Potentially Inappropriate Medication Use among Nursing Home Residents: Medication Errors Associated with Pro re nata Medications and the Importance of Pill Burden

Fatma Özge Kayhan Koçak, Emin Taşkıran, Zehra Kosuva Öztürk, Sevnaz Şahin

Division of Geriatrics, Department of Internal Medicine, Faculty of Medicine, Ege University, Izmir, Turkey

Corresponding Author:
Fatma Özge Kayhan Koçak, MD
Division of Geriatrics, Department of Internal Medicine, Faculty of Medicine, Ege University, Izmir, Turkey
E-mail: drozgekayhankocak@gmail.com
ORCID:
https://orcid.org/0000-0002-6447-2352

Background: The use of potentially inappropriate medications (PIM) has become more common among nursing home residents (NHR). This study focused on drugs initially prescribed as pro re nata (PRN) medications and pill burden in association with PIM among NHR. **Methods:** This observational cross-sectional study was conducted between March and April 2019 on 225 adult NHR aged ≥60 years. **Results:** The prevalence of PIM was 47.6% among NHR according to the Screening Tool of Older Persons' Prescriptions (STOPP) criteria version 2. The most frequent PIM was the use of any drug prescribed without evidence-based clinical indication; most medication errors were associated with PRN medications. The prevalence rates of PRN in non-PIM and PIM users were 12% and 62.4%, respectively. PRN medications that most commonly caused PIM were non-steroidal anti-inflammatory drugs and proton pump inhibitors. The cut-off value for both medications and pills to correctly identify participants with PIM was 5.5. Pill burden had a similar sensitivity to polypharmacy in identifying individuals with PIM. **Conclusion:** Medication errors associated with PRN medications were overlooked as factors that increased the risk of PIMs. The most common error related to PRN medications was the continued daily use despite symptom resolution.

Key Words: Potentially inappropriate medication list, Nursing homes, Aged, Medication errors

INTRODUCTION

The use of potentially inappropriate medication (PIM) has recently become more common among nursing home residents (NHR). Systematic reviews performed in long-term care facilities reported that up to 91% of NHR regularly took more than four medications and that the prevalence of PIM varied from 23.7% to 79.8%, according to the Screening Tool of Older Persons' Prescriptions (STOPP) criteria.[1,2] Not all treatments are prescribed by one physician, and NHR in Turkey often consult more than one hospital or physician. The number of prescribed medications had increased with increasing comorbidity. In addition, pro re nata (PRN) prescriptions contribute to an increase in the number of medications taken. PIM may be associated with medication errors related to

PRN prescriptions.[3-5] In addition, the overall prevalence of PIM use and PRN prescriptions in nursing homes (NHs) increase with extended lengths of stay.[6,7] Therefore, PRN medication should be considered when determining inappropriate medication prescriptions in NHs.[5]

Pill burden (the number of pills taken per day) is an inconspicuous cause of PIM that influences adherence in the treatment of chronic diseases, especially HIV infection, cardiovascular disease, and renal disease.[8-10] The pill burden may be underestimated, especially in the presence of comorbidities. To our knowledge, no studies have compared the effects of pill burden and polypharmacy on the prevalence of PIM.

Two of the most commonly used criteria to define PIM are the Beers Criteria and the STOPP/Screening Tools to Alert Doctors

to Right Treatment (START) criteria.[11] The START criteria are one of the most frequently used tools for evaluating the use of PIM in older people. In contrast to the Beers criteria, the STOPP/START criteria do not include PRN medications. This study investigated the prevalence of PIM and the association of medications initially prescribed as PRN with PIM in NHR. This study focused on the association between pill burden, polypharmacy, and PIM in NHR.

MATERIALS AND METHODS

Setting and Participants

This observational cross-sectional study was conducted between March and April 2019 in an NH. The study participants were recruited among adults ≥ 60 years of age, with Katz activities of daily living (Katz-ADL) scores of 5 or higher, and institutionalized in NHs. No sampling was performed because this study planned to include all eligible NHRs who provided written informed consent.

