Eur J Clin Pharmacol
DOI 10.1007/s00228-013-1506-8

PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

Potentially inappropriate medication use among patients with Alzheimer disease in the REAL.FR cohort: be aware of atropinic and benzodiazepine drugs!

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Received: 7 November 2012 / Accepted: 18 March 2013

Abstract
Objective Few studies have investigated potentially inappropriate medication (PIM) use in patients with Alzheimer's disease (AD). The aim of our study was to assess the prevalence of PIM in community-dwelling patients diagnosed with mild-to-moderate AD and identify the clinical factors associated with PIM prescriptions.
Methods REAL.FR is a 4-year, prospective, multicenter French cohort of AD patients recruited in centers of expertise. We analyzed patient baseline data at entry into the study. PIMs were assessed using the Laroche list. A multivariate logistic regression was conducted to assess factors associated with PIMs.
Results A total of 684 AD patients were enrolled in the study [mean age 77.9±6.8 years, 486 (71.0 %) females]. According to the Laroche list, 46.8 % [95 % confidence interval (CI) 43.0–50.5 %] of the patients had at least one PIM. "Cerebral vasodilators" were the most widely used class of PIM, accounting for 24.0 % (95 % CI 20.9–27.3 %) of all prescriptions, followed by atropinic drugs (17.0 %, 95 % CI 14.1–19.8 %) and long half-life benzodiazepines (8.5 %, 95 % CI 6.4–10.6 %). Atropinic drugs were associated with cholinesterase inhibitors in 16 % of patients. In the multivariate analysis, only two factors, namely, female gender [odds ratio (OR) 1.5, 95 % CI 1.1–2.2] and polypharmacy (≥5 drugs; OR 3.6, 95 % CI 2.6–4.5) were associated with prescriptions for PIMs.
Conclusions These results reveal that approximately one out of two community-dwelling patients with mild-to-moderate AD treated by AD specialists use PIMs. They also indicate that the characteristics of the disease and the pharmacodynamic/pharmacokinetic profile of the drugs prescribed are not sufficiently taken into account by physicians when prescribing for AD patients.

Keywords Alzheimer's disease · Potentially inappropriate medications · Atropinic drugs · Benzodiazepines

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Published online: 16 April 2013

Introduction

Elderly patients are major drug consumers, and polypharmacy is commonly defined as an indicator of adverse drug reactions (ADRs) [1]. The prevalence of ADRs in the Alzheimer's disease (AD) population is estimated to be between 5 and 10 % [2, 3], and cognitive impairment seems to be a risk factor for ADRs [4].

The quality of prescriptions among elderly people has been often studied, and several lists of potentially inappropriate medications (PIMs) have emerged [5–8]. A PIM is defined as a drug "with an unfavourable benefit-to-risk ratio when safer or equally effective alternatives are available" [7]. However, although several studies on PIM use in the elderly have been published, few of these focused on patients with AD. Most of the studies investigating prescribing practices in AD were performed in America where the healthcare policy and cultural background context, as well as the PIM lists, widely differ from European ones [8–11]. Moreover, few have also investigated factors potentially associated to PIMs.

The aim of this study was to assess the prevalence of PIM use in community-dwelling patients with mild to moderate AD (main objective) and to identify factors associated with such prescriptions.

Methods

Study design and participants

We used the baseline data of the French cohort REAL.FR of AD patients. This 4-year prospective cohort has been previously described in an earlier study [12]. From 2000 to 2002, it included subjects with DSM-IV and NINCDS-ADRDA criteria for Alzheimer-type dementia at mild to moderate stage [Mini-Mental State Examination (MMSE) score ranging from 10 to 26]. Participants were living at home and cared for by an informal caregiver. They were recruited for the study during consultation in a university hospital-based network of AD expert centers (neurology, geriatrics or psychiatry). Before inclusion, patients were followed either by general practitioners (GPs) or specialists. Informed consent was obtained from all patients and caregivers.

