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Evaluation of Potential Drug-drug Interactions in the Prescriptions in Outpatient Settings

Ayaktan Tedavi Edilen Hasta Reçetelerinde Potansiyel İlaç-ilaç Etkileşimlerinin Değerlendirilmesi

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ABSTRACT

Introduction: Drug-drug interactions (DDIs) are an important component of drug-related adverse events, leading to morbidity and mortality worldwide. The aim of the present study was to evaluate the frequency and severity of potential DDIs (pDDIs) in the prescriptions written in outpatient primary care clinics in Trabzon, Turkey. **Material and Methods:** A retrospective descriptive study was carried out in 169 prescriptions from 15 primary care clinics. pDDIs were identified by using Lexi-Interact™ software program. **Results:** A total of 169 prescriptions involving 506 drugs were analyzed, of which 59 had at least one pDDI. The prevalence of pDDIs was 34.91%. The mean number of drugs per prescription was 2.99±1.08. A total of 124 pDDIs were identified with mean of 0.73±1.45 per each prescription. Hydrochlorothiazide was the most frequently prescribed drug involved in pDDIs (n=15, 12.10%). The most common pDDIs was between hydrochlorothiazide and metformin (n=4, 3.22%). The number of pDDIs are positively correlated with increasing age (r=0.33 p<0.01) and the number of prescribed drugs (r=0.41, p<0.01). The majority of pDDIs (n=96, 77.42%) were in the risk category C (monitor therapy). **Conclusion:** Our findings indicate that polypharmacy and age were associated with the risk of having pDDIs. Physicians and pharmacists should be aware of pDDIs to improve drug safety, patient compliance and, prevent adverse drug reactions. Analyzing of DDIs with softwares should be effective for management of risks associated with pDDIs.

Key words: family practice, interaction, polypharmacy, primary care, prescription

ÖZET

Giriş:İlaç-ilaç etkileşimleri, dünya çapında morbidite ve mortaliteye yolaçan ilaçlarla ilgili advers olayların önemli bir bileşenidir. Bu çalışmada, Trabzon'da aile sağlığı merkezlerinde ayakta tedavi gören hastalara ait reçetelerdeki potansiyel ilaç-ilaç etkileşimlerinin yaygınlığını ve ciddiyetini değerlendirmek amaçlandı. **Materyal ve Metot:** Trabzon'da bulunan 15 farklı aile sağlığı merkezinden çıkmış olan 169 reçetede retrospektif tanımlayıcı bir çalışma yapıldı. Potansiyel ilaç-ilaç etkileşimleri Lexi-Interact™ programı kullanılarak analiz edildi. **Bulgular:** Beş yüz altı adet ilaç içeren toplam 169 reçetenin 59 tanesinde en az bir potansiyel etkileşim saptandı. Potansiyel ilaç-ilaç etkileşimi prevalansı %34.91 ve reçete başına düşen ortalama ilaç sayısı 2.99 ± 1.08 idi. Reçete başına ortalama 0.73±1.45 adet olmak üzere toplam 124 potansiyel etkileşim tanımlandı. Hidroklorotiyazid potansiyel ilaç etkileşimlerinde en fazla yer alan ilaçtı (n = 15,% 12.10). En yaygın potansiyel ilaç-ilaç etkileşimi hidroklorotiyazid ve metformin arasındaydı (n = 4,% 3.22). Potansiyel etkileşim sayısı ile hastaların yaşı (r = 0.33, p <0.01) ve ilaç sayısı (r = 0.41, p <0.01) arasında pozitif korelasyon mevcuttu. Etkileşimlerin büyük çoğunluğu C grubu (n=96, 77.42%) risk kategorisine aitti. **Sonuç:** Bulgularımıza göre polifarmasi ve ileri yaş, potansiyel ilaç-ilaç etkileşim riskini artırmaktadır. Hekimler ve eczacılar ilaç güvenliği ve hasta uyumunu iyileştirmek, ve olumsuz ilaç reaksiyonlarını önlemek için potansiyel etkileşimlerin farkında olmalıdır. İlaç-ilaç etkileşimlerinin yazılımlarla analiz edilmesi, potansiyel etkileşimlere ilişkili risklerin yönetimi için etkili olabilir.

