BPSD [6].

The impact of BPSD on direct and indirect costs of AD [7] leads to higher institutionalization rate [8, 9]. BPSD impair the quality of life of the caregivers [10], contributing to AD intangible costs, an aspect which is still overlooked, but which deserves attention and should thus be accurately evaluated [7]. On the other hand, BPSD raise ethical questions about care, autonomy, safety, and treatment. For instance, a reasonable question is what interventions and treatments could be recommended for dementia-related behaviors and if anti-psychotic medications are an acceptable therapy for the treatment of dementia-related behavioral disturbances. This due to the reported increased risk of mortality associated with antipsychotics in patients with BPSD [8–10]. Several other ethical concerns come from the use of electronic tracking for AD individuals at risk for wandering [11].

Four clusters of BPSD have been described: mood disorders (depression, anxiety, and apathy/indifference), psychotic symptoms (delusions and hallucinations), aberrant motor behaviors (pacing, wandering, and other purposeless behaviors), and inappropriate behaviors (agitation, disinhibition, and euphoria), the last two more associated to faster cognitive and functional decline [12]. Genetic factors are related to each cluster [13, 14]. BPSD causes are still unclear. Besides the contribution of psychological and social aspects, including the premorbid personality, the environmental modifications, and the caregiving style, alterations of several neurotransmitters (GABA, serotonin, noradrenaline) and of the related pathways are certainly involved. Among them, the main role is attributed to acetylcholine reduction and consequent dysfunctions of the brain cholinergic system [15].

The treatment of BPSD [16] is essentially based on antipsychotics, antidepressants, and benzodiazepines. Antipsychotics can ameliorate the symptoms in the short term [17], but older subjects are very sensitive to their undesirable effects that may lead to a further functional decline and the risk of pharmacological interactions [18]. The safety profile of these compounds is also questionable in elderly people, having been reported that these compounds may increase the risk of cerebrovascular events [19–21]. Antidepressants are effective essentially on depressive aspects [16]. Benzodiazepines, which are used if other agents have failed [22], may lead to increased confusion and falls, and rarely to a paradoxical increase of agitation in the elderly [23].

BPSD treatment is therefore unsatisfactory, and the anticholinergic propriety of many drugs used for treating various disorders, occurring often in the elderly, represents a further limitation [24]. Cholinergic dysfunctions are not only associated with cognitive impairment, but probably also with BPSD [25, 26]. This hypothesis is further supported by the reported benefits of treatment with cholinesterase inhibitors on BPSD [25, 26]. Rivastigmine, in fact, has been shown to reduce apathy, anxiety, depression, and delusions [27] and donepezil and galantamine to decreased delusion, hallucinations, agitation [28, 29], depression, apathy, and anxiety [27, 28].

From a theoretical point of view, symptoms caused directly or indirectly by impaired brain cholinergic neurotransmission could benefit from an enhanced cholinergic neurotransmission and by increasing acetylcholine bioavailability. In this study, we have explored this hypothesis by evaluating BPSD in two matched groups of AD subjects, treated for 24 months with a cholinesterase inhibitor alone (group A) or with the association of the same cholinesterase inhibitor to the cholinergic precursor choline alphoscerate (alpha-glyceryl-phosphorylcholine) (group B). Preclinical studies have shown that choline alphoscerate alone or in association with an acetylcholinesterase-inhibitor (AChE-I) has an enhancing effect on cholinergic transmission [30–33]. Starting from these observations, we have investigated in a clinical trial the effect of association of choline alphoscerate with the AChE-I donepezil on BPSD in AD. The activity of the association was compared to that of donepezil alone.

METHODS

Patients and study type

Patients described here were all included in the double blind randomized trial ASCOMALVA (Association between the Cholinesterase Inhibitor Donepezil and the Cholinergic Precursor Choline Alphoscerate in Alzheimer's Disease). This trial was aimed to compare the cognitive effects of the treatment with donepezil plus the cholinergic precursor choline alphoscerate versus donepezil only in subjects with mild/moderate AD.

