JRP Journal of Research in Pharmacy

Research Article

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# Evaluation of inappropriate drug use in geriatric patients using the TIME-to-STOP/TIME-to-START criteria in a tertiary hospital

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Received: 28 February 2022 / Revised: 17 October 2022 / Accepted: 18 October 2022

**ABSTRACT**: This study aimed to determine the frequency and factors affecting inappropriate drug use and polypharmacy in geriatric patients. The data on 318 geriatric patients hospitalized between January 1, 2020, and July 1, 2020, in the internal medicine clinic of a tertiary hospital were analyzed retrospectively. Inappropriate drug use was evaluated according to the Turkish Inappropriate Medication Use in the Elderly (TIME) TIME-to-STOP/ TIME-to-START criteria. Of the 318 patients, 157 (49.4%) used at least one potentially inappropriate drug. The most frequently used inappropriate drugs according to TIME-to-START criteria were related to (B) the central nervous system (n = 28; 53.89%), (A) the cardiovascular system (n = 26; 33.33%), and (I) supplements (n = 24; 30.77%). The most frequently used inappropriate drugs according to TIME-to-STOP criteria were related to (B) the central nervous system (n = 258; 45.18%), (C) the gastrointestinal system (n = 224; 39.23%), and (D) the respiratory system (n = 44; 7.71%). A total of 225 (70.8%) patients engaged in polypharmacy at least once**.** Conclusion: There is a high rate of potentially inappropriate drug use and polypharmacy among Turkish geriatric patients. The use of published guidelines should be expanded in Turkey.

**KEYWORDS**: inappropriate drug use; geriatrics; polypharmacy; prescribing

## 1. INTRODUCTION

Inappropriate drug use-related problems among geriatric patients constitute a challenging global public health issue [1]. Age-related pharmacokinetic and pharmacodynamic changes may be the reason for the development of adverse drug reactions (ADRs), as well as drug–drug, drug–disease, and drug–nutrient interactions in the elderly [1, 2, 3, 4, 5]. Inappropriate drug use is defined as the use of drugs in inappropriate doses, durations, and indications [6, 7, 8]. Inappropriate drug use can reduce therapeutic efficacy, cause adverse effects, increase the cost of treatment, and sometimes lead to prolonged hospital stays or death [9, 10]. Studies conducted in various countries have reported that the frequency of potentially inappropriate drug use varies between 24% and 98.2% in the geriatric population [11, 12, 13, 14, 15]. The use of inappropriate medications among hospitalized geriatric patients in Turkey was reported to be 32% according to Beers criteria [16] and 59.4% according to the European Union Potentially Inappropriate Medication (EU[7]-PIM) list [6]. No criteria have been adapted/validated for the Turkish population regarding potentially inappropriate medication (PIM) use in geriatric patients. Recently, Bahat et al. developed the Turkish inappropriate medication use in the elderly (TIME) TIME-to-STOP/START criteria [17]. Another related aspect of inappropriate drug use is polypharmacy. Polypharmacy is defined as the use of multiple medications in one day [18]. The literature has reported various definitions, including cut-off numbers for used drugs, with polypharmacy most commonly indicated by the taking of five or more medications [19]. Polypharmacy prevalence varies between 11.3% and 76.3%, depending on the country where the study was conducted, the definition of polypharmacy, and the definition of old age [20, 21, 22, 23]. Studies conducted among hospitalized geriatric patients in different regions and hospitals in Turkey reported polypharmacy rates to be 74.5% and 80.2%, respectively [6, 24]. The high prevalence of polypharmacy in the geriatric population is a

**How to cite this article:** Hodzic Kuerec A, Terzioglu Bebitoglu B. Evaluation of inappropriate drug use in geriatric patients using the TIME-to STOP/TIME-to-START criteria in a tertiary hospital. J Res Pharm. 2023; 27(2): 685-695.


ISSN: 2630-6344

http://dx.doi.org/10.29228/jrp.350

consequence of the presence of more than one disease [25]. Prior clinical studies excluded older patients with multiple diseases [26], patients who engaged in the frequent use of non-prescription drugs [27], and patients demonstrating symptoms of the prescription cascade—where adverse effects of drugs are confused with other disease symptoms, leading to additional unnecessary medication prescriptions [28]. Furthermore, polypharmacy causes ADRs and drug-drug interactions and negatively affects treatment costs [29, 30, 31, 32]. It has also been noted that polypharmacy causes cognitive problems and is associated with an increased risk of hip fractures [33, 34].

