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ORIGINAL REPORT

Adverse drug reactions in patients with Alzheimer's disease and related dementia in France: a national multicentre cross-sectional study

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ABSTRACT

Purpose To assess the prevalence of adverse drug reactions (ADRs) occurring in patients with Alzheimer's disease (AD) or other dementia in France.
Methods A cross-sectional multicentre study was conducted by the French network of the 31 regional pharmacovigilance centres on a given day. The subjects were selected by random draw to be a representative sample of French patients with dementia: consultations of dementia clinics, nursing-homes, acute and long care geriatric units, rehabilitation care geriatric units. The staff of each medical structure together with that of the pharmacovigilance centre defined a day for including the patients. Socio-demographic data, history, ADR and drugs given were registered.
Results There were 1332 subjects included, 51.1% living at home, 48.8% in institutions, aged 82.0 ± 8.0 years (46–108); 61.3% suffered from AD. Mean number of drugs was 6.3 ± 3.1. Anti-dementia drugs were given to 66.4% subjects. ADR prevalence was 5.0% (95% CI: 3.9–6.2) without a significant difference between at home and institutionalized patients. ADR consisted of gastro-intestinal (23.2%), central nervous system (17.4%) and psychiatric disorders (8.7%). Of the ADR, 31.9% were serious, and 47.8% preventable. The drugs most often involved were anti-dementia (28.9%), cardio-vascular (28.9%) and psychotropic drugs (26.4%, anxiolytics, hypnotics, antidepressants, neuroleptics).
Conclusion This national scale study showed that iatrogenesis in patients with AD and related dementia can at times be serious and preventable. Therefore, special attention is required when prescribing psychotropic and anti-dementia drugs, as they are frequently used and induce half of the ADR in this population. Copyright © 2013 John Wiley & Sons, Ltd.

KEY WORDS—Alzheimer's disease; dementia; adverse drug reaction; pharmacovigilance; cross-sectional study; pharmacoepidemiology

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INTRODUCTION

Dementia is characterized by a global cognitive decline that significantly alters a person's ability in daily life. Alzheimer's disease (AD) AD, the most common dementia, has become a major public health problem as the proportion of older people continues to increase.[1,2] In 2050, 107 million patients will be affected worldwide.[3] In France, one million people suffer from AD or related dementia; more than 95% are over 65 years [3–5].

The management of dementia is an important challenge for health professionals and caregivers. In patients with impaired cognition, the reduction of adherence, polymedication and the increased sensitivity to drugs with anticholinergic properties could be risk factors for adverse drug reactions (ADRs.)[6–8] While ADR related to cholinesterase inhibitors (ChEI)[9–11] or drug-induced cognitive impairment[12,13] are often studied and well described, few studies have evaluated the relationship between dementia and ADR occurrence.[14–17]

One of the objectives of the Alzheimer's Plan 2008–2012, fixed by the French government, was to improve the knowledge on iatrogenesis in subjects with dementia. To this end, we devised a pharmacovigilance study to assess ADR prevalence in patients with dementia in France and to describe the drugs involved, the severity and preventability of ADR.

METHODS

A multicentre prospective cross-sectional study was conducted on a given day within a representative sample of French subjects with AD or related dementia.

The subjects included originated from consultations in dementia clinics in public and private hospitals or within the French memory centres network, from nursing homes with public or private funding, from acute and long care geriatric units, and from rehabilitation care geriatric units in public or private hospitals. All patients with a diagnosis of dementia syndrome (AD or other dementia) medically confirmed in these structures were eligible. The diagnosis of dementia was based on declarative data from the practitioners in charge of the patients, after confirmation by a specialist using standardized criteria (NINCDS-ADRDA, National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association). Patients with dementia diagnosed on the inclusion day, patients and/or caregivers who refused to participate were not included.

