

Usage of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) And Their Interaction With Other Concurrently Used Drugs in Elderly Patients

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Abstract

Background: The elderly consume a disproportionate amount of prescription and non-prescription medications. Thus, elderly patients are highly susceptible to poly-pharmacy, which may cause drug-drug interactions. The main objective of this study is to evaluate usage of non-steroidal anti-inflammatory drugs (NSAIDs) and its interaction with other concurrently used drugs in elderly patients.

Methodology: A cross sectional study was performed with sample size 580 older patients of age 60 or above. Prescription, medical card, questionnaire and US-FDA drug interaction checker software (www.drugs.com) were used to collect information. . Odds ratio (95%CI) was used in all logistic regression analysis. All analyses were considered significant when $p < 0.001$.

Results: Average number of NSAIDs prescribed per prescription was 2.09 and average number of drugs per prescription was 6.49. Drug interactions were found in 231 participants among 237 participants suffering from hypertension and in 168 participants among 176 participants suffering from diabetes.

Conclusion: Moderate and few severe drug-drug interaction among the elderly were common that warrants attention of prescribers and pharmacists. With the age number of chronic illnesses are common in elderly patients which increases the number of drug in prescription or polypharmacy. Polypharmacy increases the risk of drug interaction.

Key words: Non-steroidal anti-inflammatory drugs, polypharmacy, drug interaction, elderly participants

Introduction

In 1897, Felix Hoffman synthesized acetylsalicylic acid and the first non-steroidal anti-inflammatory drug (NSAID) was discovered. NSAIDs are the most commonly used medications on account of their anti-pyretic, anti-inflammatory, and analgesic properties. Due to their easy availability, more than 30 million people worldwide use NSAIDs every day. However, they have broad spectrum of side effects^[1].

NSAIDs account for approximately 5-10% of all medications prescribed each year^[2]. A Brazilian study in elderly patients indicated a mean drug consumption of two to four drugs per person per day^[3]. The elderly consume a disproportionate amount of prescription and non-prescription medications. The increase in drug consumption among the elderly population might be due to the prevalence of

chronic diseases, the physiology of aging, the influence of the pharmaceutical industry on prescriptions and the medicalization that is common in the training of the health professionals^[3]. Thus, inappropriate medication use is highly prevalent among elderly patients (age ≥ 65 years)^[4]. Virtually all medications can produce undesirable side effects. The elderly are more likely to experience adverse drug reactions (ADRs) as a result of age-related increases in the frequency of drug use, sensitivity to drug effects, and prevalence of predisposing conditions that can increase the frequency and severity of ADRs^[5]. Thus, elderly patients are highly susceptible to poly-pharmacy, which may cause drug-drug interactions (DDIs) and ADR related complications and hospitalizations^[5]. A study conducted on elderly population with a family health

program showed that anti-inflammatory and analgesics were used by 28.8% elderly persons ^[6]. Among the classes of anti-inflammatory and analgesic, 70.6% ingested non-opioid analgesics, 41.7% ingested NSAIDs, 16.5% used glucocorticoids and 1.4% took opioid analgesics. In a study which was conducted in Jordan by Qoul et al., a total of 25,692 prescriptions were reviewed ^[7]. 52% of the collected prescriptions had NSAIDs. Out of this, 40.6% was prescribed for elderly patients (aged 60-80). The average number of drugs per prescription was 3.76 with a range of 1-8 drugs. About 72% of the patients used 3 or more medications. In a study conducted in Brazil, 10.30% of the 573 elderly respondents reported the regular use five or more medications ^[8].

A study done in United Arab Emirates (UAE) by Mubarek et al. reported that 89% of the included participants were exposed to polypharmacy^[9].

A study conducted in elderly at Trondheim, Norway recommended that co-prescription of NSAIDs and interacting drugs in the elderly constitutes a major problems ^[10].

