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Prescribing for geriatrics in Tehran; is it appropriate and rational?

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Abstract

Background: The world's population is growing older. Inappropriate and irrational use of drugs in the elderly is a considerable health concern due to consequences such as increased morbidity and adverse drug events. This study aimed to evaluate the rationality of prescribing and determining the extent of inappropriate prescribing in a sample of geriatric patients in Tehran.

Methods: This cross sectional study was performed on 1512 prescriptions of patients aged ≥ 65 years from 5 pharmacies affiliated to Tehran University of Medical Sciences in 2014. Prescription of potentially inappropriate medications (PIMs) was investigated using the Beers Criteria along with WHO prescribing indices. Date were analyzed using SPSS software, and significance level was set at less than 0.05.

Results: Mean (SD) age of patients was 73.9(6.7) years. A total of 472 (31.2%) patients received at least 1 PIM. Benzodiazepines were the most frequent drug class and general practitioners (GPs) were the most frequent prescriber of PIMs. The highest and the lowest percentage of prescriptions containing brand-names were prescribed by subspecialists (62.5%) and GPs (42.2%), respectively. Antibiotics and injectable medications were prescribed for 26.8% and 28.5% of patients by GPs. Mean (SD) number of drugs per prescription was 3.57 (1.92). Prescriptions containing systemic antibiotics and PIMs had significantly higher mean number of drugs compared to those without these items (both $P < 0.001$).

Conclusion: There is a need for interventions to improve the quality of prescribing for elderly patients, especially by GPs. Also, there are still some problems in rational use of drugs based on prescribing indices, especially, prescribing brand-names and injectable medications.

Keywords: Aged, Beers criteria, potentially inappropriate medication list, Inappropriate prescribing, Drug prescriptions, World Health Organization prescribing indices, Antibacterial agents, Injections

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Introduction

Older people often experience higher prevalence of chronic and multiple diseases that may lead to increased medication use (1). Moreover, prescribing for elderly is challenging due to altered pharmacokinetics, pharmaco-

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↑What is "already known" in this topic:
Potentially inappropriate medications (PIMs) can predispose geriatrics to adverse drug events. Additionally, WHO prescribing indices can help to determine the rationality of administrations. Using the prescriptions, rather than the insurance claim data, can provide a more precise picture that can help to identify the prescribing problems and target the interventions more effectively.

→What this article adds:
Almost one-third of the patients received at least 1 PIM based on the Beers Criteria in Tehran, and general practitioners prescribed PIMs more frequently. On average, patients received 3.57 medications per prescription. Only 76.77% of all drugs were prescribed by generic names. Vitamins and corticosteroids were among the top injectable medications in this study.

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dynamics, and age-related changes in body composition and physiology (2). In previous studies, it has been shown that medication use increases with age in developed countries. It is not surprising that elderly are the highest group of drug consumers (3). Prescribing inappropriate medications for the elderly that result in wastage of health care resources due to adverse drug reactions (ADRs) is now a considerable concern (4). These medications can cause fall, fracture, delirium, and other preventable adverse drug events (5). In fact, it has been demonstrated that inappropriate prescribing can lead to mortality and morbidity along with the need for health care utilization in the elderly (6). Generally, inappropriate medications are defined as the medications that "pose more risk than benefit". Medications that are administered with either inappropriate dose/duration or drugs that can expose patients to considerable drug-drug or drug-disease interactions can also be included among the inappropriate medications (6). The importance of the detection of inappropriate prescribing is more pronounced considering the population aging. It is predicted that by 2020 the world will have 1 billion habitants older than 60 years of age, representing 22% of the global population (7). Iran is no exception (8), and it has been demonstrated that "the structure of the age pyramid has been reversed" in Iran in the last 2 decades (9).

Validated screening tools have been developed to identify potentially inappropriate medications (PIMs) in older adults. Among explicit prescribing indicators, the Beers Criteria is the most frequently cited tool to detect PIMs (4) and was first published in 1991 when used to assess medications of the residents of nursing homes (10). Then, it was expanded in 1997 to include "community-dwelling elderly" (11), revised in 2003 (12), and updated later (13). The 2012 version of the Beers Criteria divide inappropriate medications into 3 categories: (1) PIMs in older adults, (2) PIMs in older adults due to drug–disease or drug–syndrome interactions that may exacerbate the disease or syndrome, and (3) PIMs to be used with caution in older adults (13).

Another important issue in pharmacotherapy is the rational use of drugs. Based on the World Health Organization (WHO), use of drugs is considered rational when "patients receive medications appropriate to their clinical needs, in doses that meet their own individual requirements for an adequate period of time, and at the lowest cost to them and their community" (14). It was proposed that in developing countries, using WHO indicators for the evaluation of prescribing is important for promoting the rational use of drugs (14). The average number of drugs per prescription, the percentage of antibiotics, injectable drugs, drugs prescribed by generic name, and drugs prescribed from the essential drug list are among the prescribing indices developed by WHO (15). The average number of drugs per prescription was reported 1.3 to 2.2 in developed countries and 1.4 to 4.8 in developing countries in the general population (16). According to the WHO International Network of Rational Use of Drugs (INRUD), the optimal mean number of drugs per prescription is 3 or fewer. Additionally, the optimum percentage of prescriptions containing antibiotics and injectable drugs are up to 30% and 10%, respectively. Moreover, all of the drugs should be prescribed by generic name and within the essential drug list (17).

