

Is inappropriate medication use a major cause of adverse drug reactions in the elderly?

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What is already known about this subject

- Several studies have shown that inappropriate medications induce adverse health outcomes in the elderly.
- The hypothesis of Beers *et al.* that these inappropriate medications increase the likelihood of adverse drug reactions is debated and checked in patients admitted to hospital.

What this study adds

- Inappropriate medications do not seem to be the major cause of adverse drug reactions in the elderly.
- More than the inappropriateness of the drugs themselves, it is the inappropriate use of drugs that is to be tackled when treating the elderly.
- The main preventable factor is the reduction in the number of drugs given.

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Aim

To study the occurrence of adverse drug reactions (ADRs) linked to inappropriate medication (IM) use in elderly people admitted to an acute medical geriatric unit.

Methods

All the elderly people aged ≥ 70 years admitted to the acute medical geriatric unit of Limoges University hospital (France) over a 49-month period were included, whatever their medical condition. For all the patients, clinical pharmacologists listed the medications given before admission and identified the possible ADRs. The appropriateness of these medications and the causal relationship between drugs (either appropriate or not) and ADRs were evaluated.

Results

Two thousand and eighteen patients were included. The number of drugs taken was 7.3 ± 3.0 in the patients with ADRs and 6.0 ± 3.0 in those without ADRs ($P < 0.0001$). Sixty-six percent of the patients were given at least one IM prior to admission. ADR prevalence was 20.4% among the 1331 patients using IMs and 16.4% among those using only appropriate drugs ($P < 0.03$). In only 79 of the 1331 IM users (5.9%) were ADRs directly attributable to IMs. The IMs most often involved in patients with ADRs were: anticholinergic antidepressants, cerebral vasodilators, long-acting benzodiazepines and concomitant use of two or more psychotropic drugs from the same therapeutic class. Using multivariate analysis, after adjusting for confounding factors, IM use was not associated with a significant increased risk of ADRs (odds ratio 1.0, 95% confidence interval 0.8, 1.3).

Conclusion

Besides a reduction in the number of drugs given to the elderly, a good prescription should involve a reduction in the proportion of IMs and should take into consideration the frailty of these patients.

Introduction

Adverse drug reactions (ADRs) in older people are a major public health issue. The elderly are more likely to experience ADRs because of age-related changes in the pharmacokinetics and pharmacodynamics of the drugs they are given to treat their multiple pathological conditions. ADRs are up to seven times more frequent in 70–79-year-olds than in those aged 20–29 years [1]. In Europe, 20% of ambulatory elderly people suffer from ADRs; nearly 10–20% of acute geriatric hospital admissions are believed to be drug related [2, 3].

Lindley *et al.* have investigated the relationship between inappropriate medications (IMs) and the occurrence of ADRs and shown that nearly 50% of ADRs were due to drugs that had absolute contraindications and/or were unnecessary [4]. Beers proposed explicit criteria to identify IM use in elderly patients, first in nursing homes and then wherever they lived [5, 6]. These criteria were based on a drug list compiled from reviews of the literature and submitted to a consensus of experts using a modified Delphi technique. Potential IMs were drugs with an unfavourable risk/benefit ratio when safer or equally effective alternatives were available. Thus, it was hypothesized that taking these drugs was a major factor influencing the likelihood of ADR occurrence among the elderly.

Several authors have studied the influence of IM use, as defined by Beers, on health outcomes in the elderly. There seems to exist a positive relationship between IM use on one hand and healthcare costs on the other [7, 8] or use of healthcare services (hospitalizations, in- or outpatient visits, emergency department admissions) [8–11]. Nevertheless the direct influence of IM use on mortality is difficult to assess from the conflicting results published, especially as all adverse health outcomes are not necessarily ADRs [7, 9–14]. Only a few investigators have studied the association between IM use as defined by Beers and the occurrence of ADRs [13, 15]. Onder failed to show any association between IM use and ADRs in hospitalized older adults [13], whereas Chang found a positive association in elderly outpatients on their first visit [15]. However, in these studies neither the involved IMs nor the seriousness of ADRs were detailed.