Table 1
Patient dropout causes in ASCOMALVA trial

Dropout causes in ASCOMALVA trial						
Causes of dropouts	No.	Donepezil + placebo		No.	Donepezil + choline alphoscerate	
Total		12			17	
Death	0			1		
Lack of efficacy	0			2	Disease worsening	
Non compliance	3	Transferred to geriatric homecare support		3	Transferred to geriatric homecare support	
Lack tolerability	3	1	Hallucinations, asthenia	3	1	Hallucinations, insomnia
					1	Diarrhea, vomiting
		2	Diarrhea, vomiting		1	Cutaneous rash
Other reasons	6	5	Difficulty to displace	8	3	Difficulty to displace
					2	Home change
		1	Unknown		3	Unknown

For clarity, the main characteristics of the ASCOMALVA study are detailed below. Further details are reported in previous studies of our group [34–36]. Patients, diagnosed according to NINCDS-ADRDA criteria, were all in a mild/moderate-stage, showed brain ischemic lesions (in CT or MRI), and had at least two vascular risk factors (such as hypertension, diabetes, obesity, ischemic heart disease, hypercholesterolemia, hyperhomocysteinemia, smoking, previous cerebrovascular events, or family history of cardio-cerebrovascular diseases). This to confirm the diagnosis of cerebrovascular impairment [37, 38]. Two matched groups were analyzed: one (group A) treated with donepezil 10 mg/day plus choline alphoscerate 1,200 mg/day (associative therapy), the other (group B) with donepezil 10 mg/day + placebo (mono therapy). 175 subjects out of the originally planned 210 were recruited and 29 dropped out (12 in the donepezil only group, and 17 in the associative therapy group) for different causes, indicated in Table 1. The interim results reported in this paper involved 113 subjects treated for 24 months. It was found, at 24 months of treatment, that group A subjects performed significantly better than group B on cognitive [Mini Mental State Examination (MMSE), Alzheimer's Disease Assessment Scale Cognitive subscale (ADAS-Cog)], functional [Basic Activities of Daily Living (BADL), Instrumental Activities of Daily Living (IADL)], and behavioral scales [Neuropsychiatric Inventory (NPI)] [34–36].

This paper refers to the same patient population already described [34–36] and was aimed to provide a more accurate evaluation of the behavioral effect observed on the different sub-items of the NPI. This to assess if any specific symptom or symptoms cluster was influenced by the therapy. BPSD presence and severity was investigated at the baseline, after 12 months and after 24 months by the NPI relatively to each of its sub-items. The severity of the caregiver distress by the NPI-Distress of caregiver was assessed as well. The sample consists of 113 subjects, whose demographic characteristics are reported in Table 2. All subjects were community dwelling, were enrolled in the study at least 6 months after the diagnosis, and none had received any specific previous treatment. The other psychoactive drugs assumed by each patient at the baseline and the follow up were registered together with their eventual dosage changes. These drugs were classified into three categories: antipsychotics, antidepressants, and anxiolytics.

Table 2
Demographic characteristics of patients participating to the ASCOMALVA trial

113 subject (43 males)		
	Monotherapy	Associative
Age (y)	78 ± 5	76 ± 8
Sex	20 males	23 males
	36 females	34 females
Education (y)	7 ± 3	8 ± 5
Mean MMSE at baseline	20.3 ± 2.9	19.9 ± 3.1
MMSE 24–21	42.9%	37.5%
MMSE 20–18	39.3%	25%
MMSE <17	17.9%	37.5%

Procedures

BPSD presence and severity were measured by the subscales of the Neuropsychiatric Inventory NPI [39]. The NPI assesses the frequency

