**Evaluation of Polypharmacy and Its Effects in Geriatric Age Group Patients Applying to the Internal Diseases Outpatient Clinic**

Sinem GÜRCÜ1, Melisa ŞAHİN TEKİN2, Pınar YILDIZ2, Göknur YORULMAZ3

*1 Eskisehir City Hospital, Department of Pharmacy, Eskişehir, Turkey*

*2 Eskisehir Osmangazi University, Faculty of Medicine, Department of Internal Medicine Eskişehir, Turkey*

*3* *Eskisehir Osmangazi University, Faculty of Medicine, Department of Endocrinology, Eskişehir, Turkey*

*Address for Correspondence:*

*Assoc. Prof. Pınar Yıldız*

*Eskisehir Osmangazi University, Faculty of Medicine, Department of Internal Medicine Eskişehir, Turkey*

*e-mail:* *pinaresogu@gmail.com*

*ORCID ID:* *0000-0002-3625-9829*

**ABSTRACT**

The world population is aging and the elderly population is trying to cope with chronic diseases and multiple drug use. Polypharmacy can be defined as the combined use of 4 or more drugs. Pharmacokinetic and pharmacodynamic changes of drugs and drug-drug interactions in old age may affect this age group much more. In this study, drug-drug interactions were investigated in outpatients over the age of 65 who had 4 or more drugs prescribed. 119 prescriptions were included in the study. The average number of drugs in prescriptions is 5.23 (min 4 max 12). The group of drugs that interact most frequently is antidiabetic drugs. In second place are diuretics and nonsteroidal anti-inflammatory drugs (NSAIDs); angiotensin converting enzyme (ACE) inhibitor drugs are in the third place. Prevention of polypharmacy and its related problems will benefit both the patient and the cost. By avoiding polypharmacy or at least by following guidelines when prescribing, geriatric patients' drug compliance will increase, all side effects and interactions that may be caused by inappropriate drug use will be kept to a minimum, and possible hospitalizations and health expenses will be reduced in this way.

**Key Words:** *Geriatrics, polypharmacy, drug-drug interaction*

**INTRODUCTION**

The world population is aging rapidly with each passing day with economic progress, decrease in birth rate and increase in the practices of modern medicine. The aging of the population emerges as a very important phenomenon both individually and socially. According to 2001 data, in the United States of America (USA), approximately 35 million Americans are over the age of 65 and this number is expected to reach 70 million by 2030 [1]. The World Health Organization (WHO) states that, in 2025, approximately 2 million people will be the age of 60 years or older, and in 2050, 80% of the 2 million elderly population will continue to live in developing countries [2]. Chronic diseases that increase with aging bring about the use of many drugs. Pharmacodynamic and pharmacokinetic changes in drug metabolism, increasing side effects and interactions between drugs in geriatric patients make it difficult to regulate treatments. There are different definitions of polypharmacy in the literature. Polypharmacy is defined as the use of four or more drugs by the National Service Framework (NSF) [3]. Although it can be thought that polypharmacy may benefit the patient when it is regulated in a way that drugs can positively affect each other in some treatments, such as hypertension, it may also cause potential problems due to predicted and/or unpredictable side effects, toxic effects and drug interactions. Changes in physiological functions in systems with aging affect the pharmacokinetic and pharmacodynamic properties of drugs, and therefore drug side effects can be seen more seriously in the elderly. With aging, gastrointestinal motility slows down, salivation decreases, body fat mass increases while muscle mass decreases. Renal and hepatic blood flow, which play an important role in drug metabolism, decreases, and these alterations cause changes in the effect of the drugs in the body [4, 5]. For many reasons, the geriatric population is a sensitive group and drug use should not be considered as in other adult individuals. In this study, prescriptions for geriatric patients were analyzed. Especially drug interactions were evaluated in prescriptions and it was aimed to raise awareness that ordinary outpatient prescriptions could lead to important complications for patients.

**MATERIALS AND METHODS**

In the study, prescriptions of patients over the age of 65 who applied to the Internal Medicine Outpatient Clinic between January 2021 and June 2021 were retrospectively analyzed. The study was approved by the ethics committee (14.12.2021/36).