Considering the importance of assessing rational drug use and identifying the extent of inappropriate prescribing for geriatrics, which has not been widely documented in Iran, this study was conducted. In fact, having knowledge about the prevalence and quantifying the problem can help researchers to conduct interventional studies to improve medication therapy. Thus, the aim of the present study was to find the prevalence of prescribing PIMs using the Beers Criteria. Additionally, we intended to assess the rationality of prescribing using the WHO prescribing indices in a sample of geriatric prescriptions.

Methods

Study design

This retrospective cross sectional study, conducted from January to March 2014, was part of a project that evaluated different aspects of pharmacotherapy for outpatient geriatrics (18, 19). Data of 1512 insurance prescriptions of patients aged ≥ 65 years were collected from 5 pharmacies (Amini, Booali, Isar, Taleghani and Abedini) affiliated to the Faculty of Pharmacy, Tehran University of Medical Sciences (TUMS). The study was approved by the ethic committee of TUMS.

At the time of the study, there were 4 main insurance organizations that paid medical expenses of the majority of the population in Iran. Number of prescriptions from insurance organizations was determined based on the proportion of the population under their coverage. The data of prescriptions, including the specialty of the prescriber, number, dosage form, dose of each medicine, and the demographics of patients were entered into Excel (Microsoft office). Physicians were categorized based on both their specialty and their level of education. To compare different medical specialty branches, all specialists and subspecialists of the same branch were assessed together.

Investigation of PIMs

The 2012 version of the Beers Criteria was applied to identify PIMs prescribed for older adults (13). Inappropriate medications that should generally be avoided regardless of the drug–disease or drug–syndrome interactions were evaluated in this study. Selection of this category was due to the unavailability of medical records of patients in pharmacies. However, in the selected list, which included 34 medications or medication classes, there were still items that needed some modifications. The medications of the mentioned category were divided into 2 groups: the first group "the generally inappropriate medications (GIM)" consisted of the items that the criteria recommended to be avoided or the researcher could determine their appropriateness based on the criteria using the prescription data; the second group included medications whose appropriateness could be judged only based on additional data.

In fact, based on the selected list of the criteria, several drugs should be considered inappropriate if they are prescribed exceeding a certain dose (eg, doxepin > 6 mg/d

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and digoxin >0.125 mg/d) or duration (eg, zolpidem > 90 days, nitrofurantoin for long-term suppression). For some medications, prescribing for special indications are deemed to be inappropriate: i.e. α_1 blockers for hypertension; antipsychotics for behavioral problems of dementia unless non-pharmacological options have failed and the patient is a threat to self or others; clonidine as a first-line antihypertensive, and benzodiazepines for the treatment of insomnia, agitation, or delirium. Moreover, in some cases, medications are considered inappropriate if they are prescribed for patients with special medical conditions such as nitrofurantoin in creatinine clearance < 60 mL/min.

Among the above-mentioned cases, whenever the appropriateness could be judged based on the prescription data, the medications were categorized in the GIM group. The complete list of the modified Beers Criteria is available in Supplementary Table 1. Whenever the data that could help to clarify the appropriateness of the medications were not provided in the prescriptions, the medications were considered to be conditionally inappropriate medications (CIMs). Moreover, the total number of PIMs was calculated by summing up the number of encounters with GIM and CIM.

Prescribing indices

The core drug use indicators of the WHO were used (15): percentage of medicines prescribed by generic name, number of drugs per prescription, and percentage of encounters with injectable drugs and antibiotics.

Antibiotics were selected based on the WHO model list presented by INRUD (20). To have a more comprehensive list, several antibiotics were added from the essential drug list of the WHO. For example, since ciprofloxacin is included in the WHO model list, levofloxacin the same class agent, was added as well. Other drugs that were added due to their similarities were nalidixic acid, ofloxacin, gemifloxacin, moxifloxacin, tetracycline, amikacin, streptomycin, tobramycin, and gentamicin. Additionally, several cephalosporins (cefuroxime, ceftizoxime, and cefepime) and penicillins (benzathine salt of phenoxymethyl penicillin), along with ampicillin/sulbactam, piperacillin/tazobactam and meropenem, were added to the list. Moreover, different strength of the included dosage forms of the medications were included. The ophthalmic dosage form of ofloxacin, ciprofloxacin, and erythromycin were also included in the antibiotic list since their systemic dosage forms were already in the list. The complete list of the antibiotics that was used in the present study is available in Supplementary Table 2.

To evaluate the extent of generic-name prescribing, medication names listed in Iran Drug List were considered as generic names. Others, including the name of herbal medicines and branded generics, were considered as brands.

Polypharmacy was defined as the presence of 5 or more drugs per prescription. Moreover, due to the tendency of the elderly patients to use herbal medicines, this category of drugs was reported separately.

Statistical analysis

Descriptive statistics were reported using mean (SD) for quantitative variables and frequency (percentage) for the qualitative. The mean number of inappropriate medications and the number of prescribed drugs within different prescribers' educational levels and specialties were compared using Kruskal-Wallis test. Number of drugs prescribed as CIM, GIM, and PIM per prescription were also compared by Kruskal-Wallis test. In addition, the comparison between the number of inappropriate medications and the number of prescribed drugs was performed using the Spearman's correlation. Date were analyzed using the SPSS software, and significance level was set at less than 0.05.