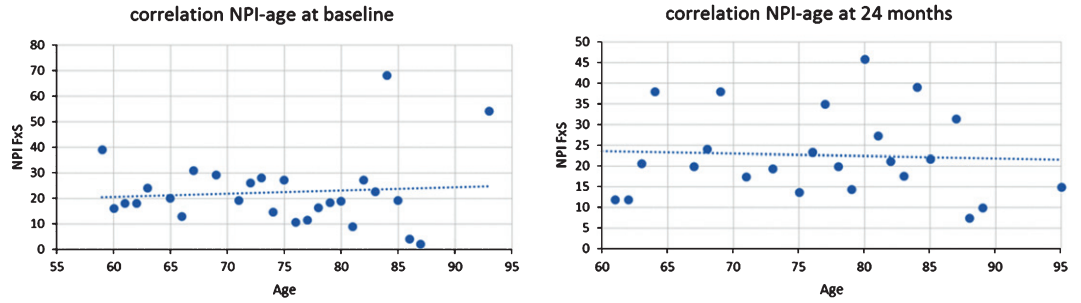

Fig. 1. Correlation between the age of the whole sample and the severity of behavioral symptoms (NPI-F) at baseline and after 24 months of treatment assessed by the test of Pearson. NPI, neuropsychiatric inventory.

and the severity of the symptoms and the caregiver distress in 12 behavioral domains (delusions, hallucinations, depression/dysphoria, anxiety, agitation/aggression, elation/euphoria, disinhibition, irritability/lability, apathy/indifference, aberrant motor activity, sleep/night time behavior, and appetite/eating) [39]. NPI is given as an interview questionnaire, and neuropsychiatric manifestations within each domain are rated by the caregiver in terms of both frequency (1–4) and severity (1–3), yielding a composite symptom domain score (frequency × severity: NPI-F). The caregiver distress (NPI-D) is rated for each positive neuropsychiatric symptom domain by scores from 0 (no distress) to 5 (extreme distress). The total composite score is obtained by summing up the single item score, which may range from 0 to 144, with higher scores indicating more behavioral problems. In addition, a score for the caregiver stress is assigned for each type of the abnormal behavior found. The total distress score may range from 0 to 60, with higher scores indicating more severe distress suffered by the caregiver.

Statistics

The correlation between the age and gender of the whole sample and the severity of behavioral symptoms (NPI-F) was assessed by the test of Pearson.

NPI-F, NPI-D, and each sub-item was evaluated at baseline and each follow up. Analysis of variance (ANOVA) and multivariate ANOVA were used. A two tailed Student "t" test was then used to evaluate the significance of differences between each group. To assess if the use of antidepressants, anxiolytics, and antipsychotics modified significantly the severity of symptoms, chi square test (χ^2) was employed.

RESULTS

The 113 patients investigated (43 M), were treated with donepezil (10 mg/day) + choline alphoscerate (1200 mg/day) ($n = 57$, group A) or with donepezil + placebo (10 mg/day) ($n = 56$, group B). Groups were matched for age (76 ± 8 y in group A, 78 ± 5 y in group B) and sex (23 males in group A, 20 in group B) and MMSE at baseline. The distribution of mild/moderate cases within the two groups are detailed in Table 2. Vascular risk factors were found in both groups. Arterial hypertension was the most common (87.4%), followed by a family history of cardio-cerebrovascular diseases (74.8%), hypercholesterolemia (61.4%), diabetes (29.9%), smoking (28.3%), obesity (26.8%), hypertriglyceridemia (24.4%), previous ischemic stroke (20.5%), transient ischemic attack (17.3%), ischemic heart disease (14.2%), and hyperhomocysteinemia (0.8%). No differences between groups in the total number of vascular factors were noticeable (Table 3). Composite cardiovascular [40] and cerebrovascular [41] burden were also calculated, and showed no significant differences within the two groups (data not shown).

The correlation between the age of the whole sample and the severity of behavioral symptoms (NPI-F) showed no differences at the baseline nor after 24 months (Fig. 1). At baseline, the severity of behavioral symptoms (NPI-F) was greater in females (NPI-F = 22) than in males (NPI-F = 16). After 24 months, the NPI-F female averaged 24.9 and the NPI-F male 24.2 (Fig. 2), indicating that baseline differences did no longer occur at the end of the observation time. Among the different neuropsychiatric symptoms, agitation (13%), depression (21%), anxiety (15%), apathy (18%), and irritability (12%) were mostly found (Fig. 3).