De Lima et al. conducted a prospective, exploratory and descriptive based study to analyze potential drug interactions and adverse reactions to NSAIDs in elderly^[3]. Their results showed the importance of monitoring the use of NSAIDs among the elderly due to the increased risk of drug interactions and adverse reactions associated with age, concomitant diseases, multi-prescriptions and polypharmacy^[3].

A study which took place in India focusing in elderly individuals practicing self-medication revealed that 88.5% reported self-medication in 6-month recall period ^[11]. The researchers concluded that Self-medication is highly prevalent in elderly people who are unaware of risks involved. However, self-medication may leads to unwanted consequences due to interactions with the prescribed drug therapy for chronic diseases^[11].

Methodology

A cross sectional descriptive study was performed with quantitative approach to study usage of NSAIDs and their interactions with other concurrently used drugs in elderly

patients who visited hospitals of Mehsana selected for study during August 2021 to April 2022. Four different hospitals were selected for study. In order to get representative samples from each hospital stratified sampling technique was implemented. Four hospitals were considered as strata. 580 participants were selected as sample size during study period. Face to face communication was used for interaction with patients. The study and study related information were explained to participants by oral presentation in their local language. Subjects were encouraged to ask questions and clarify their doubts regarding any aspects of study.

Inclusion criteria: (i) Elderly patients (≥ 60 years) who came up with formal prescriptions containing one or more NSAIDs. (ii) Subjects who were willing to participate in the study.

Exclusion criteria: (i) Subjects who came up with prescriptions containing no NSAIDs. (ii) People who were unwilling to participate. (iii) People of obvious debilitating conditions and who couldn't pass on reliable information. (iv) Prescriptions that were not legibly written.

Prescription, medical card, questionnaire and US-FDA drug interaction checker software (www.drugs.com) were used to collect information. Prescription was used to get information of the prescribed NSAIDs, while medical cards were used to assess disease and medication status of the patients. The questionnaire was aimed at exploring information on patients' socio-demographic characteristics. The study population consisted of randomly selected elderly patients (≥ 60 years) receiving prescriptions containing NSAIDs from the respective out-patient departments (OPDs) of the hospitals. The investigators explained purposes of the study to the subjects and those who gave consent were enrolled in the study.

Exit interview was conducted for each patient based on a structured questionnaire. Then, information contained in their prescriptions was recorded. After that, the patients' medical cards were assessed. Finally, the drug-drug interactions were screened using drugs.com. For interactions where results could not be available in drugs.com, we utilized WebMD

interaction checker. All the obtained data were documented to be analyzed and no follow ups were made.

The entered data were exported to SPSS (version 22) for statistical analysis. Descriptive summaries of the socio-demographic variables was done using mean (SD) or median (IQR) based on the normality of the quantitative variables. Frequencies and percent were used for qualitative variables. Graphs and tables were used to present the data. Chi-square test and logistic regression were used to find out the existence of trend as well as magnitude of association for number of drug and its subsequent interaction respectively. Odds ratio (95%CI) was used in all logistic regression analysis. All analyses were considered significant when $p < 0.001$. The protocol, informed consent form and questionnaire were reviewed by the Independent Ethics Committee (IEC) and the study was commenced after a written approval was obtained from IEC.

Result:

According to survey, out of 580 participants 316 (54.48%) male and 264 (45.52%) female participants with age ≥ 60 year were included in this study. Among total old participants 356 (61.38%) participants were between age 60-69 year, 176 (30.34) were between age 70-79 year and remaining 48 (8.28%) were 80 year or above age. Out of total participants 378 (65.17%) were married, 196 (33.79%) were widowed and remaining 6 (1.04%) participants were unmarried. More than half participants [398 (68.62%)] were illiterate and 182 (31.38%) were literate. (Table 1)

Among 580 participants, 238 (41.03%) were suffering from hypertension, 176 (30.34%) were suffering from diabetes, 72 (12.41%) from asthma, 46 (7.93%) had other cardiac problems, 13 (2.24%) had mental illness, 11 (1.90%) had renal problems and 219 (37.75%) had no chronic illness. (Figure 1)