Therefore, we aimed to determine the frequency of and factors affecting inappropriate drug use and polypharmacy in 314 geriatric inpatients using the newly published TIME-to-STOP/TIME-to-START criteria.

## 2. RESULTS

Of the 318 patients, 175 (55%) were female. The mean age ± standard deviation (SD) of the patients was 79.69 ± 8.26 years, and the min–max age range was between 65 and 99 years. The largest group of patients was aged 85 years and older (33.3%). The number of female patients aged 85 years and older was significantly higher than the number of male patients of this age (p = 0.001). There was no significant difference in terms of hospitalization type (whether the patient came from the emergency department) (p = 0.206), duration of hospitalization (p = 0.128), discharge status (p = 0.472), and Charlson Comorbidity Index (CCI) (p = 0.107) values between age groups. A significant difference in the number of diagnoses was found among patients 85 years and older, who most commonly had 1–4 diagnoses (p = 0.012) (Table 1).

The 318 patients included in the analysis had 532 diagnoses; the mean ± SD of the number of comorbidities for each patient was 3.63 ± 1.92. The patients had a minimum of one diagnosis and a maximum of 12 diagnoses. According to the International Classification of Diseases (ICD)-10 classification, the most common diagnosis groups were respiratory system diseases (n = 178; 33.4%), anemia and blood diseases (n = 53; 9.96%), and urinary system diseases (n = 49; 9.21%). The most common diagnoses were pneumonia (n = 146; 27.4%), pain (n = 48; 9.02%), and acute renal failure (n = 33; 6.2%) (Supplement 1). Among all patients, n = 131 (41.19%) had at least one chronic disease. The most common chronic diseases were hypertension (n = 94; 32.19%), diabetes mellitus (n = 60; 20.55%), and heart failure (HF) (n = 37; 12.67%).

A total of 32,206 prescriptions, including 321 different drugs, were made for all patients included in the analysis. The number of different medications administered to patients in one day during the hospitalization period was at least 1, at most 40, and the mean ± SD was 13.65 ± 6.94. According to ATC 1 level, the prescribed drugs were mostly for the digestive system and metabolism (A) (44.93%), cardiovascular system (C) (14.61%), and nervous system (N) (9.1%) groups.

The most frequently prescribed generic drugs were A02BC02 (pantoprazole) (13.63%), A10AE04 (insulin glargine) (4.68%), and A10AD05 (insulin aspart) (4.53%) (Table 2). A total of n = 225 (70.8%) patients underwent polypharmacy (≥ 10 medications) at least once during the hospitalization period. Continuous polypharmacy was present for an average of 3.4 ± 4.48 days, with a min-max of 1–38 days.

PIM use was detected at least once during their hospitalization in n = 157 (49.4%) patients according to the TIME-to-STOP/TIME-to-START criteria. In total, 657 drugs were identified as PIMs, with 78 according to the TIME-to-START criteria and 571 according to the TIME-to-STOP criteria. The number of days PIM use was continued (according to the TIME-to-STOP criteria) during hospitalization was at least one and at most 15, and the mean ± SD was 1.18 ± 0.134 days.

Table 3 shows the distribution of the TIME-to-START criteria. According to the TIME-to-START criteria, the most common drug omissions were (B3) (n = 26; 33.33%). Although it was appropriate to initiate cholinesterase inhibitors in early-middle-stage Alzheimer's disease, they were not prescribed (I1) (n = 24; 30.77%). When nutritional counseling and increasing dietary supplement intake were not sufficient in patients suffering malnutrition or malnutrition risk, oral nutritional supplements (ONS) should have been initiated but were not (A5) (n = 13; 24.36%). In the presence of systolic HF (EF <= 40%) or ST-elevation myocardial infarction (MI), the ACE inhibitor was not prescribed where appropriate.