Procedure

Nursing staff members were interviewed using a structured questionnaire. The functional status of NHRs was assessed as described below. NHR data on the number of chronic diseases and prescribed medications, falls (in the last 12 months), the presence of urinary and/or fecal incontinence, dizziness, visual impairment, hearing loss, walking disability (the use of a cane, crutches, or walking frame), nutritional support, amputation, having a pacemaker, and admission to a hospital in the last 6 months were obtained from their medical records. Information from the medical records was verified by interviewing the attending nurse.

Definitions

Functional status

We evaluated the functionality of the NHR using the KATZ-ADL score.[12] This score is used to measure the dependence of an individual regardless of their disability status. This index assesses six basic activities of daily living: eating, bathing, dressing, transferring, toileting, and continence. To prevent heterogeneity in disability status among the study population, NHRs with KATZ-ADL scores < 5 points were excluded.

Polypharmacy

Polypharmacy was defined as the daily use of five or more different medications.[13,14]

Pill burden

Pill burden was defined as the number of pills (tablets or capsules, oral solid dosage forms) that a patient regularly consumed. The number of pills taken in the last 30 days was included to calculate the pill burden.

PIM

We defined PIM as the use of more medication than clinically necessary or the use of potentially harmful medication for an individual. The START criteria are a medication assessment tool intended to identify drugs with a potentially higher risk when used in patients aged 65 years and over.[15] The START criteria were initially published in 2008 and revised in 2014.[15,16] We applied the STOPP criteria version 2 (STOPP-2) to evaluate the presence of PIM.[15,16] Each medical history was obtained from the medical records and daily medication lists in the nurse desks. The STOPP-2 criteria checklist was applied to all NHR medical histories of currently used medications.

PRN prescriptions

PRN prescription refers to the administration of prescribed medication "when required" or "as needed". PRN medication was determined through the examination of clinical records, including drug, dose, indications for use, and maximum daily dose. Each prescription was assessed with the attending nurse in terms of "is this medicine used as a PRN?" and "are there written instructions such as 'as needed'?" The US Food Drug Administration (FDA) defines medication error as "a preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the healthcare professional, patient, or consumer."[17] The daily administration of PRN prescriptions to patients with no symptoms was considered a medication error and PIM as "to use any drug prescribed without an evidence-based clinical indication." FÖKK and ET reviewed the medication lists of these NHRs.

Ethics Approval

The study was approved by the Human Research Ethics Committee of Ege University (No. 18-11T/16-99166796-050.06.04) and received approval from the Ministry of Family, Labor, and Social Services of the Republic. Informed consent was obtained from all the participants included in the study. This study was performed in accordance with the principles of the Declaration of Helsinki.

Also, this study complied the ethical guidelines for authorship and publishing in the *Annals of Geriatric Medicine and Research*.[18]

Statistical Analyses

Data analyses were performed using IBB SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, NY, USA). Normality was assessed using Kolmogorov-Smirnov tests. Non-normally distributed quantitative variables were expressed as medians and minimum-maximum values. Qualitative variables were expressed as frequencies and percentages. Chi-squared (χ^2) and Fisher exact tests were used to analyze the qualitative variables. Mann-Whitney U tests were used to analyze quantitative variables. Multiple logistic regression analysis was performed for multivariate analysis. We applied a logistic regression model to variables that showed significant relationships in the univariate analysis. Multivariable logistic regression analysis was used to calculate the adjusted odds ratios (ORs) and 95% confidence intervals (CI) of variables for PIM in different models adjusted for potential confounders. For the multivariable logistic regression analyses, Model 1 was adjusted for medication number, pill number, and number of comorbidities, while Model 2 additionally adjusted for the presence of PRN. The optimal cut-off values for variables were determined using receiver operating characteristic (ROC) curve analysis. ROC curve analysis was also used to evaluate the ability of the number of pills (pill burden) and number of medications (polypharmacy) to predict PIM use. Differences with $p < 0.05$ were considered statistically significant.

RESULTS

We assessed the functional status of 268 NHR based on KATZ-ADL scores. Of these NHR, 225 had Katz-ADL scores of 5 or higher. To prevent heterogeneity in disability status among the study population, this cross-sectional study included data on the activities of daily living of 225 independent residents.

