Biomedical Research 2018; 29 (12): 2561-2569 *ISSN 0970-938X*
www.biomedres.info

The prevalence of drug-drug interactions and polypharmacy among elderly patients in Jordan.

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Abstract

Background: The number of people aged 60 or older is estimated to be 5.6% among Jordanian population, those elderly people need special medical care; since they have a greater prevalence of chronic diseases and therefore subjected to higher prevalence of polypharmacy and potential drug-drug interaction (pDDI). There is no data about polypharmacy and pDDI in elderly patients among the Jordanian population.
Methods: Prescriptions for patients aged 60 or older were examined and those patients were interviewed in several community pharmacies and hospitals' outpatient pharmacies. The interviews covered factors that may affect the possibility of pDDI and polypharmacy including patient's education level, number of doctors the patient see, number of drugs the patient take, does the patient live alone and does the patient take the medication by himself.
Results: 367 (51.5% male and 48.5% female) patients were interviewed and their prescriptions examined. The data showed that 334 (91%) had at least one pDDI of those 67 (18.3%) had a major pDDI and 281 (76.6%) had at least one moderate pDDI. Polypharmacy was found in 275 (74.9%) of the participants. Factors that were associated with incidence of major pDDI included polypharmacy, taking Alimentary tract and metabolism drugs or drugs acting on blood and blood forming organ, and patient taking medication by him/herself. Several factors were associated with moderate pDDI including seeing a general practitioner, while polypharmacy was associated with education level and number of diseases.
Conclusion: High incidence of major and moderate pDDI and polypharmacy was found. This study emphasizes the need for a better control over elderly prescription in Jordan

Keywords: Polypharmacy, Drug-drug interaction, Geriatrics, Jordan.

Accepted on May 07, 2018

Introduction

Drug-Drug Interaction (DDI) means that one drug alters the response of the other [1]. Depending on the effect of the DDI on patients, the DDI can be classified into beneficial, harmful or neutral [2]. The mechanism of DDI includes inhibition or induction of drug-metabolizing enzyme, inhibition of drug transporters and competition on plasma albumin which can affect the pharmacokinetic parameters [3]. In addition, some drugs may influence the pharmacodynamics of other drugs, such as warfarin and vitamin K interaction [4]. It is reported that DDI accounted to cause 4.8% of total hospitalization cases, which increases the medical costs and mortality among patients [5,6].

Polypharmacy has been defined as concurrent consumption of several medications. However, the exact definition varies in literature. While some studies required the usage of 5 or more medications a day to be labelled "polypharmacy", other defined it as the usage of two or more medications [7-9].

Polypharmacy is more common in aged people with chronic diseases [8]. It is estimated that more than 40% of adults aged 65 or older are on polypharmacy [10]. As number of drug medications increase, the potential of DDI may increase [11]. In addition, polypharmacy was associated with several adverse outcomes including hospitalization, nursing home placement, death, hypoglycemia, fractures, impaired mobility, pneumonia, and malnutrition [12].

The number of people aged 60 or older is estimated to be 5.6% among Jordanian population, which is lower than the worldwide elderly population percentage (12%) [13]. Those elderly people need special medical care; since they have a greater prevalence of chronic diseases and therefore exposed to a high number of drugs administration and higher risk of DDI [14]. It is reported that the prevalence of DDI among elderly patients is 13-58%, leading to greater hospital admissions and mortality [15,16].

There is no data regarding polypharmacy and DDI in elderly patients among Jordanian population. Therefore, the aim of this study was to find the prevalence and type of potential drug-drug interaction and the prevalence of polypharmacy among

Jordanian elderly patients. The study also examined the factors associated with pDDIs and polypharmacy.

Methods

Post graduate students in pharmaceutical science in AlZaytonah University examined prescriptions for patients aged 60 or older and interviewed these patients in several pharmacies and hospitals in Amman, Madaba and Zarqa in Jordan during the period from October 2017 to January 2018. The interviews covered factors that may affect the possibility of DDI and/or polypharmacy including patient's education level, how many doctors does the patient see, how many drugs does the patient take, does the patient live alone and if the patient takes the medication by himself, does the patient suffer from any chronic disease. The severity of the potential drug-drug interaction (pDDI) was classified in accordance with drugs.com and Lexicomp Online® into 3 categories [17,18]:

1. **Minor:** Minimally clinically significant which are equivalent to lexicomp category B;
2. **Moderate:** Moderately clinically significant which are equivalent to lexicomp category C.
3. **Major:** Highly clinically significant, generally avoid or modify drug regimen; the risk of the interaction may outweigh the benefits which is equivalent to Lexicomp categories D and X.

