BMJ Open   Identification and prevalence of adverse drug events caused by potentially inappropriate medication in homebound elderly patients: a retrospective study using a nationwide survey in Japan

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ABSTRACT

Objectives: A nationwide large-scale survey was conducted to identify the prevalence and causal medications of adverse drug events (ADEs) that are caused by potentially inappropriate medications (PIMs) given to homebound elderly patients, factors associated with ADEs, and measures taken by pharmacists to manage ADEs and their effects on ADEs.

Settings: A questionnaire was mailed to 3321 pharmacies nationwide. It asked about the details of PIMs and ADEs of up to 5 patients for whom home visits were provided by a pharmacist. Questionnaire forms were filled in by pharmacists who visited the patients.

Design and participants: Between 23 January and 13 February 2013, comprehensive assessment forms were sent to 3321 pharmacies. Data collected from 1890 pharmacies including data of 4815 patients were analysed and 28 patients of unknown sex were excluded. Their average age was 82.7 years. PIMs were identified based on the 2003 Beers Criteria Japan.

Results: There were 600 patients who did not provide valid answers regarding the medications. In the remaining 4243 patients, one or more medications that were considered to be PIMs had been prescribed to 48.4% of patients. PIM-induced ADEs were found in 8% of these patients by pharmacists during home visits. The top ADE-inducing medications were strong anticholinergic antihistamines, benzodiazepines, sulpiride and digoxin. The most common ADEs associated with benzodiazepines were frequent lightheadedness, somnolence and sleepiness, which increase the risk of falls and subsequent fractures in elderly patients. The following factors associated with ADEs were identified: sex, pharmacist awareness of prescription issues, frequency of visits and time spent at patients' homes, and the frequency of detailed checks for patient adverse reactions by pharmacists.

Conclusions: The PIM prevalence associated with home healthcare in Japan was relatively high, as reported in previous studies. The present study suggests that

Strengths and limitations of this study

- The incidence of potentially inappropriate medication (PIM) use and associated adverse drug events (ADEs) were evaluated, independent of the views of medical care providers, by conducting a nationwide survey of pharmacists who were providing services to homebound elderly patients.
- PIMs were prescribed to 48.4% of patients, which is higher than the 2.9–38.5% in previous studies based on Beers Criteria 2003, suggesting that our approach identified PIMs that might have been previously overlooked.
- ADEs were experienced in 8% of patients who were prescribed PIM, and were mostly related to the central nervous system, which could potentially lead to more serious conditions. This highlights the importance of vigilance for PIM.
- Responses of visiting pharmacists to ADEs were helpful in preventing serious situations. Home visits by pharmacists should be further encouraged.
- Despite the relatively low rate of response (56.9%) to the initial inquiry, and the reporting means that were rather open to interpretation by the pharmacist on site, the present study provides important insights in reducing the use of PIMs and associated ADEs.

pharmacists could reduce the incidence of PIMs and consequent ADEs.

INTRODUCTION

There are numerous reports on the evaluation of prescriptions for elderly patients,

based on the Beers Criteria. A systematic review of 19 studies—14 of which used the Beers Criteria (the 2003 version was used in 11 papers, the 1997 version was used in 2 papers and the 1991 version was used in 1 paper)—on elderly patients in the primary care setting revealed that the median rate of inappropriate medication prescription was 20.5% among elderly patients 65 years of age or older, and that diphenhydramine and amitriptyline were most commonly associated with high-risk adverse drug events (ADEs), while propoxyphene and doxazosin were often associated with low-risk ADEs.[1]

A study of Swiss outpatients based on data collected from a health insurance company revealed that the prevalence of potentially inappropriate medication (PIMs) according to 2003 Beers Criteria or PRISCUS list was 21% in patients 65 years of age or older,[2] while a study of 2707 homebound elderly patients receiving home care in eight European countries revealed that the average percentage of PIM, according to all expert panel criteria for community-living elderly persons (Beers and McLeod) was 19.8%.[3] ADEs caused by PIMs in elderly patients are serious drug-related issues.