The aim of the present study was to assess the prevalence of ADRs and describe those ADRs directly linked to IMs among elderly patients admitted to an acute medical geriatric unit.

Methods

Study population

A systematic and prospective drug surveillance study was carried out in the acute geriatric unit of Limoges

University Hospital, France. From January 1994 to April 1996 and from May 1997 to January 1999, all patients aged ≥ 70 years were included, whatever their medical condition. Subjects admitted repeatedly were excluded if less than 1 month had elapsed between admissions. Patients were admitted from their own homes, from nursing homes, other care units or other hospitals.

The following data was collected: age, gender, weight, origin of the patient (own home or institution: hospital, nursing home), medical history, serum concentration of common analytes, number of drugs and length of hospital stay. Subjects were classified into three age categories: 70–79 years, 80–89 years and ≥ 90 years. In order to take into account the complexity of the patient's health status, a simplified version of the Charlson Comorbidity Index was used [11, 16]. This index covers nine diagnoses with a maximum sum of 11 (weight in parentheses): myocardial infarction (1), congestive heart failure (1), cerebrovascular disease (1), dementia (1), chronic obstructive pulmonary disease (1), connective tissue disease (1), diabetes (1), impaired renal function (2) and any tumour (2). Creatinine clearance was computed using the Cockcroft–Gault formula [17]. Patients with creatinine clearance $< 30 \text{ ml min}^{-1}$ were classified as having impaired renal function.

Potential IM use

On admission of the patients, pharmacologists established the list of all drugs received from written prescriptions; when possible, patients and their families were asked about the treatment given and eventually the in-charge general practitioners or carers most familiar with the patients were questioned. The list of drugs thus established at admission was considered to reflect as precisely as possible the treatment received before hospitalization.

Potential IMs were identified using the 1997 Beers criteria adapted to French practice. This list has been used in several studies in France [16, 18] to estimate the prevalence of potential IM use. Most of the Beers criteria were included in the French list, except meperidine (not available in France), drugs necessitating dose information (digoxin, iron supplements, some benzodiazepines such as lorazepam, oxazepam, alprazolam, triazolam, temazepam and a benzodiazepine analogue, zolpidem) and drugs that should not be used in the elderly with specific medical conditions. Three criteria were added: concomitant use of two (or more) nonsteroidal anti-inflammatory drugs (NSAIDs), concomitant use of two (or more) psychotropic drugs from the same

therapeutic class and use of any medications with anticholinergic properties other than those listed by Beers (Table 2).

Determination of ADRs

According to the World Health Organization, an ADR is defined as any response to a drug which is noxious and unintended and which occurs at doses normally used in human beings for diagnosis, prophylaxis or therapy of disease, and excluding a failure to accomplish the intended purpose [19]. The presence of ADRs was identified from the clinical manifestations observed on admission, from the laboratory tests and hospital reports. Two physicians from the Pharmacovigilance Centre (L.M., Y.N.) jointly judged the probability that any drug taken prior to admittance had caused or contributed to signs or symptoms suggesting an ADR according to the French causality scale [20]. Only 'definite' and 'probable' ADRs were taken into account.

An ADR was considered to be serious when signs and symptoms were directly responsible for hospitalization and/or were life threatening or fatal. ADRs were classified according to type of mechanism: type A reactions are dose-dependent ADRs related to the pharmacological effects of the medication and type B reactions are neither dose dependent nor related to the known drug pharmacological properties and do not improve when the dose is reduced (reactions often immunologically mediated or having a genetic basis) [21].

Signs and symptoms were classified into nine groups of disorders: cardiovascular, ionic or renal, neuropsychological, digestive, digitalis toxicity, metabolic, haematological, cutaneous and others. Only ADRs present at the time of admission – whether or not they were the reason for admission – were considered to be relevant.

