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ARAŞTIRMA / RESEARCH

Evaluation of the potential drug-drug interactions at orthopedics and traumatology outpatient clinics of a tertiary care hospital

Üçüncü basamak bir hastanenin ortopedi ve travmatoloji polikliniklerinde olası ilaç-ilaç etkileşimlerinin değerlendirilmesi

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Abstract

Purpose: The aim of the present study is to determine the frequency and severity of possible drug-drug interactions (DDIs) in the prescriptions of patients who admitted to the orthopedics and traumatology outpatient clinics.

Materials and Methods: This cross-sectional, retrospective study analyzed the prescription data of patients that admitted to orthopedics and traumatology outpatient clinics of a tertiary care hospital from January 1, 2020 to February 15, 2020. The severity of DDIs was interpreted using the Lexi-comp® drug interaction database. Relationship between the presence of DDIs and the number of prescribed drugs were evaluated.

Results: Out of 753 patient data evaluated, a total of 2248 drugs were prescribed. Among 669 polypharmacy patients, 293 (43.8%) patients had one or more potential DDIs. A total of 437 DDIs were detected of which 300 (68.6%) were D, 82 (18.8%) were X, 49 (11.2%) were C and 6 (1.4%) were B risk category interactions. The most common DDIs were between systemic Diclofenac and topical Diclofenac, (14.4%) The presence of potential DDIs was significantly associated with adult age and female gender.

Conclusion: Although, the severity of the potential DDIs in orthopedics and traumatology outpatient clinics were generally moderate and manageable, it is crutial for physicians to be aware of the interactions between the most frequently prescribed drugs in orthopedics and traumatology outpatient clinics, monitor patients for the safe use of drugs.

Keywords:. Drug interactions, polypharmacy, orthopedics

Öz

Amaç: Bu çalışmanın amacı, ortopedi ve travmatoloji polikliniklerine başvuran hastaların reçetelerinde olası ilaç-ilaç etkileşimlerinin sıklığını ve şiddetini belirlemektir.

Gereç ve Yöntem: Bu kesitsel retrospektif çalışma, 1 Ocak 2020- 15 Şubat 2020 tarihleri arasında üçüncü basamak bir hastanenin ortopedi ve travmatoloji polikliniklerine başvuran hastaların reçete verilerini analiz etti. İlaç-ilaç etkileşimlerinin şiddeti, Lexi-comp® ilaç etkileşimi veri tabanı kullanılarak yorumlandı. İlaç-ilaç etkileşimi varlığı ile reçetelenmiş ilaç sayısı arasındaki ilişki değerlendirildi.

Bulgular: Değerlendirilen 753 hasta verisinde toplam 2248 ilaç reçete edildi. 669 polifarmasi hastasından, 293 (%43.8) hastanın bir veya daha fazla potansiyel ilaç- ilaç etkileşimi vardı. 300'ü (%68.6) D, 82'si (%18.8) X, 49'u (%11.2) C ve 6'sı (%1.4) B risk kategorisi etkileşimleri olmak üzere toplam 437 ilaç-ilaç etkileşimi tespit edildi. En sık ilaç- ilaç etkileşimleri sistemik diklofenak ve topical diklofenak arasındaydı (%14.4). Olası ilaç-ilaç etkileşimlerinin varlığı erişkin yaş ve kadın cinsiyet ile anlamlı olarak ilişkiliydi.

Sonuç: Ortopedi ve travmatoloji polikliniklerinde olası ilaç-ilaç etkileşimlerinin şiddeti genel olarak orta düzeyde ve yönetilebilir olsa da, ortopedi ve travmatoloji polikliniklerinde en sık reçete edilen ilaçlar arasındaki etkileşimlerden haberdar olmak ve ilaçların güvenli kullanımı için hastaları izlemek hekimler açısından önem taşımaktadır.

