Saudi Journal of Biological Sciences (2017) **24**, 200–207

King Saud University

Saudi Journal of Biological Sciences

www.ksu.edu.sa
www.sciencedirect.com

ORIGINAL ARTICLE

Potentially inappropriate medications prescribed for elderly patients through family physicians

Abdulaziz Al Odhayani *, **Ayla Tourkmani, Mohammed Alshehri, Hala Alqahtani, Adel Mishriky**

Family and Community Medicine Department, College of Medicine, King Khalid University Hospital, King Saud University, Riyadh, Saudi Arabia

Received 21 March 2016; revised 27 April 2016; accepted 1 May 2016
Available online 12 May 2016

KEYWORDS

Inappropriate;
Prescribing;
Medications;
Elderly;
Adverse effects

Abstract The elderly population is increasing throughout the globe, resulting in higher healthcare costs. Potential inappropriate medication (PIM) prescriptions are a major health problem affecting the elderly persons. Due to limited studies in PIM use in primary care and home healthcare in Saudi Arabia, we aim to examine the extent of PIM prescription for and use by elderly patients. This study was carried out with 798 elderly patients, arbitrarily selected from Prince Sultan Medical Military City through the patient register. The mean age of the patients were in the range of 75.2 ± 5.5; 37.8% were males and 62.2% were females. The elderly patients are affected majorly with diabetes (73.9%), hypertension (83.2%) and lipid abnormalities (73.8%). The maximum patients involved in this study were affected with lower hemoglobin levels i.e. 99.2%. Renal impairment was found in 64% and iron supplements were the most commonly used in 23.1%, followed by analgesics and opioids (17%). The 52.5% of participants were using one or more PIMs. Kidney was the only functions and had influence on prescribed decisions. This study indicates PIM is a concern in elderly patients attending clinics and home residents and commonly prescribed ones are atypical antipsychotics, iron overdose, benzodiazepines and opioids. Prescription of drug–drug interactions, cascades and inappropriate drug doses results in preventable adverse effects.

1. Introduction

The elderly population is increasing globally, resulting in higher healthcare costs and demand for services (Klarin et al., 2005; Fick et al., 2001). The estimation of current statistics suggests that 2.9% of the affected elderly persons were more than 65 years of age in the Saudi population (WHO, 2011). One of the challenges in the provision of healthcare to elderly persons is inappropriate prescriptions, drug-related is inappropriate prescriptions and complications. The earlier

* Corresponding author at: Family and Community Medicine Department, College of Medicine, King Khalid University Hospital, King Saud University, Riyadh 1135, Saudi Arabia. Tel.: +966 114692767; fax: +966 114671231.
E-mail address: drodhayani12@yahoo.com (A. Al Odhayani).
Peer review under responsibility of King Saud University.

ELSEVIER Production and hosting by Elsevier

http://dx.doi.org/10.1016/j.sjbs.2016.05.006
1319-562X

studies from the western population indicates 12% and 23% of more than 65 years of age consumed at least 10 medications at any given time, and five prescription drugs monthly (Kaufman et al., 2002). One of the study from European population showed that the older people in community-dwelling received ~2.8–5.0 drugs (Brekke et al., 2008). An earlier study in the 90s concluded the person who receives two, four and seven drugs experienced with 13%, 38% and 82% risk (Goldberg et al., 1996). Duplicate use of drugs within the same class is common and often unrecognised. The side effects of drugs are leading to polypharmacy, coupled with continued prescription of cascades (example; prescribing levodopa for parkinsonian symptoms resulting from neuroleptic drugs side effects) (Col et al., 1990). Older individuals are at a higher risk of developing drug-related adverse events because of age-related changes and reduced organ reserve capacity (Byles et al., 2003). Furthermore, age-related changes in drug pharmacokinetics and pharmacodynamics and coexisting diverse underlying medical morbidities contribute towards serious adverse drug interaction and toxicity (Handler et al., 2006). Polypharmacy, non-prescription drugs and inadequate treatment adherence carry a substantially high risk for morbidity and mortality. Hospital admission, functional impairment, falls, cognitive decline, drug toxicity and poor quality of life are common, due to inappropriate prescription of medication (Williams, 2002; Chin et al., 1999; Buajordet et al., 2001). In total, 5% of total hospitalisations are reportedly drug-related; 17% thereof are of older adults (Lazarou et al., 1998).