Statistical analysis

Data was analysed using STATA 8 software (Stata Corp., College Station, TX, USA). Statistical analyses were performed with χ^2 tests for dichotomous variables and *t*-test for continuous variables. Logistic regression was used to estimate the effect of the number of drugs taken, of sex, patient origin and comorbidity index on ADR outcome. In a subsequent analysis, logistic regression was used to estimate the effect of IM use on ADR outcome; variables considered for adjustment were those associated with ADR outcome at $P \leq 0.25$ in bivariate analysis. A P -value < 0.05 was considered to be statistically significant.

Results

Patient characteristics

During the 49-month observation period, 2018 patients aged ≥ 70 years were admitted. Characteristics of the subjects are shown in Table 1. The mean (\pm SD) age of the patients was 85.2 ± 6.6 years. Only 59 (3%) of the 2018 subjects studied were not taking any drugs at the time of hospital admission.

The proportion of patients receiving at least one potential IM on admission was 66.0% [95% confidence interval (CI) 63.8, 68.0]. Cerebral vasodilators (36.4%) were the drugs most frequently used, then long-acting benzodiazepines (23.2%), dextropropoxyphene (7.9%), anticholinergic antidepressants (7.4%) and concomitant use of two or more psychotropic drugs of the same therapeutic class (6.6%) (Table 2).

ADRs

Four hundred and sixty ADRs were considered 'definite' or 'probable' and involved 385 patients (19% of the study population). In 201 patients, ADRs were the cause of hospital admission. The three main ADR symptoms were cardiovascular (31.5%), ionic or renal (24.3%) and neuropsychological (13.7%) (Table 3). Of ADRs, 78.4% were classified as type A reactions and 3.2% type B. ADRs were serious in 57.1% of patients suffering from an adverse effect (220/385); 36 patients died: 14 from digitalis toxicity, eight from dehydration (aggravated by diuretics), five from hyperkalaemia (spironolactone, amiloride), one from acute renal failure (lisinopril), four from haemorrhage with an anticoagulant or antiplatelet drug (heparin, acenocoumarol, fluidione, ticlopidine), three from cytopenia (cytarabine, cyclophosphamide, etoposide) and one from severe hypoglycaemia (glipizide). The outcome was favourable in 96.9% of the moderate ADRs. After adjustment for potential confounders, the number of drugs taken was associated with a significantly increased risk of ADR (four to six drugs vs. three or less, OR 3.4, 95% CI 2.1, 5.5; seven to nine drugs vs. three or less, OR 4.6, 95% CI 2.8, 7.4; ≥ 10 drugs vs. three or less, OR 5.9, 95% CI 3.6, 9.9).

The 460 ADRs detected were caused by 810 drugs, either singularly or in combination (Table 4). Cardiovascular drugs were the most commonly involved drugs in ADRs (47.5%).

IMs and ADRs

ADR prevalence was 20.4% among the 1331 patients using IMs and 16.4% among those using only appropriate drugs ($P < 0.03$) (Figure 1). However, after adjusting for potential confounders, the use of IMs was not associated with a significantly increased risk of ADR (OR

Table 1

Characteristics of the study population

Characteristics	Patients with ADRs (N = 385) % (n)	Patients without ADRs (N = 1633) % (n)	P-value
Age			0.3
70–79 years	17.4 (67)	20.4 (333)	
80–89 years	54.8 (211)	51.4 (840)	
≥90 years	27.8 (107)	28.2 (460)	
Female	72.2 (278)	68.7 (1122)	0.2
Origin			0.004
Home-dwelling	67.6 (227)	75.3 (1096)	
Institution	32.4 (109)	24.7 (360)	
Use of inappropriate drugs	70.6 (272)	64.8 (1059)	0.03
Number of drugs (mean ± SD)	7.3 ± 3.0	6.0 ± 3.0	<0.0001
Days of hospitalization (mean ± SD)	13.7 ± 7.3	13.4 ± 8.7	0.5
Comorbidity Index			0.7
0	5.4 (21)	6.6 (108)	
1–2	28.6 (110)	28.9 (472)	
3–4	43.4 (167)	44.3 (723)	
>6	22.6 (87)	20.2 (330)	
Impaired renal function	73.8 (284)	68.8 (1124)	0.06
Dementia	16.6 (64)	19.7 (321)	0.15
Myocardial infarction	19.5 (75)	21.2 (347)	0.5
Congestive heart failure	30.4 (117)	25.4 (415)	0.05
Cerebrovascular disease	16.6 (64)	16.6 (271)	0.99
Chronic obstructive pulmonary disease	20.6 (79)	22.7 (371)	0.35
Connective tissue disease	30.6 (118)	30.9 (506)	0.9
Diabetes	11.2 (43)	10.7 (175)	0.8
Tumour	15.3 (59)	15.8 (258)	0.8

