Journal of Alzheimer's Disease 31 (2012) 325–334
DOI 10.3233/JAD-2012-112003
IOS Press

Apathy and Depression in Mild Alzheimer's Disease: A Cross-Sectional Study Using Diagnostic Criteria

Michel Benoit[a,*], Gilles Berrut[b], Johanna Doussaint[c], Serge Bakchine[d], Sylvie Bonin-Guillaume[e], Patrick Frémont[f], Thierry Gallarda[g], Pierre Krolak-Salmon[h], Thierry Marquet[i], Claude Mékiès[j], François Sellal[k], Stéphane Schuck[c], Renaud David[l] and Philippe Robert[l]
[a]*Clinique de Psychiatrie et de Psychologie Médicale, Pole des Neurosciences Cliniques, CHU Nice, France*
[b]*Pôle de Gérontologie clinique, Hôpital Bellier, Nantes, France*
[c]*Kappa Santé, Paris, France*
[d]*Service de Neurologie et CMRR, CHU de Reims, France*
[e]*Assistance Publique des Hôpitaux de Marseille, Institut des Neurosciences de la Timone, Université Aix Marseille, France*
[f]*Service de Psychiatrie, C.H. Lagny – Marne La Vallée, France*
[g]*Université Paris-Descartes, Inserm, UMR 894, Laboratoire de physiopathologie des maladies psychiatriques, Centre de Psychiatrie et Neurosciences, Service Hospitalo-Universitaire, Centre Hospitalier Sainte-Anne, Paris, France*
[h]*CMRR – Hospices Civils de Lyon, Inserm U1028, CNRS UMR5292, Université Lyon 1, France*
[i]*Eisai France – Région Europe du Sud, Paris, France*
[j]*Polyclinique du Parc, Toulouse et clinique des Cèdres, Cornebarrieu, France, Representing the ANLLF*
[k]*CMRR – Hôpitaux Civils de Colmar et INSERM U-692, Université de Strasbourg, France*
[l]*CMRR – EA CoBTeK- CHU – Université de Nice Sophia Antipolis, France*

Accepted 10 April 2012

Abstract. Apathy and depression are the most frequent neuropsychiatric symptoms in Alzheimer's disease (AD). In a cross-sectional observational study of 734 subjects with probable mild AD, we evaluated the prevalence of apathy and depression. After the use of specific diagnostic criteria, we tested the interaction between the two syndromes and their relation with specific comorbidities, and different functional outcomes. Depression was diagnosed using the diagnostic criteria for depression in AD, and apathy with the diagnostic criteria for apathy in neuropsychiatric disorders. According to the specific diagnostic criteria, depression had a 47.9% prevalence, while apathy prevalence was 41.6%. Apathy and depression were associated in 32.4% of patients ($n = 225$). 9.4% ($n = 65$) had only apathy, 15.4% ($n = 107$) had only depression, and 42.9% had no apathy and no depression ($n = 298$). The three most frequent depressive symptoms were fatigue or loss of energy (59.4%), decreased positive affect or pleasure in response to social contacts and activities (46.2%), and psychomotor agitation or retardation (36.9%). Concerning apathy, loss of goal-directed cognition was the most frequently altered (63.6%), followed by loss of goal-directed action (60.6%) and loss of goal-directed emotion (43.8%). Patients with both apathy and depression more frequently required a resource allowance for dependency. Neurological comorbidities were more frequent in the "apathy and depression" and

*Correspondence to: Dr. Michel Benoit, Clinique de Psychiatrie et de Psychologie Médicale, Pole des Neurosciences Cliniques, Hôpital Pasteur, BP 69, 06002 Nice Cédex 1, France. Tel.: +33 492 037 753; Fax: +33 492 038 011; E-mail: benoit.m@chu-nice.fr.

ISSN 1387-2877/12/$27.50

"depression alone" groups ($p < 0.001$). Apathy and depression overlap considerably, and this might be explained by the presence of some non-specific symptoms in both diagnostic criteria. The need for social support is higher when a patient fulfills the two diagnostic criteria.

Keywords: Alzheimer's disease, apathy, depressive symptoms, dementia

INTRODUCTION

Neuropsychiatric symptoms (NPS) are usually associated with cognitive deficits during the course of Alzheimer's disease (AD) and related disorders. Apathy and depression are the two most frequent NPS in AD [1, 2], and both have a negative impact on the evolution of the disease [3, 4] and are predictive of early institutionalization.

Marin was the first to present apathy as a disorder of motivation, defined as "the direction, intensity and persistence of goal-directed behaviour" [5]. Most of the current descriptions acknowledge this point and consider apathy in terms of a lack of goal-directed behavior, cognition, or emotion [6–8], with lack of interest as one of the core clinical features [9] or as "an absence of responsiveness to stimuli as demonstrated by lack of self initiated action" [10]. Prevalence of apathy in the early stages of dementia is estimated at between 36% and 65% in mild AD [1, 11, 12] and is also frequently reported in the pre-demented stage and in mild cognitive impairment (MCI) with frequency between 15 and 41% in MCI [12–17].

Average frequency of depression in mild AD is between 20–50% [12, 18, 19] and is lower in MCI subjects [1, 20]. Apathy and depression syndromes share common symptoms [3, 21] but it has been shown that they have distinct neural pathways as demonstrated by several neuroimaging studies [22]. Additionally, apathy, but not depression, was found to predict progression from amnestic MCI to AD [9, 16, 23].