The median age of the study population was 76 years (range, 61–96 years), including 123 (54.7%) men and 102 (45.3%) women. Only 15 (6.7%) participants were married and had a living spouse. A total of 210 (93.8%) participants had been staying in the institution for > 6 months. Among the NHRs, 19.4% had diabetes mellitus, 10.1% had arrhythmia, 27.2% had cardiovascular disease, 7.4% had heart failure, 58.5% had hypertension, and 6.9% had cerebrovascular disease. Various medications were used by the NHRs. Proton pump inhibitors (PPIs) were administered to one-third of NHRs. Moreover, almost half of the NHRs were taking antiplatelet medication. The most commonly used medication classifications are presented in Table 1.

In this study, 107 NHR were on PIM, corresponding to a PIM prevalence of 47.6% according to the STOPP-2 criteria. The most frequent PIM was the use of "any drug prescribed without an evi-

Table 1. The most used medication classes of all residents (n=225)

Medication classification	n (%)
Gastrointestinal system	
Proton pump inhibitors	81 (36)
Cardiovascular system	
Antiplatelet drugs	97 (43.1)
ACE inhibitor or ARB	99 (44)
Diuretic	91 (40.4)
Beta blocker	67 (29.8)
Calcium channel blocker	44 (19.6)
Vasodilator	41 (18.2)
Lipid lowering drugs	27 (12)
Piracetam	25 (11.1)
Anticoagulant drugs	14 (6.2)
Respiratory system	
Inhaler beta mimetic	43 (19.1)
Inhaler steroid	40 (17.8)
Inhaler ipratropium	31 (13.8)
Central nervous system & psychotropic drugs	
SSRI/SNRI	40 (17.8)
Antipsychotics	24 (10.7)
Atypical anti-depressant	15 (6.7)
Donepezil	15 (6.7)
Endocrine system	
Thyroid therapy	31 (13.8)
Metformin	24 (10.7)
DPP4 inhibitor	15 (6.7)
Musculoskeletal system	
NSAIDs	14 (6.2)
Calcium-vitamin D	11 (4.9)
Urogenital system	
Alpha blocker	40 (17.8)
Non-classified drugs	
Anticholinergic	39 (17.3)
Vitamin supplement	45 (20.1)

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; SSRI, selective serotonin reuptake inhibitors; SNRI, serotonin and norepinephrine reuptake inhibitors; DPP-4, dipeptidyl peptidase-4; NSAIDs, non-steroidal anti-inflammatory drugs.

dence-based clinical indication." Most occurred as medication errors associated with PRN medications. The detailed PIM subclasses are shown in Table 2.

PIM users had higher numbers of medications; numbers of pills; PRN use; polypharmacy prevalence; and comorbidity prevalence such as chronic obstructive pulmonary disease (COPD), constipation, muscle-skeletal disease, dizziness, visual impairment, and urinary incontinence compared to non-PIM users. We observed no significant differences in terms of the length of stay in the institu-

Table 2. PIM prevalence according to drug classes described in STOPP criteria version 2