Variable		Number	Percent
Age			
	60 to 69	356	61.38
	70 to 79	176	30.34
	80 or above	48	8.28
Gender			
	Male	316	54.48
	Female	264	45.52
Marital Status			
	Married	378	65.17
	Widowed	196	33.79
	Unmarried	6	1.04
Level of Education			
	Illiterate	398	68.62
	Literate	182	31.38

Table 1: Distributions of elderly persons according age, gender, marital status and level of education (n = 580)

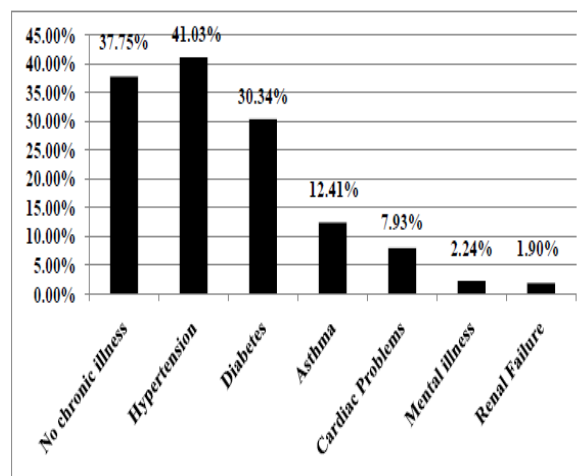


Figure 1: Distribution of chronic illness among elderly patients

In the prevalence of NSAIDs prescribed, 352 (60.69%) participants were prescribed paracetamol, 133 (22.93%) were prescribed aspirin, 124 (21.37%) were prescribed aceclofenac, 123 (21.21%) were prescribed etoricoxib, 107 (18.45%) were prescribed diclofenac and followed by ibuprofen 84 (14.48%), Tramadol 78 (13.45%), Naproxen 62 (10.69%), nimesulide 54 (9.31%), Indomethacin 34 (5.86%), mefenamic acid 27 (4.66%), piroxicam 21 (3.62%) and lornoxicam 16 (2.76%). (Figure 2)

