**ORIGINAL ARTICLE / ÖZGÜN MAKALE** 



# INTERVENTIONS IN INTERNAL MEDICINE WARDS WITH SCOPE OF CLINICAL PHARMACY RESIDENCY PROGRAM: A RETROSPECTIVE STUDY

KLİNİK ECZACILIK UZMANLIK PROGRAMI KAPSAMINDA İÇ HASTALIKLARI SERVİSLERİNDEKİ MÜDAHALELER: RETROSPEKTİF BİR ÇALIŞMA

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# ABSTRACT

**Objective:** Drug-related problems are a common health problem in hospitalized patients, affecting optimal patient outcomes. The aim of the study is to classify the drug-related problems detected by clinical pharmacy resident in hospitalized patients during their rotations and evaluate their interventions to the healthcare team.

**Material and Method:** This is a retrospective study in which the drug-related problems of the patients hospitalized in the internal medicine wards between April and November 2018 were examined during the rotations of the clinical pharmacy resident. Patients' demographics, prescribed medicine, laboratory findings were recorded. Drug-related problems are classified with the Pharmaceutical Care Network Europe Version 9.1 system.

**Result and Discussion:** *Ninety-two patients were included in the study. The median age of patients was 60.5 years and 59.8% of them were female. Most of the patients (63%) had three or more comorbidities. The most frequent comorbidities were hypertension (21.70%) and diabetes mellitus (10.64%). One hundred forty-seven drug-related problems were detected in 57 patients (62%). Potential drug-drug interactions (55.78%), errors in dosing timing instructions (9.52%), and inappropriate drug use according to guidelines (8.16%) were the most common causes of drug-related problems. The acceptance rate of interventions for resolving drug-related problems was 65%. The most common drug-related problems in this study were due to drug selection. The acceptance rate of recommendations for drug-related problems was lower than in the literature. However, this initial acceptance rate can be considered successful in a center where clinical pharmacy services have not been established.* 

Keywords: Clinical pharmacy, drug-related, internal medicine

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# ÖΖ

Amaç: İlaçla ilgili sorunlar, hastanede yatan hastalarda optimal hasta sonuçlarını etkileyen yaygın bir sağlık sorunudur. Çalışmanın amacı, klinik eczacılık asistanının rotasyonları sırasında hastanede yatan hastalarda tespit ettiği ilaçla ilgili sorunları sınıflandırmak ve sağlık ekibine yapılan girişimleri değerlendirmektir.

Gereç ve Yöntem: Bu çalışma, Nisan-Kasım 2018 tarihleri arasında iç hastalıkları servislerinde yatan hastaların klinik eczacılık asistanının rotasyonları sürecinde ilaçla ilgili sorunlarının incelendiği retrospektif bir çalışmadır. Hastaların demografik bilgileri, reçete edilen ilaçlar, laboratuvar bulguları kaydedildi. İlaçla ilgili sorunlar, Avrupa Farmasötik Bakım Ağı Versiyon 9.1 sistemi ile sınıflandırıldı.

**Sonuç ve Tartışma:** Çalışmaya 92 hasta dahil edilmiştir. Hastaların ortanca yaşı 60.5'tir ve %59.8'i kadındı. Hastaların çoğunda (%63) üç veya daha fazla ek eşlik eden hastalık vardır. En sık eşlik eden hastalıklar hipertansiyon (%21.70) ve diabetes mellitus'tur (%10.64). Hastaların 57'sinde (%62) 147 adet ilaçla ilgili sorun saptandı. Potansiyel ilaç-ilaç etkileşimleri (%55.78), doz zamanlama talimatlarındaki hatalar (%9.52) ve kılavuzlara göre uygunsuz ilaç kullanımı (%8.16) ilaçla ilgili sorunların en yaygın nedenleri olarak belirlenmiştir. İlaçla ilgili sorunların çözümüne yönelik önerilerin kabul oranı %65'tir. Bu çalışmada en yaygın karşılaşılan ilaçla ilgili sorunlar ilaç seçiminden kaynaklanmaktadır. İlaçla ilgili sorunlar için önerilerin kabul oranı literatüre kıyasla daha düşüktür. Ancak klinik eczacılık hizmetinin henüz kurulmadığı bir merkezde bu ilk kabul oranları başarılı olarak kabul edilebilir.