Results

A total of 1512 prescriptions containing 5450 drugs, which were obtained from 5 pharmacies affiliated to TUMS, were evaluated in this study. The mean (SD) age of the patients was 73.9(6.7) years, and 790 (52.4%) patients were male. General practitioners (GPs), by 474 (31.3%) prescriptions, were the largest group of prescribers followed by internists and cardiologists among the specialists (357 and 214 prescriptions, respectively).

PIM

At least 1 GIM and CIM was detected in 399 (26.4%) and 125 (8.3%), prescriptions respectively. From 5450 medications in the prescriptions, 481 (8.25%) and 132 (2.4%) drugs were among the GIMs and CIMs, respectively. In fact, in 472 (31.2%) prescriptions, at least 1 PIM was encountered, which consisted of 613 (11.24%) medications (Table 1).

The mean (SD) number of GIMs, CIMs, and PIMs per prescription was 0.32 (0.57), 0.09 (0.29), and 0.40 (0.67), respectively. The most frequent GIMs were chlorpheniramine (n=86, 17.9%), glibenclamide (n=66, 13.72%), alprazolam (n=55, 11.4%), chlordiazepoxide (n=29, 6%), clonazepam (n=26, 5.4%), clidinium-c (n=25, 5.2%), and prazosin (n=21, 0.43%). Among the CIMs, diphenhydramine (n=40, 30.3%) was the most frequently prescribed medication (Tables 2 and 3). Benzodiazepines (n=153) and anticholinergics (n=140) were the most frequently

Table 1. Frequency of inappropriate medications in prescriptions

Categories of Inappropriate Medications	Number of Inappropriate Medications in Prescriptions				
	0	1	2	3	4
	N (%)	N (%)	N (%)	N (%)	N (%)
CIM	1387(91.7)	118(7.8)	7(0.5)	0	0
GIM	1113(73.6)	321(21.2)	74(4.9)	4(0.3)	0
PIM	1040(68.8)	349(23.1)	107(7.1)	14(0.9)	2(0.1)

N: Number of prescriptions, CIM: Conditionally Inappropriate Medications, GIM: Generally Inappropriate Medications, PIM: Potentially Inappropriate Medications

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Table 2. Frequency of prescribed conditionally inappropriate medications (drugs/drug class)

	CIM drugs or drug class	n
1	Antipsychotics	45
2	Anticholinergics	40
3	Spironolactones	19
4	Antiarrhythmics	10
5	Metoclopramide	9
6	Estrogens	5
7	Digoxin	4
	Total	132

CIM: Conditionally Inappropriate Medications

Table 3. Frequency of prescribed generally inappropriate medications (drugs/drug class)

	GIM drugs or drug class	n
1	Benzodiazepines	153
2	Anticholinergics	100
3	Sulfonuurea, Antidiabetics	66
4	Antispasmodics	43
5	Alpha Blockers	25
6	Tricyclic Antidepressants	21
7	Muscle Relaxants	16
8	Antithrombotics	12
9	Indomethacin	12
10	Non-Steroidal Anti-Inflammatory Drugs	9
11	Ketorolac	7
12	Antiparkinson agents	5
13	Digoxin	3
14	Thioridazine	3
15	Barbiturates	2
16	Nifedipine	2
17	Estrogen	1
18	Non-Benzodiazepine Hypnotics	1
	Total	481

GIM: Generally Inappropriate Medications

prescribed medication classes considered inappropriate in this survey.

GPs were responsible for the highest proportion of potentially inappropriate prescribing compared to other prescribers' groups. We found at least 1 PIM in 228 prescriptions by GPs (48.1%). Among specialists with > 50 prescriptions, PIMs were more frequently prescribed by neurologists (26 prescriptions, 38.8%). Cardiologists (54 prescriptions, 25.2%) and internists (90 prescriptions, 25.2%) were the following groups of specialists with similarly high frequency of prescribing inappropriate medications. Additionally, it was found that the differences between the mean numbers of inappropriate medications per prescription were statistically significant among prescribers with various educational levels (Table 4). This significant difference was also found in multiple comparisons.

The results of this study showed that the mean number of drugs in prescriptions with at least 1 CIM, GIM, and PIM were significantly higher than the prescriptions that did not contain them (4.4 vs 3.5, 4.5 vs 3.2, and 4.4 vs 3.1 for prescriptions with and without CIM, GIM, and PIM, respectively $p<0.001$ in all cases).

Prescribing indices

The mean (SD) number of drugs per prescription was 3.57 (1.92) and ranged from 1 to 10. Prevalence of polypharmacy in the prescriptions by GPs, internists, and cardiologists was 14.5%, 19.3%, and 29.9%, respectively. Totally, polypharmacy was detected in 29.9% of prescriptions. Moreover, the mean number of medicines per prescription was higher in women's prescriptions (3.7) vs men's (3.4) ($p<0.001$).

Among the total medications, 1266 (23.22%) prescribed items were brand-name drugs. The highest and lowest percentage of prescriptions with at least 1 brand-name drug was prescribed by subspecialists (62.5%) and GPs (42.2%), respectively. Cardiologists (76.6%), neurologists (70.1%), and orthopedists (62.7%) had the higher percentages of prescriptions with at least 1 of brand-name medication among the specialists, respectively.

This study showed that 352 (23.3%) prescriptions included at least 1 injectable drug. Orthopedists (54.9%), GPs (28.5%), and internists (24.6%) were the first 3 groups with higher percentage of injectable drugs in the prescriptions, respectively.