Drug-related problems are common in primary care (Doshi et al., 2005) and up to 35% of older patients attending outpatient clinics develop preventable adverse drug interactions (Mallet et al., 2007). Prescription of inappropriate medications is an important preventable drug-related problem (Beijer and de Blaey, 2002). A potentially inappropriate medication (PIM) refers to prescription of drugs carrying risks outweighing the expected clinical benefits, especially when there is evidence for an equally or more effective and safer alternative medication (Spinewine et al., 2007; Chang and Chan, 2010). There are few international evidence-based studies on a comprehensive clinical approach comprising appropriate drug prescription for elderly people. Beers' criteria, published in 1991 and updated in 2003 and 2012 (Beers et al., 1991; Fick and Semla, 2012; Fick et al., 2003), are the most widely used tool for appropriate prescription and monitoring of elderly persons in ambulatory settings and long-term facilities. Recently, Beers' criteria updated PIMs to include up to 53 drugs in three classes, which may carry negative outcomes and limited effectiveness for elderly people. The criteria had been well described and emphasised, to improve the care of older adults and reduce exposure to PIMs (Fick and Semla, 2012). PIMs fall under three major therapeutic classes, organs and systems, namely: PIMs and classes to avoid in older adults, PIMs and classes to avoid in older adults with certain diseases and syndromes and medications to be used with caution in older adults.

There is insufficient evidence regarding PIM use in primary care and home healthcare in Saudi Arabia. One economic-focused, cross-sectional study, conducted from 2002 to 2004, at Riyadh Military Hospital, using outpatients' pharmacy-dispensary records, found that 43.6%, 18% and 38.4% of patients took at least one, two and three or more PIMs, respectively (Al-Omar et al., 2012). Since there are limited qualitative and quantitative data locally on appropriate drug use among elderly persons, in ambulatory settings and home healthcare, the majority of prescriptions are by family physicians; improving the quality of family physicians' prescriptions would improve patients' quality of life and minimise drug hazards. Hence, we conducted this study, to identify and analyse the medications taken by elderly persons consulting family physicians at the Family and Community Medicine and the Home Healthcare departments at Prince Sultan Military Medical City, Riyadh, and to classify the dispensed drugs, based on Beers' criteria, as PIMs.

This study aimed to establish the extent of inappropriate drug prescription for and use by elderly patients, by determining the proportion of: (1) ambulatory medical care visits by elderly patients resulting in inappropriate drug prescription (visit-level analysis), and (2) elderly, community-dwelling recipients of inappropriate drugs (person-level analysis). Secondly, the study examined trends in these outcomes for recent years and, thirdly, factors associated with a higher risk of inappropriate drug prescription/use.

2. Materials and methods

The target population was elderly patients, aged $\geqslant 65$ years, despite gender and ethnicity. Common medical co-morbidities possibly influencing the number of medications and pharmacokinetics, and the number of medications used by the elderly, were recorded. Only Prince Sultan Medical Military City (PSMMC) items and non-over–the-counter (non-OTC) medications were counted and registered for each patient. Non-PMMSC items, OTC medication and herbal supplements were excluded from the analysis, as they were not well recorded for each patient. We pooled and documented laboratory results possibly indicating functional impairment of common organs (renal function, liver function, uncontrolled diabetes, etc.) and increasing the potential hazards of some medications for each patient.

Data were collected from patients' medical electronic and non-electronic records, and from the main hospital laboratory framework. Data were captured and managed on EXCEL. Demographic data, a list of commonly used medications, comorbidities, laboratory data sheets and prescribed medication multiplicity were prepared and used by investigators.

All registered elderly patients who visited family medicine chronic disease clinics (CDCs) and those involved in the Home Health Care (HHC) programme were included in this study; institutionalised patients were excluded. 798n patients were randomly selected through the patient registry programme, from the data registries at Wazarat Family Medicine Center and Home Health clinics. We excluded patients attending other hospitals, with multiple medication prescriptions.