In case conflicting results were found between drugs.com and Lexicomp we would classify the interaction according to the more severe category

All medications were classified according to the Anatomical Therapeutic Chemical Classification System (ATC) [19].

The ethical approval was obtained from AlZaytonah University Ethical Committee before beginning this study.

In addition, the present study examined the number of drugs used and the prevalence of polypharmacy among the studied sample. Polypharmacy in this study was defined as concurrent consumption of 5 medications or more per day.

Statistical analysis

All continuous variables were expressed as means (M) ± standard deviations (SD). For categorical variables, frequencies and percentages were reported.

Chi-square (χ^2) test was performed between different categorical variables including polypharmacy and pDDI (All, moderate and major), with different classes of drugs, gender, visiting a general practitioner (GP), age group, education level, and taking the medicine by himself.

A univariate and forward stepwise multivariate binary logistic regression models were performed, the binary outcome variable in the models was (moderate pDDI, no pDDI), the independent variables considered include: age group, gender, education level, does the patient live alone, does the patient take the medicine by himself, polypharmacy, different types of medication, number of doctors seen by the patient, and does the patient see a GP. Other univariate and forward stepwise multivariate binary logistic regression models were performed to investigate the relation between several factors and polypharmacy, the multivariate regression model included all the previously stated predictors and the outcome was (polypharmacy, no polypharmacy). All binary logistic regressions assumptions were evaluated including multi-collinearity and linearity of independent variables and log odds. The data were analyzed using SPSS software [20].

Results

The demographics of the studied sample are shown in Table 1. The total sample studied was 367 (51.5% male and 48.5% female). Major pDDI's were found in 18.3% of the participants. The average of number of drugs involved in a major pDDI in participants that had major pDDI was 2.98 ± 1.57 and the maximum reported number of drugs was 7. Polypharmacy was found in 74.9% of the participants and the average number of drugs per patient was 5.5 ± 2.1. Most of the patients (78.5%) were currently seeing more than one doctor (1.67 ± 0.81).

Table 2 shows the number of drugs used by the participants and their ATC classes. The participants were on 2022 medications of those 1745 (86.3%) were involved in polypharmacy and 154 (7.6%) in major pDDI. The most commonly ATC class used was cardiovascular (783, 38.7%), 35.3% of those were agents acting on the renin-angiotensin system. Alimentary tract and metabolism drugs were 27.2% of the drugs used; most of those drugs were for diabetes and drugs for acid-related disorders. Drugs acting on blood and blood forming organs were 12.7%, the majority of which were antithrombotic agents. The majority of drugs involved in a major pDDI were cardiovascular drugs (61, 39.6%), followed by drugs acting on blood and blood forming organs (47, 30.5%) and alimentary tract and metabolism drugs (18, 11.7%). However, the most common subgroup involved in major pDDI were antithrombotic agents (45, 29.2%), followed by lipid modifying agents (22, 14.3%) and acid-related disorders (14, 91%).

Table 3 shows the percentage of patients on different ATC drug classes. As the table shows most of the patients were taking cardiovascular drugs, followed by Alimentary tract and metabolism drugs and drugs acting on blood and blood forming organ.

Chi-square test (Table 4) showed statistically significant correlations between all pDDI and the following: polypharmacy, being on alimentary tract and metabolism, being on blood and blood forming organ and cardiovascular system medications, while major pDDI was significantly associated with alimentary tract and metabolism drugs, drugs acting on blood and blood forming organ and patient taking the medication by her/himself; polypharmacy was significantly correlated with alimentary tract and metabolism drugs, drugs acting on blood and blood forming organ, drugs acting on the

nervous system, anti-infective drugs for systemic use, patient taking the medication by her/himself, education and age group.

Stepwise logistic regression (Table 5) was performed to analyze factors associated with moderate pDDI. As mentioned previously the model included age group, gender, education level, does the patient live alone, does the patient take the medicine by himself, polypharmacy, different types of medication, number of doctors seen by the patient, and does the patient see a GP. The model showed good fit as Hosmer-Lemeshow test p value was above 0.05 (p=0.9) and Cox and Snell R square indicated that the model explained 14.5% of the variances while Nagelkerke R square indicated that 21.9% of the variances were explained. The results showed that the probability of having a moderate pDDI increases with cardiovascular and nervous system medications and polypharmacy and decreases with seeing a GP.