The distribution of subjects with dementia in France is as follows: 60% at home, 40% in an institution; 10% of the at-home patients and 10% of those in an institution were likely to be hospitalized on the study day.[4,5] Thus, the following distribution of patients was hypothesized: 50% in dementia clinics, 30% in nursing homes, 5% in acute care geriatric units, 5% in long care geriatric units and 10% in rehabilitation care geriatric units.[4,5] The prevalence of ADR in the French population has been shown to range from 10% to 20%.[18,19] We assumed that the prevalence of ADR in patients with dementia could be similar. Therefore, 1400 subjects were necessary, with the following distribution: 700 subjects in dementia clinics, 420 in nursing homes, 140 in rehabilitation care geriatric units, 70 in acute care geriatric units and 70 in long care geriatric units. The inclusion of subjects was carried out by the French Regional Pharmacovigilance Centres network. Within each region, the number of subjects to be included was defined according to the prevalence of persons aged over 65 years, the age of most patients with dementia. The number of subjects to include was then assigned to randomly selected medical structures using a list issued by the French Health Ministry and the Méderic Alzheimer Foundation. The staff of each medical structure together with the regional pharmacovigilance centre chose a day to visit the structure and include patients between 15/2/2010 and 15/5/2010. Patients in each medical structure category were randomly selected.

Using a standardized report form, socio-demographic characteristics, history of dementia, cognitive status, comorbidities and medications (including those used over-the-counter) were recorded. Drugs were coded according to the Anatomical Therapeutic and Chemical classification, and diseases according to the MedDRA v13 and the Charlson comorbidity index.[20] The severity of dementia was estimated using an Mini Mental State Examination (MMSE) score dating from less than 1 year.

The pharmacovigilance staff in the various regional centres investigated all suspected adverse reactions (SARs), gathering information from the patients and their caregivers, the in-charge nurses and physicians, and from a review of the various charts and records. A SAR was defined as the presence, on the given day, of any untoward medical occurrence present during treatment with pharmaceutical products, whatever its severity, date of onset and nature of the drugs involved. Clinical, biological and complementary abnormalities were taken into account to identify these SAR. For each SAR, the description, the drugs, the severity and the evolution after a supervision of up to 15 days were recorded.

All collected SAR were evaluated by an independent committee including 10 experts in pharmacovigilance, geriatrics and neurology. The committee used the French ADR causality assessment.[21] This causality assessment

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method is the standard method that is part of the French national regulations. To date, no method has demonstrated superiority over the others, and most give similar results within the main causality categories.[22] One of the main criteria used was the time relationship between drug administration and SAR onset. Each ADR was identified according to the World Health Organization definition, which refers to any noxious, unintended and undesired effect of a drug, occurring at doses normally used in humans for prophylaxis, diagnosis or therapy.[23] Possible, probable and definite ADRs were taken into account. Therapeutic failure, intentional or accidental overdose and drug abuse were excluded. ADR were coded according to the MedDRA v13 classification. Any ADR leading to death, hospitalization or prolongation of existing hospitalization, to persistent or significant disability/incapacity or life threatening, was qualified as serious. The causality of drug interactions was assessed with the French causality method. The preventability of ADR was evaluated from an ADR preventability scale and classified as preventable, potentially preventable, not preventable and not assessable.[24]

A descriptive analysis of the subjects' characteristics comprised proportions for qualitative variables and mean values ± standard deviation for quantitative variables. The prevalence of ADR was defined as the number of subjects with ADR out of the number of enrolled subjects with dementia. A bivariate analysis using Chi2 or Fischer's test for dichotomous variables and Student's or Mann–Whitney test for continuous variables was performed. A backward multivariate logistic regression analysis was performed to determine factors associated with ADR occurrence using adjusted odds ratios (ORs) and their 95% confidence intervals (CIs). Independent variables associated with a *p*-value inferior to 0.25 in bivariate analysis were included in the initial model. The goodness of fit of the final model was assessed using the Hosmer–Lemeshow test. The level of significance was set at 0.05 (two sided), and all analyses were carried out using SAS 9.2 software.

All subjects and/or their caregivers gave informed written consent. This study was approved by the Ethics Committee of Poitiers' University Hospital and the National Committee on Information technology and Liberties (CNIL, Commission Nationale de l'Informatique et des Libertés, Paris).

