ARAŞTIRMA MAKALESİ / RESEARCH ARTICLE
TIBBİ FARMAKOLOJİ / MEDICAL PHARMACOLOGY

ATLJM 2024; 4 (11): 156-163
https://doi.org/10.54270/atljm.2024.69

PREDICTING AND DETECTING POLYPHARMACY-RELATED DRUG INTERACTIONS AND FRAILTY : GERIATRICS

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ABSTRACT

Background: Frailty is a situation that has become increasingly important in recent years. The study's objective was to investigate the connection between frailty and drug-drug interactions brought on by polypharmacy in older adults.
Methods: 180 older adults admitted from the family practice medicine department between January 2022 to June 2022 were included. People over the age of 65 who applied to the family medicine outpatient clinic were included in the study.
Results: The most prevalent comorbidities were hypertension (71.6%), diabetes (31.1%), and arthrosis (19.4%) in individuals with polypharmacy-related drug-drug interactions, antihypertensive medicines had the most interactions across all interaction classes. Polypharmacy-related drug-drug interactions were found in 130 (72.2%) of 180 patients included in the study.
Conclusions: In the study, the frailty score was found to be statistically significantly worse in the 65 years and older with polypharmacy-related drug-drug interactions, according to age, comorbidities, and the number of drugs.
Keywords: Frailty, Drug-drug interactions, Polypharmacy

POLİFARMASİ İLE İLİŞKİLİ İLAÇ ETKİLEŞİMLERİNİN VE KIRILGANLIĞIN ÖNGÖRÜLMESİ VE TESPİTİ : GERİATRİ

ÖZET

Giriş ve Amaç: Kırılganlık son yıllarda önemi giderek artan bir durumdur. Çalışmanın amacı, yaşlı yetişkinlerde polifarmasinin neden olduğu ilaç-ilaç etkileşimleri ile kırılganlık arasındaki bağlantıyı araştırmaktır.
Yöntemler: Ocak 2022 ile Haziran 2022 tarihleri arasında aile hekimliği bölümüne başvuran 180 yaşlı yetişkin çalışmaya dahil edildi. Aile hekimliği polikliniğine başvuran 65 yaş üstü kişiler çalışmaya dahil edildi.
Bulgular: Polifarmasi ilişkili ilaç-ilaç etkileşimi olan bireylerde en yaygın komorbiditeler hipertansiyon (%71,6), diyabet (%31,1) ve artroz (%19,4) olup, antihipertansif ilaçlar tüm etkileşim sınıflarında en fazla etkileşime sahipti. Çalışmaya dahil edilen 180 hastanın 130'unda (%72,2) polifarmasi ilişkili ilaç-ilaç etkileşimi saptanmıştır.
Sonuçlar: Çalışmada, polifarmasi ile ilişkili ilaç-ilaç etkileşimi olan 65 yaş ve üzeri hastalarda kırılganlık skoru yaş, komorbiditeler ve ilaç sayısına göre istatistiksel olarak anlamlı derecede daha kötü bulunmuştur.
Anahtar Kelimeler: Kırılganlık, İlaç-ilaç etkileşimi, Polifarmasi

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KETENCİ S, AKPINAR NG. PREDICTING AND DETECTING POLYPHARMACY-RELATED DRUG INTERACTIONS AND FRAILTY : GERIATRICS. ATLJM. 2024;4(11):156-163.