Anahtar kelimeler: İlaç etkileşimleri, polifarmasi; ortopedi

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INTRODUCTION

Drug-drug interactions (DDIs) are important public health issues worldwide which may cause undesired adverse reactions, decrease in patients' quality of life and enhance hospitalizations and health care expenses[1]. Polypharmacy which is known as a major risk factor for DDIs, is commonly described in the literature as prescribing five or more drugs daily[2]. The elderly population are known to be at high risk for polypharmacy and DDIs. Particularly, increased comorbidities with age and age-related pharmacokinetic and pharmacodynamic changes makes elderly population more susceptible to polypharmacy related adverse events and DDIs[3].

DDI is defined as the alterations in the pharmacologic effect of a drug resulting from another drug used concomitantly for the same or different disorders. The prevalence of DDIs varies between 16% and 96% in several studies conducted on different patient groups and settings[4-11]. DDIs are significant risk factors for adverse drug reactions and hospitalizations. In a systematic review and meta-analysis, hospital admissions due to DDIs have been reported as 1.1%[12].

It is known that orthopedics and traumatology outpatient clinics have an important role in the treatment and management of many musculoskeletal diseases. The prevalence of these muscoloskeletal diseases rises especially over the age of 40[13]. Commonly prescribed drugs for musculoskeletal diseases in orthopedics and traumatology outpatient clinics such as nonsteroidal anti-inflammatory drugs (NSAIDs) and antibiotics may be associated with several adverse effects such as gastritis, leukopenia, thrombcytopenia, hepatotoxicity, stomatitis etc.[13]. In this respect, it is important to know the rates of polypharmacy and related DDIs in orthopedics and traumatology outpatient clinics, particularly for elderly population.

The aim of the present study is to determine the frequency and severity of possible DDIs in the prescriptions of patients who admitted to the orthopedics and traumatology outpatient clinics of a tertiary care hospital.

MATERIALS AND METHODS

This cross-sectional, retrospective study analyzed the prescription data of patients that admitted to orthopedics and traumatology outpatient clinics of a tertiary care hospital from January 1, 2020 to February 15, 2020. After obtaining approval from Marmara University Ethics Committee (IRB No: 09.2020.1258, December 4, 2020), files of the patients were assessed retrospectively.

Table 1. Lexi-comp® online interaction risk rating levels (14)

Risk Rating	Description
A	No known interaction
B	The specified agents may interact with each other, but there is little to no evidence of clinical concern due to their concomitant use
C	The specified agents may interact with each other in a clinically significant manner. The benefits of concomitant use generally outweigh the risks. Monitoring the therapy is recommended
D	The two medications may interact with each other in a clinically significant manner. Aggressive monitoring and considering therapy modification is recommended
X	The specified agents may interact with each other in a clinically significant manner. Concomitant use of these agents are contraindicated. Avoiding the combination is recommended

A total of 2767 registry files of patients that admitted to orthopedics and traumatology outpatient clinics within the given time period were determined. Among these, the files of 2014 patients who were not prescribed any drugs were excluded from the study. The files of 753 patients that admitted to orthopedics and traumatology outpatient clinics and prescribed drugs were further analyzed. The inclusion criteria were patients 18 years of age or older who were prescribed drugs. All orthopedics and traumatology outpatient clinic prescriptions with at least twoor more prescribed drugs were included in the assessment. Parameters such as age, gender, diagnoses, International Classification of Disease (ICD-10) codes, number of drugs prescribed, drug names, the Anatomical Therapeutical Chemical (ATC) codes, dosage forms of drugs, route of administration, number of the DDIs and risk category of the interactions were evaluated. Repeated prescriptions of the same patient were not evaluated. We prevented the duplications by enrolling the first prescription of the patient in the registration system.

Analysis of DDIs

The severity of DDIs was interpreted using the Lexi-comp® drug interaction database, an electronic platform that categorizes the interaction as A, B, C, D and X. Lexi-comp® online interaction risk rating levels are depicted Table 1[14].