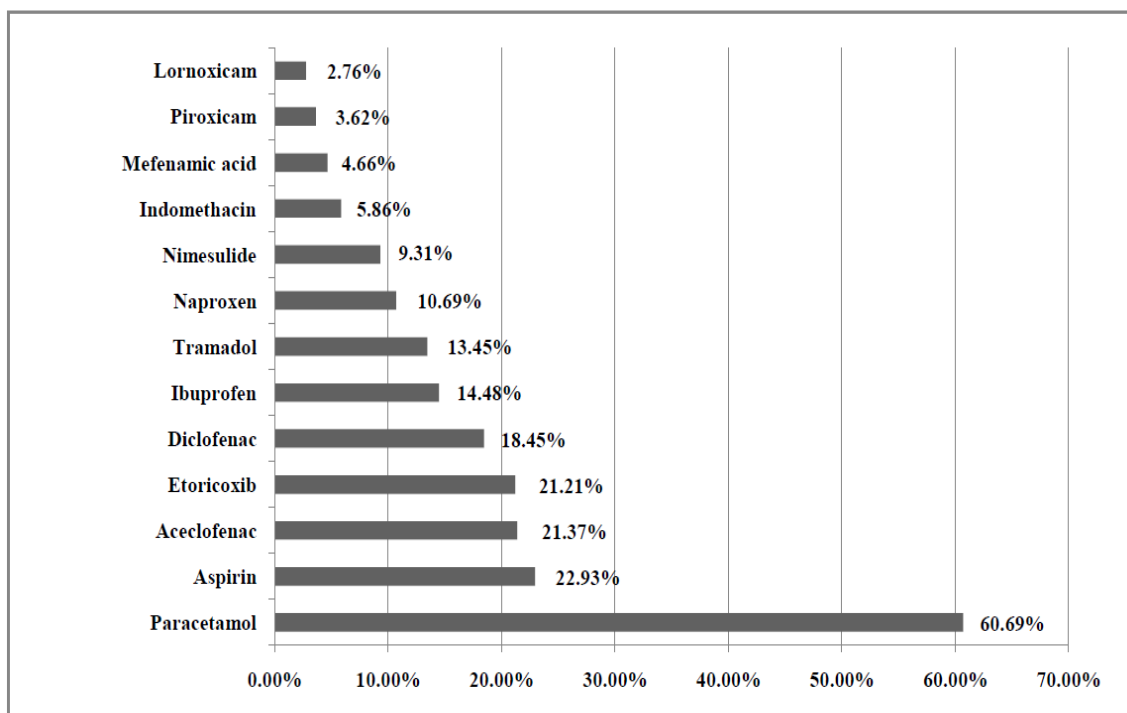


Figure 2: Prevalence of type of NSAIDs prescribed

Description of number of NSAIDs per prescription and total number of drugs per prescription is given in Table 2. Among 580 prescriptions, one NSAID was prescribed to 78 (13.45%) prescriptions, two NSAIDs were prescribed to 369 (63.62%) prescriptions and 3 NSAIDs were prescribed to 133 (22.93%) prescriptions. Maximum eleven different drugs were prescribed to 39 (6.72%) patients, followed by ten drugs to 51 (98.79%), nine drugs to 65 (11.21%), eight drugs to 56 (9.66%), seven drugs to 77 (13.28%), six drugs to 60 (10.34%), five drugs to 70 (12.07%), four drugs to 59 (10.17%) and three drugs to 103 (17.76%) patients.

In the prescription pattern, 103 (17.76%) patients were prescribed 3 drugs and remaining 477 (82.24%) were prescribed 4 or more than 4 drugs (Table 2). If four or more than four drugs were prescribed, it was considered as polypharmacy. The prevalence of polypharmacy was 82.24%. Average number of NSAIDs prescribed per prescription was 2.09 and average number of drugs per prescription was 6.49.

Variable		Number	Percent
Number of NSAID per prescription			
	1	78	13.45%
	2	369	63.62%
	3	133	22.93%
Total number of drugs per prescription			
	3	103	17.76%
	4	59	10.17%
	5	70	12.07%
	6	60	10.34%
	7	77	13.28%
	8	56	9.66%
	9	65	11.21%
	10	51	8.79%
	11	39	6.72%

Table 2: Description of NSAIDs per prescription and total number of drugs per prescription

Out of 580 participants, 112 (19.31%) participants were practicing self-medication and among them 86 prescriptions showed drug interaction with NSAIDs prescribed giving total 96 potential drug interaction. Out of these 96 drug interaction 6 (6.25%) were severe, 64 (66.67%) were moderate and 26 (27.08%) were mild drug interaction. (Table 3) Potential NSAID drug interactions with other prescribed drugs were observed in 492 respondents giving total of 638 drug

interactions, of which 51 (7.99%) classified as severe, 396 (62.07%) classified as moderate and 191 (29.94%) as mild. (Table 4) Number of drugs prescribed the frequency of potential drug interactions and their linear-by-linear associations are described in Table no.

It is showing that drug interactions are increases with increasing of total number of drug prescribed. It was analyzed by chi square test. The chi square value was 76.781 and p value was less than 0.001 which indicates that data were statistically significant. (Table 5)

Severity of DrugInteraction	Number of Drug interaction(n=96)	Percentage
Mild	26	27.08%
Moderate	64	66.67%
Severe	6	6.25%

Table 3: Analysis of NSAID drug interaction with selfmedicated drugs

Severity of DrugInteraction	Number of Drug interaction(n=638)	Percentage
Mild	191	29.94%
Moderate	396	62.07%
Severe	51	7.99%

Table 4: Analysis of NSAID drug interaction with other prescribed drugs

		Total Number of Drugs in Prescription									Total	Linear by Linear Association	
		3	4	5	6	7	8	9	10	11		X ² Value	P value
Interaction	No	29	23	14	12	8	2	0	0	0	88	76.781	<0.001
	Yes	74	36	56	48	69	54	65	51	39	492		