RESULTS

A total of 1332 patients with dementia were included, 919 women (69.0%) and 413 men (31.0%). Mean age was 82.0 ± 8.0 years (46–108) (women: 83.1 ± 7.9 years; men: 79.7 ± 7.8 years, $p < 0.0001$); 1280 (96.1%) subjects were aged 65 years and more. The recruitment complied with the random selection planned in each region: 51.1% of the subjects were living at home, 38.6% in nursing homes and 10.3% in long-term care geriatric units.

Patients with dementia suffered from 4.0 ± 2.4 (0–16) comorbidities; 67.6% of the subjects had a Charlson index below 2. Patients living at home suffered from 3.6 ± 2.2 comorbidities and institutionalized patients from 4.4 ± 2.5 comorbidities. Overall, 50.1% of the patients suffered from hypertension, 50.9% from renal failure, 37.3% from diabetes and 25.6% from depression (Table 1).

The distribution of dementia was as follows: AD (65.5%), mixed dementia (14.8%), vascular dementia (7.1%), dementia with Lewy bodies (4.4%), fronto-temporal dementia (3.9%) and other dementia (4.3%). In 78.7% of the cases, dementia had been evolving for at least 5 years. Mean MMSE was 15.3 ± 7.2 (women: 14.7 ± 7.1, men: 15.6 ± 7.2, $p < 0.0001$). When considering the severity of the disease, 25.3% of the patients suffered from mild dementia, 53.7% from moderate dementia and 21.0% from severe dementia. Lastly, 32.9% of the subjects in institutions versus 12.4% at home suffered from severe dementia.

The mean number of medications was 6.3 ± 3.1 (0–18) and 5.5 ± 3.1 after excluding medications for dementia. Polymedication (≥5 drugs) was encountered in 928 patients (69.7%). Overall, 885 (66.4%) subjects had 1067 medications for their dementia. Donepezil was the most often prescribed ChEI (276 prescriptions), followed by rivastigmine (240 prescriptions) and galantamine (177 prescriptions). Memantine was prescribed as a single drug in 190 patients, and together with a ChEI in 182 patients (76 times with donepezil, 57 with

Table 1. Description of comorbidities in patients with Alzheimer's disease and related dementia (1332 patients, 5306 comorbidities)

Medical history (MedDRA SOC) $N = 5306$	Number *n* (%)
Vascular disorders	857 (16.2)
Renal and urinary disorders	827 (15.6)
Metabolism and nutrition disorders	784 (14.8)
Cardiac disorders	546 (10.3)
Psychiatric disorders	412 (7.8)
Musculoskeletal and connective tissue disorders	311 (5.9)
Eye disorders	277 (5.2)
Nervous system disorders	244 (4.6)
Gastrointestinal disorders	188 (3.5)
Endocrine disorders	153 (2.9)
Respiratory, thoracic and mediastinal disorders	137 (2.6)
Other	570 (10.7)

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rivastigmine, 49 with galantamine). Two patients used trazodone within a temporary authorization utilization scheme.

Four pharmaco-therapeutic classes involved 88% of the medications used (Table 2). The most common classes used were nervous system drugs (excluding dementia medications) (33.8%), cardio-vascular drugs (23.3%) (with 50.1% of these drugs exerting vasodilator properties [C03 diuretics, C04 peripheral vasodilators, C08 calcium channel blockers, C09 drugs acting on the renin–angiotensin system]), gastro-intestinal and metabolic drugs (20.6%), haematology drugs (10.1%).

The pharmacovigilance centres altogether collected 100 SAR. Following the independent committee analysis, 69 were confirmed as ADR in 67 patients. The prevalence of ADR in the population, whatever their severity, was 5.0% (95%CI: 3.9%–6.2%). This prevalence was not significantly different between institutionalized subjects and those living at home (OR = 0.79 [CI95%: 0.48–1.29], $p = 0.35$) (Table 3). No significant risk factors were identified with the logistic regression analysis adjusted on age, categories of dementia, Charlson index and polymedication.

Among the 69 ADR, 22 (31.9%) were serious, and 33 (47.8%) were preventable. Most frequent ADRs involved the gastro-intestinal tract (23.2%), nervous system (17.4%) and psychiatric field (8.7%); these ADRs were most often not serious (Table 4). After a 15-day follow-up, ADRs were not resolved in half of the cases (50.7%), 34.8% of the patients were cured, and in the other cases, the outcome was unknown.