The discrepancies between the reported prevalence of apathy and depression in AD and MCI may be related to several methodological issues, such as tool validity, threshold of scores for diagnosis, socio-environmental factors in selected populations, or severity of cognitive deficits. Global and symptom-specific scales have been developed to assess the presence and severity of NPS in dementia. The diversity of available assessment methods testifies the interest in this field but also constitutes a limitation in the comparability of publications and clinical trials. As diagnosis of depression and apathy is most often based on a quantitative assessment (i.e., scores on specific scales), diagnostic criteria for depression [18] and apathy [24] are currently available. Data with application of these qualitative methods is limited [25].

The main objective of this study is to evaluate the prevalence of apathy and depression, and their interaction, using specific diagnostic criteria among recently diagnosed AD subjects. Secondary objectives are to assess the relationships 1) between both apathy and depression and the impact on patients' dependency, and 2) between both apathy and depression and physical comorbidities.

MATERIALS AND METHODS

Population

A cross-sectional national epidemiological study was conducted by a national representative sample of clinicians. The investigators were private practice neurologists, geriatricians, or psychiatrists working in a memory clinic. They were randomly selected on the basis of their main specialty.

Each clinician had to check for the presence of apathy and depression according to the specific diagnostic criteria in consecutive patients with the following inclusion criteria: people older than 65, Mini Mental Score Examination (MMSE) score higher than 19 [26], and diagnosis of probable AD according to the NINCDS-ADRDA criteria [27]. The diagnosis had to have been established within the previous 6 months. The study protocol has been approved by the French ethical committee for data management (CNIL). The demographic data recording process was the same as the data recording used in the French National Data Bank for dementia [28] and includes age, gender, education level, and the presence or absence of the French official financial support for elderly people with loss of autonomy (APA). More specifically, the patient or his/her family, in relation with the general practitioner, can apply for APA from the regional health administration in order to partially cover costs related to loss of autonomy (e.g., nurse, home help, home delivered meals, day hospital charges, nursing home charges). The decision on whether to grant this allowance is made after a patient home visit and a fully independent standardized interview with a social worker from the regional administration.

Table 1
Diagnostic criteria for depression [18] and apathy [24]

Depression	Apathy
A. Three or more of the following criteria over the same 2-week period, representing a change from previous functioning:	**A. Loss of or diminished motivation in comparison to the patient's previous level of functioning and which is not consistent with his age or culture. These changes in motivation may be reported by the patient himself or by the observations of others**
At least one of criteria 1 or 2 must be present	**B. Presence of at least one symptom in at least two of the three following domains for a period of at least four weeks and present most of the time**
1. Depressed mood (sad, hopeless, discouraged, tearful)	Domain B1 ACTION: Loss of, or diminished, goal-directed behavior as evidenced by at least one of the following:
2. Decreased positive affect or pleasure in response to social contacts and activities	- Loss of self-initiated behavior (for example: starting conversation, doing basic tasks of day-to-day living, seeking social activities, communicating choices)
3. Social isolation or withdrawal	- Loss of environment-stimulated behavior (for example: responding to conversation, participating in social activities)
4. Disruption in appetite	Domain B2 COGNITION: Loss of, or diminished, goal-directed cognitive activity as evidenced by at least one of the following:
5. Disruption in sleep	- Loss of spontaneous ideas and curiosity for routine and new events (i.e., challenging tasks, recent news, social opportunities, personal/family and social affairs)
6. Psychomotor agitation or retardation	- Loss of environment-stimulated ideas and curiosity for routine and new events (i.e., in the persons residence, neighborhood or community)
7. Irritability	Domain B3 EMOTION: Loss of, or diminished, emotion as evidenced by at least one of the following:
8. Fatigue or loss of energy	- Loss of spontaneous emotion, observed or self-reported (for example, subjective feeling of weak or absent emotions, or observation by others of a blunted affect)
9. Worthlessness, hopelessness or excessive guilt	- Loss of emotional responsiveness to positive or negative stimuli or events (for example, observer-reports of unchanging affect, or of little emotional reaction to exciting events, personal loss, serious illness, emotional-laden news)
10. Recurrent thoughts of death or suicidal ideation	**C. These symptoms (A-B) cause clinically significant impairment in personal, social, occupational, or other important areas of functioning**
B. All criteria are met for dementia of the Alzheimer's type	**D. The symptoms (A-B) are not exclusively explained or due to physical disabilities (e.g., blindness and loss of hearing), to motor disabilities, to diminished level of consciousness or to the direct physiological effects of a substance (e.g., drug of abuse, a medication)**
C. Symptoms cause distress or disruption in functioning	
D. Symptoms do not occur exclusively during delirium	
E. Symptoms are not due to substances (medications or drugs of abuse)	

Diagnosis and assessment

Depression was diagnosed using the diagnostic criteria for depression in AD [18], and apathy with the diagnostic criteria for apathy in AD and neuropsychiatric disorders [24] (Table 1).

Among the diagnostic criteria of apathy, criterion B describes the three core clinical domains of apathy, namely reduced goal-directed behavior, goal-directed cognitive activity, and emotions. Criterion B is based on the premise that change in motivation can be assessed by examining a patient's responsiveness to internal or external stimuli. To be fulfilled, clinical criterion B requires the presence of a minimum of one symptom in at least two of the three domains for a period of at least four weeks and most of the time.