Table 5: Number of drugs prescribed, the frequency of potential drug interactions and their linear-by-linear associations

Association of NSAID potential drug interactions with age, gender and chronic illness was performed by using odds ratio with confidence interval 95%. Since higher number of patients was suffering from hypertension and diabetes, they were taken as chronic illness. In the age group 60 to 69 year, drug interactions were present in 298 prescriptions out of 356 prescriptions. In the age group 70 to 79 year, drug interactions were present in 152 prescriptions out of 176 prescriptions. In the age group 80 year or above, drug interactions were present in 42 participants out of 48. Here age group 60 to 69 year was taken as reference and the correlation coefficient for age group 70 to 79 year and age group 80 year or above were 1.23 and 1.36 respectively.

Drug interactions were found in 269 male participants out of 316 and 223 female participants out of 264. Female participants were taken as reference and the correlation coefficient for male participants was 1.05.

Drug interactions were found in 231 participants among 237 participants suffering from hypertension and drug interactions were found in 261 participants among 342 participants not suffering from hypertension. Patients without hypertension were taken as reference and patients with hypertension were taken as test value. The correlation coefficient was 10.24 and p-value was less than 0.001.

From the selected sample size, 176 participants were suffering from diabetes. Out of these 176 prescriptions, drug interactions were found in 168 prescriptions. From remaining 404 prescriptions without diabetes, drug interactions were found in 324 prescriptions. Patients without diabetes were taken as reference and the correlation coefficient for patients with diabetes was 5.19 and data were statistically significant ($p < 0.001$).

Variable		Interaction		Crude Odds Ratio (95%CI)	P-value
		Yes n(%)	No n(%)		
Age					
	60-69	298 (60.57%)	58 (65.91%)	Ref.	
	70-79	152 (30.89%)	24 (27.27%)	1.23 (0.74, 2.06)	0.425
	80 or above	42 (8.54%)	6 (6.82%)	1.36(0.55, 3.35)	0.501
Gender					
	Male	269 (54.67%)	47 (53.41%)	1.05 (0.67, 1.67)	0.826
	Female	223(45.33%)	41 (46.59%)	Ref.	
Hypertension					
	Yes	231 (46.95%)	7 (7.95%)	10.24(4.64, 22.62)	<0.001
	No	261 (53.05%)	81 (92.05%)	Ref.	
Diabetes					
	Yes	168 (34.15%)	8 (9.09%)	5.19 (2.45, 10.98)	<0.001
	No	324 (65.85%)	80 (90.91%)	Ref.	

Table 6: Associations of NSAID potential drug interactions with age, gender and clinical condition

Discussion:

In this study total 580 older patients were evaluated. Among them different demographic data like age, gender, marital status, education, and chronic illness were taken. In the age it was found that maximum respondents were between the ages 60 to 69 year (61.38%). Similar data were found from study performed in Brazil 2015 where 60.50% participants were between the age 60 to 69 year.^[6] Study conducted in UAE also found the higher number of patients between 60 to 69 year age group (39%).^[9] From the 580 included participants more number of male respondents had found than female respondents. However, the study conducted at Brazil found 55.67% female and 44.33% male participants.^[8] Another study conducted at Brazil in 2015 also found more female (64.20%) patients than male (35.80%).^[6] But study conducted in 2014 in UAE found 44% female and 56% male elder responders.^[9] Of the 580 elder patient surveyed, 65.17% were married, 1.06% were unmarried and 30.32% were widowed. Similar data were found in Brazilian study where maximum participants (53.58%) were married and 46.43% patients were single / other.^[8] More than 50% participants were illiterate in present study. Participants who had not completed their primary education were considered as illiterate. Similar data were found in Brazilian study where 27.30% were illiterate / educated outside school, 57.30% incomplete primary

education and only 15.40% completed primary education or more.^[6]