The frequency of potential DDIs was calculated as the number with at least one of these potential DDIs divided by the total number potential DDIs and then multiplied by 100.

Statistical analysis

The statistical data analyses were carried out by using SPSS v25.0 software (SPSS, Inc., Chicago, IL). Frequency tables were used to show qualitative data. The chi-square test was usedto evaluate the effect of variables (gender, age and number of drugs) on the presence of DDIs. Categorical data were expressed as percentages. The comparisons were considered as statistically significant at $p< 0.05$.

Table 2. Patients' demographic characteristics and clinical diagnoses (n=753)

Variables	n (%)
Gender	
Female	544 (72.2%)
Male	209 (27.8%)
Age groups (in years)	
18-44	222 (29.5%)
45-64	378 (50.2%)
≥65	153 (20.3%)
Top 10 Diagnoses (ICD-10 Codes)	
Pain in joint (M25.5)	319 (42.4%)
Pain in knee (M25.56)	51 (6.8%)
Pain in unspecified joint (M25.50)	36 (4.8%)
Osteoarthritis of knee, unspecified (M17.9)	34 (4.5%)
Bilateral primary osteoarthritis of knee (M17.0)	27 (3.6%)
Pain in shoulder (M25.51)	22 (2.9%)
Other shoulder lesions (M75.8)	20 (2.7%)
Low back pain (M54.5)	17 (2.3%)
Pain in elbow (M25.52)	14 (1.9%)
Soft tissue disorder, unspecified, other site (M79.98)	12 (1.6%)
Age (Mean± SD)	52.5±13.5

RESULTS

A total of 753 data of patients that admitted to orthopedics and traumatology outpatient clinics and were prescribed at least one or more drugs between January 1, 2020 and February 15, 2020 were evaluated retrospectively. The mean age of the patients was 52.5±13.5 years and most of them (72.2%) were female (Table 2). Most of the patients were in 45-64 years of age group (50.2.%), (Table 2). 'Pain in joint' was the most common diagnosis (ICD-10 code: M25.5; 42.4%), followed by 'pain in knee' (M25.56; 6.8%) and 'pain in unspecified joint' (M25.50; 4.8%), (Table 2).

Table 3. Drug use characteristics and number of drugs per patient (n=753)

Variables	n (%)
Number of drugs per patient	
1	84 (11.2%)
2	154 (20.5%)
3	273 (36.3%)
4	184 (24.4%)
≥5	58 (7.7%)
Pharmaceutical forms	
Tablet	607 (80.6%)
Topical gel	581 (77.2%)
Capsule	237 (31.5%)
Sugar-coated pill	96 (12.7%)
Effervescent tablet	79 (10.5%)
Ampoule	75 (10.0%)
Vial	27 (3.6%)
Topical cream	18 (2.4%)
Oral drop	12 (1.6%)
Pre-filled syringe	10 (1.3%)
Topical spray	8 (1.1%)
Sachet	6 (0.8%)
Pomade	3 (0.4%)
Liquid	1 (0.1%)
Route of administration	
Oral	697 (92.6%)
Topical	603 (80.1%)
Intraarticular	57 (7.6%)
Intramuscular	19 (2.5%)
Subcutaneous	10 (1.3%)
Average number of drugs per patient (Mean± SD)	2.9±1.1

Out of 753 patient data evaluated, a total of 2248 drugs were prescribed. Most of the patients (88.8%) were prescribed two or more drugs (Table 3). The average number of drugs per patient was 2.9 ±1.1 with a minimum of 1 and a maximum of 7 drugs (Table 3). As to the pharmaceutical forms of drugs, tablets (80.6%) and topical gels (77.2%) were present in most of the prescriptions. Oral (92.6%) and topical (80.1%) uses were the most common routes of administration (Table 3).

The ATC/DDD (Anatomical Therapeutic Chemical/ Defined Daily Dose) methodology is an important globally accepted comparison technique used in drug use research in order to eliminate the difficulties related to the differences of quantity, dose, duration etc. and make comparisons (http://www.whocc.no/atc_ddd_index/).