The cognitive, behavioral, and functional assessment included the MMSE and the scale of Instrumental Activities of Daily Living (IADL) [29] detection score. Dependency and loss of autonomy was estimated by the percentage of subjects receiving APA. Physical comorbidity assessment used the Cumulative Illness Rating Scale (CIRS) 5-point Likert scale, measuring degree of severity (ranging from "1 = none" to "5 = extremely") [30]. The CIRS has been used excluding from the list of comorbidities the psychiatric

Table 2
Prevalence of depression and apathy symptoms in the overall population

	Total ($n = 734$)
Depression diagnostic criteria [18]	
Depressed mood	177 (24.4%)
Decreased positive affect or pleasure in response to social contacts and activities	335 (46.2%)
Disruption in appetite	170 (23.4%)
Disruption in sleep	226 (31.1%)
Psychomotor agitation or retardation	266 (36.9%)
Fatigue or loss of energy	431 (59.4%)
Worthlessness, hopelessness or excessive guilt	155 (21.5%)
Lack of concentration	496 (68.7%)
Recurrent thoughts of death or suicidal ideation	59 (8.2%)
Social isolation or withdrawal	286 (39.7%)
Irritability	270 (37.4%)
()Data are missing for 16 patients	
Apathy diagnostic criteria [24]	
Loss of, or diminished, goal-directed behavior	430 (60.6%)
Loss of, or diminished, goal-directed cognitive activity	460 (63.6%)
Loss of, or diminished, emotion	316 (43.8%)
Data are missing for 24 patients	

and behavioral comorbidities, which can overlap with apathy. All these assessments were based on the caregiver's interview and the examination by physician.

Statistical analysis

Statistical analyses were performed using SAS software (v 9.1, SAS Institute, North Carolina). Two-group comparisons for quantitative variables were made using a Student test after verifying the equality of variances (in case of unequal variances, the Satterthwaite approximation method was used). For other group comparisons (>2), quantitative variables were compared using analysis of variance in case of equality of variance (Levène test) and normality of distributions (visual analysis of histograms or the Shapiro-Wilk test). Otherwise, a non-parametric analysis was performed (Kruskal-Wallis test). A 0.05 threshold of significance was implemented. Post hoc analysis used a Bonferroni procedure with a correction for multiple comparisons. For ordinal variables, group comparisons were made using a chi-square test. A 0.05 threshold of significance was chosen for all analyses.

RESULTS

A total of 1,034 patients with mild AD were screened by 115 physicians (75 private practice neurologists and 40 physicians working in a memory clinic). 307 subjects (age = 77.5 ± 7.6 years; M/F = 43/57%; MMSE = 23.2 ± 3.6) were not included in the analysis. The main reasons for non-inclusion were the patient's or accompanying person's refusal to participate in the study (27%) and lack of time for the physician to perform the screening (34.2%). Among the screened patients, 734 AD patients were included (age = 80 ± 6.6 years; M/F = 38/62%; MMSE = 23.1 ± 2.2; range 20–29). Included patients were slightly older than the screened patients ($p < 0.001$). No difference for these populations was observed for gender ($p = 0.15$) or for MMSE ($p = 0.67$). These characteristics are similar to previously described cohorts of AD patients with mild severity [1, 2]. Mean time between AD diagnosis and inclusion was 2.6 ± 5.9 months. 15.4% of the patients received the APA.

According to the specific diagnostic criteria, depression had a 47.9% prevalence, with apathy prevalence at 41.6%. Frequency of Apathy criterion B alone was 54.8%.

Table 2 details the most frequent symptoms observed among the diagnostic criteria of apathy and depression. The three most frequent depressive symptoms are fatigue or loss of energy (59.4%), decreased positive affect or pleasure in response to social contacts and activities (46.2%), and psychomotor agitation or retardation (36.9%). Depressed mood was less frequent (24.4%). Concerning apathy, Domain B2 (cognition) is the most frequently altered (63.6%), followed by Domains B1 (action; 60.6%) and B3 (emotion; 43.8%).

Apathy and/or depression according to the diagnostic criteria are present in more than half of patients. The population was divided into four clinical groups: "apathy only", "depression only", "depression and apathy" associated, and "no apathy/no depression". The four

subgroups are similar with regard to the prescription of acetylcholinesterase inhibitors and memantine. However, the prescription of antidepressants was significantly higher in the subgroups presenting either solely with depression criteria or criteria of both "apathy and depression". Data for the four subgroups is presented in Table 3.

Post hoc analysis indicated that the "apathy and depression" subgroup had a significantly lower MMSE score than the "no apathy no depression" subgroup, together with a lower IADL score than the "no apathy no depression" subgroup, the "apathy" subgroup and the "depression "subgroup. We calculated the effect size of the MMSE difference between "apathy and depression" and "no apathy no depression" groups (0.28) and of the MMSE difference between "apathy alone" and "depression alone" (0.39). These effect size values are estimated to be « low » according to Cohen's conventional ranges.

In addition, the "apathy and depression" subgroup had a significantly higher time since diagnosis than the "no apathy no depression" subgroup.

Among the depressive symptoms (depression diagnostic criteria A), depressed mood was only detected in 24% of the patients with depression either alone or associated with apathy. Likewise, decreased positive affect or pleasure in response to social contacts and activities is present in 62.9% of the "depression alone" subgroup and 81.3% of the "apathy and depression" subgroup.