Japan is the most rapidly ageing country among industrialised nations. However, sufficient medical care of elderly patients and control of its costs are common issues that are shared by many countries. The Japanese government is promoting home healthcare as a national policy to improve quality of life and control inpatient medical costs associated with the care of elderly patients. Several studies have already found clinical and economic advantages of home healthcare over inpatient healthcare.[4–8] An understanding of the prevalence of PIM-induced ADEs and factors associated with ADEs in elderly patients in home healthcare settings is necessary for establishing safe pharmacotherapy and formulating policy for optimising medical costs associated with home healthcare in the future. To date, most prevalence studies have been small-scale studies in which biases are difficult to avoid and therefore lack sufficient credibility or validity. Large-scale studies are needed to obtain accurate and more detailed information.

The objective of this study was to conduct a nationwide, large-scale survey to shed light on the occurrence of PIM-induced ADEs in homebound elderly patients receiving home healthcare services, and to identify the drugs that cause such ADEs, factors associated with ADEs, measures taken by pharmacists to manage such ADEs and the effectiveness of such measures.

METHODS
Patients
First, we conducted a screening survey to identify pharmacists who routinely provide home visit services to elderly patients, by using a questionnaire that was inserted in selected issues of the *Journal of the Japan Pharmaceutical Association*. Members of the Association were asked to send a single response (per pharmacy) via

FAX, and 3321 pharmacies were identified as providers of home visit services. A second questionnaire was mailed to those pharmacies, which was filled and mailed back by a pharmacist who represented their pharmacy between 23 January and 13 February 2013. On the basis of the results of a pilot study that was conducted prior to the present study, which had indicated that each pharmacy provides home visit services to a maximum of five patients per month,[9] we asked the pharmacies to provide details of up to five patients who were recipients of their home visit service (excluding cases of medication delivery only), regardless of the presence of a possible PIM. When a pharmacy provided home visit services to more than five patients, the pharmacist was asked to describe the most recent five home visit cases. Requested patient information included: a physician's order for the home visit (with a summary of the patient's medical conditions), records of home visits and drug management.

Data collection
The following variables were studied: patient characteristics (sex, age, primary disease (defined as disease that had the most impact on the general condition of the patient), living arrangement, family composition); number of medications that were being taken; whether prescribed medication included those in the Beers Criteria list (PIMs); whether the pharmacist had any experience of discovering PIM-induced ADEs during visits (ADEs, if any), and details of such an episode (name of the drug (including specification), daily dose, description of ADEs, care provided by the pharmacist with physician and degree of improvement of ADEs as a result of care provided); pharmacist awareness of prescription issues (contraindications, duplication, drug interactions and unnecessary continuation of treatment); home visit service-related work load (frequency of visits, time spent at patients' homes); and the frequency of detailed pharmacist checks for ADEs that were based on test results, vitals and activity of daily living (ADL).

Measurements
The frequencies of ADEs and their characteristics described in the survey responses were assessed on the following factors based on "medications that should be avoided in elderly individuals regardless of disease or clinical condition" in the "Beers Criteria: The Japanese V.2003"[10]: the number and details of ADEs that occurred; the responses of pharmacists to ADEs; and the degree of improvement in ADEs as a result of such measures. ADEs were classified based on the "Geriatric Care Medication Management Manual: ADL and Medication."[11]

In the present study, we used the 2003 Beers Criteria in Japan, which was independently developed using the same strategy that was used to develop the original 2003 Beers Criteria with supervision by Dr Beers to better

reflect the healthcare situation in Japan. The major differences in the Japanese version compared with the original Beers Criteria are: (1) medications that were not available at the time were excluded, (2) the upper limits for the dosage of short-acting benzodiazepines were stated and (3) four of the H_2 blockers, which are commonly prescribed in Japan, that are metabolised in the liver and excreted from the kidneys, were included.

In the home healthcare system in Japan, a home visiting pharmacist is provided with patient data, as needed, by the physician in charge, and the pharmacist collects information regarding drug adherence and possible signs of adverse drug effects on each visit. Such information is then relayed to the physician, and the physician will determine whether the observed symptom is related to PIM, and if additional intervention and/or cessation of the medication is necessary.