Table 3
Vascular risk factors of the subjects participating to the ASCOMALVA trial

		A	B	C	D	E	F	G	H	I	J	K
Total	no	12.6	70.1	38.6	75.6	73.2	79.5	85.8	82.7	71.7	99.2	25.2
	yes	87.4	29.9	61.4	24.4	26.8	20.5	14.2	17.3	28.3	0.8	74.8
Monotherapy	no	8.6	69.0	44.8	72.4	72.4	81.0	82.8	82.8	72.4	98.3	32.8
	yes	91.4	31.0	55.2	27.6	27.6	19.0	17.2	17.2	27.6	1.7	67.2
Association therapy	no	15.9	71.0	33.3	78.3	73.9	78.3	88.4	82.6	71.0	100.0	18.8
	yes	84.1	29.0	66.7	21.7	26.1	21.7	11.6	17.4	29.0	0.0	81.2

A) arterial hypertension; B) diabetes; C) hypercholesterolemia; D) hypertriglyceridemia; E) obesity; F) ischemic stroke; G) ischemic heart disease; H) transient ischemic attack; I) smoking; J) hyperhomocysteinemia; K) family history; No, absent; Yes, present.

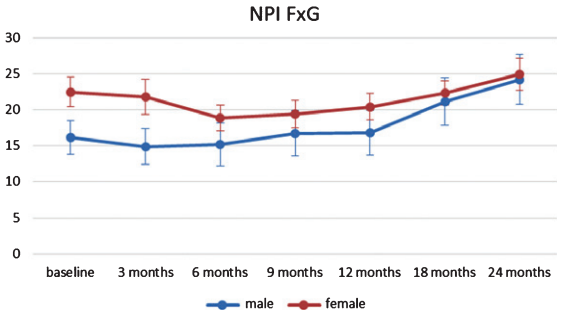

Fig. 2. Correlation between sex and severity of the behavioral symptoms (NPI-F) in the whole sample.

At the baseline, the global NPI severity and frequency (NPI-F) and the caregiver distress (NPI-D) were not different between groups (Table 4), whereas after two years of treatment the NPI-F and NPI-D in group A subjects were significantly lower than in group B (Table 4). Variations from baseline of NPI-F and NPI-D are shown in Fig. 4a and 4b, respectively. Assessment of each single NPI item showed that, after treatment, group A subjects had less depression and apathy than group B subjects (Table 4), whereas anxiety was reduced significantly in group A and not in group B subjects (Table 5).

Table 6 summarizes data on patients taking psychoactive drugs (antidepressants, anxiolytics, and antipsychotics), including the mean doses of different compounds used. After 24 months, the global assumption of antidepressants and anxiolytics decreased, whereas administration of antipsychotics increased (Fig. 5). On comparing the two treatment