Anahtar kelimeler: aile hekimliği, etkileşim, polifarmasi, birincil bakım, reçete

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INTRODUCTION

Drug-drug interactions (DDIs) defined as an altered response of one drug by concurrent use of another drug, is a major concern in pharmacotherapy. DDIs may result in adverse drug reactions (ADRs) and decreased or increased efficacy of drugs leading to increased rate of hospitalization, prolonged hospital stay, morbidity, mortality and higher healthcare expenditures. DDIs is one of the most common drug-related problems causing poor patient compliance and decreased quality of patients' life.[1,2]

Numerous studies have been conducted to determine DDIs, possible risk factors and potential clinical outcomes. It is well established that age (commonly elderly), number of drugs, duration of combination therapy, drugs with narrow therapeutic index and underlying diseases are the main risk factors for DDIs. Elderly patients are considered to be more prone to develop DDIs due to age-related physiological changes and co-morbid conditions.[3,4,5] It has been also reported that the incidence of potential DDIs (pDDIs) is about 40% in patients receiving 5 drugs and 80 % in patients receiving 7 or more medications.[6] The incidence of DDIs-related hospital admissions has been estimated to range from 2.8% to 23%.[5,7] DDIs are considerable cause of ADRs, accounting for 5-41% of all ADRs.[8,9] Therefore, identification of pDDIs could help to prevent ADRs and improve quality of medical care by increasing knowledge and awareness of clinicians.

Many studies based on primary care reports have revealed the prevalence for pDDIs range from 12% to 80%.[11] The variations in outcomes of these studies are attributed to experimental design, patient characteristics and DDI software programs.[10,11] However, limited data is available on the evaluation of pDDIs in the outpatient settings. The purpose of this study was to analyze the frequency and severity of pDDI in prescriptions of outpatients from a selected region in Turkey.

MATERIALS AND METHODS

Study Design and Setting

This is a retrospective descriptive study that was designed to evaluate pDDIs in prescriptions randomly reported by the pharmacy students who were doing an internship in fifteen family practice centers in the city of Trabzon, Turkey two half days per week as a part of their mandatory pharmaceutical care course during February to May 2016. Data on patients' demographic information (age and gender), prescription details and the number of additional drug use (co-administreted drugs out of reported prescriptions) were recorded by the students during that period. A total of 169 prescriptions were analyzed in this study. Prescribed drugs were classified into groups according to Anatomical Therapeutic Chemical Classification (ATC Code) as recommended by World Health Organization.[12] pDDIs were analyzed by using Lexi-Interact™, an online software program available on the website www.uptodate.com and pDDIs were also categorized into risk categories named as A (no known interaction), B (no action needed), C (monitor therapy), D (consider therapy modification) and X (avoid combination) according to the software.[13] For a medicine that contains two or more active substances, each active substance was considered for pDDIs separately. All data were recorded in Microsoft Excel v.2010 spread sheet® and analyzed using GraphPad Prism 5.0 (GraphPad Software, Inc., San Diego, CA). Data were tested for normality using the Shapiro-Wilk test and presented as mean±standard deviation (SD) or percentage of case. Data were compared by Mann– Whitney U test for continuous variables and the chi-square test for categorical variables when appropriate. Spearman correlation coefficient was used to determine the relationship between two variables. $p<0.05$ was considered statistically significant.

RESULTS

Demographic Profile of Patients

A total of 169 patients were included in the study, of which 101 (59.76%) were female and 68 (40.24%) were male. The patients were classified into three age groups as 0-14 years, 15-64 years, and ≥65 years. The mean age of the patients was 42.10±25.20 years and the majority of patients' age was between 15-64 years old. The age distribution of patients was 0-14 years (n=37, 21.90%), 15-64 years (n=96, 56.80%) and ≥65 years (n=36, 21.30%).

Drug Prescription Details

Totally 506 drugs were prescribed for 169 patients. The mean number of drugs per prescription was 2.99±1.08, 101 of prescriptions (59.76%) contained at least two drugs, 10 (5.92%) of prescriptions contained only one drug. Three-drug containing prescriptions were the most prevalent (n=63, 37.28%). The highest number of drugs prescribed in a single prescription was 8 (Table 1).

Table 1. The distribution of number of drugs per prescription	
Number of drugs per prescription	**Number of prescriptions (%)**
1	10 (5.92)
2	46 (27.22)
3	63 (37.28)
4	40 (23.67)
5	7 (4.14)
6	2 (1.18)
8	1 (0.59)
Total	**169**

Respiratory system drugs were the most frequently prescribed (n = 78, 15.42 %), followed by the drugs effecting the alimentary tract and metabolism (n=77, 15.22%), and cardiovascular system drugs (n=70, 13.83%). Musculoskeletal system drugs were the most frequently prescribed group for the female patients whereas cardiovascular system drugs were most common in the prescriptions of male patients (Table 2).