Table 4 shows the distribution of the TIME-to-STOP criteria. According to the TIME-to-STOP criteria, proton pump inhibitors (PPI) (n = 166; 29.07%) (C5; not appropriate due to multiple drug use) followed by anticholinergic GIS antispasmodics (n = 84; 14.71%) (B18; long-term use of betahistine, trimetazidine, and dimenhydrinate in the treatment of vertigo), and anticholinergic GIS antispasmodics (n = 47; 8.23%) (C6; not suitable in the elderly due to increased anticholinergic side effects, such as dizziness, decreased cognitive abilities, blurred vision, arrhythmia, and bloating-constipation) were the most common potentially inappropriately used drugs.

Table 5 shows PIM use and polypharmacy distribution according to sociodemographic characteristics. Patients 85 years and older (p = 0.01), patients with 5–8 diagnoses (p = 0.012), CCI (3–4) (p = 0.019), and patients with at least one chronic disease (p = 0.001) experienced a significantly higher rate of polypharmacy. After conducting a multivariate logistic regression analysis, only the presence of at least one chronic disease (p = 0.002; OR: 2.421; 95% CI: 1.373–4.269) increased polypharmacy. Among chronic diseases, polypharmacy was found to be significantly more frequent in patients with hypertension (p = 0.001), chronic HF (p = 0.035), and malignancy (p = 0.031). After the multivariant logistic regression analysis, only chronic HF (p = 0.042; OR: 3.19; 95% CI: 1.043–9.757) and malignancies (p = 0.027; OR: 9.91 95% CI: 1.292–76.049) increased polypharmacy. Polypharmacy (p = 0.026; OR: 1.77; 95% CI: 1.072–2.944) and the presence of at least one chronic disease (p = 0.036; OR: 1.639; 95% CI: 1.033–2.602) increased PIM use.

## 3. DISCUSSION

In this study, the data on 318 inpatients aged 65 years and older who received treatment in the internal medicine clinic of a tertiary hospital were retrospectively examined. Most patients were 85 years and older, and there was a significantly higher number of women in this age group. The reason for the mentioned distribution could be the poorer general health conditions of older patients and because the overall proportion of women (10.4%) is higher than men (8.4%) in this age group in Turkey [35]. The age distribution in our study was similar to that in Bozkurt et al.'s study, where they also assessed the rate of PIM use and polypharmacy in geriatric patients [6]. The average hospital stay duration of our group was longer than that of Bozkurt et al.'s study (mean ± SD = 5.74 ± 4.70 days), which included geriatric patients from other departments rather than internal medicine, but shorter than Pereira et al.'s study population (mean ± SD = 17.5 ± 19.9 days), which included geriatric patients from the cardiology department in a general hospital [6, 36]. The difference in the study setting and the included departments could have been the reason for the difference in hospital stay length. Furthermore, the patients in our study were less frequently diagnosed with severe diseases, such as malignancy, end-stage organ damage, hemiplegia, and AIDS. Hence, the patients had a lower CCI ($n \leq 2$), which was different from Fahrini et al.'s study conducted among geriatric patients who reported higher CCI ($n \geq 3$) scores [37]. There was no difference in hospitalization and discharge type, duration of hospitalization, or CCI according to age group. However, the fact that there was no difference in the CCI scores between men and women showed that they had similar morbidities.

Similar to our study, another study in Turkey reported that respiratory system diseases were the most common diagnosis in hospitalized geriatric patients. Respiratory diseases were followed by circulatory and gastrointestinal diseases, while in our study, anemia, blood diseases, and urinary system diseases followed respiratory diseases [6].

In our study, cardiovascular, digestive-metabolic, and nervous system drugs were the most frequently used. Periera et al. reported similar results to our study [36]. Furthermore, pantoprazole, insulin preparations, and furosemide were the most commonly used drugs. This can be explained by the fact that the patients received therapy in accordance with their underlying chronic disorders in addition to their hospitalization-related conditions. Similar to our study, PPIs were the most commonly prescribed drugs in the elderly in studies conducted in Turkey [38] and Italy [39].