We collected cases in which a home visiting pharmacist had documented possible symptoms of ADE after which the physician judged that the reported symptom was related to an ADE and modified the prescription as needed. The physician may have visited the patient with the pharmacist when the possible symptom(s) were identified or approximately within 1 week after the pharmacist's initial report, to further examine the situation. The physician in charge evaluated the patient's condition at her/his next visit after cessation or decrease in dose of the medication; this normally happens within 2 weeks, but the patient may be followed up for 4–8 weeks depending on the characteristics of the medication and/or the symptoms identified.

Statistical analysis

To screen for factors associated with PIM-induced ADEs, the occurrence of ADEs and the following variables were analysed by univariate analysis using the χ^2 test: patient characteristics (sex, age, living arrangement, family composition), number of medications that were being taken, pharmacist awareness of prescription issues (contraindications, therapeutic duplication, interactions and unnecessary continuation of treatment), frequency of visits, time spent at patients' homes and the frequency of pharmacist checks for ADEs that were based on test results, vitals and ADL. Patients who had been prescribed PIMs were included in the subsequent analyses, and patients missing demographical information were excluded from the subsequent analyses. All the statistical analysis was performed using SPSS V.18.

RESULTS

Data for 5447 patients were collected from 1890 pharmacies (56.9% response rate), of which 4843 patients were 65 years of age or older. The frequency of home visits was more than once a week in 17.3%, twice a month in 63.2% and less than once a month in 19.5%. The median duration of the visit was 15 min; it was less than 10 min in 33%, 11–15 min in 19.4%, 16–20 min in 16.8% and more than 20 min in 30.8%. Patients were followed up for 26.5 months on average (median, 17 months).

Patient characteristics

The cohort of elderly patients (65 years of age or older) included 1716 men, 3099 women and 28 patients whose sex was unknown. The average age was 82.7 years (SD 7.7 years). A total of 600 patients did not provide valid information on prescribed medications and were therefore excluded, leaving 4243 patients. One or more medications that were defined as PIMs had been prescribed in 48.4% of patients (2053 patients, table 1). Signs of PIM-induced ADEs were discovered by pharmacists in 8% of patients (165 of 2053 patients who had been prescribed PIMs (table 2)) during home visits.

The proportion of women was higher. There were more male patients with cerebral infarction, chronic respiratory failure and cancer, while osteoarthritis, osteoporosis and dementia were more prevalent in female patients. A higher percentage of female patients were living independently, and a higher percentage of males were living with their spouses. The sex distribution was similar when the analysis was limited to patients who had been prescribed PIMs.

PIM-induced ADEs

Table 3 shows the details of the PIMs and the number of ADEs that had occurred. A total of 2991 PIMs had been prescribed. The top five most common medications, by drug category, were: H_2 blockers (23.9% (714/2991)); short-acting benzodiazepines (21.6% (646/2991)); stimulant laxatives for chronic use (12.1% (362/2991)); long-acting benzodiazepines (7.3% (218/2991)) and digoxin (5.3% (159/2991)).

The top five medications frequently associated with ADEs that had been observed during home visits were: strongly anticholinergic antihistamines (13.3% (17/128)); ultra-long-acting benzodiazepines (11.5% (11/96); sulpiride (10.7% (13/122)); short-acting benzodiazepines (9.9% (61/646)); and digoxin (8.8% (14/159)).

Specific details of ADEs caused by PIMs

Among 182 ADEs associated with PIMs, as shown in table 3, specific details were retrieved in 154 cases (table 4). The top five medications associated with ADEs were: short-acting benzodiazepines (triazolam, etizolam and alprazolam), 40.9% (63 events); intermediate-acting benzodiazepines (flunitrazepam and lorazepam), 11% (17 events); long-acting benzodiazepines (diazepam and quazepam), 8.4% (13 events); sulpiride, 7.1% (11 events); and ultra-long-acting benzodiazepines (ethyl loflazepate and flutoprazepam), 6.5% (10 events). The most common ADEs associated with short-acting, intermediate-acting and long-acting benzodiazepines were lightheadedness and sleepiness, while the most common ADE associated with ultra-long-acting

Table 1 Characteristics of patients 65 years of age or older* (n=4223)