Table 2. Gender-distribution of drugs according to the first level of ATC code				
Anatomical group of drugs	Total (n,%)	Female (n,%)	Male (n,%)	*P* value
Respiratory system	78 (15.42)	44(14.81)	34 (16.27)	0.258
Alimentary tract and metabolism	77 (15.22)	43 (14.48)	34 (16.27)	0.305
Cardiovascular system	70 (13.83)	32 (10.77)	38 (18.18)	0.475
Anti-infectives for systemic use	66 (13.04)	40 (13.47)	26 (12.44)	0.085
Musculo-skeletal system	65 (12.85)	45 (15.15)	20 (9.57)	0.002
Nervous system	50 (9.88)	35 (11.79)	15 (7.18)	0.005
Blood and blood forming organs	21 (4.15)	11 (3.70)	10 (4.78)	0.827
Systemic hormonal preparations, excl. sex hormones and insulins	20 (3.95)	14 (4.72)	6 (2.87)	0.074
Dermatologicals	19 (3.75)	9 (3.03)	10 (4.78)	0.819
Genitourinary system and sex hormones	17 (3.36)	10 (3.37)	7 (3.35)	0.467
Sensory organs	13 (2.57)	9 (3.03)	4 (1.92)	0.166
Others	10 (1.98)	5 (1.68)	5 (2.39)	1.000
Total number of drugs	**506**	**297**	**209**	

ATC: Anatomical Therapeutic Chemical Classification

The mean numbers of drugs were for female and male patients were 3.15±0.14 and 2.88±0.09, respectively (Figure 1). No significant difference was found between male and female patients regarding the mean number of drugs per prescription ($p>0.05$). A weak positive correlation was observed between patients' age and the number of prescribed drugs (Spearman correlation coefficient $r=0.26$, $p<0.01$).

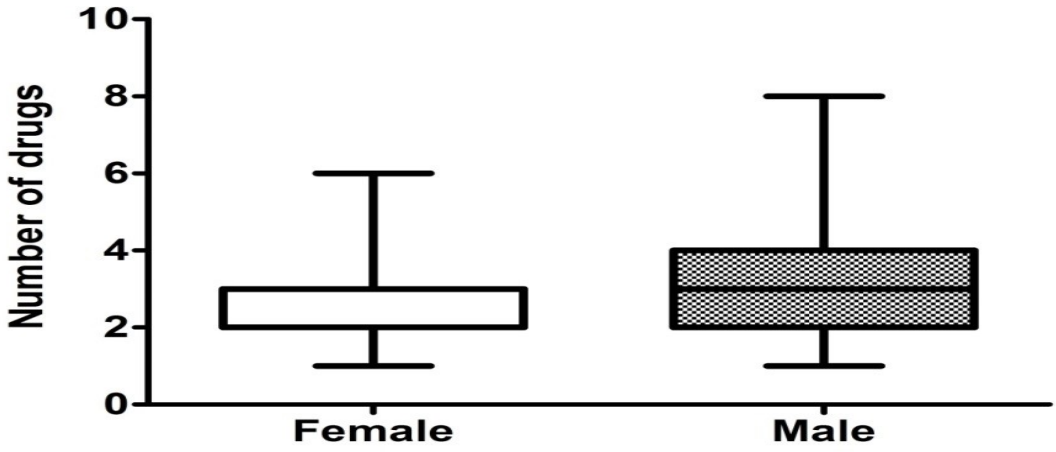

Figure 1.The distribution of the number of drugs per prescription in both genders

Drug Interactions

The total of 124 pDDIs were identified including the additional drugs (drugs were taken by patients, which were out of analyzed prescriptions). Seventeen of total pDDIs were between the additional drugs and currently prescribed drugs. The mean number of pDDIs per prescription was 0.73±1.45. Among 169 prescriptions, 59 had pDDIs ranging from 1 to 11. Thirty (17.75%) of prescriptions had one pDDI. Highest number of pDDIs in a single prescription was 11(Table 3).

Table 3. Distribution of the number of pDDIs in the prescriptions

Number of pDDIs	Number of prescriptions	Frequency (%)
0	110	65.09
1	30	17.75
2	15	8.88
3	6	3.55
4	4	2.37
6	2	1.18
7	1	0.59
11	1	0.59
Total	**169**	**100**

pDDI: Potential drug-drug interactions

The prevalences of pDDIs in prescriptions of females and males were 53.23% and 46.77%, respectively Prescriptions with one pDDI was common for both genders (Table 4).