Drug classes	Number of residents
Any drug prescribed without an evidence-based clinical indication.	89
Any drug prescribed beyond the recommended duration, where treatment duration is well defined.	47
Any duplicate drug class prescription, e.g., two concurrent NSAIDs, SSRIs, loop diuretics, ACE inhibitors, anticoagulants (optimization of monotherapy within a single drug class should be observed prior to considering a new agent).	5
Beta-blocker in combination with verapamil or diltiazem (risk of heart block).	2
Loop diuretic as first-line treatment for hypertension (safer, more effective alternatives available).	3
Loop diuretic for treatment of hypertension with concurrent urinary incontinence (may exacerbate incontinence).	1
Aspirin plus clopidogrel as secondary stroke prevention, unless the patient has a coronary stent(s) inserted in the previous 12 months or concurrent acute coronary syndrome or has a high grade symptomatic carotid arterial stenosis (no evidence of added benefit over clopidogrel monotherapy).	2
Antiplatelet agents with vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors in patients with stable coronary, cerebrovascular or peripheral arterial disease (no added benefit from dual therapy).	1
NSAID with concurrent antiplatelet agent(s) without PPI prophylaxis (increased risk of peptic ulcer disease).	1
Anticholinergics/antimuscarinics in patients with delirium or dementia (risk of exacerbation of cognitive impairment).	5
Neuroleptics as hypnotics, unless sleep disorder is due to psychosis or dementia (risk of confusion, hypotension, extra-pyramidal side effects, falls).	3
First-generation antihistamines (safer, less toxic antihistamines now widely available).	9
Prochlorperazine or metoclopramide with Parkinsonism (risk of exacerbating Parkinsonian symptoms).	1
PPI for uncomplicated peptic ulcer disease or erosive peptic esophagitis at full therapeutic dosage for > 8 weeks (dose reduction or earlier discontinuation indicated).	23
Drugs likely to cause constipation (e.g., antimuscarinic/anticholinergic drugs, oral iron, opioids, verapamil, aluminum antacids) in patients with chronic constipation where non-constipating alternatives are available (risk of exacerbation of constipation).	2
Antimuscarinic drugs with dementia, or chronic cognitive impairment (risk of increased confusion, agitation) or narrow-angle glaucoma (risk of acute exacerbation of glaucoma), or chronic prostatism (risk of urinary retention).	6
Selective alpha-1 selective alpha blockers in those with symptomatic orthostatic hypotension or micturition syncope (risk of precipitating recurrent syncope).	3

PIM, potentially inappropriate medication; NSAIDs, non-steroidal anti-inflammatory drugs; SSRI, selective serotonin reuptake inhibitors; ACE, angiotensin-converting enzyme; PPI, proton pump inhibitor.

tion, cerebrovascular disease, peripheral vascular disease, walking disability, nutritional support, peptic ulcer disease, hypertension, malignancy, asthma, cardiovascular disease, arrhythmia, chronic prostatism, hearing loss, depression, diabetes mellitus, amputation, number of hospital admissions in the last 6 months, and having a pacemaker between the groups with and without PIM (p > 0.05). The p-values, numbers, and percentages for the descriptive statistics for the PIM users and non-PIM users are shown in Table 3.

The prevalence rates of PRN in non-PIM and PIM users were 12% and 62.4%, respectively. PRN medications that most commonly cause PIM are non-steroidal anti-inflammatory drugs (NSAIDs), PPIs, and betahistine dihydrochloride. Except for two residents, those NHR using piracetam were taking it as a PIM. Univariate analysis showed that PPIs, anticholinergic drugs, antiplatelet drugs, alpha-blockers, and inhaler beta mimetics were significantly associated with PIM prescription (Tables 4, 5). PPIs, betahistine dihydrochloride, and NSAIDs were initiated as PRN medications. However, there are no written instructions for the administration of PRN medication. These medica-

Table 3. Descriptives according to existence of PIM

	PIM users (n = 107)	Non-PIM users (n = 118)	p-value
Age (y)	77 (61–110)	75 (62–96)	0.240
Sex, male	59 (55.1)	64 (54.2)	0.892
Length of stay in institution (mo)			
0–6	6 (5.6)	8 (6.9)	0.730
>6	100 (94.3)	110 (93.2)	
Medication number	7 (1–17)	4 (0–13)	< 0.001*
PRN	67 (62.6)	15 (12.7)	< 0.001*
Pill number	8 (0–25)	5 (0–17)	< 0.001*
Pill burden	83 (77.6)	62 (52.5)	< 0.001*
Polypharmacy	83 (77.6)	58 (49.2)	< 0.001*
Comorbidities	4 (1–8)	2 (0–7)	< 0.001*
COPD	29 (27.1)	14 (11.9)	0.004*
Urinary incontinence	21 (19.6)	7 (5.9)	0.002*
Dizziness	23 (21.5)	7 (5.9)	0.001*
Vision impairment	37 (34.6)	20 (16.9)	0.002*
Muscle-skeletal disease	20 (18.7)	7 (5.9)	0.003*
Constipation	10 (9.3)	2 (1.7)	0.011*

Values are presented as median (min-max) or number (%).
PIM, potentially inappropriate medication; PRN, pro re nata; COPD, chronic obstructive pulmonary disease.
*p<0.05.

tions were administered daily to NHRs as long-term medications without the knowledge of PRN. In multivariable logistic regression analysis, piracetam and anticholinergic medications were significant in both models, whereas PPI was significant in Model 1 only. The logistic regression results are presented in Tables 4 and 5.