Distribution of comorbidities (excluding dementia and psychiatric domains) is presented in Table 4. For the whole population, mean comorbidity and severity indexes are mild to moderate (1.3 ± 1.4 for the CIRS, excluding psychiatric and behavioral comorbidities). The most frequent comorbidities are hypertension (59.3%), cardiac (34.7%), endocrine (26.3%), and vascular (20.6%). Post hoc analysis indicated that CIRS was significantly higher for the "apathy and depression" subgroup in comparison to the three other subgroups ($p < 0.05$). Patients belonging to the "apathy and depression" and "depression alone" groups have more frequent neurological comorbidities ($p < 0.001$) than the two other subgroups.

DISCUSSION

This study using diagnostic criteria concludes that apathy, either alone or associated with depression, affects 41.8% and depression, alone or associated with apathy, affects 47.8% of a representative sample of patients with mild AD. Concerning apathy, these figures are in the range of previous studies using quantitative scales as Neuropsychiatric Inventory (NPI) or qualitative criteria. In Van Reekum's review on apathy, apathy ranges from 55% to 80% in studies using the NPI and from 37% to 86% in studies using specific apathy scales [31]. In a recent study using the diagnostic criteria of apathy, Mulin et al. [25] found a higher prevalence of apathy in AD subjects (55% versus 41.6% in the present study). The lower percentage might be explained by the low severity of AD in the present sample (MMSE score 23.1 ± 2.2 versus 18.3 ± 4.6).

Concerning depression, Vilalta-Franch et al. [19] found a prevalence of 27.4% when using Olin's criteria (versus 47.9% in our study), and 10.6% when using the DSM-IV criteria in a cohort of AD subjects characterized by a lower mean MMSE score (17.1 ± 4.1). Nevertheless, previous studies using quantitative scales showed that the prevalence of depression in AD increases with the progression of cognitive decline [11, 32–34], as other studies found a relative stability or decrease of depression prevalence [35, 36]. In a five-year longitudinal cohort study, prevalence of depression increased during four years of follow-up, then decreased in year 5 [36]. More generally, the use of categorical diagnostic criteria, such as the DSM-IV and the ICD-10, provides lower prevalence of depression compared with the use of specific diagnostic criteria. This consistent finding in literature may be due to the fact that non-specific criteria for depression are more restrictive than Olin's criteria which require only three depressive symptoms or more to diagnose depression in AD, instead of the five or more symptoms required to diagnose major depressive episode [18].

The high prevalence of the association between apathy and depression raises some concern about the possible overlap between the two syndromes. The present study revealed that more than 56% of patients presenting with apathy or depression have both syndromes. This was shown in previous cohort studies showing that about half of the patients with apathy have depression and vice-versa [1, 37].

One possible explanation lies at the symptomatic level. In the overall population, results indicated that decreased positive affect in response to social contacts or activities, one of the clinical symptoms of depression criteria, is more frequent than the depressed mood (46.2% versus 24.4%). With the same criteria, the high prevalence of social isolation and withdrawal (39.7%) may account to some overlap with apathy.

Table 3
Socio-demographic and clinical variables according to the presence or absence of apathy and depression using diagnostic criteria

		Apathy and depression ($n=225$)	Apathy alone ($n=65$)	Depression alone ($n=107$)	No apathy no depression ($n=298$)	p (before correction)	After Bonferroni correction
Gender	Male	83 (37.1%)	30 (46.2%)	36 (33.6%)	105 (35.5%)	*0.37*	*NS*
	Female	141 (62.9%)	35 (53.8%)	71 (66.4%)	191 (64.5%)		
Age	Mean (±SD)	79.9 (±6.5)	80.5 (±7)	78.1 (±7.4)	80.5 (±6.2)	*0.01*	*0.13 (NS)*
Social level	Low	26 (12%)	10 (15.4%)	5 (4.9%)	25 (8.4%)		
	Middle	147 (67.7%)	35 (53.8%)	70 (68%)	217 (73.1%)	0.04	0.52 (NS)
	Well off	42 (19.4%)	20 (30.8%)	28 (27.2%)	52 (17.5%)		
MMSE score	Mean (±SD)	22.7 (±1.9)*	22.7 (±2)°	23.6 (±2.4)°,£	23.3 (±2.3)*,£	*<0.0001*	*<0.001*
APA	Yes	58 (25.9%)*	7 (10.8%)*	9 (8.4%)*	33 (11.1%)*	*<0.0001*	*<0.001*
	No	161 (71.9%)	58 (89.2%)	96 (89.7%)	251 (84.2%)		
	No information	5 (2.2%)	0 (0%)	2 (1.9%)	14 (4.7%)		
Social worker assistance	None	202 (90.2%)	56 (88.9%)	94 (88.7%)	276 (92.9%)	*0.35*	*NS*
Time since diagnosis (months)	Mean (±SD)	3.7 (±6.3)*,°	0.9 (±2.7)°	2.9 (±5.5)	2.2 (±6.3)*	*<0.0001*	*<0.001*
Pharmacological treatment	No: 52 (7.1%)	5 (2.2%)	2 (3.1%)	5 (4.7%)	30 (10.1%)		
	Yes: 682 (92.9%)	220 (97.8%)	63 (96.9%)	102 (95.3%)	268 (89.9%)	<0.002	<0.05
If yes	Cholinesterase inhibitors 487 (71.4%)	167 (75.9%)	43 (68.3%)	69 (67.6%)	189 (70.5%)	0.06	NS
	Memantine 53 (7.8%)	30 (13.6%)	4 (6.3%)	5 (4.9%)	11 (4.1%)	–	
	Antidepressant 249 (36.5%)	123 (55.9%)	10 (15.9%)	50 (49%)	55 (20.5%)	*<0.0001*	*<0.0001*
IADL detection score							
Depressive symptoms	Mean (±SD)	2.4 (±1.1)*,°,£	2.9 (±1)°	3 (±1)£	3 (±1)*	*<0.0001*	*<0.001*
Depressed mood		101 (44.9%)	7 (10.8%)	47 (44.3%)	13 (4.4%)		
Decreased positive affect or pleasure in response to social contacts and activities		183 (81.3%)	25 (38.5%)	66 (62.9%)	41 (13.8%)	*<0.0001*	*<0.0001*

Post hoc Analysis: *2 groups with the same symbol show a statistically significant difference ($p<0.05$).