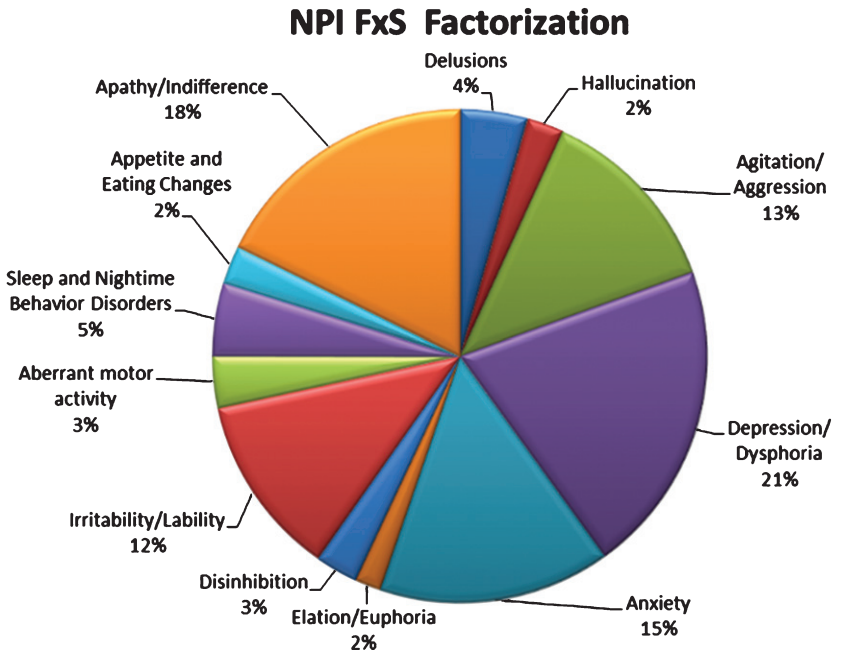

Fig. 3. Presence of the different BPSD (NPI-F) in the patients participating to the trial.

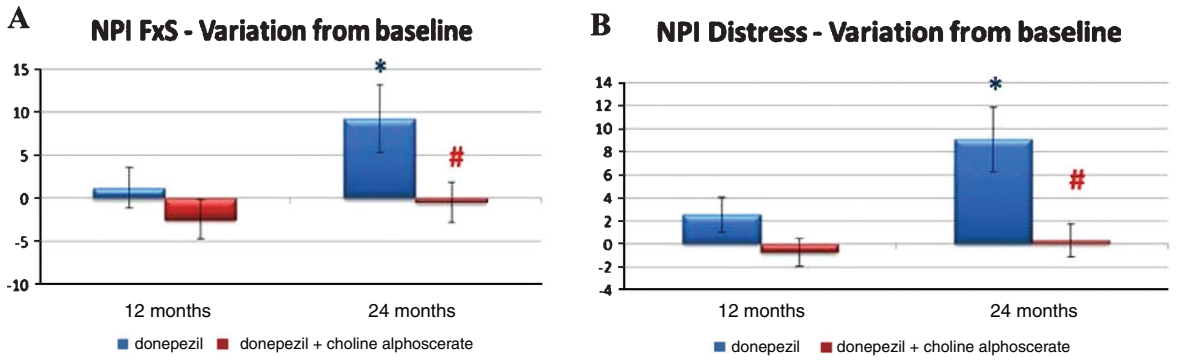

Fig. 4. Variations from baseline of severity and frequency of symptoms of NPI (NPI-F) (A) and of the caregiver distress measures of NPI (NPI-D) (B) *Significantly different $p < 0.05$ by t-Student test versus baseline. #Significantly different $p < 0.05$ by ANOVA test versus donepezil.

Table 4
Severity and frequency (NPI-F) and caregiver distress (NPI-D) assessed by NPI at the baseline, at 12 and 24 months in the two patient groups of the trial

	113 SUBJECTS (43 males)							
	Baseline		12 months		24 months		Difference between baseline and 24th month	
	MT	AT	MT	AT	MT	AT	MT	AT
NPI (FxS)	19.7 ± 13.8	22.6 ± 15.8	18.6 ± 15.4	20.1 ± 17.4	29.0 ± 19.0*	22.1 ± 16.1**	9.2 ± 23.3	–0.5 ± 14.1**
NPI (stress)	9.6 ± 6.7	11.5 ± 8.3	12.2 ± 8.7	10.8 ± 10.2	18.7 ± 15.6*	11.9 ± 9.6**	9.1 ± 16.4	0.4 ± 8.7**

Values are expressed as the means ± S.D. NPI, FxS (Neuropsychiatric Inventory severity multiplied by gravity); NPI stress, Neuropsychiatric Inventory caregiver distress; MT, monotherapy, donepezil + placebo; AT, association therapy: donepezil + choline alphoscerate. *Significantly different $p < 0.05$ by t-Student test versus baseline, **Significantly different $p < 0.05$ by ANOVA test versus monotherapy.