Data collection

Each participant underwent a comprehensive assessment that included a neuropsychological evaluation. The following parameters were recorded: sociodemographic characteristics (age, gender, and educational level), medical and surgical history, medico-social assistance (home help, nurse), expert centers (neuropsychiatric, geriatric), physical disability using both the Activities of Daily Living (ADL) scale and Instrumental Activities of Daily Living scale [13, 14], cognitive function relying on both the MMSE and Alzheimer's Disease Assessment Scale-cognitive components [15], severity of dementia using both the Reisberg GDS scale and Clinical Dementia Rating scale [16], nutritional status with the Mini Nutritional Assessment (MNA) [17], and NeuroPsychiatric Inventory (NPI) [18]. Questions on medical and social assistance were also included. Caregiver burden was assessed using the Zarit scale [19].

Medications prescribed by GPs or specialists, as well as over-the-counter drugs, were recorded based on caregiver reports and bought prescriptions when possible. Drugs were classified according to the Anatomical Therapeutic Chemical classification [20]. Polypharmacy was defined as five or more medications [21, 22]. The total number of drugs refers to all drugs, including PIMs and specific medication(s) for AD.

PIM use

Potentially inappropriate medications were identified using the 2007 Laroche list [7]. A PIM user was defined as a patient for whom at least one PIM was reported (dichotomous variable). This list is composed of 34 criteria divided into three groups: (1) drugs with an unfavorable benefit to risk ratio [25 criteria, such as atropinic (antimuscarinic), long half-life benzodiazepine, centrally antihypertensive, stimulant laxative drugs…), (2) drugs with questionable efficacy (1 criterium; for example, cerebral vasodilators such as ergot derivatives, ginkgo-biloba, nicergoline, piribedil, piracetam, vincamine…), and (3) drugs with both an unfavorable benefit to risk ratio and a questionable efficacy (8 criteria; for example, meprobamate, dipyridamole, nitrofurantoin, and associations of two or more psychotropic drugs from the same therapeutic class or anticholinesterase + atropinic drugs). Criteria involving a particular clinical situation (criteria 21–25) and those based on the dose were not considered (criteria 14, 27), as the database did not contain these data.

We also created another class merging all drugs with atropinic properties. Our list of atropinic drugs was established through an expert consensus of three experts (FM, VG, JLM) among the authors. These experts included in the whole final list of atropinic drugs all drugs described in Laroche's [7], La Revue Prescrire's [23] and the Anticholinergic Cognitive Burden Scale's [24, 25] lists. Table 1 describes the different atropinic drugs included in the study. Non-phenothiazine neuroleptics (olanzapine, clozapine) and paroxetine, all atropinic drugs, were included in the study but are not listed in Laroche's list.

Table 1 List of atropinic drugs[a]

Atropinic (INN) or atropinic class
Imipraminic antidepressants
Phenothiazine neuroleptics
Atropinic hypnotics
Atropinic H1 antihistamines
Atropinic antispasmodics (urinary, gastrointestinal)
Others atropinics (metopimazine, promethazine, buclizine…)
Memantine
Atropine
Carbamazepine
Neuroleptics (clozapine, olanzapine, quetiapine)
Paroxetine
Atropinic antiparkinsonians (trihexyphenidyle…)

INN, International nonproprietary names

[a] The list was established using data contained in Laroche [7], La Revue Prescrire [23] and the Anticholinergic Cognitive Burden Scale (ACBS) 2011 [24, 25]

To compare our results with data from studies performed in the USA, we also identified PIM through the 2003 Fick and Beers' list [26]. Criteria involving a special clinical situation and those based on the dose were not considered.

Statistical analysis

Descriptive analyses of the population are presented as the mean value ± standard deviation (SD) and quantitative and qualitative variables as proportions.

We first conducted a bivariate analysis using Pearson's χ^2 test or Fisher's exact test for theoretical numbers of <5 for qualitative variables and Student's *t* test or Mann–Whitney parametric test for quantitative variables. A backward multivariate logistic regression analysis was performed to determine factors associated with PIM use using adjusted odds ratios (OR) and their 95 % confidence intervals (CI). Independent variables associated with a *p* value of <0.20 in the bivariate analysis and known confounding factors, whatever their significance level, were included in the initial model. The following factors were therefore included in the model: gender, monthly household income (Euros), education level, dementia status (MMSE score), polypharmacy (≥5 drugs), functional status (ADL score), behavioral and psychological symptoms (NPI score) and nutritional status (MNA score). Statistical interactions were verified in the final model. The goodness of fit of the final model was assessed using the Hosmer and Lemeshow test. The level of significance was set at 0.05 (2-sided) and all analyses were conducted using STATA software ver. 11 [27].