From 580 evaluated responders maximum numbers of participants were suffering from hypertension (41.03%) and diabetes (30.34%). This was similar with findings of a Brazilian study where 78.50% elder participants were suffering from cardiovascular disease and 28.80% were suffering from diabetes mellitus.^[6]

In the present study, the most prescribed NSAIDs were paracetamol followed by aspirin, aceclofenac, etoricoxib and diclofenac. However, diclofenac tops the list followed by ibuprofen and indomethacin in the study conducted by Qoul et al.^[7]

In our study average number of NSAIDs prescribed per patient was 2.09. Jayakumari et al reported average number of NSAIDs prescribed per patient was 1.86.^[12] The mean number of drugs per prescription was 6.49 which is much lower than the 11.36 reported by Jayakumari et al^[12] and higher than the 3.67 reported by Maschio de Lima DCF et al^[3] and 3 reported by Qoul et al.^[7]

In the present study polypharmacy was identified in 84.24% of respondents. This was similar with the study conducted in UAE that reported polypharmacy in 89% of elderly patients.^[9] But higher than the Nigerian study on geriatrics that shows 23.4%^[13] and Indian study that shows 57.80%.^[7] In Brazilian study polypharmacy was found to be in only few of the respondents (10.3%).^[8] Polypharmacy was however predominant in majority of our

study participants who had co-morbidities like hypertension and diabetes. In the Indian study, clinical conditions including hypertension, gastritis, osteoarthritis, and diabetes mellitus were identified as the main reasons for the practice of polypharmacy.^[8] The variability in incidence of polypharmacy among the different studies could be due to variations in clinical practices, patient behaviors in different countries, definition of polypharmacy, study design, data sources used and/or the slight age difference among the studies. Despite the difference in incidence of polypharmacy among studies, it is clear that polypharmacy is a significant problem in the elderly that warrants immediate attention from healthcare professionals.

About 19.31% (112) of the respondents of our study who self-medicated themselves were at risk of potential drug interactions with prescribed NSAIDs. This is consistent with the study conducted by Nunes and colleagues where they reported that self-medicated NSAIDs were implicated in DDIs with a variety of prescribed drug classes.^[14] Older persons seem to have a particular susceptibility to self-medication possibly owing to multiple morbidities.^[11] This tendency normally puts the elderly in a dangerous situation and aggravates the risk of potential drug interactions. This finding mandates prescribers to responsibly take medication history into account and pharmacists to strictly advise the elderly not to self-medicate any medical products without the knowledge of the prescriber or without consulting a pharmacist.

In the present study, 7.99% severe drug interactions between the NSAIDs and other prescribed drugs were indentified which is commendable than the similar Brazilian study reported 24% highly significant drug interaction.^[13]

In this study, the most frequently documented DDI was the concurrent use of aceclofenac and telmisartan followed by diclofenac and glimepiride as well as aspirin and clopidogrel. This is a reflection of comorbidities frequently encountered in the elderly, namely, hypertension, diabetes and cardiac problems. The presence of diabetes and hypertension as comorbidities were significantly associated

with the incidence of drug interactions which is consistent with the findings reported by Soherwardi et al.^[15]

Conclusion:

Evaluating the relationship between age, gender and chronic illness with drug interaction in old age patients revealed that there is clear relationship between chronic illness and drug interaction. Moderate and few severe drug-drug interaction among the elderly were common that warrants attention of prescribers and pharmacists. With the age number of chronic illnesses are common in elderly patients which increases the number of drug in prescription or polypharmacy. Polypharmacy increases the risk of drug interaction. Therefore, a step-wise approach should be developed in all hospitals to decrease the exposure of elderly patients to poly-pharmacy.

Limitations:

Since the follow up was not made, this investigation did not confirm the occurrence of possible problems related to the drugs prescribed, such as and drug interactions, through prolonged systematic monitoring. Due to the nature of the study, there was a risk of recall bias as patients could not remember everything happened in the past like self-medicated drugs and duration of recently taken NSAIDs.