Overall, 121 medications were involved (Table 2). The most common drugs were medications for dementia (35, i.e. 28.9% of the drugs inducing ADR), cardio-vascular drugs (29, 24.0%), antipsychotics (11, 9.1%), antidepressants (9, 7.4%), anxiolytics (8, 6.6%), antithrombotics (6, 5.0%) and hypnotics (3, 2.5%). The frequency of ADR induced by nervous system medications was lower (0.03%) than that with cardiovascular drugs (1.7%). Within the nervous system medications, this frequency was the highest with antipsychotics (4.0%) followed by antidementia drugs (3.3%) (Table 2). Among the medications for dementia, donepezil and rivastigmine were involved 11 times each, galantamine five times, memantine seven times and trazodone once. Medications for dementia induced digestive disorders (13 cases), neurologic and psychiatric disorders (9), and cutaneous intolerance with rivastigmine patches (6).

Table 5 shows the drug–drug interactions involved in 13 ADR (nine severe ADR and nine preventable ones). In 10 out of 13 cases, the association of several drugs with hypotensive properties or altering vigilance led to hypotension and falls.

DISCUSSION

In this study, the prevalence of ADR in the French population suffering from AD and related dementia was 5.0% (95%CI: 3.9%–6.2%). To our knowledge, this is the first national study that evaluates the occurrence of ADR—whatever the medications—in an essentially geriatric population composed of ambulatory and institutionalized patients with dementia. The prevalence of ADR in old people ranges from 5% to 20% according to the recruitment place.[8] In Italy, this prevalence in patients with cognitive impairment admitted to geriatric and internal medicine wards was 4.8% during hospital stay.[14] In another study, 9.9% of patients with dementia or mild cognitive impairment attending dementia clinics in Toronto (Canada) suffered from ADR within 6 months after the initial clinical interview.[15] This ADR occurrence was an important problem as these ADRs were serious in one-third of the cases and potentially preventable in half of the cases. These results are consistent with a previous study in which the drugs used by patients with AD were involved in 25% of emergency hospitalizations.[16] In another cohort of patients with cognitive impairment, 37% of hospitalizations were related to ADR, half of which were preventable.[17]

In fact, considering cognitive function as a risk factor for ADR occurrence remains a debatable subject. Some studies showed that the risk of ADR increased with greater cognitive impairment (lower MMSE score),[15,25] whereas others showed that cognitive impairment was associated with a reduced risk of ADR (but this may have been confounded by age).[14] This discrepancy can be explained by the detection methods and the different patterns of ADR. Physicians at times struggle to identify ADR in patients with dementia as these patients find it difficult to express the symptoms they feel or to remember certain details. Symptomatic disorders (e.g. gastro-intestinal discomfort) are seldom reported by patients with cognitive impairment.[26] Doctors may also find it difficult to distinguish between an ADR and a clinical comorbidity in a patient with dementia.[14] Moreover, it seems that these patients do not benefit from a close enough clinical and biological monitoring. So, a lack of ADR follow-up by the medical staff is often encountered.[27]

This study showed that ChEI and memantine were the medications most often involved in the occurrence of ADR (28.9% of the drugs inducing ADR). The ADR were essentially not serious, such as gastro-intestinal discomfort or cutaneous reactions with rivastigmine patches. This high ADR number related to dementia medications could be explained by the number of patients using this treatment. The benefit/risk ratio of these drugs

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Table 2. Description of drugs used by 1332 patients with Alzheimer's disease and related dementia and drugs involved in ADRs