Overall, 271 (18.0%) prescriptions included at least 1 antibiotic. The mean (SD) number of antibiotics was 0.22 (0.52) per prescription and consisted of 0.21 (0.50) systemic, and 0.01 (0.11) topical agents. GPs (26.8%), ophthalmologists (15.4%), and internists (14%) had higher percentages of antibiotics in their prescriptions. It was also found that 52.6% of local antibiotics were prescribed by ophthalmologists. Prescriptions with at least 1 systemic antibiotic had significantly higher mean number of drugs per prescription compared to prescriptions without these medications (3.9 vs 3.1 respectively, $p<0.001$).

Herbal drugs were prescribed for 73 (4.8%) patients. Orthopedists were the most frequent prescribers of herbal medicines (11.8% of their prescriptions). The most frequent injectable drugs, herbal medicines, local and systemic antibiotics, and brand-name drugs are summarized in Table 5.

Prescribing indices in the prescriptions by GPs

The mean (SD) number of drugs in prescriptions was 3.63 (1.8), and the mean (SD) number of brand-name drugs in these prescriptions was 0.56 (0.8) which consisted of 267 items (15.49%). In the prescriptions of GPs, 127

Table 4. Mean number of potentially inappropriate medications in the prescriptions of prescribers with different level of education

Specialty	Mean number of CIM (SD)¥	Mean number of GIM (SD)	Mean number of PIM (SD)
General practitioner (n=474)	0.1(0.32)	0.54(0.69)	0.64(0.77)
Resident (n=115)	0.09(0.32)	0.13(0.42)	0.22(0.57)
Specialist (n=620)	0.09(0.30)	0.25(0.51)	0.34(0.64)
Subspecialist (n=296)†	0.04(0.21)	0.19(0.39)	0.23(0.46)
P value ‡	0.015	<0.001	<0.001

¥ Mean numbers are reported per prescription
† The remaining 7 prescriptions were written by dentists
‡ Kruskal Wallis Test
CIM: Conditionally Inappropriate Medications, GIM: Generally Inappropriate Medications, PIM: Potentially Inappropriate Medications

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Table 5. The most frequently prescribed injectable drugs, herbal drugs, antibiotics, and brand-name drugs in 1512 prescriptions

Injectable drugs		Herbal drugs		Brand-name drugs		Systemic antibiotics	
Drug	n (%)	Drug	n (%)	Drug	n (%)	Drug	n (%)
Amp Vitamin D3	58 (11.1)	Tab C lax	15 (18.7)	N.C®	115 (9.1)	Tab Cefixime200 mg	55 (17.1)
Amp Betamethasone 4 mg	30 (5.7)	Syr Thymex	10 (12.5)	Tab Metoral® 50 mg	105 (8.3)	Tab Ciprofloxacin 500 mg	41 (12.7)
Amp Dexamethasone 8 mg	30(5.7)	Syr Prospan	7 (8.7)	Tab Lozar® 25 mg	69 (5.4)	Cap Azithromycin 250 mg	30 (9.3)
Amp Vitamin B complex	28 (5.4)	Drop C.M	5 (6.6)	Tab Lasix® 20 mg	36 (2.8)	Cap Amoxicillin 500 mg	29 (9.0)
Amp Vitamin B12	23 (4.4)	Cap Pias-clidin	5 (6.6)	Spray Atrovent®	33 (2.6)	Cap Cephalexin 500 mg	21 (6.5)
Vial Insulin NPH	22 (4.2)	Oint Rose-mari	4 (5.0)	Amp Neurobion®	28(2.2)	Tab Metronidazole 250 mg	18(5.6)
Pen Insulin Novomix®	15 (2.9)	Oint Rahamin	3 (3.7)	Tab Amlopress® 5 mg	27 (2.1)	Tab Cefixime 400mg	14 (4.3)
Amp Enoxaparin40 mg	15 (2.9)	Cream Depi	3 (3.7)	Tab Plavix®	26 (2.0)	Vial Cefazolin 1 gr	12 (3.7)
Vial Insulin Regular	14 (2.7)	Tab Ginkgo	3 (3.7)	Spray Seretid® 250 mic	25 (2.0)	Vial Penicillin Ben-zathine 1200000	11 (3.4)
Amp Piroxicam20 mg	13 (2.5)	Drop Pros-tatan	3 (3.7)	Tab Sustac® 2.6	24 (1.9)	Vial Ceftriaxone 1g	11(3.4)

Injectable drugs: n = 521 in 352 prescriptions, Herbal drugs: n = 80 in 73 prescriptions, Brand-name drugs: n = 1266 in 824 prescriptions, Systemic antibiotics: n = 322 in 259 prescriptions, Topical antibiotics: n = 19 in 19 prescriptions.
Cap Coamoxiclave 625 mg was prescribed with the same frequency as the vial Penicillin Benzathine and vial Ceftriaxone 1g
Amp: Ampule, Tab: Tablet, Syr: Syrup, Cap: Capsule, Oint: Ointment
Topical antibiotics (not shown in the table) were 19 items in 19 prescriptions. They consisted of Eye Drop Erythromycin 6 (31.7%), Eye Drop Ciprofloxacin 5 (26.3%), Eye Oint Tetracycline 4 (21.0%), and Oint Mupirocin 4 (21.0%).