The number of drugs in the prescription was determined as a minimum of 4, prescriptions with 3 or fewer drugs were not included in the study. Drug interactions are classified into three levels, “Low”, “Moderate” and “Major”, according to the clinical severity of the interaction. Low-level interactions, such as decreased elimination of vitamin B12; moderate interactions include additive interactions that are not serious when some drugs are used together, and major-level interactions include interactions that can be life-threatening.

**RESULTS**

119 prescriptions were included in the study. 46.22% (n=55) of the prescriptions belonged to women and 53.78% (n=64) of them belonged to men. The average number of drugs in prescriptions was 5.23 (min 4 max 12). The average age of prescription holders was 69.44 years. The mean age of female patients was 69.56 (min 65 max 85); mean age of male patients was 69.32 (min 66, max 82). There was no significant difference between the mean age of women and men (p>0.05).

A total of 4 major, 46 moderate and 10 low-level interactions were detected in 119 prescriptions in the study, and no interaction was detected in 22 prescriptions. The interaction contents are indicated in Table 1.

|  |  |
| --- | --- |
| **Interaction** | **Number** |
| *Major* |   |
| Quinolone x Antidiabetics | 3 |
| Antigut x Diltiazem | 1 |
| *Moderate* |   |
| Antidiabetics x Beta-blockers | 5 |
| Antidiabetics x Angiotensin-Converting Enzyme (ACE) inhibitors | 5 |
| NSAID x Corticosteroid | 5 |
| Diuretics x Digitals | 4 |
| NSAID x ACE inhibitors | 4 |
| Diuretics x ACE inhibitors | 4 |
| Antidiabetics x Thiazide | 4 |
| Antiplatelets x Statins | 4 |
| PPI x Oral iron preparations | 3 |
| Antiplatelets x PPI | 3 |
| Antiplatelets x Pentoxifylline | 3 |
| Quinolones x Oral iron preparations | 2 |
| *Low* |   |
| Metformin x B12 | 6 |
| Iron x Zinc | 4 |

Table 1. Drug Interactions and Classification

When all interactions are examined, the most frequently interacting group of drugs was antidiabetic drugs. In second place were diuretics and nonsteroidal anti-inflammatory drugs (NSAIDs); Angiotensin Converting Enzyme (ACE) inhibitors were in third place.

**DISCUSSION**

The purpose of drug therapy is to improve the management of diseases and thus to increase the patients’ quality of life. Drug-related side effects or drug interactions are more common in older ages due to the increased frequency of chronic diseases, the increase in the number and types of drugs used, the use of prescription or non-prescription drugs, herbal treatments, dose repetition due to forgetfulness, and differences in the pharmacokinetic and pharmacodynamic properties of drugs. The problems associated with polypharmacy can be listed as drug side effects, drug-drug interactions, increased treatment expenditures, compliance issues to treatment, increased hospitalization and increased medication errors [6].

In a study in Italy, it was reported that almost all patients aged 75 and over used at least one drug per day, and one-third of them used five or more drugs [7]. In the meta-analysis Rollason et al. published, they reported that 20% of geriatric patients aged 70 and overuse five or more drugs [8]. In studies about geriatric patients, the number of daily drug use was reported as 2-5 [9]. In this study, we found the average number of drugs in prescriptions is 5.23, which is consistent with the literature. It is important because the increase in the number of drugs used is associated with the increase in drug interactions and drug side effects.