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Gönderim Tarihi: 02 NİSAN 2024
Kabul Tarihi: 23 TEMMUZ 2024

INTRODUCTION

It has been discovered that older adults, particularly those with multimorbidity, are more likely to have adverse drug reactions. This is thought to be related to polypharmacy and complex drug-drug interactions, which are both strongly influenced by changes in pharmacokinetics and pharmacodynamics that are linked with aging (1). Frailty is becoming more widely recognized as a unique clinical state that predicts adverse health consequences in older persons, including death, hospitalizations, institutionalization, falls, fractures, impairments, and lower quality of life (2). Frailty was reported to be linked to risk variables such as polypharmacy, multimorbidity, and functional impairment in a study (3). Frailty is related to more exposure to medications with anticholinergic and sedative side effects as well as polypharmacy, which may increase the likelihood of adverse consequences like falls. Due to drug use and probable changes in pharmacokinetics and pharmacodynamics, adverse drug events in the frail are more common and severe in them. These patients require continual examination and monitoring when using drugs, taking into account the effects of each drug as well as the increasing drug burden, comorbidities, functioning, and care objectives. Frailty is a multifactorial condition that can affect anyone at any age and is linked to functional impairment, increased vulnerability to disease, disability, and mortality. According to the clinical definition, frailty is a state of inadequate homeostatic recovery after the stress that results from a lifetime's worth of accumulated physiological system degradation (4). When older people became frail, the pharmacological reaction to medications is further affected. Among older persons, frailty is a geriatric syndrome linked to functional impairment and increased susceptibility to illness, disability, and mortality. Frail people are more likely to take more medications and are more prone to experience negative drug effects (5). The European Geriatric Advisory suggests utilizing a hybrid measure, the "FRAIL" scale, which incorporates elements taken from both the Phenotype of Frailty and the Frailty Index (6). The Physical Frailty Phenotype method is used in the FRAIL scale, which evaluates five domains: weariness, resistance (ability to ascend 10 steps), ambulation (ability to walk several hundred yards), diseases (more than five), and weight loss (more than 5%). As a result, the scale has a range of 0 to 5. Scores of 0 show robustness, 1-2 suggest pre-frailty, while 3 indicate frailty (7,8). The World Health Organization (WHO) describes aging as a diminution in someone's capacity to adapt to environmental variables (9). Age-related comorbidities are more prevalent. Frail 65 years and older people are those who have diminished mobility and nutritional inadequacies as a result of age-related loss of neuromuscular, metabolic, and immune system function (10). It might be challenging to prescribe medication to frail 65 years and older people. As a result, drug use in the 65 years and older should be carefully examined, and all factors, including frailty, should be taken into account before writing a prescription. The most frequent issues in the frail patient category are polypharmacy, inadequate treatment, overtreatment, drug-drug interactions, and difficulty adhering to treatment, in addition to the pharmacokinetic and pharmacodynamics changes that come with aging (11). The term "polypharmacy" refers to the concomitant use of four or more pharmaceuticals and is used to describe the usage of numerous medications. The risk of several adverse outcomes, including incorrect prescribing, drug-drug interactions, impaired functionality, frailty, cognitive decline, urine incontinence, malnutrition, falls, and an elevated risk of fractures, is exacerbated by polypharmacy and inappropriate medication use (12). The Disease Management Platform, which was developed to enable family physicians to monitor citizens' chronic diseases in an electronic environment in an integrated manner with other systems of the Turkish Ministry of Health, in the light of current medical algorithms, has been made available to all family physicians as of January 1, 2021 (13). This platform enables healthcare professionals to make an early diagnosis of chronic diseases and to control symptoms and signs with appropriate treatment plans in line with the recommendations of evidence-based medicine guidelines. It facilitates the early diagnosis of chronic diseases by performing periodic scans, and the periodic follow-up of the diagnosed patients in line with the recommendations of the evidence-based medical guidelines, providing the appropriate treatment and early detection of complications. Detection of drug-drug interactions is also important for adjusting the most appropriate treatment regimen (14).

Despite numerous studies showing a link between polypharmacy and frailty, no research has been conducted to determine whether drug-drug interactions caused by polypharmacy represent a risk factor for frailty in older Turkish adults. Our study's objective was to investigate the connection between frailty and drug-drug interactions caused by polypharmacy in older adults. This will

provide for the appropriate management of drug use in 65 years and older people who are frail by determining the effects of drug-drug interactions related to polypharmacy on frailty.