Results

Characteristics of the population

The baseline characteristics of the patients are shown in Table 2. After exclusion of two patients due to lack of information about their drug treatment, 684 subjects were included in this analysis [mean age 77.9±6.8 years, 486 (71.0 %) females]. The range in the MMSE score of these patients was: between 26–21 in 50.1 %, 20–16 in 32.7 %, and 15–10 in 17.2 %. Eighty-nine percent of the patients were treated with cholinesterase inhibitors (63.4 % with donepezil, 24.0 % with rivastigmine, 2.2 % with galantamine). Sixty-three patients received only one cholinesterase inhibitor without any other associated drug. None of the patients received memantine since this drug was not licensed during this period. Only five patients had zero medications. Forty-six percent of the patients required assistance with activities of daily living, and 26 % lived alone at home. Over half of the patients (51.8 %) had a monthly income of more than 1,500 Euros and most of them (84 %) were followed in geriatric centers. High-level polypharmacy (≥5 medications) was identified in 43.0 % of patients.

Potentially inappropriate medications

According to the Laroche list, 320 patients (46.8 %; 95 % CI 43.0–50.5 %) had at least one PIM. Based on Beers criteria, 173 (25.3 %; 95 % CI 22.0–28.6) patients were PIM users. Among the 320 patients who received at least one PIM according to Laroche, 102 (14.9 % of study population) were also identified as PIM users according to Beers list (Kappa=0.12). Based on the combined Laroche and Beers criteria, 293 patients (42.8 %) received no PIM.

Figure 1 shows an increasing trend in prevalence of PIM users up to five prescribed drugs. Beyond five medications (polypharmacy), the prevalence of PIM users remains stable at around 60 % (except for 12 prescribed drugs).

Table 3 shows the distribution of the PIM pharmacological classes. The drugs which were most commonly prescribed fell into one of three drug classes: "cerebral vasodilators" (*n*=165/684 patients; 24.1 %; 95 % CI 20.9–27.3 %), atropinic drugs (*n*=116/684; 17.0 %; 95 % CI 14.1–19.8 %), and long half-life benzodiazepines (*n*=58/684; 8.5 %; 95 % CI 6.4–10.6 %). Among the atropinic drugs non-listed in the Laroche list, we found four and 72 patients who had been prescribed non-phenothiazine neuroleptics and paroxetine, respectively. In addition, inappropriate antihypertensive drugs were identified in 6.0 % of patients (*n*=41/684; 95 % CI 4.1–7.7 %) and H1 antihistamines in 2.2 % (*n*=15/684; 95 % CI 1.1–3.3 %). Prevalence of atropinic, benzodiazepine, antidepressant and nonsteroidal anti-inflammatory drug associations was 1.2, 1.9, 0.7,

Table 2 Medical and sociodemographic characteristics of the study population (n=684)

Population characteristics[a]	Values
Female gender (n=684)	486 (71.1)
Age class (n=684)	
50–75 years	232 (33.9)
76–85 years	357 (52.2)
>85 years	95 (13.9)
Anticholinesterase inhibitors (n=684)	610 (89.2)
Donepezil	431 (63.0)
Rivastigmine	164 (24.0)
Galantamine	15 (2.2)
Previous history of depression (n=599)	223 (37.2)
ADL score (≥1 incapacity) (n=684)	312 (45.6)
Polypharmacy (≥5) (n=684)	299 (43.7)
Medico-social assistance	
Home help (n=678)	300 (44.3)
Nurse (n=661)	43 (6.5)
Living arrangement (n=684)	
Home with spouse	403 (58.9)
Home alone	180 (26.3)
Home with family	80 (11.7)
Group home/other	21 (3.2)
Monthly household income (€) (n=680)	
<1500	328 (48.2)
1,500–2287	161 (23.7)
>2,287	191 (28.1)
Education level (n=679)	
Primary or no education	145 (21.3)
Completed primary school	246 (36.2)
Secondary school	129 (19.0)
High school, technical school	159 (23.5)
Centers (n=684)	
Neuropsychiatric	112 (16.4)
Geriatric	572 (83.6)
Age distribution (years) (n=684)	77.86±6.8
Number of drugs (with ChEI) (n=684)	4.36±2.3
MMSE score (range 26–10) (n=682)	20.00±4.2
ADL score (range 0–6) (n=684)	5.43±0.9
NPI score (range 0–144) (n=681)	15.32±15.3
ZARIT score (range 0–88) (n=636)	22.61±15.9
CDR score (range 0–3) (n=680)	1.09±0.6
MNA score (range 0–30)	23.92±3.2