Age: *No apathy no depression versus depression alone.

MMSE: *No apathy no depression versus apathy and depression/°apathy alone versus depression alone/£apathy and depression versus depression alone.

APA: *apathy and depression versus the other groups.

Time since diagnosis: *No apathy no depression versus apathy and depression/°apathy and depression versus apathy alone.

IADL detection score: *No apathy no depression versus apathy and depression/°apathy and depression versus apathy alone/£apathy and depression versus depression alone.

Table 4
Comorbidities index, severity index, and comorbidities frequency associated with the presence or absence of apathy and depression

		Total ($n = 734$)	Apathy and depression ($n = 225$)	Apathy alone ($n = 65$)	Depression alone ($n = 107$)	No apathy No depression ($n = 298$)	p	p (After Bonferroni correction)
Comorbidity index*	Mean (±SD)	2.3 (±1.9)	**2.7 (±2.2)**	**2.1 (±1.6)**	**2.4 (±2.2)**	**2 (±1.5)**	**<0.01**	
Severity index	Mean (±SD)	1.3 (±1.4)	**1.6 (±1.6)**	**1.3 (±1.4)**	**1.1 (±1.4)**	**1.2 (±1.2)**	**<0.01**	
Comorbidities	Cardiologic	236 (34.7%)	**84 (41.6%)**	**20 (32.8%)**	**23 (23.2%)**	**89 (31.7%)**	**0.01**	**0.14**
	Hypertension	403 (59.3%)	**121 (59.9%)**	**33 (54.1%)**	**58 (58.6%)**	**165 (58.7%)**	**0.88**	**NS**
	Vascular	140 (20.6%)	**48 (23.8%)**	**14 (23%)**	**17 (17.2%)**	**50 (17.8%)**	**0.33**	**NS**
	Haematology	22 (3.2%)	**3 (1.5%)**	**2 (3.3%)**	**6 (6.1%)**	**10 (3.6%)**	**0.21**	**NS**
	Respiratory	65 (9.6%)	**22 (10.9%)**	**5 (8.2%)**	**12 (12.1%)**	**23 (8.2%)**	**0.6**	**NS**
	Head and neck (eye. ear. noose. pharynx. larynx)	66 (9.7%)	**15 (7.4%)**	**6 (9.8%)**	**11 (11.1%)**	**27 (9.6%)**	**0.73**	**NS**
	Upper digestive system (esophagus, stomach, duodenum, bladder, pancreas)	60 (8.8%)	**26 (12.9%)**	**4 (6.6%)**	**12 (12.1%)**	**17 (6%)**	**0.04**	**0.56**
	Lower digestive system (bowels. hernia)	66 (9.7%)	**33 (16.3%)**	**4 (6.6%)**	**10 (10.1%)**	**16 (5.7%)**	**<0.01**	**0.10**
	Liver	18 (2.6%)	**12 (5.9%)**	**0 (0%)**	**2 (2%)**	**3 (1.1%)**	**<0.01**	**NS**
	Kidney	46 (6.8%)	**22 (10.9%)**	**4 (6.6%)**	**6 (6.1%)**	**11 (3.9%)**	**0.03**	**0.42**
	Urogenital	104 (15.3%)	**42 (20.8%)**	**10 (16.4%)**	**13 (13.1%)**	**33 (11.7%)**	**0.05**	**0.70**
	Dermatology and osteoarticular (muscles. bones. skin)	104 (15.3%)	**32 (15.8%)**	**10 (16.4%)**	**20 (20.2%)**	**39 (13.9%)**	**0.52**	**NS**
	Neurology (brain. bone marrow. nerves)	77 (11.3%)	**109 (54%)**	**16 (26.2%)**	**48 (48.5%)**	**78 (27.8%)**	**<0.0001**	**<0.001**
	Endocrine and mammary	179 (26.3%)	**62 (30.7%)**	**14 (23%)**	**28 (28.3%)**	**69 (24.6%)**	**0.42**	**NS**

The comorbidity and severity index do not include psychiatric and behavioral comorbidities. *CIRS scale. The comorbidity and severity index do not include psychiatric and behavioral comorbidities.

Likewise, within the diagnostic criteria of apathy, loss of or diminished cognitive activity is the most frequent symptom in the diagnostic criteria (63.6%).

As already observed in Parkinson disease, there is a probable overlap between symptoms considered both as apathetic and depressive symptomatology [38]. In fact, loss of directed-goal cognitive activity is usually interpreted [24] as a loss of or diminished interest that is most observed in leisure activities. This domain indicates that the patient is less interested in the activities and plans of others, in friends and family members, or in their own usual leisure activities. This meaning is close to the meaning of the decreased positive affect symptoms of the depression criteria, which is considered as decreased interest or pleasure in things in the DSM IV. The present study confirms that these "overlapping" symptoms are present in 62.9% of the patients presenting the depression criteria alone and in 81.3% of the patients presenting both apathy and depression diagnostic criteria. Due to the cross-sectional design of our study, we could not determine if apathy or depression were present before the onset of dementia and may be risk factors or prodromes. It was also not possible to evaluate the dynamics and interrelation of these symptoms with time.