In our study, we found that quinolones and antidiabetics were used together in 3 different prescriptions. Quinolones have been associated with disorders in blood glucose homeostasis resulting from their effects on ATP-sensitive potassium channels of the pancreatic beta cell that regulate insulin secretion. For this reason, serious abnormalities in blood glucose levels may occur when these two drug groups are used together [10, 11]. Diltiazem, an inhibitor of CYP450 3A4, when co-administered with colchicine can significantly increase serum concentrations of colchicine. One interaction was determined in our study. If colchicine is to be used together with CYP450 3A4 inhibitor drugs, it is recommended to reduce the dose of colchicine [12]. Absorption of quinolones is significantly reduced due to chelation by cations such as iron salts. In our study, this interaction was observed in 2 prescriptions. However, the gap between the intake times of these two drugs (2-4 hours before or 4-6 hours after the quinolone intake) may not be clinically significant as it will minimize the interaction [13]. Beta-blockers present pharmacodynamic interactions with antidiabetic drugs. Beta-blocker drugs may mask the symptoms of hypoglycemia such as tremors and sweating caused by antidiabetic drugs. It is known that cardioselective beta-blockers are safer than non-cardioselective agents in diabetic patients. However, the same risks associated with hypoglycemia apply to cardioselective beta-blockers. In our study, we detected this interaction in 5 prescriptions, and therefore, in clinical practice, patients should be warned about the symptoms of hypoglycemia if they use these drugs together [14, 15]. Diuretics may predispose patients who are using digoxin to arrhythmias due to hypokalemia and hypomagnesemia. These two groups of drugs, which are included in 4 different patient prescriptions in our study, can be frequently prescribed by physicians. Therefore, when these drugs are used together, if patients experience symptoms of possible digoxin toxicity or electrolyte disturbances, such as weakness, drowsiness, muscle aches or cramps, nausea, anorexia, visual disturbances, or irregular heartbeat, they may be advised to consult a physician [16, 17]. When nonsteroidal anti-inflammatory drugs are used together with Angiotensin Converting Enzyme (ACE) inhibitors, the risk of renal failure and a decrease in hypotensive effect are observed. In the study, interactions between NSAIDs and ACE inhibitors were observed in 4 prescriptions. When the past medical records of these four patients were analyzed, it was thought that they had taken NSAIDs for a short time. The use of NSAIDs for more than one week may pose a risk in terms of interaction, and it is recommended to monitor the patient's blood pressure [18].

Because thiazide diuretics antagonize the hypoglycemic effect of antidiabetics, they increase blood sugar levels [19]. By competitively blocking the binding of the Intrinsic Factor-Vitamin B12 complex to its receptor depending on calcium, metformin may result in decreased oral vitamin B12 absorption [20]. ACE inhibitors can increase the effectiveness of oral antidiabetics [21]. When diuretics and ACE inhibitors are used together, the hypotensive effect is increased additively. This interaction may be a convenient effect in clinical practice [22]. When clopidogrel and proton pump inhibitors (PPI) are used together, pantoprazole may decrease the serum concentrations of clopidogrel's active metabolites. The bioactivation of clopidogrel occurs by the enzyme CYP450 2C19. Since proton pump inhibitors have been shown to inhibit CYP450 2C19, an interaction is possible leading to decreased therapeutic efficacy and formation of the active metabolite of clopidogrel [23]. Pentoxifylline prolongs the prothrombin time. Since clopidogrel inhibits platelet aggregation, the risk of bleeding increases when used simultaneously with pentoxifylline [24]. Atorvastatin may inhibit the antiplatelet activity of clopidogrel by preventing its conversion to its active metabolite via CYP3A4 [25]. The combined use of proton pump inhibitors (PPIs) and oral iron, which is seen in 3 prescriptions of our study group patients, is seen much more frequently in our geriatric patient prescriptions in our daily practice. Since PPIs reduce gastric acidity, gastrointestinal absorption of iron, which is dependent on an acidic environment, is impaired and iron absorption decreases [26]. Concomitant use of corticosteroids and nonsteroidal anti-inflammatory drugs (NSAIDs) may increase the potential for serious gastrointestinal (GI) toxicity, including inflammation, bleeding, ulceration, and perforation. In this study, this interaction was observed in 5 different prescriptions [27]. The interactions of oral iron and zinc preparations seen in four different prescriptions are potentially due to decreased absorption of each other [28].