Table 5
Anxiety, depression, and apathy subscale of NPI at the baseline, 12 and 24 months in the two groups of patients of the trial

	113 SUBJECTS (43 males)							
	Baseline		12 months		24 months		Difference between baseline and 24th month	
	MT	AT	MT	AT	MT	AT	MT	AT
Anxiety	3.1 ± 4.1	3.3 ± 3.9	2.0 ± 2.4	2.1 ± 3.3	3.0 ± 3.8	1.5 ± 2.4*	–0.1 ± 5.6	–1.8 ± 3.9**
Depression	4.2 ± 4.2	4.7 ± 4.4	3.7 ± 3.4	3.3 ± 3.1	6.3 ± 4.4*	4.6 ± 4.2	2.1 ± 6.4	–0.1 ± 5.0**
Apathy	3.2 ± 3.9	4.2 ± 4.5	4.9 ± 4.7	3.3 ± 4.3	6.8 ± 4.8*	4.8 ± 4.9	3.6 ± 4.8	0.6 ± 6.1**

Values are expressed as the means ± S.D., MT, monotherapy, donepezil + placebo; AT, association therapy: donepezil + choline alphoscerate, *Significantly different $p < 0.05$ by t-Student test versus baseline; **Significantly different $p<0.05$ by ANOVA test versus monotherapy.

groups investigated, after 24 months, the use of antipsychotic drugs increased and the use of anxiolytics decreased in both groups. Antidepressants use remained the same as in the group A, but decreased in the group B (Fig. 6).

Consumption of antidepressants and anxiolytics was compared versus the improvement in apathy and anxiety by the chi square test (χ^2) (Fig. 7). Among subjects in which depression was improved, 56% were in group A and only the 12% of those used antidepressants for 24 months. In subjects in which apathy improved, one half was in group A, and none of them were treated with antidepressants. In subjects with anxiety improved, 62.1% belonged to the group

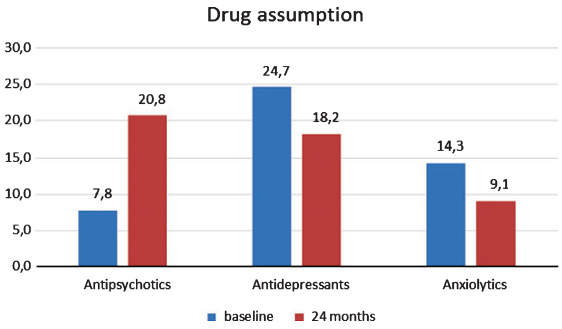

Fig. 5. Drug consumption from global sample at baseline and after 24 months of treatment.

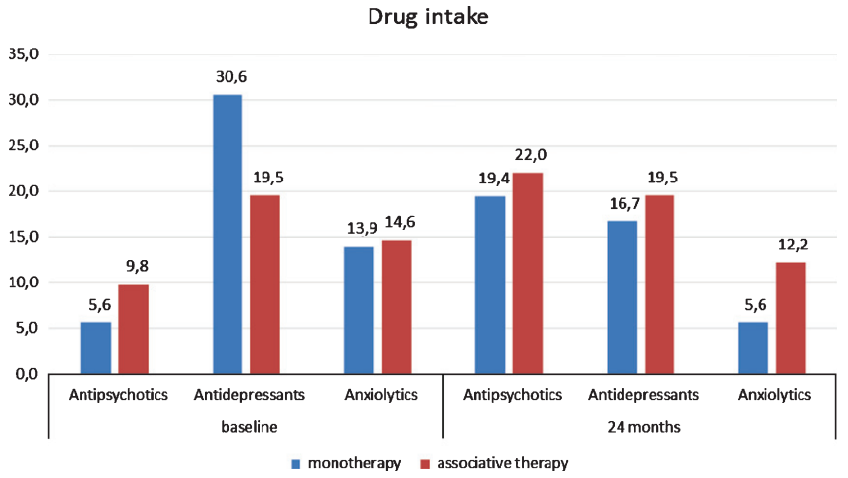

Fig. 6. Drug consumption in monotherapy group versus association therapy group.