It also has been hypothesized that depressive symptoms in AD are more often related to vegetative or action disturbances than to negative mood or affective distress, and therefore may be similar to apathy symptoms [3, 39, 40].

This study also indicated that patients with apathy and depression more frequently required a resource allowance for dependency (APA) than patients with only depression or none of these syndromes, even with a small difference in cognitive level between groups. We also demonstrated that the patients with both syndromes have a lower IADL score when compared to other subgroups. This suggests that the association of apathy and depression may be more closely associated with lack of autonomy, as was demonstrated in other studies showing that these patients are more functionally impaired, independently of their cognitive deficit [2, 4, 41]. However, we could not provide any evidence of an association between apathy alone or depression alone and loss of autonomy. This suggests that depression and apathy may have a cumulative negative effect on functional outcomes.

Concerning physical comorbidities, we also observed that a majority of patients in all clinical groups had hypertension. Moreover, apathetic patients with or without depressive symptoms had a higher prevalence of cardiological comorbidities than patients in the other groups. Other studies on diverse elderly populations have found similar results. Longitudinal studies after strokes reported a high prevalence of both apathy and depression symptoms [42–44]. In dementia, apathy as mental slowness was more frequently associated with vascular white-matter changes [45]. In a community-dwelling elderly subject sample, an association was found between apathy and hypertension and white matter lesions [46]. This relation had been otherwise considered as a depression-executive dysfunction syndrome of late life [47].

The question of the association between vascular factors and specific depressive symptoms provided conflicting results. In our study, AD subjects having isolated depressive symptoms exhibited less frequently cardiological comorbidities (23.2%). Previous reviews or large cohort studies in the elderly confirmed this relationship between depressive symptoms and cardiovascular risk factors [48, 49], while others studies did not find a direct relation. In many cases, depressive symptoms may precede cardiovascular comorbidities or share only some of pathophysiological factors [50]. Conversely, depression alone or associated with apathy is more frequently associated with neurological disorders (47.3%). One hypothesis is that neurological disturbances may have more depressive consequences due to the incapacity associated with this group of disorders.

The fact that this study was largely conducted among private sector specialists is a positive point since, in France, these doctors are very often consulted by the public at an early stage. It is also a drawback, as it is more difficult to access para-clinical details leading to the diagnosis or the register of associated treatment. A further limitation with regard to this study stems from the fact that it was conducted at a given time and that there is no data describing developments in these four subgroups. This data is, however, of interest as it provides an overview of the associations between apathy and depression in a significant population.

In conclusion, this study confirms that an accurate qualitative assessment, using diagnostic criteria of depression and apathy, reveals these syndromes both have a high prevalence. They overlap considerably and this may due to the fact that diagnostic criteria shared the same symptoms. When a patient fulfills the two diagnostic criteria, there is a greater need for social support. Neurophysiological studies looking at the relationship with vascular factors will probably be improved by taking this symptomatic overlap into account.

ACKNOWLEDGMENTS

This study was supported by a grant from EISAI (ESTIME study for Estimation de la prévalence des troubles apathiques et dépressifs chez les patients atteints de la MA à un stade léger, nouvellement diagnostiqués par des spécialistes en neurologie ou au sein de consultation mémoire).

Authors' disclosures available online (http://www.j-alz.com/disclosures/view.php?id=1263).

REFERENCES

[1] Lyketsos CG, Lopez O, Jones B, Fitzpatrick AL, Breitner J, DeKosky S (2002) Prevalence of neuropsychiatric symptoms in dementia and mild cognitive impairment: Results from the cardiovascular health study. *JAMA* **288**, 1475-1483.

[2] Landes AM, Sperry SD, Strauss ME (2005) Prevalence of apathy, dysphoria, and depression in relation to dementia severity in Alzheimer's disease. *J Neuropsychiatry Clin Neurosci* **17**, 342-349.

[3] Tagariello P, Girardi P, Amore M (2009) Depression and apathy in dementia: Same syndrome or different constructs? A critical review. *Arch Gerontol Geriatr* **49**, 246-249.

[4] Benoit M, Andrieu S, Lechowski L, Gillette-Guyonnet S, Robert PH, Vellas B (2008) Apathy and depression in Alzheimer's disease are associated with functional deficit and psychotropic prescription. *Int J Geriatr Psychiatry* **23**, 409-414.

[5] Marin RS (1990) Differential diagnosis and classification of apathy. *Am J Psychiatry* **147**, 22-30.

[6] Marin RS, Fogel BS, Hawkins J, Duffy J, Krupp B (1995) Apathy: A treatable syndrome. *J Neuropsychiatry Clin Neurosci* **7**, 23-30.

[7] Starkstein SE, Petracca G, Chemerinski E, Kremer J (2001) Syndromic validity of apathy in alzheimer's disease. *Am J Psychiatry* **158**, 872-877.

[8] Brown RG, Pluck G (2000) Negative symptoms: The 'pathology' of motivation and goal-directed behaviour. *Trends Neurosci* **23**, 412-417.

[9] Robert PH, Berr C, Volteau M, Bertogliati-Fileau C, Benoit M, Guerin O, Sarazin M, Legrain S, Dubois B (2008) Importance of lack of interest in patients with mild cognitive impairment. *Am J Geriatr Psychiatry* **16**, 770-776.