2.1. Statistical analysis

Data were analysed using an SPSS software programme (version 20). Both descriptive and analytic statistics were applied. Percentages, mean and standard deviation were used for descriptive statistics. For analytical statistics, Chi squared test was applied for categorical data, and Student's t test and ANOVA were applied for numerical data. Statistical significance was considered at $p < 0.05$. The intended sample size

was 400 participants. We used Beers' criteria due to their wide use in clinical practice; they are the best-known criteria for identifying PIM use among the elderly (Nagendra Vishwas et al., 2012). Evidence-based methodology enabled the development of the AGS 2012 Updated Beers' Criteria, to help healthcare providers improve medication safety in older adults. To determine the number of PIMs, we applied the latest criteria by Beers et al., published in 2012, and a review of scientific literature. Apart from explaining the drugs and doses to be avoided among elderly persons, to prevent adverse effects, these criteria evaluate the severity of potential adverse effects. We did not record treatment duration and indication of any inappropriate prescribed drugs, due to difficulties with data documentation.

3. Results

The study participants were elderly, as defined by the World Health Organisation (WHO). The mean age was 75 years; with SD (75.2 ± 5.5) with no significant differences between CDC and HHC patients after using chi-square test. Female patients made up 62.2% of the sample. Table 1 and Fig. 1 depict common chronic diseases among elderly participants. The majority of patients were diabetic (73.9%), hypertensive (83.2%) and with lipid profile abnormalities (73.8%). Almost all participants had haemoglobin abnormalities (99.2%), with no significant difference between CDC and HHCS patients. About 64% had some renal impairment.

Table 2 and Fig. 2 depict the medication groups used by the patients. Iron supplements were the most commonly used (23.1%), followed by analgesics and opioids (17%). Different types of antipsychotics were used by 7.6% of the participants. Some patients were using two types of analgesic drugs (2%); few (0.1%) were using three types. Some patients (1%) were using two kinds of antipsychotics simultaneously.

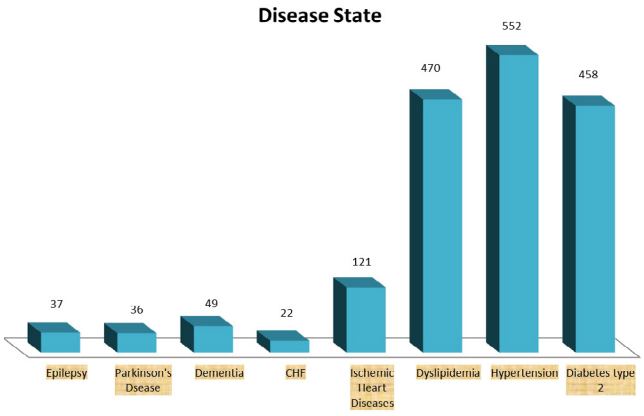

Figure 1 Participants' medical conditions.

Almost 52.5% of participants were using one or more PIMs as in Table 3. At least 17.3% were using two; the majority were using <4. One patient was using 10 PIMs simultaneously and another using 12.

Antispasmodics and muscle relaxants, tolterodine and chlorpheniramine, were frequently prescribed to 13 and 11 HHC patients respectively while two CDC patients were found to take tolterodine. Risperidone was one of the atypical antipsychotic medications prescribed to 39 HHC patients, and quetiapine to 29. Only one CDC patient was taking quetiapine. Other commonly prescribed medications were iron supplements (ferrous sulphate for 184 patients), oral muscle relaxants for 40 patients, hypoglycaemic (glibenclamide) for 49, diclofenac for 42 and tizanidine for 40. The most common PIM was a high dose of ferrous sulphate, in about 33% of the participants compared to the rest of the group ($p < 0.001$). There was no statistical difference between the two patient

Table 1 Age, sex and medical history of homecare and CDC patients.