Variable	Classification	Distribution (%)	
		Male (n=1495)	Female (n=2728)
Age (years)	65–69	9.5	3.6
	70–79	33.8	23.1
	80–89	44.6	49.7
	90–99	11.5	22.3
	100 or older	0.5	1.4
Primary disease	Circulatory disease	12.9	14.0
	Cerebral infarction	20.0	9.6
	Osteoarthritis	1.5	4.9
	Fracture/osteoporosis	1.0	5.6
	Rheumatoid arthritis	0.7	2.9
	Amyotrophic lateral sclerosis	1.7	0.7
	Dementia	11.6	19.6
	Parkinson's disease	4.3	3.8
	Other neurological disease	3.5	3.0
	Chronic respiratory failure	6.4	3.9
	Cancer	6.9	3.0
	Renal failure	1.5	1.0
	Other	16.2	14.5
	Unknown	11.9	13.5
Living arrangement	Home	77.6	69.1
	Assisted-living housing	19.3	25.5
	Special elderly nursing home	2.4	4.8
	Unknown	0.7	0.5
Family composition	Independent	30.9	39.6
	Living with spouse	32.8	12.7
	Living with family	24.2	29.9
	Living with non-family member	11.0	16.5
	Unknown	1.1	1.4

*Data shown with the patients who provided valid answer to the question regarding medication, and 65 years or older. Twenty patients whose sex was unknown were excluded.

benzodiazepines was somnolence. The most common ADEs associated with sulpiride were lightheadedness, tremor and sialorrhoea. Among the medications for which maximum daily doses had been defined, 63 ADEs related to short-acting benzodiazepines and 9 ADEs related to digoxin, and were reported at doses below the defined upper daily dose limit.

For these ADEs, pharmacists had contacted a physician and had taken the following measures: discontinuation of the causative drug (47%); dose reduction (27.4%); change of medication (11.6%); and other measures (11%). It was unknown whether appropriate measures had been taken in 3% of cases. ADEs had improved in 82.3% of cases, while no improvement was reported in 14.6%, and the outcome was unknown in 3.1%.

Univariate analysis of factors associated with ADEs

The following factors were associated with PIM-induced ADEs: sex, pharmacist awareness of prescription issues (contraindications, therapeutic duplication, interactions and unnecessary continuation of treatment), frequency of visits and time spent at the visit, and the frequency of a detailed pharmacist check for adverse reactions (table 5).

DISCUSSION
Prevalence of PIMs

The percentage of PIM prescription in this study (48.4%) was relatively high compared with previously reported figures. PIM ranged from 2.9% to 38.5% in 11 previous studies utilising the Beers Criteria 2003, which were analysed in a systematic review.[1] Large databases in industrialised nations indicate prevalence of PIMs were 20.5%, 21.0% and 19.8%, respectively,[1–3] and studies conducted in New Zealand and Brazil found the rates were 42.7%, 48.0% and 49%, respectively.[12–14]

As we had stated in Methods section, patients in the present study were reported by the participating pharmacists regardless of the presence of possible PIM. Therefore, we believe that the relatively high rate of PIM shown in the present study was not due to selection bias. The national health insurance system in Japan covers all prescription medications without limitations, and out-of-pocket expense is minimal. Therefore, prescriptions for medicines were occasionally continued for unnecessarily long periods, which may have contributed to the higher incidence of PIMs caused by polypharmacy in the present study.[15]

This study found that the majority of PIMs were benzodiazepines, consistent with other reported

Table 2 Characteristics of patients 65 years of age or older who were prescribed a medication on the Beers Criteria list* (n=2039)

Variable	Classification	Distribution (%)	
		Male (n=707)	Female (n=1332)
Age (years)	65–69	9.3	3.5
	70–79	34.8	23.8
	80–89	44.1	49.4
	90–99	11.3	21.5
	100 or older	0.4	1.8
Primary disease	Circulatory disease	14.6	14.7
	Cerebral infarction	19.4	10.0
	Osteoarthritis	2.0	4.7
	Fracture/osteoporosis	1.0	6.4
	Rheumatoid arthritis	0.6	2.6
	Amyotrophic lateral sclerosis	2.0	0.5
	Dementia	10.2	17.4
	Parkinson's disease	3.8	4.1
	Other neurological disease	3.3	3.2
	Chronic respiratory failure	6.4	4.2
	Cancer	6.1	2.6
	Renal failure	2.1	1.0
	Other	15.3	13.9
	Unknown	13.4	14.7
Living arrangement	Home	77.4	71.5
	Assisted-living housing	19.9	24.1
	Special elderly nursing home	2.0	4.0
	Unknown	0.7	0.5
Family composition	Independent	32.8	40.5
	Living with spouse	33.7	12.5
	Living with family	21.5	30.2
	Living with non-family member	11.0	15.2
	Unknown	1.0	1.5

*Sex unknown was excluded (n=14).

studies,[2] [12–14] [16] but there were also many cases of H_2 blockers and chronic stimulant laxatives use, indicating that these medications tend to be prescribed regardless of the presence or absence of symptoms.