We found that 157 (49.4%) patients experienced PIM use at least once during hospitalization. In Bahat et al.'s study, the rate of PIM use was 39.1% according to STOPP version 2 and 33.3% according to Beers 2012 criteria [40]. In Kara et al.'s study, PIM use was 41.2% according to STOPP/START criteria [41]. In Bozkurt et al.'s study, PIM use was 48.1%, according to the EU(7)-PIM list [6]. We found a higher percentage of PIM use in Turkey than in the studies mentioned above. Furthermore, unlike in our study, another study reported no inappropriate drug use according to the START criteria for elderly patients in Turkey [42]. This difference is thought to stem from the inclusion of the section on oral nutritional support in the TIME-to-START criteria [6]. Our study showed a lower PIM use percentage than in Malaysia, where, according to STOPP/START criteria, the PIM use rate was 58.5% [37], and in Brazil, where the PIM use rate was found to be 99.3% according to STOPP/START criteria [36]. However, the results of our study showed a higher PIM percentage compared to a study conducted in Lithuania, where PIM use was reported at 24.1% according to the 2003 Beers criteria, 25.9% according to 2015 Beers criteria, but lower according to the EU(7)-PIM list at 57.2% [13].

Our study determined that cholinesterase inhibitors (ChEIs) were the most commonly omitted drugs (33.33%). According to the TIME-to-START (B3) criteria, they should have been started in early-middle stage Alzheimer's disease but were not. The fact that ChEIs were not initiated despite the presence of an Alzheimer's disease diagnosis could stem from the consultant neurologist's intention to differentiate whether the Alzheimer's disease symptoms might have been caused by the condition that caused the hospitalization. However, this is open to further discussion. Furthermore, oral nutrition supplements (ONSs) were the second most common omitted drugs (30.77%). ONSs should have been started according to the TIME-to-START criteria (I1) if nutritional counseling and increased dietary supplement intake were insufficient to treat patients with malnutrition or at risk of malnutrition. Malnutrition in the elderly may occur for many reasons, such as low economic status, chronic disease, and chronic drug use. The presence of malnutrition can affect drug pharmacodynamics and pharmacokinetics in the elderly in many ways. Reduced protein intake can change the distribution of drugs and microsomal enzyme activity by causing hypoalbuminemia.

Moreover, since it increases the free fraction of drugs, it may lead to the faster elimination of drugs and a decrease in their half-life [43]. ONSs have been included in reimbursement lists in Turkey and many other countries. Due to their favorable effects, it is recommended that physicians prescribe ONSs to old, malnourished patients [17]. In a study conducted on the elderly in the internal medicine service in Greece, it was observed that ONSs were initiated in 8 out of 25 malnutrition patients, and the rate was higher than in our study [44]. In our study, only 7 of 31 malnutrition patients were administered ONSs, which suggests that dietitians were not consulted and that doctors and nurses need more training about ONSs. According to TIME-to-START criteria, in the presence of systolic HF (EF <= 40%) or MI, ACE inhibitors are recommended. However, in our study, ACI inhibitors were the third most frequently omitted drugs (24.36%). The low number of ACE inhibitor prescriptions might stem from most elderly patients being admitted to the hospital due to HF and usually concomitantly having acute kidney failure.

According to the TIME-to-STOP criteria, PPI use is inappropriate when multiple drugs are being used (no benefit and potential harm). However, in our study, besides being the most frequently prescribed drugs, PPIs were also the most frequently PIMs (29%). Our results showed a lower rate of PPI prescription compared to the results of Ozturk et al., who used EU(7)-PIM criteria [45], where PPIs were also the most commonly prescribed drugs (38.5%). However, our study showed a higher rate than Periera et al., where the most common possible unsuitable drugs taken at home or in the hospital according to STOPP criteria were PPIs (18.2%) [36]. Antivertigo drugs (AVI) were the second most frequently and potentially inappropriately prescribed drugs. The inappropriate use of AVI in our study was higher than in Maarsingh et al.'s study, in which general practitioners inappropriately prescribed AVI during the first consultation (9.2%) with elderly patients for non-vestibular dizziness. An irrational prescription could be a result of the patient's medical needs, expectations, or the (wrong) perception of the patient's expectations. Since AVIs can cause serious side effects, such as dystonia and parkinsonism, in geriatric patients, clinicians should take extra precautions while prescribing them [46]. Scopolamine (hyoscine-N-butyl bromide), another frequently potentially inappropriately prescribed drug in our study, is an antimuscarinic drug that causes side effects, such as constipation, urinary retention, blurred vision, skin flushing, and tachycardia. A study reported that hemodynamic instability was the most frequent ARD of scopolamine [47]. A recent case reported that hypotension and acute MI developed after the intravenous injection of hyoscine-N-butyl bromide as a premedication therapy for colonoscopy. The frequency of the potentially inappropriate use of hyoscine-N-butyl bromide in our study was higher than in another study conducted among elderly outpatients [48]. These data indicate that physicians should avoid using anticholinergic hyoscine-N-butyl bromide in geriatric patients.