According to the the ATC-1 distributions, "Musculoskeletal system drugs" (ATC-1 code: M; 69.3%) were the most frequently prescribed group, followed by "Alimentary tract and metabolism drugs" (A; 20.9%) and "Nervous system drugs" (N; 4.3%), (Table 4). As to the ATC-2 group distributions, "Anti-inflammatory and antirheumatic products" (ATC-1 code: M01; 39.2%) was the most common group, followed by "Topical products for joint and muscular pain" (M02; 21.6%) and "Drugs for acid related disorders" (A02; 17.3%), (Table 4).

Pantoprazole (ATC-5 code: A02BC02; 11.6%) was the most common drug in the prescriptions, followed by dexketoprofen + thiocolchicoside (M02AA27+M03BX05; 7.1%) and escin+diethylamine salicylate (M02AC55; 7.0%). The top 20 drugs prescribed are depicted at Figure 1.

Table 4. ATC-1 and ATC-2 classification of the prescribed drugs (n=2248)

ATC-1 classification	**n (%)**	**ATC-2 classification**	**n (%)**
Alimentary Tract and Metabolism (A)	469 (20.9%)	Drugs for Acid Related Disorders (A02)	390 (17.3%)
		Drugs for Functional Gastrointestinal Disorders (A03)	8 (1.0%) 1 (0.0%)
		Antidiarrheals, Intestinal anti-inflammatory/anti-infective Agents (A07)	1 (0.0%)
		Drugs Used in Diabetes (A10)	1 (0.0%)
		Vitamins (A11)	41 (1.8%)
		Mineral Supplements (A12)	35 (1.6%)
Blood and Blood Forming Organs (B)	11 (0.5%)	Antithrombotic Agents (B01)	10 (0.4%)
		Antianemic Preparations (B03)	1 (0.0%)
Cardiovascular System (C)	6 (0.3%)	Vasoprotectives (C05)	3 (0.1%)
		Calcium Channel Blockers (C08)	1 (0.0%)
		Agents Acting on the Renin-Angiotensin System (C09)	2 (0.1%)
Dermatological (D)	8 (0.4%)	Antifungals for Dermatological Use (D01)	2 (0.1%)
		Preparations for Treatment of Wounds and Ulcers (D03)	2 (0.1%)
		Antibiotics and Chemotherapeutics for Dermatological Use (D06)	3 (0.1%)
		Corticosteroids, Dermatological Preparations (D07)	1 (0.0%)
Systemic Hormonal Prep. excluding Sex Hormones (H)	59 (2.6%)	Corticosteroids for Systemic Use (H02)	59 (2.6%)
General Anti infectives for Systemic Use (J)	21 (0.9%)	Antibacterials for Systemic Use (J01)	21 (0.9%)
Musculoskeletal System (M)	1557 (69.3%)	Anti-inflammatory and Antirheumatic Products (M01)	882 (39.2%)
		Topical Products for Joint and Muscular Pain (M02)	486 (21.6%)
		Muscle Relaxants (M03)	187 (8.3%)
		Drugs for Treatment of Bone Diseases (M05)	2 (0.1%)
Nervous System (N)	97 (4.3%)	Anesthetics (N01)	14 (0.6%)
		Analgesics (N02)	78 (3.5%)
		Antiepileptics (N03)	4 (0.2%)
		Psychoanaleptics (N06)	1 (0.0%)
Respiratory system (R)	20 (0.9%)	Nasal Preparations (R01)	1 (0.0%)
		Throat Preparations (R02)	1 (0.0%)
		Cough and Cold Preparations (R05)	17 (0.8%)
		Antihistamines for Systemic Use (R06)	1 (0.0%)