ADL, Activities of daily living (coded "0" for no incapacity, "1" for at least one incapacity); MMSE, Mini-Mental State Examination; NPI, neuropsychiatric inventory; ZARIT, caregiver burden; CDR, clinical dementia rating; MNA, Mini Nutritional Assessment; ChEI, cholinesterase inhibitors

Data are presented as the number (of patients) with the percentage in parenthesis, or as the mean ± standard deviation (SD), as indicated

[a] Numbers in parenthesis represent the total number of data sets (taking into account missing values)

and 0.3 %, respectively. No neuroleptic association was found.

Sixteen percent (95 % CI 12.9–18.4 %) of patients concomitantly received drugs with atropinic properties and cholinesterase inhibitors.

Associated factors to PIM

Bivariate analysis of the social and clinical features associated with PIM prescription is reported in Table 4. The multivariate analysis initially included the following factors: gender, monthly household income (Euros), education level, dementia status (MMSE score), polypharmacy (≥5 medications), ADL score, NPI score and MNA score. After backward logistic regression, only female gender (OR 1.5; 95 % CI 1.1–2.2) and polypharmacy (OR 3.6; 95 % CI 2.6–4.5) were associated with PIM use.

It is interesting to note that another model of multivariate analysis that included the same factors as above + age led to the same conclusions (data not shown). Thus, age was not associated with PIM use. We emphasize the lack of interactions between the variables age and gender.

Finally, sensitivity analyses on the final model did not change the values of associations. In particular, dementia severity (MMSE score) did not change the effect of associations and was not associated with PIM prescription.

Discussion

The aim of our study was to investigate the prevalence of PIM use in community-dwelling patients with mild to moderate AD and to identify factors associated with these prescriptions. Little data at the European level is currently available on this important topic of everyday prescriptions

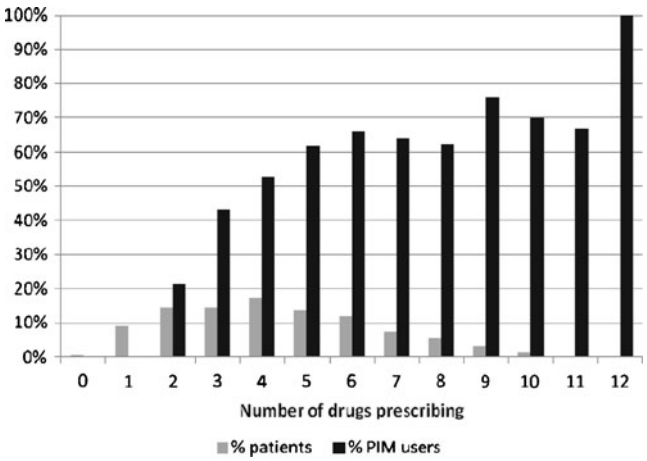

Fig. 1 Prevalence of potentially inappropriate medication (PIM) use according to the total number of drugs prescribed to patients in the REAL.FR baseline (n=684)

Table 3 Prevalence of potentially inappropriate medications according to the 2007 Laroche list at baseline in the REAL.FR[a]