The results of the univariate ROC analysis are presented in Table 6. ROC analysis of the pill numbers showed an AUC of 0.692 with a cutoff value of 5.5, above which PIM could be diagnosed.

DISCUSSION

This study investigated the association of medications initially prescribed as PRN with PIM in NHR patients who were independent according to KATZ-ADL scores. As this study did not include NHRs with a score Katz-ADL scores < 5, we excluded the effect of dependency. We found that PRN medications were administered daily to asymptomatic NHRs. Poor understanding of PRN administration also led to medication errors. PRN also refers to the use of a medication without an evidence-based clinical indication, which is a PIM. We found that the prevalence of PIM increased

due to this medication error. Another important finding of this study was the observation that pill burden had similar sensitivity to polypharmacy for predicting PIM use.

The groups did not differ significantly in terms of the length of hospital stay. In addition, PIM users and non-PIM users did not differ significantly in terms of the rate of hospital admission. We noticed that PRN medications were administered daily to NHRs after nursing home transition. Dorks et al.[5] reported that 74.9% of the NHRs received at least one PRN medication. PRN medications can reduce the workload of nursing staff, and directions for use "as needed" should be noted on the prescription. Therefore, prescribers should regularly reconsider the need for each PRN medication.

The most common cause of PIM was the use of any medication prescribed without an evidence-based clinical indication. In this

Table 4. Effect of some variables on PIM for the whole group (logistic regression results from the univariate analysis)

Variable	Univariate		
	OR	%95 CI	p value
Medication number	1.264	1.151–1.388	0.000*
Pill number	1.156	1.080–1.237	0.000*
Comorbidities number	1.607	1.332–1.940	0.000*
Piracetam	15.881	3.644–69.204	0.000*
PPI	2.671	1.523–4.685	0.000*
Anticholinergic	5.609	2.445–12.867	0.000*
Antiplatelet	1.777	1.043–3.028	0.035*
Inhaler beta mimetic	2.434	1.218–4.863	0.012*

PIM, potentially inappropriate medication; OR, odds ratio; CI, confidence interval; PPI, proton pump inhibitor.
*p<0.05.

Table 5. Effect of some variables on PIM for the whole group (logistic regression results from the multivariate analysis)

Variable	Multivariate		
	OR	95% CI	p-value
Model 1			
Medication number	1.106	0.854–1.433	0.445
Pill number	0.943	0.793–1.122	0.508
Comorbidities number	1.249	0.947–1.648	0.115
Piracetam	19.304	4.160–89.586	0.000*
PPI	2.320	1.181–4.556	0.015*
Anticholinergic	5.196	2.112–12.786	0.000*
Antiplatelet	1.576	0.822–3.022	0.171
Inhaler beta mimetic	2.050	0.808–5.203	0.205
Model 2			
PRN	10.631	4.914–22.999	0.000*
Piracetam	31.310	6.355–154.266	0.000*
PPI	1.602	0.761–3.372	0.215
Anticholinergic	4.889	1.835–13.025	0.002*
Antiplatelet	2.118	1.049–4.279	0.036*
Inhaler beta mimetic	2.480	1.005–6.123	0.049*

PIM, potentially inappropriate medication; OR, odds ratio; CI, confidence interval; PPI, proton pump inhibitor; PRN, pro re nata.
*p<0.05.