Table 6
Percentage of subjects receiving the different psychoactive drugs and their mean dose at baseline and after 24 months of treatment.

Baseline			24 months		
Drug	Dose	% of patients	Drug	Dose	% of patients
Antipsychotics					
Quetiapine	25 mg	33.3	Seroquel	25 mg	18.8
	50 mg	33.3		50 mg	25
	100 mg	16.7		100 mg	25
Risperidone	2 mg	16.7		150 mg	6.3
				400 mg	6.3
			Risperdal	2 mg	6.3
			Other drugs		12.5
Antidepressants					
Duloxetine	30 mg	10.5	Cymbalta	30 mg	7.1
	60 mg	15.8		60 mg	21.4
Citalopram	10 mg	21.1	Cipralex	10 mg	21.4
Setraline	50 mg	15.8	Zoloft	50 mg	7.1
Other drugs		36.8	Other drugs		42.9
Anxiolytics					
Lorazepam	1 mg	18.2	Lorazepam	1 mg	28.6
Prazepam	10 mg	9.1	Prazene	10 mg	0
	20 mg	18.2		20 mg	14.3
Other drugs		54.5	Other drugs		57.1

A, and only 6.9% used anxiolytics at the 24th month of observation (Fig. 7).

DISCUSSION

The BPSD, a group of very common symptoms in AD [39], can be assessed by standardized instruments such as the NPI [39, 42]. Leading to high disability and poor quality of life [43], BPSD are a further cause of distress in caregivers [44, 45] and the main reason of the early institutionalization of patients [46]. The occurrence of BPSD raises several ethical and legal medical problems such as to establish the level of remaining autonomy, such as if patients are still able to have enough understanding/knowledge about their disease to decide on their treatment and make plans for the future [47, 48]. Another relevant ethical problem is the opportunity of treating BPSD with antipsychotic drugs. These compounds are at high risk of adverse events, even at modest doses, and may interfere with the progression of cognitive impairment. Moreover, they could interact with several drugs including anti-arrhythmics and AChE-I [49].

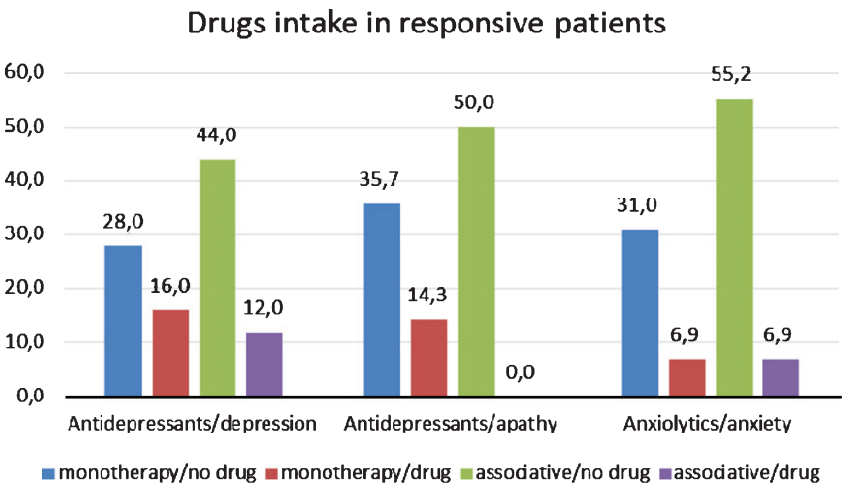

Fig. 7. Percentage of patients consuming drugs who had an improvement in the respective NPI parameter. No significant increase in frequency of patients who showed improvement in NPI subscales was seen among those patients that at the same time consumed specific drugs for their behavioral disorder.