PIM criteria	Pharmacology classes	Number of patients	Percentage (n=684)
Unfavorable benefit/risk balance			
Analgesics	Indometacin	1	0.1
	Phenylbutazone	0	0
	Association at least 2 NSAIDs	2	0.3
Drugs with atropinic properties	Imipraminic antidepressants	5	0.7
	Phenothiazines neuroleptics	4	0.6
	Atropinic hypnotics	1	0.1
	H1 antihistamines	15	2.2
	Antispasmodics and muscle relaxants	10	1.5
Sedatives, hypnotics	Benzodiazepines and benzodiazepine-like drugs with long half-life	58	8.5
Antihypertensives	Centrally acting antihypertensives	21	3.1
	Short-acting calcium-channel inhibitors	20	2.9
	Reserpine	0	
Antiarrhythmics	Disopyramide	2	0.3
Antiplatelet drugs	Ticlopidine	4	0.6
Gastrointestinal drugs	Cimetidine and Laxative drugs	0	0
Oral antidiabetics	Long-acting sulfonylureas	0	0
Other muscle relaxants non atropinic	Muscle relaxants	1	0.1
Questionable efficacy			
Cerebral vasodilators (dihydroergotamine, vincamine, ginkgo biloba, piribedil…)		165	24.1
Unfavorable benefit/risk balance and questionable efficacy			
Gastrointestinal drugs	Meprobamate	0	0
	Atropinic antispasmodic drugs	3	0.4
Other drugs with atropinic properties	Antiemetics, antidrowsiness, nasal decongestants, cough suppressants, etc.	12	1.7
Antiplatelet drugs	Dipyridamole	7	1
Antimicrobial	Nitrofurantoin	1	0.1
Association drugs	Two or more benzodiazepine drugs	13	1.9
	Two or more neuroleptic drugs	0	
	Two or more antidepressant drugs	5	0.7
Other criteria	Drugs with atropinic properties	116	17.0
	Including atropinic neuroleptics	8	1.2
	Two or more drugs with atropinic properties	8	1.2
	Association between drugs with atropinic properties and cholinesterase inhibitors	107	15.6

PIM, Potentiallyinappropriate medication

[a] Criteria for a particular clinical situation and those based on the dose were not considered, as the database did not contain these data

in AD patients. Three main results were found: (1) PIMs were prescribed for approximately one out of every two AD patients; (2) Most of the PIMs prescribed for these patients fell into the drug classes of "cerebral vasodilators", atropinic drugs (in association with cholinesterase inhibitors in 16 % of patients) and long half-life benzodiazepines; (3) factors associated with PIM prescription were only female gender and polypharmacy.

With respect to the prevalence of PIM prescriptions, we found that 46.8 % of the community-dwelling patients with mild to moderate AD used PIMs according to the Laroche list (25.3 % according to Beers list). Previous American studies (all using Beers list) found lower rates of PIM use in AD patients. In the cross-sectional study from Lau [9], PIMs were prescribed for about 15 % AD patients. Zuckerman [10] identified 20 and 19 % PIM usage in patients with dementia

Table 4 Variables associated with potentially inappropriate medications in the bivariate and multivariate analysis

Variable[a]	PIM frequency (%)	Bivariate analysis		Final model[b] n=655	
		OR [CI 95 %]	p value	OR [CI 95 %]	p value
Gender (n=684)					
Male (n=198)	40.5	1	0.042	1	0.020
Female (n=486)	49.1	1.4 [1.0–2.0]		1.50 [1.07–2.19]	
Age (years) (n=684)					
50–75 (n=232)	45.3	1	0.848		
76–85 (n=357)	47.6	1.1 [0.8–1.5]			
>85 (n=95)	47.4	1.1 [0.7–1.8]			
Dementia status (n=682) (MMSE score)					
26–21 (n=342)	47.8	1	0.191		
20–16 (n=223)	41.7	0.8 [0.5–1.1]			
15–10 (n=117)	51.3	1.2 [0.7–1.7]			
Polypharmacy (n=684)					
≥5 medications	60.6	3.8 [2.8–5.2]	0.001	3.6 [2.6–4.5]	0.001
ADL score (=312/684)					
0 (incapacity)	41.9	1	0.009		
≥1 (incapacity)	51.9	1.5 [1.1–2.0]			
Social assistance					
Home help (300/678)	48.1	1.1 [0.8–1.5]	0.510		
Nurse (43/661)	55.8	1.5 [0.8–2.8]	0.220		
Living arrangement (n=684)					
Home with spouse (n=403)	44.9	1	0.563		
Home alone (n=180)	50.1	0.8 [0.6–1.3]			
Home with family (n=80)	48.8	0.9 [0.6–1.6]			
Group home/other (n=21)	38.2	0.6 [0.3–1.5]			
Monthly household income (n=680)					
<1,500 (n=328)	50.3	1	0.132		
1,500–2,287 (n=161)	42.2	0.7 [0.5–1.1]			
>2,287 (n=191)	42 .9	0.7 [0.5–1.1]			
Education level (n=679)					
Primary or no education (n=145)	51.0	1	0.082		
Completed primary school (n=246)	50.0	0.9 [0.6–1.5]			
Secondary school (n=129)	45.0	0.8 [0.5–1.3]			
High school, technical school or higher education (n=159)	38.4	0.6 [0.4–0.9]			
NPI (quartile) (n=684)					
0–4 (n=182)	40.7	1	0.193		
5–12 (n=201)	51.8	1.6 [1.0–2.3]			
13–22 (n=140)	47.1	1.3 [0.8–2.0]			
23–144 (n=158)	46.2	1.0 [0.8–1.9]			
ZARIT score (n=636)					
0–20 (n=319)	49.4	1	0.363		
21–40 (n=234)	45.3	0.9 [0.7–1.3]			
41–60 (n=65)	43.1	0.9 [0.5–1.5]			
61–88 (n=18)	66.8	2.3 [0.8–6.3]			
MNA score modified (n=668)					
≤23.5 (n=220)	49.1	1.2 [0.9–1.6]	0.279		
Center (n=684)					
Geriatric (n=572)	46.8	1	0.620		
Neuropsychiatric (n=112)	44.6	0.9 [0.6–1.4]			