Table 6. Frequency of prescribing injectable drugs, brand-name agents, antibiotics, herbal-drugs, and mean number of agents in the prescriptions of the largest groups of prescribers

Indices			GP (n=474)	Internists (n=357)	Cardiologists (n=214)	Ophthalmologists (n= 78)
Mean number of Drugs per prescription (SD)			3.63 (1.77)	3.63 (1.99)	4.46 (2.18)	2.39 (1.10)
Injectable drugs	Prescriptions with at least one n (%)		135 (28.5)	88 (24.6)	21 (9.8)	1 (1.3)
	Mean number per prescription (SD)		0.47(0.87)	0.33(0.63)	0.12 (0.37)	0.01(011)
Brand-names	Prescriptions with at least one n (%)		199 (42.0)	220 (61.6)	164 (76.6)	44 (56.4)
	Mean number per prescription (SD)		0.56(0.77)	0.96 (0.98)	1.48 (1.23)	0.69 (0.70)
Antibiotics	Prescriptions with at least one n (%)	Systemic	127 (26.8)	49 (13.7)	10 (4.7)	5 (6.4)
		Topical	1 (0.2)	2 (0.6)	0	10 (12.8)
		Total	127 (26.8)	50 (14.0)	10 (4.7)	12 (15.4)
	Mean number per prescription (SD)	Total	0.34 (0.61)	0.17 (0.47)	0.05 (0.24)	0.19 (0.48)
Herbal drugs	Prescriptions with at least one n (%)		31 (6.5)	16 (4.5)	2 (0.9)	0
	Mean number per prescription (SD)		0.07 (0.28)	0.05 (0.24)	0.01 (0.09)	0.00 (0.00)

GP: general practitioners

(26.8%) and 135 (28.5%) prescriptions contained at least 1 systemic antibiotic and injectable drugs, respectively (Table 6).

Discussion

In the present study, the prescribing indicators and inappropriate medications were investigated in a sample of geriatric prescriptions. We found that 31.2% of the patients were exposed to at least 1 PIM. This consisted of both CIMs and GIMs, which were observed in 8.3% and 26.4% of the prescriptions, respectively. The frequency of PIMs in this study was similar to the previous studies in Iran that reported the frequency of 20%-30% based on the Beers Criteria. However, the studies were conducted using either the 2003 or 1997 version of the criteria (21-24). To the best of the authors' knowledge, the only study that was performed with the 2012 version of the criteria in Iran was the study by Talebi-Taher et al on hospitalized geriatric patients (25). They reported the frequency of PIMs to be 22.3%. Due to the availability of patients' charts in the hospital, it was assumed that the researchers could have detected drug–disease interactions. However, the study method was vague and data were not presented clearly.

Benzodiazepines were the most frequently prescribed inappropriate class of medications in this study, which is consistent with several other reports that showed benzodiazepines among the top frequently prescribed inappropriate drug classes (22, 23, 25). Studies from Turkey, Lebanon (21), Irland (26) and Japan (27) reported the prevalence of PIMs to be 9.8%, 22%, 25%, and 43.6% according to the previous versions of the Beers Criteria, respectively. PIM prescribing based on the 2012 updated criteria was documented in some studies in different countries and ranged from 16% among Indian inpatients (28) to 59.2% in Brazilian aged population (29). Similar studies in Nigeria (30), India (31), and New Zealand (32) reported the frequency of PIMs to be 25.5%, 21.8%, and 42.7%, respectively. The diversity in the prevalence of PIMs reported in various studies can be to some extent attributed to the difference in the availability of inappropriate medications in the countries, differences in patients (31), and the accessibility of medical charts in the study

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settings. In addition, whether the practitioners included only GPs or the specialists, could also make a difference. Moreover, evaluating a single prescription or all the medications used by patients may lead to different results. For example, in a study by Baldoni et al, not only the current medications of the patient but also the medication used within the preceding month were evaluated (29). In one study in Japan, all the prescriptions of patients during the study period were evaluated and only those patients with at least 2 pharmacy claims during the study period were included (27). The considerable point is that both studies reported a high prevalence of PIM.

The most common GIMs prescribed in the present study were chlorpheniramine, glibenclamide, alprazolam, and chlordiazepoxide. Similarly, antihistamines in Nigeria (30) and both chlorpheniramine and alprazolam in India (31) were among the prevalent prescribed PIMs. The recently reported prevalence of PIMs in a large American survey was 30.9% using the qualified definition of the 2012 Beers Criteria (33). With an acceptable agreement with the method of the present study, the study by Davidoff et al generated 2 definitions for PIMs using the Beers 2012 Criteria based on the specific restrictions related to dose, route, duration, and medical conditions. The "broad definition" in which special route and dose of drugs were considered inappropriate in the elderly was almost comparable to the GIMs in the present study. In the same way, the "qualified definition" in their study was similar to the CIMs in this study, considering more restrictions such as duration and medical conditions. The main difference between the 2 studies was the unavailability of patients' diagnosis, coexisting diseases, and medical conditions in the present study. Among the 5 most frequently prescribed categories of PIMs, benzodiazepines, first generation antihistamines, and sulfonylureas were similar inappropriate medications in the present study as well as in the study by Davidoff et al (33).

The evaluation of rational prescribing based on the WHO prescribing indices has been previously performed in several studies (16, 34-37). WHO indicators were not primarily developed for the elderly; rather, they are assessment tools for GPs' prescribing practice, irrespective of patients' age.