In Steinman et al.’s study, it was observed that 128 of 196 patients (65%) had at least one inappropriate drug use, and the frequency of inappropriate drug use increased as the number of drugs used increased [9]. According to the data of the Ministry of Health of the Republic of Turkey, 2 billion 19 million boxes of drugs were consumed in 2016 [29]. In these data, analgesics are in the first place and antibiotics are in the second. According to Organization for Economic Co-operation and Development (OECD) data, Turkey ranks first place in the world with 42.2 per thousand antibiotic consumption [30]. According to Masoodi et al.’s study in 2008, it was shown that adverse drug effects can be seen in 15% frequency with the use of two drugs; and raise to 58% with the use of five drugs [31]. Adverse drug effects include drug side effects and drug interactions, and drug interactions are preventable adverse drug effects. For this reason, drug interactions should also be considered when prescribing.

There is a need for widespread use of algorithms such as BEERS and TIME TO STOP, TIME TO START that provide physicians with the opportunity to evaluate before prescribing drugs, to prevent problems associated with the irrational use of prescriptions and polypharmacy in the geriatric patient group [32, 33]. In these criteria, drugs that are not suitable for use in the elderly patient group and potential interactions have been brought to the attention of physicians. Again, in line with the TIME criteria, physicians will have the chance to review drug contents and interactions before starting a new drug, and this will reduce drug side effects that elderly individuals frequently encounter in daily life.

Polypharmacy, which is very common in the elderly, is an important medical condition that increases morbidity and mortality. It impairs quality of life and increases costs in both developed and developing countries. This situation makes it even more important to raise awareness of polypharmacy and take precautions, if possible. Because of this, before starting a new drug to elder people, a comprehensive geriatric evaluation should be made with an interdisciplinary approach, the indication should be made sure, the current functional capacity should be evaluated, and a new drug should be started by considering other drugs that are constantly used.

As a result, the most important condition for the prevention of polypharmacy, and the problems that may develop due to it, is awareness. It is necessary to act with the knowledge that prescribing medication for an elderly patient is as important as making a diagnosis, and to be aware that we can provide benefits without harming the patient. By avoiding polypharmacy, or at least by following guidelines when prescribing, geriatric patients’ quality of life will increase, all side effects and interactions that may result from inappropriate drug use will be kept to a minimum, and possible hospitalizations and health expenses will be reduced.

**Limitations:** Due to the retrospective design of the study, the inability to differentiate the drugs used by the patients and the duration of use is the limitation of our study. Larger data can be obtained with longer periods and larger samples.