Anahtar Kelimeler: İç hastalıkları, ilaçla ilgili, klinik eczacılık

# **INTRODUCTION**

Drug-related problems (DRPs) are a common health issue among inpatients that can negatively impact patient outcomes, increase morbidity and mortality, and increase healthcare costs. To improve patient outcomes, it is important to prevent, detect, and resolve DRPs [1,2]. A review of studies found that when clinical pharmacists were involved in clinical rounds and medication reconciliation, there were reductions in DRPs and shorter hospital stays [3]. The involvement of pharmacy students in healthcare team meetings, pharmacist-patient interactions, medication reconciliation, and post-discharge counseling and follow-up has been shown to improve patient outcomes [4,5].

Many studies on DRPs in inpatients have been conducted, with reported rates varying depending on factors such as location. In studies conducted with pharmacy students in Turkey and Lebanon, at least one drug-related problem (DRP) was found in 80% and 15% of patients, respectively. The main causes of DRPs are drug and dose selection, with common risk factors including renal failure, polypharmacy, and prolonged hospital stays [6-9]. Studies have shown that student interventions to resolve DRPs are well accepte [7-10].

Clinical pharmacy has been present in Turkey since 1991, but clinical pharmacists are not widely employed in hospitals. Most research in Turkey has been conducted as part of undergraduate and graduate programs. A clinical pharmacy residency program was established in 2018 under the Ministry of Health, in which, clinical pharmacy residents (CPRs) rotate through 15 different clinics and make recommendations to the healthcare team to resolve DRPs. These recommendations are generally accepted, but there is currently no system in place to record them.

The aim of this study is to examine the interventions made by a clinical pharmacy resident (CPR) to the healthcare team for identifying, preventing, and resolving DRPs internal medicine wards during the CPR's rotations.

#### **MATERIAL AND METHOD**

#### **Study Design and Sample Size**

This retrospective study was conducted in the 40 beds internal medicine wards of a training and research hospital in Turkey. Patients hospitalized in endocrinology (2 months), rheumatology (1 month), gastroenterology (1 month), nephrology (1 month) and chest diseases (2 months) services were

examined. In this study, DRPs detected by CPR during rotations within the clinical pharmacy residency program scope were evaluated retrospectively between April and November 2018. The detected DRPs, which include issues related to dosage, indication, treatment duration, drug-drug interactions, therapeutic drug monitoring, dosage form, and administration route, and the recommendations made by the CPR were presented to the healthcare team. The DRPs were classified according to the Pharmaceutical Care Network Europe (PCNE) Version 9.1 DRP classification system.

This study included patients aged 18 years and older who used at least one drug, were hospitalized for more than 24 hours, and were followed by CPR. Eligible patients were included in the study without randomization to eliminate potential selection bias. Patients who could not reach sufficient information and data were excluded from the study by the researchers. One CPR conducted the study. The CPR made interventions for DRPs during patient visits and discussed them with the patient's primary physician. The CPR documented implementation and acceptance of suggestions and interventions are recorded routinely. The CPR participated in weekday patient rounds and made interventions during the day. These interventions covered any stage of the medication treatment process and included recommendations such as discontinuation/addition of the drug, alternative therapy, or dose adjustment.

### **Data Collection**

The study was collected data on patients' demographic information, medication use and medical history, laboratory test results and length of hospital stay. The appropriateness of drug selection and dosage was assessed by comparing to local and international guidelines. Treatment was considered appropriate when drug and dose selection complied with these guidelines. In the study, UpToDate (Wolters Kluwer Health Inc.) and Micromedex® Drug Information (Truven Health Analytics Inc.) were primarily used as references for clinical decision making, drug administration, and drug-drug/nutrition/disease interactions. Lexicomp was used through the UpToDate database to identify drug-drug interactions. Only contraindicated and major drug interactions were classified as DRPs. The Sanford Guide to Antimicrobial Therapy (Antimicrobial Therapy, Inc. Sperryville, USA) was used for information on dosage and indication of antimicrobial drugs. This study used CKD-EPI to calculate the estimated glomerular filtration rate (eGFR). eGFR values below 60 ml/min/1.73 m2 were classified as "decreased GFR" at the hospital where the study was performed. Also, normal values of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) parameters are 10-37 IU/L and 10-40 IU/L, respectively. Patients with AST and ALT values above normal values were classified as having "increased AST-ALT".