The average number of drugs per prescription in this study was 3.57, which is higher than 3.07 reported by Karimi et al in a study on the prescriptions of GPs as well as the specialists in all age groups (35). In 2 studies that evaluated the prescriptions of health centers, the average number of drugs per prescription was 3.03 (16) and 3.4 (37).

It seems that the higher need for medications by geriatrics may be presented with a higher mean number of drugs per prescription. However, in this study, this number was lower compared to 3.8 (30) and 3.9 (38) reported from studies on elderly outpatients of 2 Nigerian hospitals and 4.27 in prescriptions of elderly outpatients of a tertiary hospital clinic in India (39). However, the health care system is important in the interpretation of the results. For example, Eze et al. noted that high mean number of medications per prescription was also reported in previous studies in Nigeria (38).

Similar to the present study, a Swedish study found a higher number of drugs being prescribed for the elderly women compared to men. However, Craftman et al documented all medications used by the elderly in their study and not a single prescription (40). Considering the prescriptions by GPs, the mean number of drugs per patient in this study was 3.63, which was lower compared to the study by Ghadimi et al, in which they reported 4.4 items per prescription in the GPs' prescriptions for the elderly (21). However, as it was expected, both numbers are higher than the reported mean number of items by Safaeian et al (3.3) in a study that included the prescriptions of all age groups (41).

The results showed that the percentage of drugs prescribed by generic names was 76.77% and 84.51% among the prescription of all prescribers and GPs, respectively. The mentioned percentages were lower compared to previous Iranian studies that reported more than 95% of drug encounters were by generic names (16, 21). The difference with other Iranian studies can be attributed to the method of assessment. In fact, one of the advantages of the present study, compared to the previous studies in Iran (21, 35), was documenting the entire prescription items, not only evaluating the insurance claims data. Using the insurance data has several limitations: the uncovered items by the insurance organizations cannot be included in the data. Thus, supplements and herbal medications are underreported. Moreover, only items that were purchased by the patient (not all of the prescribed items by the physicians) can be reported. Therefore, the number of drugs per prescription was more accurate in the data of this study. Moreover, most of the times, the branded-generic names are entered in the insurance claims by their generic name in Iran. Therefore, the data by the insurance organizations generally underreport the brand-name prescribing.

The brand-name prescribing in this study was less than half of the reports from the studies in other countries like Nigeria (30, 38) and was nearly comparable to the reports from Brazil (42). To the best of the authors' knowledge, the previous studies in Iran have not evaluated the brand-name prescribing among different specialties or educational levels of prescribers. Antibiotics were prescribed by GPs in 26.8% of their prescriptions, which was much lower than the figures for both the elderly (39%) (21) and the general population (51%) of the country (35, 41). Also, the frequency of antibiotic prescription in this study was within the standard range recommended by the WHO (not higher than 30%) (35). Similarly, the percentage of the injectable drugs in the GPs' prescriptions (28.5%) was lower compared to other studies (21, 41). However, vitamins and corticosteroids were among the top injectable medications in this study, which deserve consideration.

Comparable to the previous studies (35, 36), the average number of medicines per patient differed based on the physicians' specialty. In other studies, similar to the results of this study, ophthalmologists were among the prescribers with the least number of medications in their prescriptions (35, 36).

Among the prescribers, GPs and ophthalmologists pre-

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scribed higher percentage of antibiotics in prescriptions in the present study, while antibiotics were mostly prescribed by GPs, ENT specialists (35, 36), and general surgeons (36) in other studies. Orthopedists and GPs were the first and the second highly prescribers of injections both in the present study and the study by Sadeghian et al (36).

Limitations

The main limitation of the present study was the unavailability of medical records of patients, including diagnosis and comorbidities at pharmacies. Therefore, identifying inappropriate medications in certain diseases was not possible. Moreover, the precise evaluation of appropriateness of medications that required data about specific conditions (eg, renal function, indication, and duration of treatment) was not possible. The mentioned limitation also led to the unavailability of the outcomes of the PIM administrations. In the present study, all the prescriptions for geriatrics were included with no limitation regarding the prescribers, which resulted in the limited number of prescriptions written by certain specialists, including dermatologists and gynecologists that could not be compared with other specialists.

Conclusion

Interventions are needed to improve the prescribing habits of GPs for the elderly, especially with respect to prescribing PIMs. Also, some problems still exist in rational use of drugs as evaluated by the WHO prescribing indices, especially, the prescription of the brand-name medications and injectable medications.

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Conflict of Interests

The authors declare that they have no competing interests.

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Supplementary Table 1. The modified list of the Beers criteria