**REFERENCES**

1. United States Department of Health and Human Services, 2001. A profile of
older Americans: 2001. Administration on Aging. http://www.caregiverslibrary.org/Portals/0/AOA%20Older%20American%20profile\_2001.pdf (Accessed 12/11/21)
2. Kalache A, Gatti A. Active ageing: a policy framework. Adv Gerontol. 2003;11:7-18. PMID: 12820516.
3. Medicines and older people: implementing medicines-related aspects of the NSF for older people, 2001. <http://www.wales.nhs.uk/sites3/documents/439/nsf%20for%20older%20people%20-%20medicines%20and%20older%20people.pdf> (Accessed: 26/12/21)
4. Hajjar ER, Cafiero AC, Hanlon JT. Polypharmacy in elderly patients. Am J Geriatr Pharmacother. 2007;5(4):345-351. doi: 10.1016/j.amjopharm.2007.12.002. PMID: 18179993.
5. Maher RL, Hanlon J, Hajjar ER. Clinical consequences of polypharmacy in elderly. Expert Opin Drug Saf. 2014;13(1):57-65. doi: 10.1517/14740338.2013.827660. Epub 2013 Sep 27. PMID: 24073682; PMCID: PMC3864987.
6. Linjakumpu T, Hartikainen S, Klaukka T, Veijola J, Kivelä SL, Isoaho R. Use of medications and polypharmacy are increasing among the elderly. J Clin Epidemiol. 2002 ;55(8):809-817. doi: 10.1016/s0895-4356(02)00411-0. PMID: 12384196.
7. Nobili A, Tettamanti M, Frattura L, Spagnoli A, Ferraro L, Marrazzo E, Ostino G, Comelli M. Drug use by the elderly in Italy. Ann Pharmacother. 1997 ;31(4):416-422. doi: 10.1177/106002809703100405. PMID: 9101001.
8. Rollason V, Vogt N. Reduction of polypharmacy in the elderly: a systematic review of the role of the pharmacist. Drugs Aging. 2003; 20(11):817-832. doi: 10.2165/00002512-200320110-00003. PMID: 12964888.
9. Steinman MA, Landefeld CS, Rosenthal GE, Berthenthal D, Sen S, Kaboli PJ. Polypharmacy and prescribing quality in older people. J Am Geriatr Soc. 2006;54(10):1516-1523. doi: 10.1111/j.1532-5415.2006.00889.x. PMID: 17038068.
10. Wang S, Rizvi AA. Levofloxacin-induced hypoglycemia in a nondiabetic patient. Am J Med Sci. 2006;331(6):334-335. doi: 10.1097/00000441-200606000-00009. PMID: 16775443.
11. Saraya A, Yokokura M, Gonoi T, Seino S. Effects of fluoroquinolones on insulin secretion and beta-cell ATP-sensitive K+ channels. Eur J Pharmacol. 2004;16;497(1):111-1117. doi: 10.1016/j.ejphar.2004.06.032. PMID: 15321742.
12. Şen S, Karahan E, Büyükulaş C, Polat YO, Üresin AY. Colchicine for cardiovascular therapy: A drug interaction perspective and a safety meta-analysis. Anatol J Cardiol. 2021;25(11):753-761. doi: 10.5152/AnatolJCardiol.2021.707. PMID: 34734808; PMCID: PMC8575392.
13. Lomaestro BM, Bailie GR. Quinolone-cation interactions: a review. DICP. 1991;25(11):1249-1258. doi: 10.1177/106002809102501115. PMID: 1763542.
14. May M, Schindler C. Clinically and pharmacologically relevant interactions of antidiabetic drugs. Ther Adv Endocrinol Metab. 2016;7(2):69-83. doi: 10.1177/2042018816638050. Epub 2016 Mar 31. PMID: 27092232; PMCID: PMC4821002.
15. Sinclair AJ, Davies IB, Warrington SJ. Betaxolol and glucose-insulin relationships: studies in normal subjects taking glibenclamide or metformin. Br J Clin Pharmacol. 1990;30(5):699-702. doi: 10.1111/j.1365-2125.1990.tb03838.x. PMID: 2125460; PMCID: PMC1368169.
16. Marcus FI. Pharmacokinetic interactions between digoxin and other drugs. J Am Coll Cardiol. 1985 May;5(5 Suppl A):82A-90A. doi: 10.1016/s0735-1097(85)80466-6. PMID: 2985676.
17. Wang MT, Su CY, Chan AL, Lian PW, Leu HB, Hsu YJ. Risk of digoxin intoxication in heart failure patients exposed to digoxin-diuretic interactions: a population-based study. Br J Clin Pharmacol. 2010;70(2):258-267. doi: 10.1111/j.1365-2125.2010.03687.x. PMID: 20653679; PMCID: PMC2911556.
18. Moore N, Pollack C, Butkerait P. Adverse drug reactions and drug-drug interactions with over-the-counter NSAIDs. Ther Clin Risk Manag. 2015 15; 11:1061-1075. doi: 10.2147/TCRM.S79135. PMID: 26203254; PMCID: PMC4508078.