Furthermore, we determined that gender, age groups, discharge status, length of stay, CCI, and the number of diagnoses were not affected. However, polypharmacy or chronic disease increases the potential for inappropriate drug use. Other studies have reported similar results to ours [16, 40]. However, Sayın et al. reported that potentially inappropriate drug use was statistically more common in patients over 75 years of age [42]. The CCI score was not associated with potentially inappropriate drug use in our study, similar to the study by Martin et al. [29].

Nevertheless, Fahini et al. reported an association between increased CCI and potentially inappropriate drug use [13]. The patients' low CCI scores (mild disease group) in our study may explain the lack of a statistically significant relationship between CCI and potentially inappropriate drug use. Consistent with our study, Bahat et al. and Kara et al. reported that chronic diseases increased the potential for inappropriate drug use in the elderly [40, 41]. Furthermore, similar to our study, Sayın et al. reported that polypharmacy increased potentially inappropriate drug use [42]. Another study reported no statistically significant relationship between the number of drugs used and potentially inappropriate drug use in hospitalized elderly patients [16].

In our study, during their hospital stay, 70.8% of patients experienced polypharmacy (using at least 10 or more drugs at least once during the hospital stay). Another study conducted in a geriatric medicine department in Turkey reported that 82.7% of geriatric inpatients experienced polypharmacy (use of ≥ 4 drugs) [18]. Nevertheless, it was determined that gender, discharge status, duration of hospitalization, number of diagnoses, and CCI were not affected. However, chronic disease and age 85 and above significantly increased polypharmacy. A high rate of polypharmacy in the population aged 85 years and above was also reported by Walkers et al. [49]. Similar to our findings, Walkers et al.'s study also showed no difference in the prevalence of polypharmacy between men and women. Furthermore, the relationship between chronic disease and an age of 85 and above and polypharmacy could stem from the increased multimorbidity occurring with older age. A study conducted with oncological geriatric patients reported that 46% of patients with a CCI score greater than 3 used more than ten drugs more often and that a higher CCI score was associated with multiple drug use [50]. However, this relationship was not found in our study. The reason for this could be our patients' lower CCI scores. Similar to our study, Morin et al. [51] reported that the presence of chronic disease increased the use of multiple drugs. However, unlike in our study, in the study by Harugeri et al. [52], essential hypertension, diabetes mellitus, COPD, and angina pectoris were found to increase polypharmacy during a hospital stay. In our study, chronic HF and malignancies increased polypharmacy. The high rate of polypharmacy in association with these diseases may be due to the recommendation of the concomitant use of many drugs to treat these diseases in clinical guidelines. For instance, in a study conducted with 209 HF patients, it was reported that the mean ± SD number of drugs taken by the patients was 11 ± 8–17, and 12% of the patients took more than 20 drugs [53]. Similarly, more than one drug is usually involved in cancer treatments. Cancer patients are at risk of polypharmacy due to the numerous medications prescribed for various comorbidities [54].

Reviewing supplements, over-the-counter medicines, and herbal remedies that patients take in addition to prescription medications is advised to prevent polypharmacy in geriatric patients [55, 56]. The risks of PIM use and polypharmacy can be minimized by increasing awareness among healthcare professionals and patients. It would be beneficial to expand the use of criteria developed for the elderly by incorporating them into hospitals' computerized prescribing decision support systems. It is critical to avoid treating diseases with inappropriate drugs to optimize drug use.