Factors associated with polypharmacy were also analyzed using logistic regression (Table 6). The model included the same predictors mentioned above excluding polypharmacy. The model showed good fit as Hosmer-Lemeshow test p value was above 0.05 (p=0.61) and Cox and Snell R square indicated that the model explained 27.4% of the variances while Nagelkerke R square indicated that 40.6% of the variances were explained that females had higher odds to have a polypharmacy when compared with males. The results also indicated that being on alimentary tract & metabolism drugs, blood and blood forming organs, and nervous system medications, increases the risk of having polypharmacy. The results also indicated that number of diseases increased the odds of polypharmacy, while education decreased it.

Table 1. *Demographic and clinical characteristics of participants (N=367).*

Age group	Frequency	Percent
60-69	216	58.9
70-79	99	27
>80	52	14.2
Gender		
Male	189	51.1
Female	178	48.5
Smoking habit		
Cigarette	107	29.2
Shisha	15	4.1
Ex-smoker	18	4.9
Non-smoker	227	61.9
Marital status		
Divorced	21	5.7
Married	294	80.1
Single	9	2.5
Widow/widower	43	11.4
Education		
Illiterate	55	15
Primary	102	27.8
Secondary	99	27
University	94	25.6
Post-graduate	17	4.6
Patient living alone	40	10.9
Drug interactions		
All interactions	334	91

Major interaction	67	18.3
Moderate interaction	281	76.6
Polypharmacy	275	74.9
Types of doctor seen		
Specialist only	247	67.3
General practitioner only	36	9.8
Both	84	22.9
	Mean	St. Deviation
Age	69.8	7.31
Number of drug per patient	5.5	2.13
Number of drugs involved in major pDDI in patients with major pDDI	2.98	1.57
Number of diseases per patient	2.45	1.15
How many physicians does the patient visit currently?	1.67	0.81

Table 2. *The number of drugs used by the participants and their ATC classes and codes.*

	Frequency	**Percent**
All drugs	2022	100
Polypharmacy (>5 drugs)	1745	86.3
Drugs involved major pDDI	154	7.6
Alimentary tract and metabolism (A)	594	27.2
Drugs used in diabetes (A10)	230	38.7
Drugs for acid related disorders (A03)	185	31.1
Vitamins (A11)	64	10.7
Mineral supplements (A12)	30	5
Blood and blood forming organs (B)	256	12.7
Antithrombotic agents (B01)	198	77.3
Anti-anemic preparations (B03)	32	12.5
Cardiovascular system (C)	783	38.7
Cardiac therapy (C01)	37	4.7
Diuretics (C003)	95	12.1
Beta blocking agents (C07)	109	13.9
Calcium channel blockers (C08)	78	9.9
Agents acting on the renin-angiotensin system (C09)	277	35.3
Lipid modifying agents (C10)	164	20.9
Dermatologicals (D)	13	0.6
Genito urinary system and sex hormones (G)	33	1.6
Systemic hormonal preparations, XCL. Sex hormones and insulin's (H)	24	1.2
Anti-infective for systemic use (J)	59	2.9
Antineoplastic and immunomodulating agents (L)	10	0.5

Musculo-skeletal system (M)	76	3.8
Nervous system (N)	154	7.6
Anti-parasitic products, insecticides and repellents (P)	2	0.1
Respiratory system (R)	52	2.6
Sensory organs (S)	6	0.3
Various (V)	5	0.2

Table 3. *Percentage of patients on different ATC drug classes.*

Drug type	All patients		Polypharmacy		Major drug interaction	
	Number	%	Number	%	Number	%
Blood and blood forming organ (B)	195	53.1	172	62.6	40	65.5
Alimentary tract and metabolism (A)	292	79.6	236	85.8	43	70.5
Cardiovascular system (C)	312	85	238	86.5	54	88.5
Nervous system (N)	104	28.3	93	33.8	18	29.5
Musculo-skeletal system (M)	72	19.6	59	22.1	7	11.5
Anti-infective for systemic use (J)	46	12.5	44	16	9	14.8