	Total (n = 798)		Homecare (n = 663)		CDC (n = 135)		χ^2 test	p-Value
	No.	%	No.	%	No.	%		
Age								
Mean ± SD	75.2 ± 5.5		75.8 ± 5.4		72.2 ± 5.0		t = 7.067	<0.001*
Median (Q1–Q3)	75 (71–79)		76 (72–80)		72 (68–76)			
Gender								
Male	302	37.8	238	35.9	64	47.4		
Female	496	62.2	425	64.1	71	52.6	6.317	0.012*
Disorders								
Diabetes type 2 (DM2)	590	73.9	458	69.1	132	97.8	47.933	<0.001*
Hypertension (HTN)	664	83.2	552	83.3	112	83.0	0.007	0.933
Dyslipidaemia	589	73.8	467	70.4	122	90.4	23.053	<0.001*
Ischaemic heart disease (IHD)	136	17.0	121	18.3	15	11.1	4.044	0.044*
Congestive heart failure (CHF)	31	3.9	22	3.3	9	6.7	3.368	0.066
Dementia	50	6.3	49	7.4	1	0.7	8.445	0.004*
Parkinson's disease	37	4.6	36	5.4	1	0.7	5.578	0.018*
Seizure disorders	37	4.6	37	5.6	0	0.0	7.900	0.005*
Psychiatric diseases	193	24.2	188	28.4	5	3.7	37.175	<0.001*
Renal function test abnormality	511	64.0	417	62.9	94	80.3	13.397	<0.001*
Liver function test abnormality	5	0.6	3	0.2	2	1.5	Fisher	0.200
Haemoglobin (Hb) abnormality	792	99.2	657	99.1	135	100.0	1.231	0.267

* Statistically significant at $p < 0.05$.

Table 2 Frequency of use of PIMs by medication group (n = 798).

	Frequency	Percentage
Anticholinergics/muscle relaxants/antispasmodics		
1	39	4.9
Antipsychotics		
1	61	7.6
2	8	1
Antiepileptics		
1	0	0.0
Sedative-hypnotics		
1	6	0.8
Antihypertensives		
1	12	1.5
Antidepressants		
1	17	2.1
Skeletal muscle relaxants		
1	43	5.4
Anti-infectives		
1	2	0.3
Oral hypoglycaemics		
1	49	6.1
Analgesics and opioids		
1	119	14.9
2	16	2
3	1	0.1
Platelet aggregation inhibitors		
1	4	0.5
Antiarrhythmics		
1	7	0.9
Iron supplements		
1	184	23.1

Table 3 Total number of PIMs among participants (n = 798).

Total No. of medications	Frequency	Percentage
0	379	47.5
1	103	12.9
2	138	17.3
3	54	6.8
4	69	8.6
5	23	2.9
6	17	2.1
7	3	0.4
8	9	1.1
9	1	0.1
10	1	0.1
12	1	0.1

groups regarding the use of paracetamol combinations (see Table 4).

As in Table 5, and based on Mann–Whitney U test results, liver function had no significant influence on prescription decisions. Only kidney function profile had some influence. Twelve PIMs were prescribed to patients, without adjustment of their renal impairment profile. Analgesics and opioids were the most common PIMs for patients with renal insufficiency. There was a statistically significant difference regarding prescription of iron supplements, between patients with normal kidney function and those with renal impairment.

4. Discussion

Optimal drug therapy is essential in caring for elderly persons; worldwide, elderly patients use medication. A safe prescription method for elderly persons must include the decision as to whether a drug is indicated, choosing the best drug, determining a dose and schedule appropriate for the patient's physiologic status, monitoring for effectiveness and toxicity, educating the patient about expected side effects, and indications for seeking consultation. Polypharmacy and inappropri-