Table 4. Gender-based distribution of pDDIs

Number of pDDI per prescription	Female (n,%)	Male (n,%)	Total (n,%)
0	63 (62.38)	47 (69.12)	110 (65.09)
1	19 (18.81)	11 (16.18)	30 (17.75)
2	14 (13.86)	1 (1.47)	15 (8.88)
3	3 (2.97)	3 (16.66)	6 (3.55)
4	1 (0.99)	3 (16.66)	4 (2.37)
6	1 (0.99)	1 (1,47)	2 (1.18)
7	0 (0.00)	1 (1,47)	1 (0.59)
11	0 (0.00)	1 (1,47)	1 (0.59)

pDDI: Potential drug-drug interactions

The most common drugs involved in pDDIs were hydrochlorothiazide (n=5, 12.10%) followed by metformin (n=14, 11.29%), acetylsalicylic acid (n=12, 9.68%) (Table 5).

Table 5. The most common drugs involved in pDDIs

Drugs	Number of pDDIs (%)
Hydrochlorothiazide	15 (12.10)
Metformin	14 (11.29)
Acetylsalicylic acid	12 (9.68)
Ibuprofen	10 (8.04)
Ramipril	10 (8.04)
Budesonide	6 (4.84)
Gliclazide	6 (4.84)
Metoprolol	6 (4.84)
Naproxen	6 (4.84)
Salbutamol	6 (4.84)

pDDI: Potential drug-drug interactions

The most frequent combinations with a risk of pDDI were hydrochlorothiazide-metformin (n=4, 3.22%), followed by acetylsalicylic acid-ibuprofen (n=3, 2.42%), clarithromycin-salbutamol (n=3, 2.42%) and metformin-ramipril (n=3, 2.42%). The most frequent drug pairs involved in pDDIs and their potential risk were presented in Table 6.

Table 6. The most frequent drug pairs involved in pDDIs

Drugs	Number of pDDIs (n,%)	Risk category	Potential risk	Recommended intervention
Hydrochlorothiazide -metformin	4 (3.22)	C	Decreased therapeutic effect of metformin	Serum glucose monitoring
Acetylsalicylic acid-ibuprofen	3 (2.42)	C	Increased risk of bleeding	Signs and symptoms of bleeding monitoring
Clarithromycin-salbutamol	3 (2.42)	B	Increased risk for QT interval prolongation	No action needed
Metformin-ramipril	3 (2.42)	C	Increased risk for hypoglycemia and for lactic acidosis.	Serum glucose monitoring
Metformin-indapamide	2 (1.61)	C	Decreased therapeutic effect of metformin	Serum glucose monitoring
Salbutamol-budesonide	2 (1.61)	B	Hypokalemia	No action needed
Acetylsalicylic acid -ramipril	2 (1.61)	C	Increased nephrotoxic effect and decreased therapeutic effect of ramipril	Monitoring for acute renal failure and decreased therapeutic effects of ramipril
Formoterol-budesonide	2 (1.61)	B	Hypokalemia	No action needed
Levothyroxine-pantoprazole	2 (1.61)	B	Decreased the serum concentration of levothyroxine	No action needed

pDDI: Potential drug-drug interactions

Based on severity scale, 96 (77.42%) were in the risk category C, 18 (14.52%) were in the risk category B, 9 (7.25%) in the risk category D, 1 (0.81%) was in the risk category X. The only pDDI reported in the risk category X was between dexketoprofen and flurbiprofen. Most of pDDIs (n=80, 64.52%) were identified in prescriptions of the patients aged between 15-64 years (Table 7).

Table 7. The distribution of pDDIs according to risk categories of interactions and age of the patients

Risk category	Total	0-14 years (n,%)	15-64 years (n,%)	≥65 years (n,%)	*P* value
B	18 (14.52)	5 (55.56)	11 (13.75)	2 (5.72)	0.030
C	96 (77.42)	4 (44.44)	60 (75.00)	32 (91.42)	<0.001
D	9 (7.25)	0 (0.00)	9 (11.25)	0 (0.00)	-
X	1 (0.81)	0 (0.00)	0 (0.00)	1 (2.86)	-
Total	**124**	**9**	**80**	**35**	

pDDI: Potential drug-drug interactions

Number of pDDIs was moderately positively correlated with increasing age (Spearman correlation coefficient r=0.33, p<0.01) and number of drugs prescribed (Spearman correlation coefficient r=0.41, p<0.01). Gender was not associated with increased risk of pDDIs (p>0.05, Mann–Whitney U test).

DISCUSSION

In the present study, we critically evaluated the prescriptions of outpatients of primary care clinics. Our results showed that pDDIs identified in the risk category C is more common in outpatient settings and polypharmacy and increased age are risk factors for pDDIs.