[10] Stuss DT, Van Reekum R, Murphy KJ (2000) Differentiation of states and causes of apathy. In: *The neuropsychology of emotion*, Borod JC, ed. Oxford University Press, New York, pp. 340-363.

[11] Aalten P, de Vugt ME, Jaspers N, Jolles J, Verhey FR (2005) The course of neuropsychiatric symptoms in dementia. Part I: Findings from the two-year longitudinal Maasbed study. *Int J Geriatr Psychiatry* **20**, 523-530.

[12] Fernandez-Martinez M, Molano A, Castro J, Zarranz JJ (2010) Prevalence of neuropsychiatric symptoms in mild cognitive impairment and Alzheimer's disease, and its relationship with cognitive impairment. *Curr Alzheimer Res* **7**, 517-526.

[13] Geda YE, Roberts RO, Knopman DS, Petersen RC, Christianson TJ, Pankratz VS, Smith GE, Boeve BF, Ivnik RJ, Tangalos EG, Rocca WA (2008) Prevalence of neuropsychiatric symptoms in mild cognitive impairment and normal cognitive aging: Population-based study. *Arch Gen Psychiatry* **65**, 1193-1198.

[14] Vicini Chilovi B, Conti M, Zanetti M, Mazzu I, Rozzini L, Padovani A (2009) Differential impact of apathy and depression in the development of dementia in mild cognitive impairment patients. *Dement Geriatr Cogn Disord* **27**, 390-398.

[15] Apostolova LG, Cummings JL (2008) Neuropsychiatric manifestations in mild cognitive impairment: A systematic review of the literature. *Dement Geriatr Cogn Disord* **25**, 115-126.

[16] Robert PH, Berr C, Volteau M, Bertogliati C, Benoit M, Sarazin M, Legrain S, Dubois B (2006) Apathy in patients with mild cognitive impairment and the risk of developing dementia of Alzheimer's disease: A one-year follow-up study. *Clin Neurol Neurosurg* **108**, 733-736.

[17] Hwang TJ, Masterman DL, Ortiz F, Fairbanks LA, Cummings JL (2004) Mild cognitive impairment is associated with characteristic neuropsychiatric symptoms. *Alzheimer Dis Assoc Disord* **18**, 17-21.

[18] Olin JT, Schneider LS, Katz IR, Meyers BS, Alexopoulos GS, Breitner JC, Bruce ML, Caine ED, Cummings JL, Devanand DP, Krishnan KR, Lyketsos CG, Lyness JM, Rabins PV, Reynolds CF 3rd, Rovner BW, Steffens DC, Tariot PN, Lebowitz BD (2002) Provisional diagnostic criteria for depression of Alzheimer disease. *Am J Geriatr Psychiatry* **10**, 125-128.

[19] Vilalta-Franch J, Garre-Olmo J, Lopez-Pousa S, Turon-Estrada A, Lozano-Gallego M, Hernandez-Ferrandiz M, Pericot-Nierga I, Feijoo-Lorza R (2006) Comparison of different clinical diagnostic criteria for depression in Alzheimer disease. *Am J Geriatr Psychiatry* **14**, 589-597.

[20] Panza F, Frisardi V, Capurso C, D'Introno A, Colacicco AM, Imbimbo BP, Santamato A, Vendemiale G, Seripa D, Pilotto A, Capurso A, Solfrizzi V (2010) Late-life depression, mild cognitive impairment, and dementia: Possible continuum? *Am J Geriatr Psychiatry* **18**, 98-116.

[21] Levy ML, Cummings JL, Fairbanks LA, Masterman D, Miller BL, Craig AH, Paulsen JS, Litvan I (1998) Apathy is not depression. *J Neuropsychiatry Clin Neurosci* **10**, 314-319.

[22] Starkstein SE, Mizrahi R, Capizzano AA, Acion L, Brockman S, Power BD (2009) Neuroimaging correlates of apathy and depression in Alzheimer's disease. *J Neuropsychiatry Clin Neurosci* **21**, 259-265.

[23] Palmer K, Di Iulio F, Varsi AE, Gianni W, Sancesario G, Caltagirone C, Spalletta G (2010) Neuropsychiatric predictors of progression from amnestic-mild cognitive impairment to Alzheimer's disease: The role of depression and apathy. *J Alzheimers Dis* **20**, 175-183.

[24] Robert P, Onyike CU, Leentjens AF, Dujardin K, Aalten P, Starkstein S, Verhey FR, Yessavage J, Clement JP, Drapier D, Bayle F, Benoit M, Boyer P, Lorca PM, Thibaut F, Gauthier S, Grossberg G, Vellas B, Byrne J (2009) Proposed diagnostic criteria for apathy in Alzheimer's disease and other neuropsychiatric disorders. *Eur Psychiatry* **24**, 98-104.

[25] Mulin E, Leone E, Dujardin K, Delliaux M, Leentjens A, Nobili F, Dessi B, Tible O, Aguera-Ortiz L, Osorio RS, Yessavage J, Dachevsky D, Verhey FR, Jentoft AJ, Blanc O, Llorca PM, Robert PH (2011) Diagnostic criteria for apathy in clinical practice. *Int J Geriatr Psychiatry* **26**, 158-165.

[26] Folstein MF, Folstein SE, McHugh PR (1975) "Mini-mental test". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatry Res* **12**, 189-198.