1.0, 95% CI 0.8, 1.3). In fact, in only 79 of the 1331 IM users (5.9%) were ADRs directly attributable to IMs (Figure 1). The most often involved IMs in the 385 patients with ADRs were: anticholinergic antidepressants, cerebral vasodilators, long-acting benzodiazepines and concomitant use of two or more psychotropic drugs from the same therapeutic class (Table 2). ADRs attributable to IMs mainly involved cardiovascular (40.2%), neuropsychological (22.6%), ionic or renal (19.6%) and gastrointestinal (12.4%) systems. Serious ADRs were attributable to IMs in 25.5% of cases (56/220) (Figure 2). Among the 79 patients with an ADR linked to an IM, this ADR was serious in 70.9% of cases (56/79) (Figure 2). Digoxin toxicity was encountered in 33 patients and was responsible for 21 serious ADRs. The serum digoxin concentration ($2.2 \pm 0.7 \text{ ng ml}^{-1}$) was above the usual therapeutic value ($1.0\text{--}2.0 \text{ ng ml}^{-1}$) in most patients. When comparing the populations treated or not with digoxin, women treated were older ($87.7 \pm 5.6/85.6 \pm 6.5$ years), lighter ($52 \pm 13/55 \pm 13$ kg) and had a more depressed renal function (creatinine clearance $29.2 \pm 11.9/33.1 \pm 13.4 \text{ ml min}^{-1}$),

respectively ($P < 0.001$). No such difference was detected in men.

Independent of IM use, 62 patients of the 2018 included developed an ADR linked to digoxin and 20 an ADR linked to the above-listed benzodiazepines or to zolpidem. When these two drug categories were added to the IM list, 1555 (1331 + 224) patients were receiving at least one IM on admission. The prevalence of ADRs in this population was then 10.4% (79 + 62 + 20/1555).

Discussion

In this study involving an elderly population admitted to hospital, ADR prevalence was fairly high and ADRs were encountered more often in those patients using at least one IM than in those not taking these drugs (20.4% vs. 16.4%, $P < 0.03$). However, multivariate analysis showed no relation between IM use and the risk of experiencing an ADR. After establishing the causal relationship between ADRs and drugs, it appears that only 5.9% of the patients taking at least one IM experienced an ADR attributable to IMs. When adding digoxin and the listed benzodiazepines to the existing Beers list, the

Table 2

Potentially inappropriate medications used on admission from the acute medical geriatric unit of Limoges University Hospital, and involved in ADRs and serious ADRs