In this study, the mean number of drugs per prescription was 2.99±1.08, which was lower in comparison with previous studies.[14,15] In many studies investigating pDDIs, prescriptions with a single drug were excluded. However, we included one drug containing prescriptions (n=10) in order to analyze pDDIs with patient reported drug use that is not concurrently included in the prescriptions. We found a positive correlation between patients' age and the number of prescribed drugs, which is consistent with earlier studies.[14,15] Based on our results, drugs affecting respiratory system, alimentary tract and metabolism and cardiovascular system were widely prescribed therapeutic groups accounting for 44.47% of overall prescribed drugs, which is similar to the results of previous studies.[16,17]

In our study, 59 of total prescriptions had at least one pDDI and the prevalence of pDDIs was 34.91%. The prevalence of pDDIs in previous studies has been documented in patients ranging from 12% to 80%, which might vary due to sample size, study design, analysis methods of pDDIs and characteristics of the population.[10] In prescriptions for female outpatients the prevalence of pDDIs was higher when compared to that of males, which is consistent with the previous study conducted in hospitalized patients.[5]

In our study, the most prevalent drug involved in pDDIs was hydrochlorothiazide (n=15, 12.10%) that was also reported as one of the most common drugs causing pDDIs in previous studies.[18,19] Moreover, the most common pDDIs identified in this study was between hydrochlorothiazide and metformin (n=4, 3.22%), followed by acetylsalycilic acid and ibuprofen (n=3, 2.42). Hydrochlorothiazide is a thiazide diuretic that is associated with hypokalemia and hyperglycemia. Therefore, hydrochlorothiazide may reduce the efficacy of anti-hyperglycemic drugs like metformin, which may require the dose of anti-hyperglycemic drugs to be increased. Concurrent use of hydrochlorothiazide with certain drugs such as steroids and beta agonists can also potentiate hypokalemia or electrocardiography changes.[20,21] Acetylsalicylic acid is a member of non-steroidal anti-inflammatory drugs (NSAIDs) that exert anti-inflammatory, analgesic and antipyretic effects by inhibiting cyclo-oxygenase (COX), an enzyme responsible for prostaglandin synthesis. Co-administration of acetylsalicylic acid and other NSAIDs like ibuprofen could increase the risk of serious gastrointestinal adverse events.[22] In many cases of prescriptions we analyzed, acetylsalicylic acid was prescribed for the prophylaxis of cardiovascular and cerebro-vascular events. Acetylsalicylic acid is considered to have less potential risk for DDIs when used at lower doses for the prophylaxis.[22] On the other hand, if acetylsalicylic acid and ibuprofen are taken together, both drugs can compete for the acetylation site of COX-1 in platelets, resulting in the blockade of irreversible inhibition of COX by acetylsalicylic acid and thus decrease in the anti-platelet efficacy of acetylsalicylic acid. FDA recommends that ibuprofen should be taken at least 30 minutes after aspirin or at least 8 hours before aspirin to avoid any potential interaction.[23]

We found that the majority of pDDIs was in risk category C (monitor therapy), accounting for 77.42% of all. A moderate positive correlation between the number of pDDIs and age was observed. Moreover, a positive correlation was also found between number of pDDIs and the number of drugs prescribed. There was no significant difference between genders for the number of pDDIs, which is in agreement with other studies.[8,24]

We identified only one pDDI between dexketoprofen-flurbiprofen was in risk category X, which means to be this combination to be avoided. Like dexketoprofen and flurbiprofen, concomitant use of two or more NSAIDs could increase the probability of GI bleeding.[22]

DDIs associated with increased risk for hospitalization and ADRs are growing concern in patients receiving multiple medications. Physicians and pharmacists should be aware of the pDDIs to improve patient compliance and drug safety. DDIs should be also included in the continuous vocational education and training programs to increase awareness and knowledge level. The introduction of software analyzing DDIs or lists in hospitals and pharmacies would help to reduce the risks related to DDIs.

We acknowledge several limitations of our study such as short duration, using only one DDI screening tool and small population. Further studies are required with a larger sample population, planning a longer data collection period and using more DDI databases, while increasing the clinical knowledge level and experience and inducing awareness; overall which

will help to improve quality and effectiveness of medical care.

CONCLUSION

In the present study, we reported that the majority of pDDIs was in risk category C (monitor therapy). Moreover, polypharmacy and age were found to be associated with the risk of having pDDIs. This study now provides preliminary evidence to emphasize the importance of pDDIs in the prescriptions of outpatients in family practice centers. Physicians and pharmacists should be aware of pDDIs to improve drug safety and patient compliance, and prevent adverse drug reactions.

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