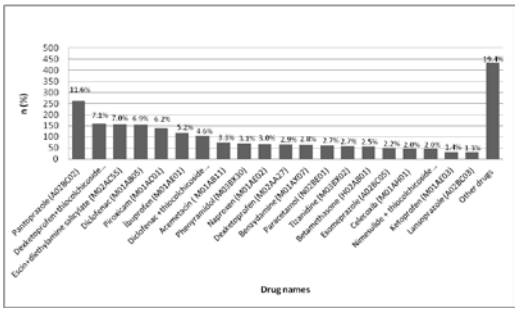

Figure 1. The most frequently prescribed 20 drugs at obesity orthopedics and traumatology clinic

A total of 669 data of patients who were prescribed two or more drugs were assessed in detail with regard to potential DDIs. Among 669 patients, 293 (43.8%) patients had one or more potential DDIs with a maximum of 7 DDIs (Table 5). The average number of DDIs per patient was 0.7. A total of 437 DDIs were detected of which 300 (68.6%) were D, 82 (18.8%) were X, 49 (11.2%) were C and 6 (1.4%) were B risk category interactions (Table 5). In terms of severity, most of the DDIs were moderate (79.8%), followed by major interactions (18.8%), (Table 5).

The most common DDIs were between systemic diclofenac and topical diclofenac, (14.4%), (Topical NSAIDs may increase the adverse/toxic effect of NSAIDs. In particular, gastrointestinal toxicity risk is enhanced). It was followed by the DDIs between systemic dexketoprofen and topical piroxicam (9.2%) and between systemic celecoxib and topical diclofenac (8.0%). The most common ten DDIs, estimated clinical outcomes and patient management are depicted at Table 6[14].

In the present study, the presence of DDIs was significantly associated with the adult age group (p=0.045) and female gender (p=0.049). On the other hand, the number of prescribed drugs were not significantly associated with the presence of DDIs (p=0.068), (Table 7).

Table 5. Frequency and the severity of potential DDIs

Variables	n(669) (%)
DDIs	
Yes	293 (43.8%)
None	376 (56.2%)
Number of DDIs	
1	223 (33.3%)
2	8 (1.2%)
3	55 (8.2%)
4	4 (0.6%)
5	2 (0.3%)
7	1 (0.1%)
Risk category of DDIs	
B	6 (1.4%)
C	49 (11.2%)
D	300 (68.6%)
X	82 (18.8%)
Severity of DDIs	
Minor	6 (1.4%)
Moderate	349 (79.8%)
Major	82 (18.8%)

Table 6. Frequency and the severity of the most common 10 DDIs at outpatient clinics (n=437)

DDIs	Risk category	Estimated clinical outcomes	Severity	Patient management	n (%)
Diclofenac (Systemic)-Diclofenac (Topical)	D	Topical NSAIDs may increase the adverse/toxic effect of NSAIDs. In particular, gastrointestinal toxicity risk is enhanced	Moderate	Coadministration is not recommended. If systemic NSAIDs and topical NSAIDs are coadministered, ensure the benefits outweigh the risks and monitor for increased NSAID toxicities.	63 (14.4%)
Dexketoprofen (Systemic)-Piroxicam (Topical)	D	Topical NSAIDs may increase the adverse/toxic effect of NSAIDs. In particular, gastrointestinal toxicity risk is enhanced.	Moderate	Coadministration is not recommended. If systemic NSAIDs and topical NSAIDs are coadministered, ensure the benefits outweigh the risks	40 (9.2%)