Table 6. Receiver operating characteristic analysis for thresholds of pill burden and polypharmacy to predict PIM use

	Cut-off value	Sensitivity	Specificity	ROC AUC (95% CI)	Asymptotic significance (p)
Polypharmacy[a]	2.5	0.972	0.364	0.698	0.000
	5.5	0.673	0.619	(0.630–0.766)	
Pill burden[b]	2.5	0.925	0.347	0.67	0.000
	5.5	0.692	0.593	(0.601–0.740)	

PIM, potentially inappropriate medication; AUC, area under ROC curve; CI, confidence interval.
[a]Number of drugs.
[b]Number of pills.

study, 74% of PRN medications continued to be used regularly, despite symptom resolution. These findings demonstrated the misuse of PRN medications by nurses and NHR. In addition, the prescription cascade increased if PRN medication was used regularly rather than "as needed."

Medications for gastrointestinal problems are frequently used in the long-term care units.[2,19] The third most common cause of PIM was PPI use at full therapeutic dosage for > 8 weeks for the treatment of uncomplicated peptic ulcer disease or erosive peptic esophagitis. Additionally, based on our observations, PPI was the most prescribed medication without an evidence-based clinical indication or beyond the recommended duration, where the treatment duration is well defined. PPI was prescribed as a PRN medication after receiving treatment for an adequate period. However, it was administered daily as a long-term scheduled medication despite the absence of symptoms and not as a PRN medication. Physicians and patients are generally afraid of symptom relapse after discontinuing PPI treatment, although on-demand therapy is recommended for gastroesophageal reflux disease and chronic gastritis. Therefore, PPI prescribed as a PRN medication but erroneously used daily was a common cause of PIM.[6,20,21]

We observed medication errors associated with the use of antipsychotics and anticholinergics. Although PRN antipsychotic medications are used for the acute control of agitation, the rescheduling of antipsychotic doses has been overlooked. Prescribers should record the indication and duration of use of PRN medication, especially to avoid misuse.[22] Although the use of anticholinergics has decreased significantly, it continues to increase in the presence of chronic diseases, such as dementia and depression, in long-term care settings.[23-25] Similarly, Kose et al.[26] reported significantly increased anticholinergic use during stroke rehabilitation. First-generation antihistamines may be used inappropriately as hypnotics in patients with behavioral and psychological symptoms of dementia or delirium.

Another notable medication among PIM users was piracetam. Piracetam is prescribed short-term to patients with peripheral vertigo.[27] However, piracetam was frequently used in this study for forgetfulness and vertigo of unknown origin. Most NHRs did not show a significant benefit from the use of piracetam. Furthermore, evidence supporting its effectiveness remains inadequate.

The most common definition of polypharmacy is the regular use of at least five medications. Polypharmacy has been associated with the risk of geriatric syndromes and the use of PIM, and lists of PIM are widely used to reduce the prevalence of geriatric syndromes.[28-32] The number of pills taken by an individual can increase, even if the number of medications used is lower, a situation

that is oven overlooked. Therefore, we investigated the pill burden and threshold number of pills, which resulted in an increased risk of PIM similar to polypharmacy. In our study, the cutoff value for the number of pills to predict PIM use was similar to the number of medications used. The most sensitive cut-off value for the number of pills based on ROC analysis was 2.5. Pill burden had similar sensitivity and specificity to polypharmacy in identifying individuals with PIM. We found that neither definition was superior in identifying participants with PIM. Studies to date have demonstrated the association of a reduced pill burden and reduced PIM use with increased medication adherence. To our knowledge, this is the first study conducted in NHs to investigate the cut-off value for the number of pills taken to predict the presence of PIM. Finally, although the number of pills was insufficient to show the PIM arithmetically, it can still be used as an important risk factor for PIM.[33]

This study was conducted at a single center, thus resulting in a relatively small sample size. Some of the STOPP-2 criteria could not be applied owing to the requirement for laboratory assessment. As not all confounding factors, such as comorbidity and START criteria, were considered, medication error may not be associated solely with PRN or pill burden. We were unable to assess the medications that were necessary for use based on comorbidities according to the START criteria.