ATC classification	Number of drugs (*n*, % of the overall number of drugs)	Number involved in ADRs (*n*, % in the category)
A. Alimentary tract and metabolism	1504 (20.6%)	7 (0.5%)
A02. Drugs for acid related disorders	327	1 (0.3%)
A03. Drugs for functional gastrointestinal disorders	71	
A06. Laxatives	434	3 (0.7%)
A10. Drugs used in diabetes	213	2 (0.9%)
A11. Vitamins	105	
A12. Mineral supplements	293	
Others	61	1
B. Blood and blood forming organs	735 (10.1%)	7 (1.0%)
B01. Antithrombotic agents	582	6 (1.0%)
Others	153	1 (0.6%)
C. Cardiovascular system	1698 (23.3%)	29 (1.7%)
C01. Cardiac therapy	258	5 (1.9%)
C02.Antihypertensives	28	1 (3.6%)
C03. Diuretics	220	4 (1.8%)
C04. Peripheral vasodilators	29	
C07. Beta blocking agents	227	5 (2.2%)
C08. Calcium channel blockers	219	3 (1.4%)
C09. Agents acting on the Renin-Angiotensin system	382	7 (1.8%)
C10. Lipid modifying agents	301	4 (1.3%)
Others	34	
D. Dermatologicals	61 (0.8%)	
D01. Antifungals for dermatological use	20	
D02. Emollients and protectives	31	
Others	10	
G. Genito-urinary system and sex hormones	146 (2.0%)	1 (0.7%)
G04. Urologicals	132	1 (0.8%)
Others	14	
H. Systemic hormonal preparations	162 (2.2%)	1 (0.06%)
H02. Corticosteroids for Systemic use	32	1 (3.1%)
H03. Thyroid therapy	127	
Others	3	
J. Anti-infectives for systemic use	49 (0.7%)	2 (4.0%)
J01. Antibacterials for systemic use	44	2 (4.5%)
Others	5	
L. Antineoplastic and immune-modulating agents	26 (0.4%)	
M. Musculo-skeletal system	178 (2.4%)	1 (0.06%)
M01. Antiinflammatory and antirheumatic products	32	
M04. Antigout preparations	29	
M05. Drugs for treatment of bone diseases	97	1 (1.0%)
Others	20	
N. Nervous system	2469 (33.9%)	72 (0.03%)
N02. Analgesics	428	3 (0.7%)
N03. Antiepileptics	177	3 (1.7%)
N04. Anti-Parkinson drugs	131	
N05. Psycholeptics	1040	22 (2.1%)
N05A. Antipsychotics	274	11 (4.0%)
N05B.Anxiolytics	538	8 (1.5%)
N05C.Hypnotics	228	3 (1.3%)
N06. Psychoanaleptics	1674	44 (2.6%)
*Antidementia**	1067	35 (3.3%)
N06A. Antidepressants	607	9 (1.5%)
Others	23	
P. Anti-parasitic products, insecticides and repellents	2 (0.0%)	
R. Respiratory system	146 (2.0%)	1 (0.7%)
R03. Drugs for obstructive airway diseases	83	
R06. Antihistamines for system use	51	1 (2.0%)
Others	12	
S. Sensory organs	109 (1.5%)	

(*Continues*)

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Table 2. (Continued)

ATC classification	Number of drugs (*n*, % of the overall number of drugs)	Number involved in ADRs (*n*, % in the category)
S01.Ophtalmologicals	109	
V. Various	8 (0.1%)	
Total	**7293**	**121**

: Antidementia drugs (N06DA02 donepezil, N06DA03 rivastigmine, NO6DA04 galantamine, N06DX05 trazodone).

is currently under debate but still considered favourable. In our personal experience, attempts to interrupt the administration of these drugs resulted rapidly in a marked behaviour deterioration that needed a resumption of the treatment. Accumulating evidence shows that they reduce cognition decline, improve daily function and delay institution placement with a relatively good safety profile.[28] So, the use of dementia medications remains justified.

Within the nervous system medications, the ADR frequency was the highest with antipsychotics (4.0%) followed by antidementia drugs (3.3%). Antipsychotics were involved in the occurrence of falls, of neurologic and psychiatric disorders. This result is not surprising; this is a recurrent problem, which makes the management of neuropsychiatric symptoms in subjects with dementia fairly complex. Guidelines helping physicians in the management of agitation and aggression are available.[29,30] According to these guidelines, the use of antipsychotic medications should be limited to short-term treatment (up to 12 weeks) of severe neuropsychiatric symptoms to limit harm. The benefits of an antipsychotic treatment for more than 12 weeks are not clearly demonstrated. Recent evidence supporting non-pharmacological approaches allows proposing a less harmful strategy as first-line management.[30–32]

Several drug–drug interactions occurred when drugs with or without different indications partly shared a common mechanism or led to common ADR (bradycardia, hypotension with a beta-blocker and a ChEI, fall with antihypertension drugs and a psycholeptic). These associations were potentially dangerous in frail elderly patients needing cardiovascular drugs but unfortunately receiving psychotropic drugs in an inappropriate way.