	All patients (N = 2018) n (%)	Patients with ADRs (N = 385) n (%)	Patients with serious ADRs (N = 220) n (%)
Any inappropriate medication	1331 (66.0)	79 (20.5)	56 (25.5)
Antiemetic drugs with extrapyramidal properties	35 (1.7)	2 (0.5)	2 (0.9)
Cerebral vasodilators*	734 (36.4)	24 (6.2)	19 (8.6)
<i>Analgesics</i>			
Propoxyphene or dextropropoxyphene	159 (7.9)	3 (0.8)	2 (0.9)
Pentazocine	0 (0.0)	–	–
<i>Sedative or hypnotic drugs</i>			
Long-acting benzodiazepines (half-life ≥ 20 h)†	468 (23.2)	23 (5.9)	18 (8.2)
Chlordiazepoxide or diazepam	24 (1.2)	3 (0.8)	1 (0.5)
Meprobamate	73 (3.6)	2 (0.5)	2 (0.9)
Barbiturates	43 (2.1)	2 (0.5)	2 (0.9)
<i>Drugs with anticholinergic properties</i>			
Anticholinergic antidepressants	150 (7.4)	26 (6.7)	16 (7.3)
Anticholinergic muscle relaxants and antispasmodic drugs	31 (1.5)	0 (0.0)	0 (0.0)
Anticholinergic H1 antihistamines	70 (3.5)	2 (0.5)	0 (0.0)
Diphenhydramine	7 (0.4)	0 (0.0)	0 (0.0)
Gastrointestinal antispasmodic drugs	6 (0.3)	1 (0.2)	0 (0.0)
Disopyramide	16 (0.8)	0 (0.0)	0 (0.0)
<i>Nonsteroidal anti-inflammatory drugs</i>			
Indomethacin	2 (0.1)	0 (0.0)	0 (0.0)
Phenylbutazone	0 (0.0)	–	–
<i>Antihypertensive</i>			
Methyldopa	15 (0.7)	5 (1.3)	3 (1.4)
Reserpine	1 (0.05)	0 (0.0)	0 (0.0)
<i>Antiplatelet drugs</i>			
Dipyridamole	81 (4.0)	0 (0.0)	0 (0.0)
Ticlopidine	25 (1.2)	2 (0.5)	1 (0.5)
<i>Hypoglycaemic</i>			
Chlorpropamide	7 (0.4)	0 (0.0)	0 (0.0)
<i>Added criteria adapted to French practice</i>			
Concomitant use of two or more psychotropic drugs from the same therapeutic class	133 (6.6)	9 (2.3)	7 (3.2)
Concomitant use of two or more nonsteroidal anti-inflammatory drugs	56 (2.8)	0 (0.0)	0 (0.0)
Other anticholinergic drugs not mentioned by Beers	91 (4.5)	5 (1.3)	5 (2.3)

*Pentoxifylline, nicergoline, dihydroergotamine, Ginkgo biloba, piracetam, ...

†Bromazepam, prazepam, clorazepate, nordazepam, ...

increase in the prevalence of ADRs, from 5.9% to 10.4%, remains limited. Consequently, we can consider that IMs overall account for only a small proportion of ADRs.

Based on our results, drugs with anticholinergic effects and long-acting benzodiazepines (half-life ≥ 20 h) were particularly unsafe. These IMs have already been considered by Beers as high-risk drugs [6].

Table 3

Signs and symptoms of adverse drug reactions

Signs and symptoms	n = 460 (%)
Cardiovascular (postural arterial hypotension, heart rhythm or conduction disorders)	145 (31.5)
Ionic or renal effect (dehydration, ionic disorders, renal failure)	112 (24.3)
Neuropsychological (vigilance impairment, agitation, confusion, extrapyramidal syndrome, sleep disorder)	63 (13.7)
Digestive (diarrhoea, vomiting, constipation, hepatic or pancreas disorders*)	40 (8.7)
Digitalis toxicity	33 (7.2)
Metabolic (dysglycaemia, dysthyroidism, gynecomastia, SIADH, adrenal failure, phosphorus-calcium disorder)	30 (6.5)
Haematological (cytopenia, coagulation disorder, haemorrhage)	25 (5.4)
Cutaneous (rash, pruritus, urticaria)	4 (0.9)
Other	8 (1.8)

*Eight hepatitis and two pancreatitis. SIADH, Syndrome of inappropriate antidiuretic hormone.

The simultaneous administration of two (or more) psychotropic drugs from the same therapeutic class, an additional criterion added by French experts, was frequently involved in ADRs. This study confirms the choice of this criterion as inappropriate prescribing in the elderly. In contrast, no ADR was linked to the concomitant use of two (or more) NSAIDs. Nevertheless, we think this association should still be considered as 'inappropriate' because the concomitant administration of NSAIDs is frequent [16] and NSAIDs are known to induce more serious gastrointestinal, renal and cardiovascular effects in the elderly [22, 23].