In conclusion, an improperly explained prescription of PRN can result in medication errors. Due to patient misunderstanding of the indication or duration of use, PRN may cause PIM as the use of "any drug prescribed without an evidence-based clinical indication." Older people who use PRN medications should be followed-up more closely. Ultimately, identifying the presence of PIM and PRN is important for identifying barriers to adherence and enhancing patient understanding of the indications and proper use of medications. To prevent the use of PIM caused by errors related to PRN medication, patients should be questioned at each visit regarding the use of each medication and prescribers should critically review the medication list.

An approach should be developed to reduce the pill burden, including reducing or stopping medications that are potentially harmful or no longer beneficial, using fixed-combination products, and reducing dose frequency. The number of pills taken is often not the same as the number of medications used and is usually more than the number of medications. Increasing the number of pills could reduce medication adherence, which, in turn, can lead to increased side effects, adverse drug reactions, or loss of efficacy. This indirectly leads to increased PIM use. Therefore, the numbers of pills and medications are important in terms of PIM use.

REFERENCES

1. Storms H, Marquet K, Aertgeerts B, Claes N. Prevalence of inappropriate medication use in residential long-term care facilities for the elderly: a systematic review. Eur J Gen Pract 2017;23:69-77.
2. Jokanovic N, Tan EC, Dooley MJ, Kirkpatrick CM, Bell JS. Prevalence and factors associated with polypharmacy in long-term care facilities: a systematic review. J Am Med Dir Assoc 2015;16:535.
3. Davies SJ, Lennard MS, Ghahramani P, Pratt P, Robertson A, Potokar J. PRN prescribing in psychiatric inpatients: potential for pharmacokinetic drug interactions. J Psychopharmacol 2007;21:153-60.
4. Mamun K, Lien CT, Goh-Tan CY, Ang WS. Polypharmacy and inappropriate medication use in Singapore nursing homes. Ann Acad Med Singap 2004;33:49-52.
5. Dorks M, Schmiemann G, Hoffmann F. Pro re nata (as needed) medication in nursing homes: the longer you stay, the more you get? Eur J Clin Pharmacol 2016;72:995-1001.
6. Morin L, Laroche ML, Texier G, Johnell K. Prevalence of potentially inappropriate medication use in older adults living in nursing homes: a systematic review. J Am Med Dir Assoc 2016;17:862.
7. Dorks M, Allers K, Hoffmann F. Pro re nata drug use in nursing home residents: a systematic review. J Am Med Dir Assoc 2019;20:287-93.
8. Hagendorff A, Freytag S, Muller A, Klebs S. Pill burden in hypertensive patients treated with single-pill combination therapy: an observational study. Adv Ther 2013;30:406-19.
9. Farrell B, French Merkley V, Ingar N. Reducing pill burden and helping with medication awareness to improve adherence. Can Pharm J (Ott) 2013;146:262-9.
10. An J, Lee JS, Sharpsten L, Wilson AK, Cao F, Tran JN. Impact of pill burden on adherence to hepatitis C medication. Curr Med Res Opin 2019;35:1937-44.
11. Levy HB. Polypharmacy reduction strategies: tips on incorporating American Geriatrics Society beers and screening tool of older people's prescriptions criteria. Clin Geriatr Med 2017;33:177-87.
12. Katz S. Assessing self-maintenance: activities of daily living, mobility, and instrumental activities of daily living. J Am Geriatr Soc 1983;31:721-7.
13. Ferner RE, Aronson JK. Communicating information about drug safety. BMJ 2006;333:143-5.
14. Masnoon N, Shakib S, Kalisch-Ellett L, Caughey GE. What is polypharmacy?: a systematic review of definitions. BMC Geriatr 2017;17:230.
15. O'Mahony D, O'Sullivan D, Byrne S, O'Connor MN, Ryan C, Gallagher P. STOPP/START criteria for potentially inappropriate prescribing in older people: version 2. Age Ageing 2015;44:213-8.
16. Gallagher P, Ryan C, Byrne S, Kennedy J, O'Mahony D. STOPP (Screening Tool of Older Person's Prescriptions) and START (Screening Tool to Alert doctors to Right Treatment): consensus validation. Int J Clin Pharmacol Ther 2008;46:72-83.
17. US Food and Drug Administration. Working to reduce medication errors [Internet]. Silver Spring, MD: Food and Drug Administration; 2019 [cited 2022 Sep 25]. Available from: https://www.fda.gov/drugs/information-consumers-and-patients-drugs/working-reduce-medication-errors#:~:text=A%20medication%20error%20is%20defined,Medication%20Error%20Reporting%20and%20Prevention.
18. Noh JH, Jung HW, Ga H, Lim JY. Ethical guidelines for publishing in the Annals of Geriatric Medicine and Research. Ann Geriatr Med Res 2022;26:1-3.
19. Resnick B, Galik E, Boltz M, Holmes S, Fix S, Vigne E, et al. Polypharmacy in assisted living and impact on clinical outcomes. Consult Pharm 2018;33:321-30.
20. Liew NY, Chong YY, Yeow SH, Kua KP, Saw PS, Lee SW. Prevalence of potentially inappropriate medications among geriatric residents in nursing care homes in Malaysia: a cross-sectional study. Int J Clin Pharm 2019;41:895-902.
21. Gaubert-Dahan ML, Sebouai A, Tourid W, Fauvelle F, Aikpa R, Bonnet-Zamponi D. The impact of medication review with ver-