Organ System or Therapeutic Category or Drug to be Avoided	Beers Criteria Descriptions	Modifications
Anticholinergics (excludes TCAs)		
First-generation antihistamines (as single agent or as part of combination products) Brompheniramine Carbinoxamine Chlorpheniramine Clemastine Cyproheptadine Dexbrompheniramine Dexchlorpheniramine Diphenhydramine (oral) Doxylamine Hydroxyzine Promethazine Triprolidine	Use of diphenhydramine in special situations such as acute treatment of severe allergic reaction may be appropriate	Cold preparations containing "chlor-pheniramine" (such as Biolenol cold®, Adult cold, Cold gel®), Expectorant, Antihistamine Decongestant and all other antihistamines listed: GIM Dimenhydrinate, Diphenhydramine and Cold preparations containing Diphenhydramine (such as Coldax®, Cold stop®): CIM
Antiparkinson agents Benztropine (oral) Trihexyphenidyl	-	GIM
Antispasmodics Belladonna alkaloids Clidinium-chlordiazepoxide Dicyclomine Hyoscyamine Propantheline Scopolamine	Avoid except in short-term palliative care to decrease oral secretions	In prescriptions without chemotherapeutic agents as a marker for palliative care: GIM Clidinium-chlordiazepoxide: GIM
Antithrombotics		
Dipyridamole, oral short acting (does not apply to extended release combination with aspirin)	-	GIM
Ticlopidine	-	GIM
Anti-infective		
Nitrofurantoin	Avoid for long-term suppression; avoid in patients with CrCl < 60 mL/min	GIM: if prescribed for > 2 weeks (prescription with > 56 tablets if daily dosing was not mentioned in the prescription) If the number of tablet was lower: CIM
Cardiovascular		
Alpha1 blockers Doxazosin Prazosin Terazosin	Avoid use as an antihypertensive	GIM: if prescribed for women, or prescribed for men along with other antihypertensive medications Otherwise: CIM
Alpha agonists, central Clonidine Guanabenz Guanfacine Methyldopa Reserpine (> 0.1 mg/d)	Avoid clonidine as a first-line antihypertensive. Avoid others as listed	GIM
Antiarrhythmic drugs (Class Ia, Ic, III) Amiodarone Dofetilide Dronedarone Flecainide Ibutilide Procainamide Propafenone Quinidine Sotalol	Avoid antiarrhythmic drugs as first-line treatment of atrial fibrillation	CIM
Disopyramide	-	GIM
Dronedarone	Avoid in patients with permanent atrial fibrillation or heart failure	CIM
Digoxin > 0.125 mg/d	-	GIM: If the daily dose was mentioned in the prescription and was > 0.125 mg/d Without daily does: CIM
Nifedipine, immediate release	-	GIM

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Spironolactone > 25 mg/d	In heart failure, the risk of hyperkalemia is higher in older adults especially if taking > 25 mg/d or taking concomitant NSAID, angiotensin converting-enzyme inhibitor, angiotensin receptor blocker, or potassium supplement Avoid in patients with heart failure or with a CrCl < 30 mL/min	CIM
Central nervous system		
Tertiary TCAs, alone or in combination: Amitriptyline Chlordiazepoxide-amitriptyline Clomipramine Doxepin > 6 mg/d Imipramine Perphenazine-amitriptyline Trimipramine	-	Doxepin was considered GIM: If the daily dose was mentioned in the prescription and was > 6 mg/d Doxepin without daily does: CIM Other TCAs as listed: GIM
Antipsychotics, first (conventional) and second (atypical) generation	Avoid use for behavioral problems of dementia unless non pharmacological options have failed and patient is threat to self or others	CIM
Thioridazine Mesoridazine	-	GIM
Barbiturates Amobarbital Butabarbital Butalbital Mephobarbital Pentobarbital Phenobarbital Secobarbital	-	GIM
Benzodiazepines Short and intermediate acting: Alprazolam Estazolam Lorazepam Oxazepam Temazepam Triazolam Long acting: Clorazepate Chlordiazepoxide Chlordiazepoxide-amitriptyline Clidinium-chlordiazepoxide Clonazepam Diazepam Flurazepam Quazepam	May be appropriate for seizure disorders, rapid eye movement sleep disorders, benzodiazepine withdrawal, ethanol withdrawal, severe generalized anxiety disorder, periprocedural anesthesia, end-of-life care Avoid benzodiazepines (any type) for treatment of insomnia, agitation, or delirium	GIM
Chloral hydrate	-	GIM
Meprobamate	-	GIM
Nonbenzodiazepine hypnotics Eszopiclone Zolpidem Zaleplon	Avoid chronic use (> 90 days)	GIM in prescription with > 90 tablets Otherwise: CIM
Ergot mesylates Isoxsuprine		GIM
Endocrine		
Androgens Methyltestosterone Testosterone	Avoid unless indicated for moderate to severe hypogonadism	CIM
Desiccated thyroid	-	GIM

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Estrogens with or without progestins	Evidence that vaginal estrogens for treatment of vaginal dryness is safe and effective in women with breast cancer, especially at dosages of estradiol < 25 lg twice weekly Avoid oral and topical patch. Topical vaginal cream: acceptable to use low-dose intravaginal estrogen for the management of dyspareunia, lower urinary tract infections, and other vaginal symptoms	GIM: if administered as oral and topical patch. Otherwise : CIM
Growth hormone	Avoid, except as hormone replacement after pituitary gland removal	CIM
Insulin, sliding scale	-	GIM
Megestrol	-	GIM
Sulfonylureas, long duration Chlorpropamide Glyburide	-	GIM
Gastrointestinal		
Metoclopramide	Avoid, unless for gastroparesis	CIM
Mineral oil, oral	-	GIM
Trimethobenzamide	-	GIM
Pain		
Meperidine	-	GIM
Non–COX-selective NSAIDs, oral Aspirin > 325 mg/d Diclofenac Diflunisal Etodolac Fenoprofen Ibuprofen Ketoprofen Meclofenamate Mefenamic acid Meloxicam Nabumetone Naproxen Oxaprozin Piroxicam Sulindac Tolmetin	Avoid chronic use unless other alternatives are not effective and patient can take gastroprotective agent (proton pump inhibitor or misoprostol)	GIM: if prescribed for >30 days In prescriptions in which daily dosing was not mentioned, GIM was determined if the number of tablet/capsules exceeded the max acceptable daily dose for 30 days
Indomethacin Ketorolac, includes parenteral	-	GIM
Pentazocine	-	GIM
Skeletal muscle relaxants Carisoprodol Chlorzoxazone Cyclobenzaprine Metaxalone Methocarbamol Orphenadrine	-	GIM