Cerebral vasodilator administration was associated with one-third of the ADRs. These drugs, whose efficacy is questionable, account for 25 different chemical entities in France. They are among the IMs most often prescribed to the French elderly [16, 18]. According to the definition by Beers, cerebral vasodilators should still be regarded as inappropriate in the elderly.

The use of dextropropoxyphene in the elderly is debated. This drug is considered by Beers to be inappropriate (although with low risk) by extrapolation of data derived from younger patients. Goldstein conducted a literature review to evaluate the efficacy and safety of dextropropoxyphene compared with other opioids in older patients and found that it appeared to provide pain

relief equivalent to that obtained from comparator agents, and to have a safety profile equivalent or superior to that of these drugs [24]. In the present study, dextropropoxyphene was involved in ADRs in only three cases (2%) out of the 159 dextropropoxyphene users, confirming this viewpoint. We therefore believe this medication should not be considered as inappropriate in the elderly. Alternatives, such as codeine, could hardly be regarded as safer.

Digoxin was not included in the French list of IMs, as information on the dose was seldom available in the studies performed [16, 18]. In our study, digoxin was involved in several ADRs, two-thirds of which were serious, whatever the administered dose. However these ADRs seemed to be related to an overdose.

Reduction of renal function is probably the main factor explaining the relationship between therapeutic dose and high steady-state serum concentrations of digoxin [25]. A reduced maintenance dose of digoxin is recommended when renal function is diminished with ageing. Physicians often tend to administer too high a digoxin dose in patients with reduced renal function, as shown in the Digoxin Intervention Group Trial (DIG trial) [26]. This situation is often found in the elderly, who are consequently overtreated and develop signs of toxicity when they are given a dose >0.125 mg day⁻¹. The serum digoxin concentration should be maintained between 0.5 and 2 ng ml⁻¹ and probably closer to the lower limit [27]. This has been confirmed in a study showing a significant relationship between digoxin serum concentration and toxicity in patients with heart failure; concentrations from 0.5 to 0.9 ng ml⁻¹ bring a beneficial effect, whereas concentrations >1.2 ng ml⁻¹ seem harmful [28].

Actually, as digoxin should no longer be the drug of choice in congestive heart failure, it is less and less often administered and is substituted by other drugs such as angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, loop diuretics, spironolactone and β -blockers [29]. Taking all these points into account, we think digoxin, whatever the dose given, should be considered as an IM if periodical monitoring of serum concentration is not undertaken.

Similarly, other studies have reported that drugs involved in most of the ADRs in the elderly were: cardiovascular drugs such as digoxin and diuretics, psychotropic agents, anti-Parkinson and anti-inflammatory drugs [2, 3, 30]. Some other drugs such as amiodarone, nifedipine and fluoxetine were often involved in ADRs; these drugs have been recently added to the last updated list of IMs [31]. However, the majority of the IMs from this last list were not involved in ADRs in our study.