sion 2 STOPP (Screening Tool of Older Person's Prescriptions) and START (Screening Tool to Alert doctors to Right Treatment) criteria in a French nursing home: a 3-month follow-up study. Ther Adv Drug Saf 2019;10:2042098619855535.

22. Geffen J, Cameron A, Sorensen L, Stokes J, Roberts MS, Geffen L. Pro re nata medication for psychoses: the knowledge and beliefs of doctors and nurses. Aust N Z J Psychiatry 2002;36:642-8.

23. Halvorsen KH, Selbaek G, Ruths S. Trends in potentially inappropriate medication prescribing to nursing home patients: comparison of three cross-sectional studies. Pharmacoepidemiol Drug Saf 2017;26:192-200.

24. Chatterjee S, Bali V, Carnahan RM, Johnson ML, Chen H, Aparasu RR. Anticholinergic medication use and risk of dementia among elderly nursing home residents with depression. Am J Geriatr Psychiatry 2016;24:485-95.

25. Lee JH, Jung HW, Jang IY, Moon SD, Lee S, Han SJ. Anticholinergic cognitive burden as a predictive factor for in-hospital mortality in older patients in Korea. Ann Geriatr Med Res 2020;24: 20-6.

26. Kose E, Hirai T, Seki T, Hayashi H. Role of potentially inappropriate medication use in rehabilitation outcomes for geriatric patients after strokes. Geriatr Gerontol Int 2018;18:321-8.

27. Agus S, Benecke H, Thum C, Strupp M. Clinical and demographic features of vertigo: findings from the REVERT Registry. Front Neurol 2013;4:48.

28. Maher RL, Hanlon J, Hajjar ER. Clinical consequences of polypharmacy in elderly. Expert Opin Drug Saf 2014;13:57-65.

29. Varga S, Alcusky M, Keith SW, Hegarty SE, Del Canale S, Lombardi M, et al. Hospitalization rates during potentially inappropriate medication use in a large population-based cohort of older adults. Br J Clin Pharmacol 2017;83:2572-80.

30. Thorell K, Midlov P, Fastbom J, Halling A. Use of potentially inappropriate medication and polypharmacy in older adults: a repeated cross-sectional study. BMC Geriatr 2020;20:73.

31. Kim MY, Etherton-Beer C, Kim CB, Yoon JL, Ga H, Kim HC, et al. Development of a consensus list of potentially inappropriate medications for Korean older adults. Ann Geriatr Med Res 2018;22:121-9.

32. Ho J, Kim B, Kim KS, Jihn CH, Kim MY, Kang DR, et al. Statin supply and polydrug use in older adults: a focus on drug combinations that reduce bone density. Ann Geriatr Med Res 2021; 25:269-77.

33. Haefeli WE, Meid AD. Pill-count and the arithmetic of risk: evidence that polypharmacy is a health status marker rather than a predictive surrogate for the risk of adverse drug events. Int J Clin Pharmacol Ther 2018;56:572-6.