Incidence of ADEs caused by PIMs
The present study found that ADEs caused by PIMs had occurred in 8% of patients. The top ADE-inducing medications were strong anticholinergic antihistamines, benzodiazepines, sulpiride and digoxin. A study on the long-term effect of anticholinergic medications (which are PIMs) on bodily and cognitive functions in elderly patients reported that bodily and cognitive functions in patients treated with PIMs were significantly compromised compared with patients who did not use PIMs.[17] Diphenhydramine has also been found to often cause high-risk ADEs.[1] Our study discovered that strong anticholinergic medications were most frequently associated with ADEs, suggesting that caution should be advised against the use of such medications, in accordance with PIM guidelines.

Benzodiazepine-induced ADEs were discovered in 28.7% of patients. According to Fujii et al, an international comparison of psychotropic drug prescriptions revealed that the percentage of sedative hypnotic

prescriptions and the number of patients using two or more concomitant hypnotic medications in Japan were greater than those in other countries. The authors attributed this to the many varieties of sedative hypnotic medications available in Japan, and to the national insurance and the medical reimbursement system that allows continued prescription and usage of such medications.[18] In particular, data indicated that the number of prescriptions for anxiolytics including benzodiazepines has been increasing every year in Japan compared with the US, and is now about six times greater than that in the US.[19] In the present study, which evaluated ADEs in elderly patients who were receiving home healthcare, the most common benzodiazepine-induced ADEs were lightheadedness, somnolence and sleepiness. As the typical features of indoor structures in Japan include high sills between rooms, where people can easily trip, steep stairways leading to a second story, and bathrooms with deep tubs, such ADEs could cause serious events such as falls, and result in fractures. Patients using benzodiazepines should therefore be frequently checked for symptoms such as lightheadedness, somnolence and sleepiness, and a reduction in dose or a change to another agent, for example, should be considered.

Table 3 PIM prescriptions (in descending order) and number of ADEs by drug category

Drug category*	Number of prescriptions	Number of ADEs	Per cent
H$_2$ blockers	714	10	1.4
Short-acting benzodiazepines	646	61	9.4
Stimulant laxatives (chronic use)	362	18	5.0
Long-acting benzodiazepines	218	16	7.3
Digoxin	159	14	8.8
Short-acting nifedipine	155	4	2.6
Strongly anticholinergic antihistamines	128	17	13.3
Ticlopidine	123	5	4.1
Sulpiride	122	13	10.7
Verapamil	104	5	4.8
Ultra-long-acting benzodiazepines	96	11	11.5
Non-COX selective NSAIDs with long half-life	94	3	3.2
Cimetidine	50	0	0.0
Amiodarone	20	2	10.0
Total	2991	179	

*Drug category is based on Beers Criteria list.
ADEs, adverse drug events; COX, cyclooxygenase inhibitor; NSAIDs, non-steroidal anti-inflammatory drugs; PIM, potentially inappropriate medications.

Factors associated with ADEs

Polypharmacy,[3] [12] [13] [20–22] centrally acting medications,[2] [3] [12] [13] [22] anti-inflammatory drugs,[2] family composition (living alone), economic status, age, presence of depression[3] and the expertise of prescribing physicians,[22] have been reported thus far as factors associated with PIMs. In contrast, factors that are associated with PIM-induced ADEs have rarely been studied. One hospital-based study showed that the number of medication prescribed per patient was the only factor that appeared to affect the incidence of ADEs.[23] Indeed, we performed a logistic regression analysis using the presence of ADEs as a covariate, but we did not find any factor significantly affecting the outcome (data not shown).