Table 3. Variables associated with ADR in patients with dementia in bivariate and multivariate analysis

Variables	ADR frequency (%)	Bivariate analysis		Final model*	
		OR (CI 95%)	*p*-value	OR adjusted (CI 95%)	*p*-value
Gender (*n* = 1332)					
Male (*n* = 413)	5.57	1			
Female (*n* = 919)	4.79	0.85 (0.51–1.43)	0.55		
Age (years) (*n* = 1332)					
<65 (*n* = 52)	9.62	1		1	
65–80 (*n* = 423)	4.49	0.44 (0.16–1.24)	0.12	0.37 (0.13–1.05)	0.06
>80 (*n* = 857)	5.02	0.47 (0.19–1.31)	0.16	0.36 (0.13–0.99)	0.05
Habitus (*n* = 1332)					
At home (*n* = 681)	5.58	1			
Institution (*n* = 651)	4.45	0.79 (0.48–1.29)	0.35		
Dementia status (*n* = 1144)					
Mild (*n* = 289)	5.88	1			
Moderate (*n* = 614)	4.40	0.74 (0.39–1.37)	0.33		
Severe (*n* = 241)	5.81	0.99 (0.48–2.05)	0.97		
Categories of dementia (*n* = 1248)					
Others (*n* = 431)	4.18	1		1	
AD (*n* = 817)	5.88	1.43 (0.82–2.49)	0.20	1.63 (0.92–2.87)	0.09
Charlson Index (*n* = 1332)					
≤2 (*n* = 901)	4.44	1		1	
>2 (*n* = 431)	6.26	1.44 (0.87–2.38)	0.16	1.58 (0.93–2.70)	0.09
Renal status (*n* = 986)					
Normal to mild (*n* = 307)	4.56	1			
Moderate to terminal (*n* = 679)	5.74	1.27 (0.68–2.38)	0.45		
Polymedication (*n* = 1332)					
<5 (*n* = 404)	3.47	1		1	
≥5(*n* = 928)	5.71	1.69 (0.93–3.08)	0.09	1.74 (0.93–3.27)	0.08

*Multivariate analysis initially included the following factors: age, categories of dementia, Charlson index, polymedication.

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Table 4. Description of ADR in patients with Alzheimer's disease and related dementia ($n = 69$)

ADR (MedDRA SOC)	Serious ADR ($n = 22$)	Not serious ADR ($n = 47$)	ADR number ($n = 69$)	ADR %
Gastro-intestinal	0	16	16	23.2
Nervous system	3	9	12	17.4
Injury, poisoning and procedural complications	7	1	8	11.6
Psychiatric	1	5	6	8.7
General and administration site disorders	0	6	6	8.7
Vascular	4	2	6	8.7
Metabolism and nutrition	1	2	3	4.3
Investigations	1	1	2	2.9
Endocrine	2	0	2	2.9
Renal and urinary	1	1	2	2.9
Respiratory, thoracic and mediastinal	0	2	2	2.9
Ocular	1	0	1	1.4
Cardiac	1	0	1	1.4
Reproduction and breast	0	1	1	1.4
Musculoskeletal and connective tissue	0	1	1	1.4

Such associations are often forgotten or their seriousness is underestimated. They require to be seriously considered according to the clinical conditions of the patients and to be closely monitored.

This multicentre study presents some peculiarities with its strengths and limits. Our results have the advantage of evaluating ADR in a national sample of the population of patients with dementia. The inclusion of patients was carried out on a given day using a random process in medical structures likely to receive these categories of patients. In our study, established from a representative selection of patients and structures regarding the usual dwelling of these patients with dementia, 51.1% were living at home and 48.8% were institutionalized. This distribution differs from that identified in a previous 2005 report showing that 60% of French subjects with dementia were living at home.[4] However, the proportion of people $\geq$65 years (96.1%), the dementia type (61.3% with AD) and the seriousness of dementia in patients living in institutions (31.9%) are characteristics of a population with dementia.[33] Because of the selection process, the results presented here in 1332 patients can reasonably be extrapolated to the whole French old population suffering from dementia.