METHOD

This was a retrospective study in a family health centre in Gebze. 180 older adults admitted from the family practice medicine department between January 2022 to June 2022 were included. The frailty index and the list of all medications within the scope of 65 years and older Patient follow-up were evaluated with the Medulla records of the patients via the Disease Management Platform (HYP). Medulla is a system in which the medical data of patients are received at other hospitals and clinics and past medical data is also stored. Statistical analysis of drug-drug interaction data over the age of 65 was analyzed using the SPSS® program. In this study, the frailty scale (7,8) was used. The FRAIL frailty assessment is a 5-item questionnaire to identify frailty in individuals. Self-rated scale, five items: fatigue, resistance, ambulation, illnesses, loss of weight (i.e., 1 point for each component; 0 = best to 5 = worst) and represent frail (3–5), pre-frail (1–2), and robust (0) health status. A patient was classified as frail if they had impairments in three or more key elements, and immediately frail if they had deficits in one to two core elements. Patients without any deficits in the core frailty measures were classified as non-frail.

Analysis of drug-drug interactions, with the Lexicomb drug interaction module in the UpToDate® program, first the chronically used drugs of the patients will be listed, and then the potential interaction levels will be evaluated by the system (Table 1). In addition, the patients included in the study were also evaluated in terms of the average number of drugs used, the total number of interactions, the most prescribed drug, and chronic disease diagnoses. To determine whether there was a statistically significant difference between the means of two independent groups, the Student's t-test was performed. Depending on the data, the chi-square or Mann-Whitney U test was used to analyze the correlations between various characteristics, including the total number of drugs used, the number of drug-drug interactions caused by polypharmacy, and the number of chronic conditions. The multivariate logistic regression model was used to explore the independent impact of several factors.

RESULTS

The study population includes 180 patients. The patients had a median age of 72.7 6.9 years, with 87 (48.3%) men and 93 (51.7%) women. All of the individuals had at least one chronic illness, although hypertension was the most prevalent, accounting for 71.6% (n=129) of all chronic illnesses (Table 2). 130 of the 180 patients who participated in the study reported drug-drug interactions related to polypharmacy, and all but three of them had at least one chronic illness diagnosis. The most prevalent comorbidities were hypertension (71.6%), diabetes (31.1%), and arthrosis (19.4%) in 180 individuals (Table 2).

Table 1. Lexi-Comp drug interaction software risk rating classifications for drug- drug interactions

Risk rating	Description	Action
A	Data have not demonstrated either pharmacodynamics or pharmacokinetic interactions between the specified agents	No Known Interaction
B	Data demonstrate that the specific agents may interact which each other, but there is little to no evidence of clinical concern resulting from their concomitant use	No Action Needed
C	Data demonstrate that the specific agents may interact which each other in a clinically significant manner. The benefits of concomitant use of these two medications usually outweigh the risk	Monitor therapy
D	A patient-specific assessment must be conducted to determine whether the benefits of concomitant therapy outweigh the risks	Consider therapy modification
X	The risks associated with the concomitant use of these agents usually outweigh the benefits	Avoid combination

Table 2. Age, gender and chronic diseases of the patients included in the study			
	Patients (n=180) n(%)	**Male (n=87) n(%)**	**Female (n=93) n(%)**
Age, Mean (SD)	72.7±6.9	72.4±6.8	72.8±6.9
Chronic Disease			
Yes	177(98.3%)	86(98.8%)	91(97.8%)
No	3(1.7%)	1(1.2%)	2(2.2%)
Chronic Diseases			
Hypertension	129(71.6%)	57(65.5%)	62(66.6%)
Type 2 Diabetes	56(31.1%)	25(28.7%)	31(33.3%)
Arthrosis	35(19.4%)	18(20.6%)	17(18.3%)
GORD	21(11.6%)	14(16.1%)	7(7.5%)
Osteoporosis	20(11.1%)	7(8.1%)	13(13.9%)
Asthma	19(10.5%)	8(9.2%)	11(11.8%)
Hyperlipidemia	17(9.4%)	9(10.3%)	8(8.6%)
Cerebrovascular Diseases	15(8.3%)	7(8.1%)	8(8.6%)
Heart Failure	12(6.6%)	6(6.9%)	6(6.4%)
BPH	11(6.1%)	11(12.6%)	-
COPD	8(4.4%)	6(6.9%)	2(2.1%)
Alzheimer's Disease	7(3.8%)	5(5.7%)	2(2.1%)
Glaucoma	6(3.3%)	4(4.6%)	2(2.1%)
Hypothyroidism	6(3.3%)	1(1.1%)	5(5.3%)
Depression	5(2.8%)	1(1.1%)	4(4.3%)