Table 4. *The relation between pDDI, major pDDI and polypharmacy with covariates and ATC drug classes.*

	Polypharmacy			pDDI			Major pDDI		
	Frequency (%)	X^2	P	Frequency (%)	X^2	p	Frequency (%)	X^2	P
Polypharmacy	N/A			268 (80.2)	55.7	p<0.01	51 (83.6)	2.93	0.08
Alimentary tract and metabolism	236 (80.8)	26.39	p<0.01*	247 (82)	13.9	p<0.01	43 (14.7)	3.7	0.04*
Blood and blood forming organ	172 (88.2)	39.02	p<0.01*	188 (56.3)	14.83	p<0.01	40 (20.5)	4.54	0.03*
Cardiovascular system medication	238 (76.3)	2.02	0.15	293 (87.7)	21.42	p<0.01	54 (17.3)	0.71	0.4
Nervous system	93 (89.4)	16.21	p<0.01*	96 (28.7)	0.3	0.58	18 (17.3)	0.05	0.8
Anti-infective for systemic use	44 (95.7)	12.02	p<0.01*	44 (13.2)	1.38	0.24	9 (19.6)	0.32	0.53
Patient taking the medication by himself	192 (71.6)	12.02	p<0.01*	240 (71.9)	2.57	0.11	38 (14.2)	4.23	0.04*
Education									
Illiterate	44 (80)			52 (15.6)			10 (18.2)		
Primary	90 (88.2)			97 (29)			19 (18.6)		
Secondary	76 (76.8)	26.38	p<0.01*	88 (26.3)	5.87	0.21	18 (18.2)	1.8	0.76
University	55 (58.5%)			83 (24.9)			12 (12.8)		
Post-Graduate	10 (58.8)			14 (4.2)			2 (11.8)		
Age Group									
60-69	152 (70.4)	6.683	0.03*	193 (57.8)	1.87	0.39	34 (15.7)	0.65	0.72
70-79	83 (83.8)			93 (27.8)			19 (19.2)		

>80	40 (76.9)	48 (14.4)	8 (15.4)

*Significant.

Table 5. *Factors associated with moderate pDDI.*

Factors	Univariate logistic regression			Multivariate logistic regression		
	Crude OR	P	95% CI	Adjusted OR**	P	95% CI
Cardiovascular system	0.41	<0.01	0.23-0.77	2.903	<0.01	1.43-5.88
Nervous system	0.38	<0.01	0.2-0.72	2.662	<0.01	1.29-5.51
GP*	0.44	<0.01	0.27-0.74	0.36	<0.01	0.21-0.63
Polypharmacy	4.22	<0.01	2.5-7.1	4.044	<0.01	2.292-7.136

*GP is an abbreviation of general precisionist.

Table 6. *Factors associated with polypharmacy.*

Factors	Univariate logistic regression			Multivariate logistic regression		
	Crude OR	P	95% CI	Adjusted OR	P	95% CI
Females	1.3	0.5	0.7-1.84	2.084	<0.01	1.074-4.042
Alimentary tract and metabolism	0.39	<0.01	2.27-6.67	4.363	<0.01	2.120-8.982
Blood and blood forming organs	5.01	<0.01	2.95-8.5	8.963	<0.01	4.598-17.474
Nervous system	0.27	<0.01	0.14-0.52	3.914	<0.01	1.748-8.763
Number of diseases	0.63	<0.01	0.49-0.81	1.71	<0.01	1.27-2.29
Education	1.62	<0.01	1.29-2.02	0.54	<0.01	0.39-0.74

Discussion

This study examined the prescriptions of outpatient Jordanian geriatrics in community pharmacies and hospitals' outpatient pharmacies. To the best of our knowledge, this study is the first report regarding the pDDIs and polypharmacy among geriatric Jordanian patients. We found a high prevalence of pDDIs and polypharmacy among Jordanian geriatric patients. Accordingly, further studies should be done to reduce the DDIs and DDI-induced mortality in Jordanians.

Prevalence of pDDI and polypharmacy

The study found that the overall prevalence of pDDI among the studied sample is 91%, of those 18.5% had at least one major pDDI. This is significantly lower than reported in other studies including a study conducted on hospitalized cardiac patients that reported that 86.3% had at least one major pDDI, but significantly higher than other studies, for example a study reported that the major DDI was only 3.4% [2,21]. This wide variation could be attributed differences in methodology including the age of the studied sample.