ADEs occur more often in women. Besides the female sex, a higher number of drugs taken by women and their greater mean age compared with men could be contributory factors. Dementia, osteoarthritis and fractures/osteoporosis are more prevalent in women than in men, and multiple drugs had been prescribed for these diseases (medians of 6.0, 7.0 and 7.0 medications, respectively; data not shown), which potentially lead to a higher incidence of PIM-induced ADEs.

More frequent home visits by pharmacists would lead to more frequent checking for ADEs through examination of test results, vitals and ADL, and a greater awareness of prescription issues (contraindications, therapeutic duplication, interactions or unnecessary continuation of treatment), which might lead to more frequent discovery of ADEs. Indeed, the majority of ADEs that were noticed by the visiting pharmacist were improved as a result of measures taken by collaboration of pharmacist and physician. Even though homebound elderly patients in this study were also receiving home healthcare provided by visiting physicians and/or nurses, our study revealed that the visiting pharmacist discovered a significant number of ADEs. Therefore, the involvement of pharmacists should be increased to assist physicians and nurses in community healthcare,[24] through checking the treatment adherence of homebound elderly patients and modifying prescriptions based on ADE vigilance.

Limitations

The essential findings of this study appear to be strong and compelling, despite a few minor limitations. First, the 56.9% rate of response to our main inquiry was not very high. The relatively low rate may reflect the fact that this was a large-scale, nationwide study, in which medical issues, such as the business of practice and data-sharing limitations between medical care providers and pharmacists, related to location, may vary. According to the survey conducted by the Ministry of Health, Labour and Welfare of Japan that was reported in September 2013, there were 4319 pharmacies that provide home visit services nationwide, of which 3321 pharmacies (76.9%) had participated in the present survey. Therefore, we believe that the results of our study accurately represent the prevalence of PIMs and consequent ADEs that affect elderly homebound patients receiving home visit pharmacist services, with minimum bias. Second, the degree of objectivity could be questioned, as the definition of ADEs, such as lightheadedness or somnolence, and the assessment of ADE improvement, were not determined in advance. However, the ADEs reported in this study were determined by a physician in charge based on the information provided by the pharmacist who had been following the patient for an extended period (26 months on average), along with information provided by a family member who was the main carer, therefore, proper assessment of ADEs appear to have been made. If similar studies are conducted under more stringent conditions in the future, a study design that includes third party assessments by physicians and other pharmacists using predefined criteria would be desirable.

Third, the potential economic impact of preventing ADEs was not addressed. A report showed that 44% of elderly patients who were prescribed a benzodiazepine received at least one PIM, resulting in an excess cost of $3076 per year because of the necessity of outpatient therapy or emergency hospitalisations.[16] Future studies will hopefully address such issues.

Table 4 Details of ADEs by the type of PIM

Classification*	Generic name	Number of ADE†	Details and number of ADEs
Short-acting benzodiazepines	Triazolam >0.2 mg	63	Lightheadedness: 29; insomnia: 4; somnolence and amnesia: 3 each; delirium, tremor, dependency, hallucination, fall, dysuria: 2 each
	Etizolam Alprazolam >2 mg		Prolonged use of massive dose, disturbed consciousness, memory impairment, hallucination, renal impairment, impaired tongue movement, insomnia, gagging, worsening of dementia, somnambulism, delusions, restlessness: 1 each
Intermediate-acting benzodiazepines	Flunitrazepam	17	Lightheadedness: 6
	Lorazepam >3 mg		Delirium, loss of motivation, oversedation, agitation, sleepiness, somnolence, insomnia, terror, dementia-like symptoms, fall, dizziness on standing: 1 each
Long-acting benzodiazepines	Diazepam	13	Lightheadedness: 7; sleepiness: 3
	Quazepam		Falling out of bed, disturbed consciousness, hallucination: 1 each
Sulpiride	Sulpiride	11	Lightheadedness, tremor, sialorrhoea: 2 each, extrapyramidal symptoms, headache, anxiety, constipation and walking difficulty: 1 each
Ultra-long-acting benzodiazepines	Ethyl loflazepate	10	Somnolence: 2
	Flutoprazepam		Lightheadedness, oversedation, panic, hallucination, falling, sleepiness, insomnia, impaired nocturnal ventilation: 1 each
Digoxin	Digoxin	9	Anorexia: 4, poisoning: 3, nausea and hallucination: 1 each
Ticlopidine	Ticlopidine hydrochloride	4	Gastrointestinal disorder, contraindication, internal bleeding, intracerebral haemorrhage: 1 each
Barbiturates	Gabapentin	3	Sleepiness: 2, lightheadedness: 1
Strongly anticholinergic antihistamines	d-chlorpheniramine maleate	4	Thirst: 2, lightheadedness and discomfort: 1 each
H$_2$ blockers	Famotidine	3	Somnolence, eczema, eruption: 1 each
Amantadine	Amantadine hydrochloride	3	Lightheadedness, delirium, hallucination: 1 each
Verapamil	Verapamil hydrochloride	3	Bradycardia: 2, poorly controlled arrhythmia: 1 each
MAO inhibitors	Selegiline	2	Hallucination, emotional instability: 1 each
Amitriptyline	Amitriptyline hydrochloride	2	Lightheadedness, hallucination: 1 each
Olanzapine	Olanzapine	2	Hypoglycaemia, ADL decreased‡: 1 each
Amiodarone	Amiodarone hydrochloride	1	Tremor: 1
Stimulant laxative (chronic use)	Bisacodyl	1	Abdominal pain: 1
Centrally acting muscle relaxants	Tizanidine hydrochloride	1	Liver function test abnormal: 1
Doxazosin	Doxazosin mesilate	1	Lightheadedness: 1
Tetracyclic antidepressants	Maprotiline hydrochloride	1	Lightheadedness: 1
Total		154	