References

1. Arain A, Rasheed M, Sallam N, Sarwaar Z, Khan M; Patients knowledge and use of oral non-steroidal anti-inflammatory drugs in a Rheumatology clinic. *Kansas journal of Medicine*.2019; 132-135.
2. Abdulla A AN, Bone M, Elliott AM, Gaffin J, Jones D Guidance on the management of pain in older people. *Age Ageing*. 2013;42(1):i1-57.
3. Maschio de Lima, Calille Atique, Patricia Di Done, Dantas Machado, Fernandes de Godoy. Analysis of potential drug interactions and adverse reactions to nonsteroidal anti-inflammatory drugs among the elderly. *Rev Bras Geriatr Gerontol*. 2016;19(3):533-44.
4. Y.S. Karandikar SRC, N.P. Dalal, M. Sharma, V.A. Pandit. Inappropriate

- prescribing in the elderly: A comparison of two validated screening tools. *Journal of Clinical Gerontology & Geriatrics*. 2013;4:109-14.
5. Emanuel Raschi CP, Vincenzo Signoretta, Lucio Lionello, Silvia Bonezzi, Marcello Delfino, Lucia Di Candia, Lucio Di Castri, Fabio Pieraccini, Daniela Carati. Clinically important drug–drug interactions in polytreated elderly outpatients: A campaign to improve appropriateness in general practice. *Br J Clin Pharmacol*. 2015;80(6):1411–20.
 6. Scheer Ely PE, Roversi Guiselli, Carlos Cardoso, Bueno Morrone, Attilio De Carli. Use of anti-inflammatory and analgesic drugs in an elderly population registered with a family health program. *Rev Bras Geriatr Gerontol* 2015;18(3):475-85.
 7. Qoul INT, Nebal Abu Ashor, Neris Hakuz. Prescribing patterns of non-steroidal anti-inflammatory drugs in outpatient clinics at royal rehabilitation center in king hussein medical center. *ZUMJ*. 2014;20(N.5):673-9.
 8. Araujo de Almeida OR, de Souza Azevedo, Cândido da Silva, Chaves Cardoso, Cegati de Souza. Prevalence of and factors associated with polypharmacy among elderly persons resident in the community. *Rev Bras Geriatr Gerontol*. 2017;20(1):138-48.
 9. Mubarak N. Al Ameri EM, Umniya Albur, Anil Kumar, Padma Rao. Prevalence of Poly-pharmacy in the Elderly: Implications of Age, Gender, Co-morbidities and Drug Interactions. *SOJ Pharm Pharm Sci*. 2014;1(3):1-7.
 10. Kathrine F. Vandraas OS, Milada Mahic, Lars Slørdal. Non-steroidal anti-inflammatory drugs: Use and co-treatment with potentially interacting medications in the elderly. *Eur J Clin Pharmacol*. 2010;66:823–9.
 11. Zankhana Parmar SM, Varsha Patel. Prevalence and pattern of self-medication in elderly individuals. *Int J Basic Clin Pharmacol*. 2015;4(6):1095-9.
 12. S.Jayakumari GK. Prescription pattern analysis of anti-inflammatory drugs in general medicine and surgery department at a tertiary care hospital. *Int J Pharm Pharm Sci*. 2016;8(7):114-118.
 13. Wuraola Akande-Sholabi LA, Olufemi Olowookere. Polypharmacy and factors associated with their prevalence among older patients attending a geriatric centre in South-West Nigeria. *West African Journal of Pharmacy*. 2018;29(1):35-45.
 14. Ana Nunes IC, Filipa Costa. Determinants of self-medication with NSAIDs in a portuguese community pharmacy. *Pharmacy Practice*. 2016; 14(1):1-9.
 15. Shahabudin Soherwardi BC, Faizal P. Surveillance of the Potential Drug-Drug Interactions in the Medicine Department of a Tertiary Care Hospital. *journal of Clinical and diagnostic research* 2012;6(7):1258-61.