The prevalence of ADR may have been underestimated as ADRs without clinical signs (e.g. biological abnormality, ECG abnormality, etc.) were not identified on the day of the survey. This under detection was kept to a minimum in our study because the identification and collection of SAR was carried out by the pharmacovigilance staff used to the complexity of adverse effects.

Causality assessment was conducted by an independent committee. This committee rejected 30% of the reported SAR. The main reasons were the occurrence of SAR out of the time window allocated or the lack of sufficient data in the medical file preventing a sound causality analysis. Unfortunately, clinical and therapeutic data encountered in the patient files were of mixed quality. Despite this limitation, the distribution of comorbidities and of treatments in these patients with dementia was coherent with previously published data.[33] The discrepancy between the evaluation of the pharmacovigilance staff and that of the independent committee could be explained by the different points of view they considered. The expert committee tended to keep to a minimum the involvement of drugs in the clinical conditions encountered as they put forward the clinical condition

Table 5. Drug–drug interactions involved in ADR according to severity and preventability

Drugs	ADR	Severity	Preventability
Amoxicilline/clavulanic acid + ciprofloxacine + macrogol 4000	Diarrhea	Mild	Potentially preventable
Valsartan/hydrochlorothiazide + atenolol	Hypotension	Mild	Not assessable but potentially preventable
Insuline + metformine + benazepril	Hypoglycemia	Mild	Potentially preventable
Clopidogrel + acetylsalicylic acid	Hematoma	Mild	Not assessable
Acebutolol + furosemide + zopiclone + clonazepam	Fall	Severe	Preventable
Donepezil + bisoprolol	Bradycardia	Severe	Potentially preventable
Atenolol + nicorandil + doxazosine	Hypotension	Severe	Potentially preventable
Bromazepam + furosemide + escitalopram	Fall	Severe	Preventable
Bisoprolol + galantamine + venlafaxine	Hypotension	Severe	Not assessable but potentially preventable
Haloperidol + zopiclone + oxazepam	Fall	Severe	Potentially preventable
Amitriptyline + risperidone + lorazepam + zopiclone	Drowsiness	Severe	Preventable
Furosemide + enalapril	Hypotension	Severe	Potentially preventable
Lercanidipine + valsartan/hydrochlorothiazide + urapidil	Hypotension	Severe	Preventable

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(history and present status of the disease). This would tend to underestimate the prevalence of ADRs. On the contrary, members of the pharmacovigilance centres tended to look for a drug origin in whatever clinical deterioration, provided that there was a reasonable explanation in the causality assessment process. So, the pharmacovigilance point of view would tend to overestimate the prevalence of ADR. Consequently, the two approaches that we used tended to guaranty the highest objectivity in the assessment of any causal link between a drug and an adverse event (AE).

We were not able to include old people with AD living at home for practical reasons. However, we assumed that a fairly good reflection of these patients could be achieved through the patients attending the outpatient clinics. This inclusion process may have selected patients with a more serious condition, seeking medical advice and receiving more drugs. Consequently, this may have tended to increase the prevalence of AE but probably not decrease it.

CONCLUSION

This pharmacovigilance study describes the pattern of ADR in patients with AD and related dementia. The ADRs were at times serious but preventable. Therefore, special attention is required when prescribing anti-dementia and antipsychotic drugs, as they are frequently used and induce half of the ADR in this population. Anti-dementia drugs are still needed by these patients and often involved in non-serious ADR. Antipsychotic drugs, which are frequently encountered, are important suppliers of preventable ADR; their use is questionable and should prompt physicians to also consider non-pharmacological therapies.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

KEY POINTS

- Few studies have evaluated the pattern of adverse drug reactions (ADR) in patients with Alzheimer's disease and related dementia.
- The prevalence of ADR in patients with dementia was estimated 5.0% (95% CI: 3.9–6.2).
- Anti-dementia and antipsychotic drugs induced half of the ADR in this population; most of them were preventable.

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