Table 4

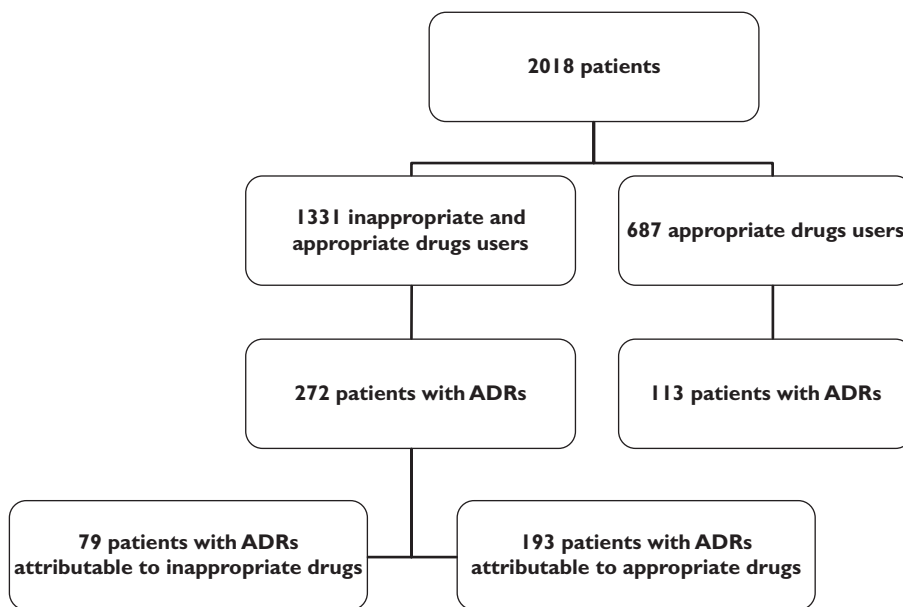
Drug classes and drugs involved in ADRs

Drug class (n,%)	Drugs (n = 810)	Nonproprietary name (n)	
Cardiovascular drugs (385, 47.5%)	Diuretics (108)	Furosemide (33) Hypokalaemia-inducing diuretics (12) Spironolactone (16) Diuretic associations (47)	
	Antiarrhythmic drugs (76)	Digoxin (62) Amiodarone (13) Flecainide (1)	
	Calcium antagonists (48)	Diltiazem (12) Nicardipine (17) Nifedipine (5) Amlodipine (4) Others (10)	
	Angiotensin-converting enzyme inhibitors (46)	Captopril (17) Enalapril (13) Ramipril (4) Others (12)	
	Anti-ischaemia drugs (42)	Piribedil (8) Buflomedil (6) Naftidrofuryl (6) Nicergoline (5) Trimetazidine (5) Others (12)	
	Nitrates (32)		
	β-Blockers (18)	Atenolol (5) Acebutolol (5) Propranolol (4) Others (4)	
	Other drugs (15)		
	Psychotropic drugs (195, 24.1%)	Antidepressants (79)	Paroxetine (16) Fluoxetine (13) Other SSRIs (3) Clomipramine (10) Amitriptyline (6) Other tricyclics (9) Mianserine (11) Tianeptine (7) Others (4)
		Antipsychotics (61)	Haloperidol (14) Tiapride (12) Thioridazine (8) Levomepromazine (6) Sulpiride (5) Others (16)
Anxiolytics, hypnotics (55)		Alprazolam (9) Bromazepam (8) Lorazepam (6) Zopiclone (5) Clorazepate, acepromazine, aceprometazine (5) Zolpidem (4) Others (18)	
Neurology drugs (51, 6.3%)	Anti-Parkinson drugs (45)	Levodopa-benserazide (27) Trihexyphenidyle (7) Bromocriptine (4) Selegiline (3) Others (4)	
	Antiepileptics (6)	Carbamazepine (4) Phenobarbital (2)	
Anti-inflammatory drugs (17, 2.1%)	NSAIDs (9)	Ketoprofene (2) Ibuprofene (1) Diclofenac (1) Piroxicam (1) Others (4)	
	SAIDs (8)	Prednisolone (6) Hydrocortisone (2)	
Analgesics (15, 1.8%)	Opioids (11)	Morphine (5) Dextropropoxyphene (3) Buprenorphine (1) Tramadol (1) Codeine (1) Paracetamol (4)	
		Non-opioids (4)	
Anti-cancer drugs (11, 1.4%)	Alkylating agents (5)		
	Anti-androgens (3)		
	LH-RH agonists (2)		
	Antimetabolites (1)		
Other drugs (136, 16.8%)			