#### **Statistical Analysis**

The study determined if the distribution of continuous variables were normal by using the Kolmogorov-Smirnov test, and as the data were not normally distributed, the relationship between patient variables and the number and presence of DRPs was analyzed using Pearson's correlation. The statistical analyses were performed using the IBM SPSS Statistics for Windows, Version 25.0. (Armonk, New York: IBM Corp.) software package. All data were considered statistically significant at p<0.05 and with a 95% confidence interval.

## **RESULT AND DISCUSSION**

One hundred nineteen patients were evaluated for eligibility and included 92 patients in the study. The median age (interquartile range [IQR]) of the patients was 60.5 (39.25-73.00) years, and 59.8% were female. The median (IQR) values of the number of medications used by the patients at admission and during discharge were 8 (6-10) and 7 (5-9), respectively. Most of the patients (63%) had three or more comorbidities. The most common comorbidities were hypertension (21.70%) and diabetes mellitus (10.64%) (Table 1). Most patients were admitted to the department of chest diseases (39.13%) and gastroenterology (20.65%).

Variable	Numbers	
Gender (n, %)		
Female	55 (59.8)	
Male	37 (40.2)	
Age, Median (IQR)	60.5 years (39.25-73.00)	
Admission wards to hospital (n, %)		
Nephrology	9 (9.78)	
Rheumatology	11 (11.96)	
Endocrinology and Metabolic Diseases	17 (18.48)	
Gastroenterology	19 (20.65)	
Chest Diseases	36 (39.13)	
Comorbidities (n, %)		
Hypertension	51 (21.70)	
Diabetes mellitus	25 (10.64)	
Chronic kidney disease	12 (5.11)	
Heart failure	10 (4.26)	
Coronary artery disease	10 (4.26)	
Hyperlipidemia	10 (4.26)	
Hypothyroidism	7 (2.98)	
Atrial fibrillation	7 (2.98)	
Other	103 (43.82)	
Charlson Comorbidity Index, Median (IQR)	3 (0-5)	
Body mass Index, Mean (± Standard Deviation)	27.28 (± 6.37)	
Length of Hospitalization Stay, Median (IQR)	13 (7.75-19)	
Kidney Function, (n, %)		
Normal	63 (68.5)	
Decreased GFR	24 (26.1)	
Hemodialysis Devites and dialaria	4 (4.3)	
Peritoneal dialysis	1 (1.1)	
Liver Function (n, %)		
Normal	85 (92.4)	
Increased AST-ALT	3 (3.3)	
Cirrhosis	2 (2.2)	
Hepatitis	2 (2.2)	
	8 (6-10)	
Number of Medications in Hospitalization, Median (IQR)		
- · · · - ·		
Number of Medications in Discharge, Median (IQR)	7 (5-9)	
- · · · - ·	• •	
Number of Medications in Discharge, Median (IQR) Discharge Status (n, %)	7 (5-9)	
Number of Medications in Discharge, Median (IQR)         Discharge Status (n, %)         Discharge	7 (5-9) 87 (94.5)	

#### Table 1. Demographic information of the patients

ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, GFR: glomerular filtration rate, IQR: Interquartile Range

In this study, 147 DRPs were detected in 57 (62%) patients. The mean (standard deviation) number of DRPs per patient was 1.59 (1.87). The most common causes of DRP were inappropriate drug selection (76.19%) and inappropriate dose selection (14.28%). The most common agents causing DRPs were quetiapine (7.72%), tramadol (6%), calcium carbonate (5.57%), methylprednisolone (4.29%), aspirin (3.86%) and pantoprazole (3.43%). Potential drug-drug interactions (pDDIs) (55.78%), errors in dose timing instructions (9.52%), and inappropriate drug use according to guidelines (8.16%) were the main causes of DRPs (Table 2). The rate of contraindicated pDDIs was 7.4%.