OR, Odds ratio; CI, confidence interval

[a] The numbers in parenthesis in the first column represent the total number of data sets (taken into account missing values)

[b] Multivariate analysis initially included the following factors: gender, monthly household income (Euros), education level, dementia status (MMSE score), polypharmacy, ADL score, NPI score and MNA score modified

before and after nursing home admission, respectively. Fick [11] found a 62.2 % prevalence of PIMs over 3 years in community-dwelling older adults with dementia. To our knowledge, our study is one of the first European evaluations of PIM use in a sample of community-dwelling patients with mild to moderate AD. Our population differs from that of the Shelter study [28], another European study, which investigated inappropriate drug use in older nursing home residents with severe cognitive impairment. The authors of the Shelter study used Holmes's list [8] and found very similar results as our study, with 44.9 % of PIMs (mainly lipid-lowering and antiplatelet drugs). All of these results are similar to our findings if the same criteria were to be used to identify PIMs (i.e. Beers list). Using the Laroche list, which is more adapted to our European context, prevalence found for PIMs increased by twofold. Moreover, availability of drugs on the market, prescribers' habits, and health system policy must also be taken into account to explain these differences.

The PIM lists were first adapted to analyze the quality of prescriptions in the elderly in general, and not in the AD patient population in particular. The prevalence of PIM use in the elderly varies from 6 to 70 %, depending on the country studied and the list used [6, 29]. In France, PIM prevalence has been evaluated to range from 33.5 % in community-dwelling settings to 66 % in acute geriatric units [30, 31]. Our study suggests that PIM prevalence in the AD population is quite similar to that observed in the elderly population without AD.

Despite a similar PIM prevalence in the AD population versus elderly people in general, our results indicate that there are some differences in the pharmacotherapeutic PIM classes involved. "Cerebral vasodilator" use (found in 24 % of AD patients) can be considered as a specificity of the French market. In fact, several studies have found that this class of drug is widely prescribed to elderly people in France without any clear pharmacological evidence [32]. Similarly, to date, no well-performed clinical trial has been able to demonstrate any benefit of these cerebral vasodilators in AD patients [33]. It would be interesting to investigate the evolution of these prescriptions in recent years since the French social healthcare system discontinued their reimbursement. Moreover, our results underline the need for French physicians to receive regular pharmacological education on the use of these inappropriate drugs in AD patients.

Another interesting finding of our study concerns the high level (17 %) of atropinic drugs prescribed in AD patients. The use of these drugs is, of course, contraindicated in AD patients since they increase the cortical cholinergic deficit and consequently cognitive impairment in AD patients. They also antagonize the pharmacodynamic effects of cholinesterase inhibitors, which were found to be associated to atropinics in 16 % of our patients. This finding is in agreement with that of a previous study showing that in 11 % of the prescriptions recorded in the French pharmacovigilance database, there was an (illogical) association between atropinic and anticholinesterase drugs [34]. Moreover, recent papers suggest that atropinic drugs could increase the cumulative risk of cognitive impairment and mortality rate in older patients [35]. This result indicates that prescribers (even AD specialists) are poorly aware of the atropinic properties of drugs used in AD, thus justifying, once again, continued pharmacological training.