*Classification: Japan Pharmacotherapeutic Classification was used as a reference.
†Number of ADE: Details unknown were excluded (n=4).
‡ADL decreased: Conditions where basic daily activities, that is, eating, cleaning, bathing and/or maintaining personal hygiene, are decreased.
ADEs, adverse drug events; ADL, activity of daily living; MAO, monoamine oxidase; PIM, potentially inappropriate medications.

Table 5 Single regression analysis of variables associated with ADEs

Characteristics	ADEs % (Number)*		p Value
	(+) (n=165)	(−) (N=1319)	
Sociodemographic characteristics			
Female sex	12.3 (119)	87.7 (846)	0.023
Age ≥75 years	10.9 (138)	89.1 (1125)	0.563
Stay at own home	11.3 (124)	88.7 (975)	0.372
Live alone	11.3 (62)	88.7 (486)	0.965
Drug-related characteristics			
Polypharmacy (≥5 drugs)	10.6 (134)	89.4 (1128)	0.068
Awareness of prescription issued by pharmacist			
Awareness of contraindications, therapeutic duplication, interactions	21.0 (17)	79.0 (64)	0.009
Awareness of unnecessarily continued treatment	20.9 (18)	79.1 (68)	0.007
Service-related characteristics			
Home visiting frequency†			
≤Once a month	9.4 (27)	90.6 (259)	0.045
About twice a month	10.4 (96)	89.6 (825)	
≥Once a week	15.4 (41)	84.6 (225)	
Work time‡ (≥20 min)	14.6 (109)	85.4 (637)	<0.001
Check of ADEs based on test results, vital, and ADL			
Not performed	6.7 (28)	93.3 (391)	0.001
≤Once a month	11.6 (73)	88.4 (554)	
About twice a month	13.7 (50)	86.3 (315)	
≥Once a week	20.3 (14)	79.7 (55)	

*Number of people excluding non-responders (n=404) from 1888.
†Frequency of visits to patients' home.
‡Work time at patient's home per visit.
ADEs, adverse drug events; ADL, activity of daily living.

Conclusion

A large amount of data collected nationwide was used to accurately investigate the occurrence of PIM-induced ADEs in homebound elderly patients receiving home healthcare, the drugs that caused such ADEs and factors associated with ADEs. PIMs had been prescribed in 48.4% of the studied patients, and PIM-induced ADEs had occurred in 8%. Of note, benzodiazepine-induced lightheadedness, somnolence and sleepiness, which increase the risk of falls and resulting fractures in elderly patients, were frequent. Measures taken by pharmacist–physician collaboration had resulted in the improvement of nearly all ADEs. The findings of this study will hopefully be useful in formulating policies for effectively preventing ADEs during home healthcare.

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