Causes	n (%)	Medications Causing Drug-Related Problems (n)*
1 During coloration	112	Problems (II)*
1. Drug selection	112	
	(76.19)	
C1.1 Inappropriate drug according to guidelines/formulary	12 (8.16)	oxybutynin (2), tenofovir (2)
C1.2 No indication for drug	7 (4.76)	pantoprazole (1), rabeprazole (1)
C1.3 Inappropriate combination of drugs. or drugs and herbal	82 (55.78)	methylprednisolone-calcium carbonate
medications. or drugs and dietary supplements		(6), quetiapine-tramadol (4),
		fluconazole-quetiapine (3)
C1.4 Inappropriate duplication of therapeutic group or active	2 (1.36)	Magnesium oxide (1), Vitamin D (1)
ingredient		0
C1.5 No or incomplete drug treatment in spite of existing	9 (6.12)	Vitamin B12 (2), Folic acid (2)
indication		
2. Drug form	10 (6.80)	
C2.1 Inappropriate drug form/formulation (for this patient)	10 (6.80)	pantoprazole (5), linezolid (2)
3. Dose selection	21 (14.28)	
C3.2 Drug dose of a single active ingredient too high	7 (4.76)	tramadol (2), ceftazidime (1)
C3.5 Dose timing instructions wrong. unclear or missing	14 (9.52)	levothyroxine (3), nifedipine (2)
4. Treatment duration	1 (0.68)	
C4.2 Duration of treatment too long	1 (0.68)	flavoxate (1)
9. Other	3 (2.04)	
C9.1 No or inappropriate outcome monitoring (incl. TDM)	3 (2.04)	hydroxychloroquine (2)
Total DRP	147	100

C: Cause, DRP: Drug-related problem

\*The active ingredients that most commonly cause drug-related problems are given.

The major and contraindicated pDDIs were mainly methylprednisolone-calcium carbonate (n=6) and atorvastatin-gemfibrozil (n=1), respectively. Details of pDDIs and levels of evidence were shown in Figure 1.

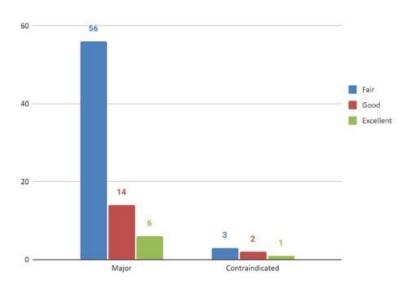
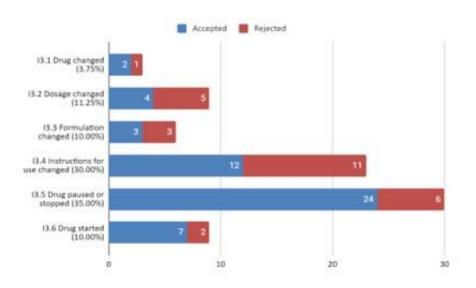


Figure 1. Frequency of potential drug-drug interactions by level of evidence (n=82)

The CPR made 80 recommendations for resolving 147 DRPs. The healthcare team accepted 52 (65%) of the recommendations. Forty-one (51.25%) of all recommendations were accepted and fully implemented. The CPR' recommendations were made only at the level of the patient's primary physician and face-to-face. Interventions were mainly made as stopping the drug (35%) and changing the instructions for the use of the drug (30%). Interventions for stopping the drug (30%) and changing the



instructions for use of the drug (15%) were accepted mainly by the healthcare team (Figure 2).

Figure 2. Classification of clinical pharmacist intervention types for DRPs (n=80)

No statistically significant difference was found when DRP numbers were compared in terms of age, gender, length of hospital stay, kidney failure, liver failure. A correlation was found between the number of DRPs and number of medications at hospitalization, number of medications at discharge, length of hospital stay and Charlson comorbidity index (Table 3).