Most studies that examined the prevalence of polypharmacy were conducted in the inpatient setting [8,22-26]. However, in this study we investigated the prevalence of polypharmacy in the outpatient settings to capture a more comprehensive insight. We found that 74.9% of the participants used 5 drugs or more. The prevalence of polypharmacy, found in this study, is significantly higher than what was reported in a previous study conducted in Jordan in 2012, which reported that 44.8% of the studied geriatrics used 5 drugs or more [27]. However, when compared to other studies in the region that used the same definition of polypharmacy, our findings were significantly lower. For example a study done in Saudi Arabia reported that 96% of the participants aged above 60 used 5 drugs or more [28]. Another study conducted in Dubai reported that 89% of the participated patients were taking more than five medications [29]. Our results were comparable to a study conducted in Oman on discharged geriatrics and reported polypharmacy in 76.3% of the participants [23].

As reported previously, our study found significant correlation between polypharmacy and major pDDI [11]; where 95.6% of participants who had at least one major pDDI where using more than 5 drugs. Therefore, the high prevalence of pDDIs, found in this study, is due mainly to the polypharmacy.

Association with gender

There are conflicting findings in the literature regarding the association between gender and pDDI and polypharmacy. For example it was reported that women had a lower probability of having potentially serious DDIs (type D), which should be

avoided, than men, while another study found that female gender was positively associated with pDDI [2,30]. Other studies in accordance with this study, found no association between pDDI and gender [31,32]. These contradicting finding maybe attributed to differences in the methodologies of the studies. However in accordance with several previous studies, we have found an association between polypharmacy and female gender [9,33,34]. Although other studies have reported that gender influence diminished in elderly population, our results did not indicate [35,36].

Association with education

The regression results showed that level of education was negatively associated with polypharmacy which is in accordance with previous studies findings [37,38]. This might indicate the importance of awareness toward drug use.

Association with comorbidities and drug classification

The results indicated that polypharmacy was positively associated with number of comorbidities as reported previously [21].

The most common prescribed groups for all patients (with or without polypharmacy) was for the cardiovascular system, mainly agents acting on the renin-angiotensin system and lipid modifying agents. Although cardiovascular system drugs were not associated with polypharmacy, they were associated with pDDI and moderate pDDI. This is an expected finding due to high prevalence of cardiovascular diseases in Jordan as it is the major reason for mortality in Jordanians aged in-between 30-70 [39]. In addition, the guidelines for treating several cardiovascular diseases including heart failure and hypertension emphasise the importance of using multiple medications [40].

Alimentary tract and metabolism drugs were associated with polypharmacy, major pDDI and pDDI. This could be due the high prevalence of diabetic elderly Jordanians, in addition to the inappropriate overuse of proton pump inhibitors in Jordan [41-43]. The proton pump inhibitors are cytochrome P450 inhibitors; therefore, these medications influence metabolism of other drugs and may cause DDI [44].

Drugs acting on blood and blood forming organ may be associated with polypharmacy, major pDDI, and pDDI due to recommendations of using antiplatelet or antithrombotic in patients with cardiovascular diseases. The antiplatelet clopidogrel is a prodrug which is activated through CYP2C19 and we found that the CYP450 inhibitors, such as proton pump inhibitors, were commonly co-administrated among the participants [45]. Anti-infectious were also associated with polypharmacy due to the high prevalence of infectious diseases as reported previously [46]. These findings are similar to findings reported by previous studies that reported a high prevalence of administration of cardiovascular system drugs, drugs acting on blood and blood forming organ, alimentary tract and metabolism drugs and anti-infectious drugs [23,25,34,46].

Role of GP

The regression results showed that visiting a GP decreased the odds of having moderate pDDI, which emphasizes the beneficial effect of GP and specialist collaboration; as the GP may act as an important link between the patient and different specialists consulting the patient. Literature has emphasized the importance of 'collaborative care' or 'coordinated care' where a teamwork with a defined member of the team taking responsibility for the coordination of care can provide the best medical outcome and may prevent adverse outcome including pDDI, these finding suggest the need to encourage more GP; as the majority (67.3%) of our participants did no see one [47].

Conclusion

High incidence of major and moderate pDDI and polypharmacy was found in the study participants. This study emphasizes the need for a better control over elderly prescription in Jordan and the need to increase the role of family doctors to form a link between different physicians seen by the patient

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