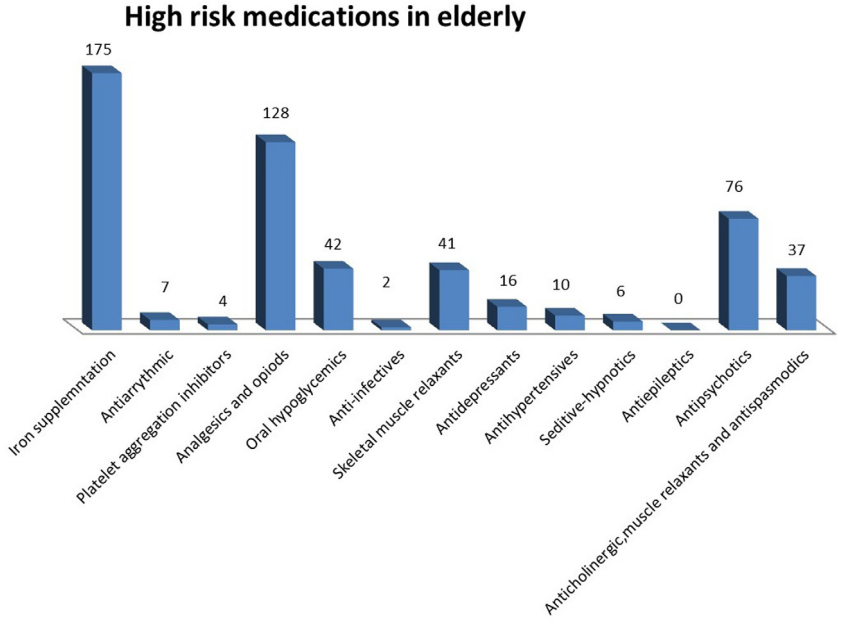

Figure 2 High-risk medications used by participants.

Table 4 Comparison of homecare and CDC patients' medication use.

	HHC (n = 663)		CDC (n = 135)		χ^2 test	p-Value
	1		2			
Anticholinergic muscle relaxants						
Oxybutynin	8	1.2	0	0.0	Fisher	0.364
Tolterodine	13	2.0	0	0.0	Fisher	0.141
Chlorpheniramine	11	1.7	0	0.0	Fisher	0.227
Hydroxyzine	2	0.3	0	0.0	Fisher	1.000
Hyoscyamine	1	0.2	0	0.0	Fisher	1.000
Scopolamine	2	0.3	2	1.5	Fisher	0.135
Antipsychotics						
Quetiapine	29	4.4	1	0.7	4.092	0.043*
Haloperidol	5	0.8	0	0.0	Fisher	0.596
Olanzapine	3	0.5	0	0.0	Fisher	1.000
Risperidone	39	5.9	0	0.0	8.349	0.004*
Sedative-hypnotics						
Diazepam	3	0.5	0	0.0	Fisher	1.000
Lorazepam	3	0.5	0	0.0	Fisher	1.000
Antihypertensives:						
Methyldopa	1	0.2	1	0.7	Fisher	0.310
Spironolactone > 25 mg	9	1.4	1	0.7	Fisher	1.000
Antidepressants						
Fluoxetine	4	0.6	0	0.0	Fisher	1.000
Clomipramine	1	0.2	0	0.0	Fisher	1.000
Amitriptyline	11	1.7	1	0.7	Fisher	0.702
Skeletal muscle relaxants						
Tizanidine	38	5.7	2	1.5	4.255	0.039*
Baclofen	3	0.5	0	0.0	Fisher	1.000
Anti-infectives						
Nitrofurantoin	2	0.3	0	0.0	Fisher	1.000
Oral hypoglycaemics						
Glibenclamide	42	6.3	7	5.2	0.257	0.612
Analgesics and opioids						
Ibuprofen	10	1.5	2	1.5	Fisher	1.000
Diclofenac	36	5.4	6	4.4	0.218	0.640
Paracetamol combination	80	12.1	18	13.3	0.167	0.683
Decongestant	2	0.3	0	0.0	Fisher	1.000
Platelet aggregation inhibitors						
Dipyridamole	4	0.6	0	0.0	Fisher	1.000
Antiarrhythmics						
Digoxin > 125 mcg	7	1.1	0	0.0	Fisher	0.609
Iron supplements						
Ferrous sulphate > 325 mg	175	26.4	9	6.7	24.607	< 0.001*

* Statistically significant at $p < 0.05$.

ately prescribed drugs cause many adverse events and, sometimes, are life threatening. Side effects are serious consequences of inappropriate prescriptions. In our study, 52.5% of the 798 elderly, CDC and homecare patients were on ⩾1 PIMs, as per Beers' criteria. One to two and five or more PIMs were prescribed to approximately 30% and 6.8% of the participants, respectively. We found less prevalence of PIMs among elderly persons in this context in Saudi Arabia, than in some Western countries (Hepler and Segal, 2003; Qato et al., 2008; Herings et al., 1995; Ay et al., 2005; Rajska-Neumann and Wieczorowska-Tobis, 2007).