				and monitor for increased NSAID toxicities.	
Celecoxib (Systemic)-Diclofenac (Topical)	D	Topical NSAIDs may increase the adverse/toxic effect of NSAIDs. In particular, gastrointestinal toxicity risk is enhanced	Moderate	Coadministration is not recommended. If systemic NSAIDs and topical NSAIDs are coadministered, ensure the benefits outweigh the risks and monitor for increased NSAID toxicities.	35 (8.0%)
Celecoxib (Systemic)-Diclofenac (Systemic)	X	NSAIDs may increase the adverse/toxic effect of other NSAIDs. In particular, gastrointestinal toxicity risk is enhanced	Major	Concurrent use of more than one nonsteroidal anti-inflammatory drug (NSAID) should be avoided	34 (7.8%)
Diclofenac (Systemic)-Piroxicam (Topical)	D	Topical NSAIDs may increase the adverse/toxic effect of NSAIDs. In particular, gastrointestinal toxicity risk is enhanced	Moderate	Coadministration is not recommended. If systemic NSAIDs and topical NSAIDs are coadministered, ensure the benefits outweigh the risks and monitor for increased NSAID toxicities.	30 (6.9%)
Naproxen (Systemic)-Piroxicam (Topical)	D	Topical NSAIDs may increase the adverse/toxic effect of NSAIDs. In particular, gastrointestinal toxicity risk is enhanced	Moderate	Coadministration is not recommended. If systemic NSAIDs and topical NSAIDs are coadministered, ensure the benefits outweigh the risks and monitor for increased NSAID toxicities.	29 (6.6%)
DDIs	Risk category	Estimated clinical outcomes	Severity	Patient management	n (%)
Benzydamine-Paracetamol	C	Methemoglobinemia associated drugs may increase the adverse/toxic effect of Local Anesthetics. In particular, methemoglobinemia risk may be enhanced.	Moderate	Monitor patients for signs of methemoglobinemia (eg, hypoxia, cyanosis) when topical local anesthetics are used in combination with other agents associated with development of methemoglobinemia.	27 (6.2%)
Piroxicam (Systemic)-Piroxicam (Topical)	D	Topical NSAIDs may increase the adverse/toxic effect of NSAIDs. In particular, gastrointestinal toxicity risk is enhanced.	Moderate	Coadministration is not recommended. If systemic NSAIDs and topical NSAIDs are coadministered, ensure the benefits outweigh the risks and monitor for increased NSAID toxicities.	23 (5.3%)
Naproxen (Systemic)-Piroxicam (Systemic)	X	NSAIDs may increase the adverse/toxic effect of other NSAIDs. In particular, gastrointestinal toxicity risk is enhanced.	Major	Concurrent use of more than one nonsteroidal anti-inflammatory drug (NSAID) should be avoided	19 (4.3%)

Vitamin D3-Calcium Carbonate	C	Calcium Salts may increase the adverse/toxic effect of Vitamin D Analogs.	Moderate	Patients receiving higher calcium doses together with a vitamin D analog should be followed closely for serum calcium (and phosphate, iPTH, etc., as appropriate) concentrations and for signs/symptoms of hypercalcemia.	9 (2.1%)

Table7. Comparison of the presence of DDIs based on patients' demographic characteristics and number of drugs (n=669)

Variables (n(%))	DDI (+)	DDI (-)	P value
Gender			
Female	222 (75.8%)	259 (68.9%)	
Male	71 (24.2%)	117.(31.1.%)	p=0.049
Age			
18-44	73 (24.9%)	121 (32.2%)	
45-64	163 (55.6.%)	174 (46.3%)	p=0.045
≥65	57 (19.5 %)	81 (21.5%)	
Number of drugs			
2-4	261 (89.1.%)	350 (93.1%)	
≥5	32 (10.9%)	26 (6.9%)	p=0.068

* Chi-square test

DISCUSSION

It is important to conduct drug utilization studies in orthopedics and traumatology clinics that commonly focus on surgical data studies. To our knowledge, this is the first study to assess the frequency and the severity of DDIs among patients admitting orthopedics and traumatology outpatient clinics in Turkey.

In our study, out of 753 patients, most of the patients (72.2%) were female. Similar to our results, two distinct drug utilization studies conducted in ortopedic departments reported female predominance over male (15, 16). These finding could be attributed to higher prevalence of musculoskeletal disorders, which were the most common diagnoses in our study, is seen in female than male (17, 18). The mean age of the patients was 52.5 and the most common age group was 45-64 (50.2%). Similar results were reported by Motgahre et al, who found that the patients admitting to orthopedics outpatient department were mostly middle aged (36%), (16).