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Supplementary Table 2. The modified list of systemic and local antibiotic medications

Systemic Antibiotics	Dosage Forms
Amoxicillin	Capule:250 mg, 500 mg
	Powder, For Suspension: 125 mg/5ml, 250 mg/5ml
Amoxicillin +Clavulanic Acid	Tablet: 375, 625 mg
	Powder, For Suspension: 156 (125+31.25)/5 ml, 228 (200+28.2)/5 ml, 312 (250+62.5)/5 ml, 457 (400+57)/5ml
Ampicillin	Capsule:250 mg, 500 mg
	Injection Powder: 500mg, 1g
	Powder, For Suspension:125 mg/5 ml, 250mg/5ml
Ampicillin+Sulbactam	Injection Powder: 1.5 g, 3 g
Penicillin 6-3-3	Injection Powder
Penicillin G Benzathine	Injection Powder, Extended Release: 1200000 U
Panicillin G Procaine	Injection Powder: 400000 U, 800000 U
Penicillin V	Tablet:500mg
	Powder, For Suspension: 125 mg/5 ml, 250mg/5ml
Cloxacillin	Capsule:250 mg, 500 mg
	Injection Powder: 250 mg, 500mg, 1g
Piperacillin+Tazobactam	Injection Powder: 1.125 g, 2.5g, 3.375 g, 4.5 g
Cefalexin	Capsule:250 mg, 500mg
	Powder, For Suspension: 125 mg/5 ml, 250 mg/5 ml
Cefazolin	Injection Powder: 500mg, 1g
Cefixime	Capsule:200 mg, 400 mg
	Powder, For Suspension: 100mg/5ml
Ceftriaxone	Injection Powder: 5oo mg, 1 g
Cefuroxim	Tablet:125 mg, 250mg, 500mg
	Injection Powder: 750 mg, 1.5 g
	Powder, For Suspension: 125mg/5ml
Cefotaxime	Injection Powder: 500mg, 1 g
Ceftazidime	Injection Powder: 500 mg, 1 g, 2 g
Ceftizoxim	Injection Powder: 500 mg, 1g
Cefepim	Injection Powder: 500 mg, 1g, 2 G
Imipenem + Cilastatin	Injection Powder: 500 mg
Vancomycin	Injection Powder: 500mg
Clindamycin	Capsule:150mg, 300mg
	Injection: 300mg/2ml
	Suspension: 75 mg/5ml
Meropenem	Injection Powder: 500mg, 1g
Azithromycin	Capsule:250 mg, 500 mg
	Powder, For Suspension: 100mg/5ml, 200mg/5ml
Erythromycin	Injection Powder: 1g
	Powder, For Suspension: 200mg/5ml
	Tablet: 200 mg, 400 mg
Clarithromycin	Tablet: 250 mg, 500 mg
Chloramphenicol	Capsule: 250mg
	Injection Powder: 1g
Ciprofloxacin	Injection, Solution: 200mg/100ml
	Tablet: 250mg, 500mg
Nalidixic Acid	Tablet: 500mg
	Suspension: 300mg/5ml
Ofloxacin	Tablet:200 mg, 300mg
Gemifloxacin	Tablet:320mg
Levofloxacin	Tablet:250 mg, 500 mg
Moxifloxacin	Tablet:400 mg
Tetracycline	Capsule:250mg
	Injection: 500mg/2ml
Doxycycline	Capsule:100mg
Gentamicin	Injection: 20mg/2ml, 40mg/1ml, 80mg/2ml
Amikacin	Injection:100mg/2ml, 500mg/2ml
Streptomycin	Injection Powder: 1g
Spectinomycin	Injection Powder: 2g
Tobramycin	Injection: 10 mg/ml,40mg/ml
Metronidazole	Injection Solution: 500mg/100ml
	Tablet:250 mg
	Suspension:125mg/5ml
Nitrofurantoin	Suspension:25mg/5 ml,12.5mg/5ml
	Tablet:100mg
Sulfamethoxazole +Trimethoprim	Injection Solution:400+80mg/5ml
	Tablet: 100+20 mg; 400+80 mg, 800+160 mg
	Suspension: 200+40 mg/5 ml
Trimethoprim	Oral Liquid: 50 mg/5 ml
	Tablet: 100 mg; 200 mg.

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Local Antibiotics	Dosage forms
Mupirocin	Ointment: 2%
Potassium Permanganate	Aqueous solution: 1:10 000
Silver Sulfadiazine	Cream: 1%
Acyclovir	Ointment: 3%
Gentamicin	Eye Drops: 0.3%
Tetracycline	Eye Ointment: 1%
Ofloxacin	Eye Drop: 0.3 %
Ciprofloxacin	Eye Ointment: 0.3 %
Erythromycin	Eye Ointment: 0.5%

Some of the medications or dosage form that was listed in the WHO model list was not available in Iran at the study time. However, we did not remove them from the table.

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