The most common PIM was a high dose of ferrous sulphate (> 325 mg/day) among about 33% of the participants. This is due to the high prevalence of iron deficiency anaemia among the elderly. High dose of iron supplement may precipitate constipation, which in turn may induce abdominal pain, loss of appetite, frequent falls and social isolation. High iron doses were prescribed to 23% of surveyed patients, for no clear reason. This is problematic and predisposes participants to serious side effects. Analgesics and opioids were the second most prescribed medications, with ⩾1 type thereof taken by approximately 17%. According to previous studies, elderly

Table 5 Comparison of the number of PIM groups used, based on renal function tests (RFT).

	Normal Renal Function Test (n = 269)							Abnormal Renal Function Test (n = 511)							Mann–Whitney (*z*)	*p*
	Mean	SD	Min	Max	Median	Q1	Q3	Mean	SD	Min	Max	Median	Q1	Q3		
Anticholinergics/muscle relaxants/antispasmodics	0.1	0.2	0	1	0	0	0	0.0	0.2	0	1	0	0	0	−1.226	0.220
Antipsychotics	0.1	0.4	0	2	0	0	0	0.1	0.3	0	2	0	0	0	−1.680	0.093
Sedative-hypnotics	0.0	0.1	0	1	0	0	0	0.0	0.1	0	1	0	0	0	−0.802	0.423
Antihypertensives	0.0	0.1	0	1	0	0	0	0.0	0.1	0	1	0	0	0	−0.527	0.598
Antidepressants	0.0	0.1	0	1	0	0	0	0.0	0.1	0	1	0	0	0	−0.071	0.944
Skeletal muscle relaxants	0.1	0.2	0	1	0	0	0	0.1	0.2	0	1	0	0	0	−0.056	0.955
Anti-infectives	0.0	0.0	0	0	0	0	0	0.0	0.1	0	1	0	0	0	−1.027	0.305
Oral hypoglycaemics	0.0	0.2	0	1	0	0	0	0.1	0.3	0	1	0	0	0	−1.520	0.129
Analgesics and opioids	0.2	0.5	0	2	0	0	0	0.2	0.5	0	3	0	0	0	−1.139	0.255
Platelet aggregation–inhibitors	0.0	0.1	0	1	0	0	0	0.0	0.0	0	1	0	0	0	−1.708	0.088
Antiarrhythmics	0.0	0.1	0	1	0	0	0	0.0	0.1	0	1	0	0	0	−1.266	0.206
Iron supplements	0.4	0.5	0	1	0	0	1	0.2	0.4	0	1	0	0	0	−6.909	< 0.001*
Total No. medications	1.7	2.0	0	10	1	0	3	1.3	1.8	0	12	0	0	2	−3.209	0.001*

* Statistically significant at $p < 0.05$.

patients require more analgesic prescriptions than do non-clinical adult populations (Pitkala et al., 2002). This could be because elderly persons experience multiple medical problems and pain, due to chronic diseases like osteoarthritis, muscular pain, headaches and joint pains. Sometimes, a physician may not have sufficient skills to care for elderly patients or time to scrutinise patient history and physical examination, to determine the exact medical problem.

In this study, antipsychotic medications were the third most commonly prescribed drugs (8.6%). Despite the strong recommendation against prescription of antipsychotics to older patients, unless necessary, more than 69 patients received $\geqslant 1$ thereof. Anti-psychotic medications reportedly predispose elderly patients to falls, fractures, sleep problems and driving problems (AGSP, 2009). Scientific geriatric organisations warn physicians against prescribing antipsychotic drugs to elderly persons for periods exceeding four weeks, to avoid serious side effects. The United States Food and Drug Administration (FDA) cautions against prescription of antipsychotics to elderly persons, due to the increased risk of cardiovascular mortality resulting from chronic use (Qato et al., 2008). Aspirin and clopidogrel were the least prescribed medications. The potential, serious side effects on the elderly include gastrointestinal upsets, gastric bleeding and bleeding disorders. The most common PIMs in our study were antipsychotics, tricyclic antidepressants, anticholinergics/muscle relaxants/antispasmodics, antiepileptics, sedative-hypnotics, antihypertensive, skeletal muscle relaxants, anti-infectives, oral hypoglycaemics, analgesics and opioids, platelet aggregation-inhibitors, antiarrhythmics, and iron supplements.