GORD, Gastro-oesophageal reflux disease; BPH, Benign prostatic hyperplasia; COPD, Chronic obstructive pulmonary disease

In terms of drug interaction classifications in individuals with polypharmacy-related drug-drug interactions, antihypertensive medicines had the most interactions across all interaction classes. Beta-blockers and calcium channel blockers interacted the most with other drugs among antihypertensive. Antirheumatic and NSAID group drugs were the second most interacting drug group at the C level, whereas antirheumatic and NSAID group drugs were the second most interacting drug group at the D level. Heart failure medications were the second most interacted with in the X category, while NSAID drugs were the third. When the drug-drug interactions in the patients included in the study were analyzed by age group, there were considerably higher interactions in the patients aged 65-74 compared to the other age groups. When drug-drug interactions were compared by gender, the number of interactions in women was significantly higher than in males (Table 3). When the interaction levels are evaluated independently, women have much higher B, C, and D levels of interaction than men. While there was no significant variation in the number of medications used by gender, there was a significant difference by age group. Considering the age groups, the drug interaction showed higher significance in the 65-74 age group compared to the other age groups (Table 3).

Table 3. The effects of sex and age on the number of potential DDIs and risk categories in patients with polypharmacy

Patient Characteristics	Patients (n)	Total DDI's	Total Drugs	DDI's of drugs by risk categories				
				A	B	C	D	X
Gender								
Male	87	273	425	**15***	18	220	17	3
Female	93	389*	505	13	**24****	**308***	**37*****	7
Total	180	662	930	28	42	528	54	10
Age								
65-74	124	384*	652*	19	18	316	35	6
75-84	43	255	248	7	16	198	16	3
≥85	13	23	30	2	8	14	3	1

**p<0.01, ** p=0.005, ***p=0.01*

Polypharmacy-related drug-drug interactions were found in 130 (72.2%) of 180 patients included in the study. The number of patients who had drug interaction due to using two or three drugs, but no drug interaction was detected due to polypharmacy is 50. The number of frail patients with drug interaction related to polypharmacy is 116 (89.2%), and the number of frail patients who do not have drug interaction related to polypharmacy is 46 (92%). The median frailty scale score of frail patients with drug-drug interactions associated with polypharmacy is 4, and the median frailty scale score of non-frail patients is 2 (Table 4). The median frailty scale score of frail patients who do not have a drug interaction related to polypharmacy is 3. While frail patients with polypharmacy-related drug-drug interactions used 7.7±2.1 drugs on average, frail patients with polypharmacy-related drug-drug interactions had 4.5±1.6 chronic conditions on average. When the frail and non-frail scores of individuals with drug-drug interactions due to polypharmacy were compared according to their comorbidities, all comorbidities showed high significance (Table 4).