[27] McKhann G, Drachman D, Folstein M, Katzman R, Pice D, Stadian EM (1984) Clinical diagnosis of Alzheimer's disease: Report of the NINCDS-ADRDA work group under the

auspices of department of Health and Human Services task force on Alzheimer's disease. *Neurology* **34**, 189-198.

[28] Le Duff F, Duport N, Gonfrier S, Lafay P, Texier N, Schück S, Pradier C, Robert P, participants. ec (2010) Plan national Alzheimer 2008–2012 – Mesure 34 mise en place du recueil épidémiologique national et premières tendances. *Rev Gériatrie* **35**, 575-582.

[29] Lawton MP, Brody EM (1969) Assessment of older people: Self-maintaining and instrumental activities of daily living. *Gerontologist* **9**, 179-186.

[30] Linn BS, Linn MW, Gurel L (1968) Cumulative illness rating scale. *J Am Geriatr Soc* **16**, 622-626.

[31] Van Reekum R, Stuss DT, Ostrander L (2005) Apathy: Why care? *J Neuropsychiatry Clin Neurosci* **17**, 7-19.

[32] Benoit M, Robert P (2003) [Depression and apathy in Alzheimer's disease]. *Presse Med* **32**, S14-S18.

[33] Wetzels RB, Zuidema SU, de Jonghe JF, Verhey FR, Koopmans RT (2010) Course of neuropsychiatric symptoms in residents with dementia in nursing homes over 2-year period. *Am J Geriatr Psychiatry* **18**, 1054-1065.

[34] Savva GM, Zaccai J, Matthews FE, Davidson JE, McKeith I, Brayne C (2009) Prevalence, correlates and course of behavioural and psychological symptoms of dementia in the population. *Br J Psychiatry* **194**, 212-219.

[35] Holtzer R, Scarmeas N, Wegesin DJ, Albert M, Brandt J, Dubois B, Hadjigeorgiou GM, Stern Y (2005) Depressive symptoms in Alzheimer's disease: Natural course and temporal relation to function and cognitive status. *J Am Geriatr Soc* **53**, 2083-2089.

[36] Steinberg M, Shao H, Zandi P, Lyketsos CG, Welsh-Bohmer KA, Norton MC, Breitner JC, Steffens DC, Tschanz JT (2008) Point and 5-year period prevalence of neuropsychiatric symptoms in dementia: The Cache County Study. *Int J Geriatr Psychiatry* **23**, 170-177.

[37] Lyketsos CG, Steinberg M, Tschanz JT, Norton MC, Steffens DC, Breitner JC (2000) Mental and behavioral disturbances in dementia: Findings from the Cache County Study on Memory in Aging. *Am J Psychiatry* **157**, 708-714.

[38] Drijgers RL, Dujardin K, Reijnders JS, Lefebvre L, Leentjens A (2010) Validation of diagnostic criteria for apathy in Parkinson's disease. *Parkinsonism Relat Disord* **16**, 656-660.

[39] Lee HB, Lyketsos CG (2003) Depression in Alzheimer's disease: Heterogeneity and related issues. *Biol Psychiatry* **54**, 353-362.

[40] Marin RS, Firinciogullari S, Biedrzycki RC (1993) The sources of convergence between measures of apathy and depression. *J Affect Disord* **28**, 7-14.

[41] Starkstein SE, Jorge R, Mizrahi R, Robinson RG (2006) A prospective longitudinal study of apathy in Alzheimer's disease. *J Neurol Neurosurg Psychiatry* **77**, 8-11.

[42] Withall A, Brodaty H, Altendorf A, Sachdev PS (2011) A longitudinal study examining the independence of apathy and depression after stroke: The Sydney Stroke Study. *Int Psychogeriatr* **23**, 264-273.

[43] Mayo NE, Fellows LK, Scott SC, Cameron J, Wood-Dauphinee S (2009) A longitudinal view of apathy and its impact after stroke. *Stroke* **40**, 3299-3307.

[44] Hama S, Yamashita H, Shigenobu M, Watanabe A, Hiramoto K, Kurisu K, Yamawaki S, Kitaoka T (2007) Depression or apathy and functional recovery after stroke. *Int J Geriatr Psychiatry* **22**, 1046-1051.

[45] Jonsson M, Edman A, Lind K, Rolstad S, Sjogren M, Wallin A (2010) Apathy is a prominent neuropsychiatric feature of radiological white-matter changes in patients with dementia. *Int J Geriatr Psychiatry* **25**, 588-595.

[46] Yao H, Takashima Y, Mori T, Uchino A, Hashimoto M, Yuzuriha T, Miwa Y, Sasaguri T (2009) Hypertension and white matter lesions are independently associated with apathetic behavior in healthy elderly subjects: The Sefuri brain MRI study. *Hypertens Res* **32**, 586-590.

[47] Alexopoulos GS, Kiosses DN, Klimstra S, Kalayam B, Bruce ML (2002) Clinical presentation of the "depression-executive dysfunction syndrome" of late life. *Am J Geriatr Psychiatry* **10**, 98-106.

[48] Rao R (2000) Cerebrovascular disease and late life depression: An age old association revisited. *Int J Geriatr Psychiatry* **15**, 419-433.

[49] Steffens DC, Helms MJ, Krishnan KR, Burke GL (1999) Cerebrovascular disease and depression symptoms in the cardiovascular health study. *Stroke* **30**, 2159-2166.

[50] Camus V, Kraehenbuhl H, Preisig M, Bula CJ, Waeber G (2004) Geriatric depression and vascular diseases: What are the links? *J Affect Disord* **81**, 1-16.