The possibility of an ADE should always be considered when evaluating elderly patients; any new symptom should be considered drug-related, until proven otherwise. Pharmacokinetic changes lead to increased plasma drug concentrations, and pharmacodynamic changes to increased drug sensitivity in older adults (Avorn et al., 1989). Various criteria have been introduced for identifying medications to avoid prescribing, or to prescribe cautiously, in older adults. Compliance with these is suboptimal. Clinicians could address this by avoiding overly prescribing inappropriate drug therapies. ADEs result in four times as many hospitalisations in elderly patients as in younger adults (AGSP, 2009). Prescription of cascades, drug–drug interactions and inappropriate drug doses result in preventable ADEs. Prescription of PIMs, as shown in this study, is a concern for elderly patients attending outpatient clinics and home residents; atypical antipsychotics, iron overdose, benzodiazepines and opioids are most commonly prescribed inappropriately. A step-wise approach towards prescriptions for older adults should include periodic review of current drug therapy; discontinuation of unnecessary medications; consideration of non-pharmacologic alternative strategies; consideration of safer, alternative medications; and prescription of the lowest possible effective dose and necessary beneficial medications only.

References

American Geriatrics Society Panel on Pharmacological Management of Persistent Pain in Older Persons, 2009. Pharmacological management of persistent pain in older persons. J. Am. Geriatr. Soc. 57, 1331–1346.

Al-Omar, H.A., Al-Sultan, M.S., Abu-Auda, H.S., 2012. Prescribing of potentially inappropriate medications among the elderly population in an ambulatory care setting in a Saudi military hospital: trend and cost. Geriatr. Gerontol. Int. 13, 616–621. http://dx.doi.org/10.1111/j.1447-0594.2012.00951.x.

Avorn, J., Dreyer, P., Connelly, K., Soumerai, S.B., 1989. Use of psychoactive medication and the quality of care in rest homes. Findings and policy implications of a statewide study. N. Engl. J. Med. 320, 227–232.

Ay, P., Akici, A., Harmanc, H., 2005. Drug utilization and potentially inappropriate drug use in elderly residents of a community in Istanbul, Turkey. Int. J. Clin. Pharmacol. Ther. 43, 195–202.

Beers, M.H., Ouslander, J.G., Rollingher, I., Reuben, D.B., Brooks, J., Beck, J.C., 1991. Explicit criteria for determining inappropriate medication use in nursing home residents: UCLA Division of Geriatric Medicine. Arch. Intern. Med. 151, 1825–1832.

Beijer, H.J., de Blaey, C.J., 2002. Hospitalisations caused by adverse drug reactions (ADR): a meta-analysis of observational studies. Pharm. World Sci. 24 (2), 46–54.

Brekke, M., Rognstad, S., Straand, J., Furu, K., Gjelstad, S., Bjørner, T., et al, 2008. Pharmacologically inappropriate prescriptions for elderly patients in general practice: how common? baseline data from The Prescription Peer Academic Detailing (Rx-PAD) study. Scand. J. Prim. Health Care 26, 80–85.

Buajordet, I., Ebbesen, J., Erikssen, J., Brørs, O., Hilberg, T., 2001. Fatal adverse drug events: the paradox of drug treatment. J. Intern. Med. 250, 327–341.

Byles, J.E., Heinze, R., Nair, B.K., Parkinson, L., 2003. Medication use among older Australian veterans and war widows. Intern. Med. J. 33, 388–392.

Chang, C.B., Chan, D.C., 2010. Comparison of published explicit criteria for potentially inappropriate medications in older adults. Drugs Aging 27, 947–957.

Chin, M.H., Wang, L.C., Jin, L., Mulliken, R., Walter, J., Hayley, D. C., et al, 1999. Appropriateness of medication selection for older persons in an urban academic emergency department. Acad. Emerg. Med. 6, 1223–1242.

Col, N., Fanale, J.E., Kronholm, P., 1990. The role of medication noncompliance and adverse drug reactions in hospitalizations of the elderly. Arch. Intern. Med. 150, 841–845.