CONCLUSION

To our knowledge, the relationship between frailty and drug-drug interactions is caused by polypharmacy in older adults. It is important to understand how frailty-related physiological changes, which increase the risk of drug reactions, interact with age-related physiological, pharmacokinetic, and pharmacodynamics changes when treating 65 years and older patients who are frail. Drug interaction was found in all of the 65 years and older with polypharmacy-related drug-drug interactions, and the frailty scores of these patients were found to be significantly higher than their chronic diseases and the number of drugs used. 180 individuals were included in the study, and 130 (72.2%) of them had drug-drug interactions linked to polypharmacy. 50 patients do not experience drug-drug interactions because of polypharmacy. The percentage of frail patients who have drug-drug interactions related to polypharmacy is 116 (89.2%), while the percentage of frail patients who do not have such interactions is 46 (92%). Patients who are frail and have polypharmacy with drug-drug interactions have a median frailty scale score of 4, while non-frail patients receive a median frailty scale score of 2. These findings demonstrated that the frailty score was statistically considerably worse in the 65 years and older when polypharmacy-related drug-drug interactions, age, comorbidities, and the number of medicines were taken into consideration. Numerous studies have found that taking multiple medications increases the 65 years and older's frailty, while others have found that taking multiple medications can result in adverse events and drug-drug interactions. There is a clear link between polypharmacy and frailty, according to studies (15-19). Similar to this, our findings showed that polypharmacy-related DDI statistically significantly enhanced frailty.

Table 4. The frailty scores of patients with drug- drug interactions associated with polypharmacy according to age, gender, number of drugs used, and comorbidities

Patients	Frail, n=162	Non-frail, n=18	P value
Age, mean (SD)	73.1±6.8	69.4±5.6	<0.01*
Gender, n (%)			1.0
Male	76	11	<0.01*
Female	86	7	<0.01*
Frailty Score Polypharmacy-related DDI, n(%), median (IQR)	116 (89.2%), 4(3-7)	14 (28.0%), 2(1-2)	<0.01*
Comorbidity number Polypharmacy-related DDI, mean (SD)	4.5±1.6	4.8±2.1	<0.01*
Hypertension, mean (SD)	3.8±1.1	1.7±0.4	<0.01*
Type 2 Diabetes, mean (SD)	4.0±0.9	1.7±0.5	<0.01*
Cerebrovascular Disease, mean (SD)	4.2±1.3	1.8±0.4	<0.05**
Gastro-oesophageal reflux disease, mean (SD)	4.3±0.8	1.1±0.4	<0.01*
Hyperlipidemia, mean (SD)	4.4±0.7	1.3±0.5	<0.01*
Arthrosis, mean (SD)	4.1±0.8	1.6±0.5	<0.01*
Osteoporosis mean (SD)	4.5±1.1	1.5±0.7	<0.01*
Asthma, mean (SD)	4.3±0.9	1.8±0.5	<0.01*
Benign Prostate Hyperplasia, mean (SD)	5.1±0.3	1.7±0.4	<0.01*
Chronic Obstructive Pulmonary Disease, mean (SD)	4.1±0.6	1.3±0.3	<0.01*
Heart Failure, mean (SD)	3.9±1.1	1.9±0.4	<0.01*
Alzheimer, mean (SD)	6.4±0.8	1.6±0.3	<0.01*
Medications number Polypharmacy-related DDI, mean (SD)	7.7±2.1	6.6±3.2	<0.05**

** p<0.01, **p<0.05*

In the study, the frequency of polypharmacy was determined as 72.2% and frailty was detected in 89.2% of the patients in whom polypharmacy was detected. While the number of drug-drug interactions in individuals without polypharmacy was 27 (0.4%), the number of drug-drug interactions in individuals with polypharmacy was found to be 662 (95.9%). This result suggests that drug interaction is inevitable when it comes to polypharmacy.

According to our study, there was no significant difference in the frailty of patients with drug interaction polypharmacy according to being male or female. However, the number of frail patients increased significantly in male and female patients compared to non-frail patients. Rawle et al. (20) found no difference between genders in terms of polypharmacy in their study, but they emphasized that drug use changes with age according to gender, and more studies are needed on this subject. The most commonly used drug group was found to be antihypertensive drugs. However, when the drug interaction classifications were examined in patients with polypharmacy-related drug-drug interactions, antihypertensive drugs were the drug group with the highest number of interactions in all interaction classes. This result may be due to the fact that they are a population that is particularly prone to cardiovascular system diseases, depending on the age group, and that the most accompanying disease is hypertension. Beta-receptor blockers and calcium channel blockers interacted most with other drugs among the antihypertensive. Antidiabetic agents were the second most interacting drug group at the C level, while the second