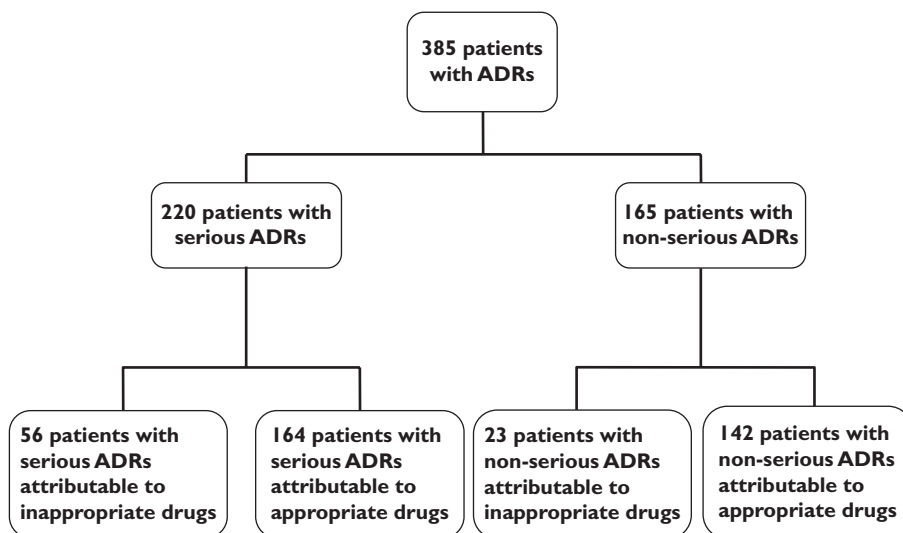
SSRI, Selective serotonin reuptake inhibitor; NSAID, nonsteroidal anti-inflammatory drug; SAID, steroidal anti-inflammatory drug.

Figure 1

Relation between adverse drug reactions (ADRs) and appropriateness of the drugs given

**Figure 2**

Relation between seriousness of adverse drug reactions (ADRs) and appropriateness of the drugs given



The causality assessment method we used could be criticised, as well as other assessment methods. However, a consensus was obtained between two senior clinical pharmacologists used to imputability evaluation for many years, which is a more accurate appreciation than an evaluation from only one expert, as is the case in some other studies.

Most ADRs belonged to the A type, i.e. were preventable. So, the use of an IM list oversimplifies the multifactorial situation of elderly patients. Besides IM use, other preventable prescribing factors in the elderly are: dosage, duration, duplication and indication of the treatment, drug–drug interactions or drug–disease interac-

tions [30, 32, 33]. These factors were not specifically evaluated in the present study. However, using multivariate analysis without adjustment in IM use, we identified a positive association between the number of drugs given and ADR occurrence. Studies of IMs have identified a positive association between the number of drugs given and IM use [8, 9, 18, 34–37]. Chang *et al.* identified a statistical interaction between these two variables [15]. This interaction may indicate that the presence of either IM prescribing or the prescription of five or more drugs will favour ADR development, but the presence of both will not further increase the risk of ADRs. In addition, a positive association was found by Chang *et al.*

between inappropriate prescription and ADR occurrence [15]. After adjustment, like Onder *et al.* [13], we did not identify this last relation. In fact, this link is probably weaker than that between the number of drugs and the occurrence of ADRs. So, two main facilitating factors of ADR development could be considered: the number of drugs on the one hand and the number of IMs on the other. However, the strength of the links is not equivalent. In our opinion, the high number of drugs is the main ADR facilitating factor, whereas the inappropriateness of drugs is a subordinate factor. So the first action to be taken in order to reduce the incidence of ADRs in the elderly is to reduce the number of drugs prescribed, so as to favour essential medications.

Other strategies can be proposed addressing both patients and treatments: minor comorbid conditions should be left out of consideration, whereas frailty, renal insufficiency and alteration in cognitive function should be taken into account. Treatments should be periodically reconsidered and adapted to the renal function [38]. Poor compliance should be hypothesized and self administration of over-the-counter drugs is to be discouraged. Occurrence of some symptoms should be identified as the adverse consequence of drug administration, the first treatment of which is drug withdrawal and not the addition of a new medication [39].

Conclusion

IM use does not seem to be the major cause of ADRs in the elderly. Other closely linked preventable factors are involved in ADR development, such as frailty and renal insufficiency, which are to be taken into account when patients in general are considered.

In order to reduce the prevalence of ADRs, IM use should be discouraged, but the first step to be taken is the reduction in the number of drugs administered. As a consequence, the number of IMs will be reduced. This is the most beneficial way to enhance the quality of the treatments given. Polymedication reduction in the elderly should be a constant preoccupation of physicians for a direct beneficial effect, allowing a decrease of the prevalence of drug–drug interactions and for easing the burden on healthcare costs.

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