### 3.1 Limitations

Since our study was carried out retrospectively, the information on the drugs used by patients and the detailed epicrisis were obtained from the hospital computer database, and the retrospective follow-up regarding the changing parameters of patients during their hospitalization constitutes limitations. Disease diagnosis and drug matching can be made based on records. However, since evaluating potentially inappropriate drug use is done by examining all data according to the specified criteria, we do not think there was a deficiency in detecting noncompliance.

## 4. CONCLUSION

This study showed a high rate of PIM use and polypharmacy in elderly patients hospitalized in an internal medicine clinic in Istanbul, Turkey. Polypharmacy was significantly more frequent in patients with chronic HF and malignancy. The frequency of PIM use was incised by polypharmacy and the presence of chronic disease.

## 5. MATERIALS AND METHODS

### 5.1 Study patients

A total of 318 patients older than 65 years who were hospitalized for longer than two days and undergoing medical therapy were included in the study after assessing a pool of 485 inpatients treated in the Department of Internal Medicine at the Goztepe Prof. Dr. Suleyman Yalcin City Hospital between January 1, 2020, and June 7, 2020. Patients with missing data were excluded. Patients' records, including age, length of hospital stay, laboratory values, diagnoses, and medications used (dose, pharmaceutical form, route of administration, and administration frequency), were obtained from the automated database of Göztepe Prof. Dr. Suleyman Yalcin City Hospital. Drugs were classified according to the Anatomical Therapeutic Chemical (ATC) classification. The hospitalization diagnoses of the patients were evaluated according to the ICD-10 code classification. The comorbidity status of the patients was evaluated by calculating their CCI scores. The Institutional Ethics Committee of Göztepe Prof. Dr. Suleyman Yalcin City hospital reviewed and approved this study on September 2, 2020 (code #2020/0565).

5.2 Assessment of inappropriate drug use using TIME-to-STOP/TIME-to-START criteria

TIME-to-STOP/TIME-to-START criteria are an updated screening tool that minimizes inappropriate drug prescriptions for the elderly. The TIME-to-START criteria include a set of 41 specifications indicating the potential benefit of using a specific group of drugs according to the conditions included in the criteria. These drugs are often overlooked in clinical practice or not given due to advanced age without a valid additional reason. Failure to use these drugs to treat the condition outlined by the criteria was considered to be potentially inappropriate drug use. TIME-to-STOP criteria include a set of 112 specifications, including the groups of drugs that have high side effect potential due to drug–disease, drug–geriatric syndrome, and drug–drug interactions in the elderly if used to treat conditions outlined by the criteria. The use of this group of drugs under the conditions outlined by the criteria was described as potentially inappropriate drug use. Each patient's prescriptions, together with the patient's diagnosis and laboratory values for each day during the whole hospitalization period, were carefully reviewed retrospectively by a team of pharmacologists and an internal medicine specialist using the TIME-to-STOP/TIME-to-START criteria. If there was at least one inappropriate drug on at least one prescription during hospitalization, this patient was defined as having a potentially inappropriate drug prescription. In addition, polypharmacy was identified in the study population as using ten or more drugs per day (excessive polypharmacy).

5.3 Statistical analysis

Descriptive values from the obtained data were calculated as means, SDs, medians, min-max numbers, and percentage (%) frequencies. Categorical data were analyzed in terms of groups using the Pearson chi-squared test or Fisher's exact test. Logistic regression analysis was performed to examine the relationships between the binary results and the variables. SPSS version 22.0 was used to perform calculations, and the level of statistical significance was accepted as $P < 0.05$.

**Author contributions:** Concept – A.HK., B.TB., E.O. Design – A.HK., B.TB., E.O. Supervision – A.HK., BTB., E.O.; B.M; N.B. Resources – A.HK., B.TB., E.O.; B.M. Materials – A.HK., B.TB., E.O., B.M. Data Collection and/or Processing– A.HK., B.TB., E.O., N.B. Analysis and/or Interpretation – A.HK., B.TB., E.O., B.M.; N.B. Literature Search – A.HK., B.TB., E.O.; B.M, N.B. Writing – A.HK., B.TB., E.O., B.M, N.B. Critical Reviews – A.HK., B.TB., E.O., B.M, N.B.

**Conflict of interest statement:** The authors declared no conflict of interest

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