Causes and pathophysiology of BPSD are incompletely understood. These problems have been associated with the imbalance of several neurotransmitters and particularly to a cholinergic dysfunction in several brain regions including the limbic system (hippocampus, amygdala, anterior thalamus, hypothalamus, basal forebrain, mammillary bodies, and septal area) and the cingulated, orbitofrontal, and parahippocampal cortices [42, 50, 51]. The high levels of acetylcholinesterase (AChE), found in the hippocampus, amygdalae, and thalamus, have suggested that the inhibition of this enzyme might be useful for treating BPSD [52]. This hypothesis was supported from studies showing a beneficial effect of ChEI on BPSD reduction [27, 53, 54, 55, 56] and specific activity of donepezil in particular on some symptoms, such as apathy, anxiety, agitation, and depression [28, 57].

In this work, we have evaluated the BPSD burden in 113 mild/moderate AD subjects, all included in the double-blind trial ASCOMALVA. We have found that subjects treated with the association of donepezil and choline alphoscerate had a lower NPI score. The caregiver stress of these subjects was, accordingly, lower. A significant difference was found in the cluster "mood disorders" of the BPSD, which refers to depression, anxiety, and apathy/indifference. This cluster of symptoms has been attributed to the disconnection between the neocortex and the basal nuclei, which would deprive the cortex of its major source of acetylcholine. Consequently, the ability to properly process the emotional significance of stimuli would be impaired [58], leading to apathy [19]. Theoretically, apathy would improve if higher levels of acetylcholine would be available, an aspect we have already described [36]. Beneficial effects of donepezil on depression and anxiety have already been reported [28, 57, 59]. This study has shown that the association of donepezil to choline alphoscerate has greater efficacy on symptoms of mood disorders such as apathy, depression, and anxiety, improving them more than when donepezil was administered alone.

It might be hypothesized that the occurrence of vascular lesions and risk factors in our sample may represent a limit to the generalization of the results to the whole AD population. However, it should be considered that the presence of cerebrovascular injury occurs in the majority of AD subjects [37]. Hence, AD degeneration plus vascular damages probably is the prevalent phenotype of these subjects [37]. It may be worthy, furthermore, to underline that the vascular burden did not show differences between the groups.

AD patients' treatment obviously included other drugs, whose potential interference has been considered. We have therefore evaluated if any significant difference in the assumption of psychoactive drugs (antipsychotics, antidepressant, and anxiolytics) occurred in the two treatment groups. This analysis has shown that the percentage of patients assuming antipsychotics was higher in both groups

after 24 months, compared to the baseline. These findings indicate the progression of AD. However, most patients with improved mood symptoms after 24 months did not take antidepressants and anxiolytics, suggesting that this improvement can be related to the cholinergic effect. The antidepressants and anxiolytics administered to our patients probably have a weak, if any, cholinergic effect as only trazodone has some anti-cholinergic activity [60], whereas duloxetine, the most used, has no effect at all. Among the antipsychotics neither quetiapine nor risperidone interfere with the cholinergic neurotransmission [61].

This study has strengths and weaknesses: the longtime of observation and treatment (24 months) represent strengths, while the size of the sample and the nature of the *post hoc* type of data are weaknesses. We are also aware that the NPI score, being dependent from the caregiver input, is influenced by the caregiver mood, his burden, and belief system [62, 63]. However, this test is, up to now, one of the most widely used in clinical trials on the BPSD. Finally, we are aware that the prescription of psychiatric drugs usually cuts across their specific categories, i.e., antipsychotics are frequently used as "tranquillizers" and antidepressants to treat anxiety [64]. Future developments of this research should include a longer observation period and the stratification of the sample according to the severity of the neuropsychiatric symptoms.

In conclusion, globally our findings suggest that the association of donepezil (10 mg/day) to choline alphoscerate (1200 mg/day) may be a beneficial option in reducing BPSD of mild/moderate AD patients and should be considered especially when BPSD are unresponsive to donepezil only, or when the caregivers are unsatisfied with donepezil alone. Beneficial effects should also be evaluated in terms of the reduction of other potentially dangerous drugs given for the BPSD. A larger clinical trial is obviously warranted to further determine the efficacy and the advantages of the treatment.

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