most interacting drugs from group D were antirheumatic and NSAID group drugs. The second group of drugs that interacted most in the X category was heart failure drugs, and the third group drug was NSAID drugs. While it is necessary to monitor treatment for drugs that interact at level C, doctors need to modify treatment more carefully at level D. In X-level interactions, avoiding the treatment and considering the benefit-risk ratio in the treatment and directing them to another more appropriate treatment may help patients to decrease their mortality, morbidity, living standards and frailty scores. The higher potential of drug-drug interactions and adverse reactions can be used to explain how polypharmacy affects frailty (12). In the study, the frailties of patients with drug-drug interactions associated with polypharmacy increased significantly according to their comorbidities. Respectively, hypertension, diabetes, cerebrovascular diseases, GORD, and hyperlipidemia diseases were the top five most common diseases in the population. This result may result from the use of multiple drugs due to the prescription of a separate drug for each accompanying disease, as well as the course of the disease and the side effects of the drug. A study determined that frailty scores were higher and walking test scores were worse in those using cardiovascular, musculoskeletal, and nervous system drugs (20). Our study's polypharmacy rate is higher than in many previous studies. This could be related to an increase in the frequency of applications to our country's healthcare system in recent years, a lack of a referral chain in primary care, and an increase in patient satisfaction when supplied the medication. Furthermore, when an unfavourable side effect occurs because of a prescription, this scenario is not always detectable, and an additional drug administered because of the patient's referral to another physician to relieve his or her complaint may also contribute to polypharmacy.

Our findings show the need for an intervention involving informing prescribers of patients whose frailty scores are higher than a particular threshold and asking them to carefully assess potential drug-drug interactions. To help doctors make clinically sound decisions in more frail, 65 years and older, comorbid patients with polypharmacy, specific educational initiatives focusing on geriatric pharmacotherapy are still required. Numerous research to date has brought up the necessity for personalized learning (21, 22). It should also be highlighted that although 65-year-old and older patients sometimes receive care from multiple medical professionals, primary care doctors are best suited to supervise the administration of their care. In the study, although the frailty score was found to be statistically significantly worse in the 65 years and older with polypharmacy-related drug-drug interactions, according to age, comorbidities, and the number of drugs, there are very few patients with polypharmacy who have no drug-drug interactions in the study population. This situation caused us to evaluate patients with polypharmacy but no drug interaction. It shows us that drug-drug interactions related to polypharmacy affect many factors and that more studies are needed to examine the relationship between frailty score and many other parameters. In addition, if the number of participants in our study had been higher, the effects of many factors would have been better evaluated.

Declarations

Ethical Approval

This research complies with all relevant national regulations, institutional policies, and the principles of the Declaration of Helsinki, and Istanbul Atlas University Ethics Committee (approval number: E-22686390-050.01.04-10991) and Kocaeli Governorship, Provincial Health Directorate Scientific Research Studies Health Facility (approval number: E-65530689-799). The rights of all participants were protected and written informed consent was obtained prior to the procedures according to the Declaration of Helsinki.

Consent to Participate

All the study participants provided their informed consent since there is no personal data, and publication consent is not requested.

Consent to Publish

Since the research does not include any information identifying individuals, there is no need for consent for the publication of this work.

Competing interests

The authors declare no competing interests.

Authors' contributions

S.K. and N.G.A.: literature review, selecting articles, and drafting the manuscript. S.K: conceptualization, analysis, editing and final approval of the manuscript.

Funding

There is no funding for this research.

Availability of data and materials

The data supporting the study's findings are available from the corresponding author on reasonable request.

Acknowledgements

We thanks for Republic of Turkey Ministry of Health and Gebze Family Health Centre.

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