19. Samardzic I, Bacic-Vrca V. Incidence of potential drug-drug interactions with antidiabetic drugs. Pharmazie. 2015 ;70(6):410-415. PMID: 26189304.
20. Andrès E, Noel E, Goichot B. Metformin-associated vitamin B12 deficiency. Arch Intern Med. 2002; 28;162(19):2251-2252. doi: 10.1001/archinte.162.19.2251-a. PMID: 12390080.
21. Herings RM, de Boer A, Stricker BH, Leufkens HG, Porsius A. Hypoglycaemia associated with use of inhibitors of angiotensin converting enzyme. Lancet. 1995;13;345(8959):1195-1198. doi: 10.1016/s0140-6736(95)91988-0. PMID: 7739305.
22. Scalbert E, Abdon D, Devissaguet M, Juggi JS. Interaction between an angiotensin converting enzyme inhibitor, perindopril, and a thiazide diuretic in the spontaneously hypertensive rat. Can J Cardiol. 1992 May;8(4):381-6. PMID: 1617521.
23. Siller-Matula JM, Spiel AO, Lang IM, Kreiner G, Christ G, Jilma B. Effects of pantoprazole and esomeprazole on platelet inhibition by clopidogrel. Am Heart J. 2009;157(1): 148.e1-5. doi: 10.1016/j.ahj.2008.09.017. Epub 2008 Nov 6. PMID: 19081411.
24. Fernandes JL, de Oliveira RTD, Mamoni RL, Coelho OR, Nicolau JC, Blotta MHSL, Serrano CV Jr. Pentoxifylline reduces pro-inflammatory and increases anti-inflammatory activity in patients with coronary artery disease--a randomized placebo-controlled study. Atherosclerosis. 2008;196(1):434-442. doi: 10.1016/j.atherosclerosis.2006.11.032. Epub 2006 Dec 28. PMID: 17196208.
25. Saw J, Steinhubl SR, Berger PB, Kereiakes DJ, Serebruany VL, Brennan D, Topol EJ; Clopidogrel for the Reduction of Events During Observation Investigators. Lack of adverse clopidogrel-atorvastatin clinical interaction from secondary analysis of a randomized, placebo-controlled clopidogrel trial. Circulation. 2003; 26;108(8):921-924. doi: 10.1161/01.CIR.0000088780.57432.43. Epub 2003 Aug 18. PMID: 12925453.
26. Humphrey ML, Barkhordari N, Kaakeh Y. Effects of Omeprazole on Vitamin and Mineral Absorption and Metabolism. Journal of Pharmacy Technology. 2012: 28(6): 243-248.
27. Wilcox CM, Shalek KA, Cotsonis G. Striking prevalence of over-the-counter nonsteroidal anti-inflammatory drug use in patients with upper gastrointestinal hemorrhage. Arch Intern Med. 1994; 10;154(1):42-46. PMID: 8267488.
28. Lind T, Lönnerdal B, Stenlund H, Ismail D, Seswandhana R, Ekström EC, Persson LA. A community-based randomized controlled trial of iron and zinc supplementation in Indonesian infants: interactions between iron and zinc. Am J Clin Nutr. 2003;77(4):883-890. doi: 10.1093/ajcn/77.4.883. PMID: 12663287.
29. Rebuplic of Turkey Ministry of Health, 2019. Turkish Pharmaceutical Market Observation Report. <https://titck.gov.tr/storage/Archive/2019/news/ffebd110-9c02-4283-b8b6-653c8d082e18.pdf> (Accessed 24/12/21)
30. Organisation for Economic Co-operation and Development, 2016. Antimicrobial Resistance Polict Insight. [https://www.oecd.org/health/health-systems/AMR-Policy-Insights November2016.pdf](https://www.oecd.org/health/health-systems/AMR-Policy-Insights%20November2016.pdf) (Accessed 24/12/21)
31. Masoodi N. Polypharmacy: To err is human, to correct divine. Br J Clin Pharmacol 2008; 1:6–9.
32. American Geriatrics Society 2012 Beers Criteria Update Expert Panel. American Geriatrics Society updated Beers Criteria for potentially inappropriate medication use in older adults. J Am Geriatr Soc. 2012 ;60(4):616-631. doi: 10.1111/j.1532-5415.2012.03923.x. Epub 2012 Feb 29. PMID: 22376048; PMCID: PMC3571677.
33. Bahat G, Ilhan B, Erdogan T, et al. Turkish inappropriate medication use in the elderly (TIME) criteria to improve prescribing in older adults: TIME-to-STOP/TIME-to-START. Eur Geriatr Med. 2020;11(3):491-498. doi: 10.1007/s41999-020-00297-z. Epub 2020 Mar 5. PMID: 32297261; PMCID: PMC7280176.