Our study also found a high prevalence (8.5 %) of prescriptions for long half-life benzodiazepines. Once again, it appears that the pharmacodynamic and pharmacokinetic profiles of these drugs are not really taken into account by physicians. From a pharmacodynamic point of view, the amnesic properties of benzodiazepines may aggravate both AD symptoms and disease evolution [36]. Moreover, recent pharmacoepidemiological studies suggest a negative impact of long-term benzodiazepine use on cognitive functions even in patients without dementia [37, 38]. From a pharmacokinetic point of view, the use of long half-life benzodiazepines by elderly people induces high blood pressure levels, explained by the decrease in renal elimination, leading to an increased risk for ADRs [39].

One of the strengths of our study is the multivariate analysis, which allows associated factors to PIMs to be discussed. In fact, most of the published studies in the field have been performed using bivariate analysis. In our AD cohort, after adjustment for several confounding factors (gender, clinical characteristics, socio-economic status, and number of prescribed drugs which we considered as a proxy for comorbidities), we only found two factors associated with PIM use: polypharmacy and female gender. The results of this logistic regression require three comments. First, polypharmacy is clearly associated to the risk of PIM prescription, as previously described [9, 40, 41]. However, beyond five medications, the increase in prevalence of PIM prescriptions seems to be less important. In our sample, the risk of PIM use increased among women (more than 50 %), and this increased risk could not be explained by an interaction with age. Lau et al. [8] did not report such an association, while Weston et al. [41] found a higher PIM prevalence in women with mild cognitive impairment than in men. These latter authors explained this result by differences in comorbidities (probably higher in women). One could also recall that women (whatever their age or medical conditions) are well known to use more drugs than men [42]. Secondly, dementia status was not associated with PIM use. This unexpected result could be explained by the fact that the underlying disease (AD) and its evolution are not really taken into account by prescribers. Third, it is interesting to

emphasize that the number of associated factors is lower in AD than in elderly people in general for whom, for example, socio-economic factors, living arrangement, and comorbidities were found to be associated [29, 43]. In the Shelter study performed in a different population than the one in our study (elderly patients with severe cognitive impairment), diabetes, heart failure, and recent hospitalization were the three factors associated with PIM use [28]. In contrast, an inverse relation was found between PIMs and presence of a geriatrician in the facility [28]. Unfortunately, it was impossible to investigate this last interesting point in our study due to the characteristics of the patients and the study design. We found that age was not associated to the risk of PIM prescription. Finally, our French multicenter study can be applied to other European countries: in fact, the characteristics of the French cohort REAL.FR and the European ICTUS cohort [44] are similar (gender, age, MMSE score, functional impairment, neuropsychiatric symptoms, social burden…) (ICTUS is a prospective longitudinal observational study including 1,380 AD patients in Europe from 2003 to 2005.)

Several limitations in our study should be discussed. Selection bias could have occurred because recruitment was based on French patients recruited in specialized centers. This study was conducted among ambulatory subjects only, which could limit the generalizability of the results, although patients with mild to moderate dementia are rarely institutionalized in France. Moreover, the conclusions should be limited, because the inclusion of the patients in REAL.FR was performed in 2000–2002, whereas the Laroche PIM list was published in 2007. It could be interesting to repeat our study after a few years in order to investigate putative changes in prescribing behavior regarding, for example, drugs with questionable efficacy (such as "cerebral vasodilators"). Another limitation is the fact that Laroche's list was developed for subjects aged ≥75 years and that, in our study, approximately 34 % of subjects were aged <75 years. Finally, due to the population included in this study, we cannot exclude underreporting (and/or misclassification) of used drugs compared with reports to administrative databases. Nevertheless, our study was based on a large real-life cohort of patients with a standardized diagnosis of AD for whom clinical data were available.

In conclusion, this study shows a high level of PIM prescriptions in mild to moderate community-dwelling AD patients, of which most belonged to the classes of "cerebral vasodilators", atropinic drugs (often in association with cholinesterase inhibitors), and long half-life benzodiazepines. Factors associated with PIM prescription were female gender and number of drugs. The results underline that the characteristics of the disease and the pharmacodynamic and pharmacokinetic profile of drugs used are not sufficiently taken into account by GPs and specialists when prescribing for AD patients.

Acknowledgments This work was supported by a grant from the Clinical Research Hospital Program from the French Ministry of Health (PHRC No. 98-47N/01-010-01).

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Conflict of interest None.

Sponsors and grants None.

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