Doshi, J.A., Shaffer, T., Briesacher, B.A., 2005. National estimates of medication use in nursing homes: findings from the 1997 medicare current beneficiary survey and the 1996 medical expenditure survey. J. Am. Geriatr. Soc. 53 (3), 438–443.

Fick, D.M., Semla, T.P., 2012. American Geriatrics Society Updated Beers Criteria for potentially inappropriate medication use in older adults. J. Am. Geriatr. Soc. 10, 1532–5415.

Fick, D.M., Waller, J.L., Maclean, J.R., Heuvel, R.V., Tadlock, J.G., Gottlieb, M., et al, 2001. Potentially inappropriate medication use in a Medicare managed care population: association with higher costs and utilization. J. Manag. Care Pharm. 7, 407–413.

Fick, D.M., Cooper, J.W., Wade, W.E., Waller, J.L., Maclean, J.R., Beers, M.H., 2003. Updating the Beers criteria for potentially inappropriate medication use in older adults: results of a US consensus panel of experts. Arch. Intern. Med. 163, 2716–2724.

Goldberg, R.M., Mabee, J., Chan, L., Wong, S., 1996. Drug-drug and drug-disease interactions in the ED: analysis of a high-risk population. Am. J. Emerg. Med. 14, 447–450.

Handler, S.M., Wright, R.M., Ruby, C.R., Hanlon, J.T., 2006. Epidemiology of medication-related adverse events in nursing homes. Am. J. Geriatr. Pharmacother. 4, 264–272.

Hepler, C.D., Segal, R., 2003. Preventing Medication Errors and Improving Drug Therapy Outcomes: A Management Systems Approach. CRC Press, Boca Raton, FL, p. 520 (ISBN: 0-8493-1576-X).

Herings, R.M., Stricker, B.H., de Boer, A., Bakker, A., Sturmans, F., 1995. Benzodiazepines and the risk of falling leading to femur

fractures. Dosage more important than elimination half-life. Arch. Intern. Med. 155, 1801–1807.
Kaufman, D.W., Kelly, J.P., Rosenberg, L., Anderson, T.E., Mitchell, A.A., 2002. Recent patterns of medication use in the ambulatory adult population of the United States: the Slone Survey. EDJAMA 287 (3), 337–344.
Klarin, I., Wimo, A., Fastbom, J., 2005. The association of inappropriate drug use with hospitalization and mortality: a population-based study of the very old. Drugs Aging 22, 69–82.
Lazarou, J., Pomeranz, B.H., Corey, P.N., 1998. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. JAMA 279, 1200–1205.
Mallet, L., Spinewine, A., Huang, A., 2007. The challenge of managing drug interactions in elderly people. Lancet 370, 185–191.
Nagendra Vishwas, H., Harugeri, A., Parthasarathi, G., Ramesh, M., 2012. Potentially inappropriate medication use in Indian elderly: comparison of Beers' criteria and screening tool of older persons' potentially inappropriate prescriptions. Geriatr. Gerontol. Int. 12 (3), 506–514.
Pitkala, K.H., Strandberg, T.E., Tilvis, R.S., 2002. Inappropriate drug prescribing in home-dwelling, elderly patients: a population-based survey. Arch. Intern. Med. 162, 1707–1712.
Qato, D.M., Alexander, G.C., Conti, R.M., Johnson, M., Schumm, P., Lindau, S.T., 2008. Use of prescription and over-the-counter medications and dietary supplements among older adults in the United States. JAMA 300, 2867–2878.
Rajska-Neumann, A., Wieczorowska-Tobis, K., 2007. Polypharmacy and potential inappropriateness of pharmaco-logical treatment among community-dwelling elderly patients. Arch. Gerontol. Geriatr. 44, 303–309.
Spinewine, A., Swine, C., Dhillon, S., Lambert, P., Nachega, J.B., Wilmotte, L., et al, 2007. Effect of a collaborative approach on the quality of prescribing for geriatric inpatients: a randomized, controlled trial. J. Am. Geriatr. Soc. 55, 658–865.
Annual report of the regional director, country statistical profile, 2011. Geneva, World Health Organization; (updated 2011 May 16; cited 2015 Jul 8). Available from: http://www.who.int/about/en/.
Williams, C.M., 2002. Using medications appropriately in older adults. Am. Fam. Physician 66, 1917–1924.