In the present study, the average number of drugs per patient, that is an important prescribing indicator evaluating rational drug use, was 2.9 which is higher than the WHO ideal values (1.6–1.8). Our finding was similar to those reported by Kumar et al. and Karki et al. (3 and 2.9, respectively),[19,20]. The most commonly prescribed drugs in this study were NSAIDs, PPIs and skeletal muscle relaxants (Figure 1). Similarly, NSAIDs and gastroprotective, anti-ulcer agents were the most frequently prescribed drugs according to the results of the several studies conducted in orthopedic departments[16,21].

We found that the frequency of the potential DDIs among polypharmacy patients was 43.8%. A study from Nepal which mainly focused on antibiotic utilization among hospitalized patients in orthopedics and traumatology clinic reported lower frequency rates of DDIs (26.0%) as compared to our study (22). In contrast, a higher prevalence of DDIs of antibiotics (73.0%) among orthopedics and traumatology unit patients was reported by Solanki et al.[15].

In terms of severity, majority of the potential DDIs were moderate interactions (79.8%), mostly in D risk category (68.6%). Our findings were comparable to those reporteed by Moura et al. who found 78% moderate and %22 major DDIs in prescriptions of hospitalized patients in Brazil (23). Unlike our results, two different studies from Palestine and Mexico which evaluated the potential DDIs in surgical

patients reported mostly major DDIs detected as 52.7% and 54.3%, respectively[24,25]. This divergence may be due to the usage of different medications in several surgical wards.

The most common DDIs in this study were between systemic NSAIDs and topical NSAIDs which combination increases the risk of gastrointestinal adverse effects. Similar to our results, a study evaluating the potential DDIs among eight major departments reported that DDIs between NSAIDs were among the most commonly seen DDIs in orthopedic deparment[26]. According to the current evidence, using a topical NSAID and systemic NSAID concomitantly has no advantage over using these agents alone, on the contrary this combination enhances the number of adverse reactions[27]. Even though, in most of the prescriptions proton pump inhibitors (PPIs), (pantoprazole, esomeprazole, lansoprazole etc.) are prescribed concomitantly with NSAIDs to decrease the risk for these gastrointestinal adverse reactions, it is important for physicians to monitor the patients in terms of increased NSAID toxicities. In addition, concurrent use of more than one systemic NSAIDs should be avoided to prevent major X risk category DDIs (Table 6).

In the present study, we found a significant association between presence of DDIs and and female gender (p=0.049), (Table 7). Similarly, the earlier studies also reported a significant association of female gender[9,23] with potential DDIs. In addition, there was also a significant association of age with DDIs (p=0.045). This association has also been reported by several studies. Nevertheless, contrary to earlier studies[4,23], the presence of DDIs decreased with increasing age in our study. The presence of DDIs was significantly more common among patients between 45-64 ages than those aged ≥65. Although, several studies reported a significant association of polypharmacy with DDIs[28,29], we found no significant association between the number of drugs and DDIs.

The limitation of the present study is that since this is a restrospective study, we don't know the co-morbid diseases of the patients and the drugs used concomitantly for their related diseases (Antihypertensives, antidiabetic agents, hypolipidemic agents etc.). Therefore, further studies are needed to assess the DDIs between precribed drugs and concomitant medications. In addition, we don't know whether DDIs actually caused the relevant changes in therapeutic efficacy of drugs or not.

The present study demonstrates that the potential DDIs in orthopedics and traumatology outpatient clinics prescriptions are strongly associated with adult age and female gender. Although, the severity of the potential DDIs in orthopedics and traumatology outpatient clinics were generally moderate and manageable, it is crutial for physicians to be aware of the interactions between the most frequently prescribed drugs in orthopedics and traumatology outpatient clinics, monitor patients for the safe use of drugs or change the drug options if necessary.

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