Variables	Number of D	Number of DRP	
	R	р	
Number of Medications in Hospitalization	0.417*	< 0.001	
Number of Medications in Discharge	0.531*	< 0.001	
Total Hospitalization Days	0.280*	0.008	
Charlson Comorbidity Index	0.115	0.275	

Table 3. Correlation between patient variables and drug-related problem numbers

R = correlation coefficient

The clinical pharmacy residency program, which started in Turkey for the first time in 2018, graduated its first specialists in 2021. In this context, universities have designed rotation programs for CPRs in nearly 15 different clinics for two years to complete their clinical training. In this process, CPRs tried to provide both their theoretical knowledge and skills in clinical practice by participating in routine patient rounds with a multidisciplinary team. During their clinical rotations, they participated in their clinics' training, patient rounds and case discussions. While trying to improve their education, they reviewed the treatments of inpatients and presented their recommendations for DRPs to the healthcare team. In this study, interventions for DRPs, determined by the CPR in the rotation of the internal medicine wards during the first seven months of clinical pharmacy residency training in Turkey and presented to the healthcare team, were examined.

Researchers have demonstrated that the recommendations made by pharmacy students during clinical rotations are crucial in enhancing patient care and decreasing costs in various clinics [4,5,11-13]. Studies have highlighted that the suggestions made by student pharmacists in the internal medicine ward aid in solving DRPs, preventing them, reducing costs, and positively impacting patient outcomes [7,8,14-16]. It is acknowledged that healthcare teams increasingly accept students who participate in CPR programs in Turkey, and physicians accept their recommendations [17].

A study conducted by a pharmacy student and a clinical pharmacy specialist in an internal medicine ward in Turkey found that the mean number of DRPs per patient (1.6) was consistent with the average number of DRPs in this study (1.6) [6]. Other studies have reported that between 15.4-80% of patients had at least one DRP [6,7,18]. The DRP rates among inpatients may vary due to factors such as the clinics where the studies were conducted, the level of knowledge of the researchers, the clinical environment, and the different DRP classification systems used.

Studies conducted by internal medicine wards and pharmacy students primarily focused on the proportion of interventions and acceptance rates. The acceptance rate of the recommendations made by the CPR in this study (65%) was lower than reported in the literature (68-96%) [7-10,14-16,19-21]. Studies that report high acceptance rates of clinical pharmacy recommendations were conducted in locations where the practice is well-established. The low acceptance rate in this study could be attributed to the hospital's lack of routine clinical pharmacy services and the uncertainty of the healthcare team's attitude towards clinical pharmacists' interventions. Additionally, postgraduate studies in clinical pharmacy in Turkey are typically conducted in the later stages of students' education [9,20,21]. In contrast, this study examines the acceptance rate during the initial residency training phase. Another potential reason for the low acceptance rate could be the level of knowledge and experience of the CPR during the rotation process.

Studies in internal medicine wards, similar to this study, have found that DRPs primarily result from drug and dose selection [6-8,14,22]. As stated in previous studies, the most common cause of DRPs is from pDDIs with a rate of 29.4-65% [6,7,9,18,23]. As reported by Vinluan et al., the rate of pDDIs was low as the medical treatment records were routinely examined for drug-drug interactions in the electronic environment [8,22]. This study found that high doses (4.76%) and inappropriate drug selection (8.16%) according to guidelines, which frequently cause DRPs, are consistent with other studies. However, DRP was not detected in this study due to the low dose compared to other studies [6–8,24]. Like other studies, interventions made to the healthcare team that were highly accepted include dose adjustment, changing the drug's instructions for use, changing the drug, stopping the drug, and adding new drugs [7,8]. While pDDIs are the most common types of DRPs encountered in studies, most drug interactions have been made for pDDIs. The acceptance of clinical pharmacists' recommendations, particularly for dosing and drug selection, indicates that pharmacists' competencies and services in this area are generally accepted.

In this study, 8.1% of DRPs were caused by inappropriate drug use according to guidelines, which is consistent with other studies that have reported rates of 2-29.5% [6,7,9,25]. Clinical pharmacists play a role in optimizing patients' treatment and providing updated treatments to the healthcare team. Another common cause of DRPs in this study was errors in the dose timing instructions (9.5%). Other studies have reported different rates (1-19.6%) of DRPs caused by errors in dose timing instructions [7,9,25]. Abunahlah et al. did not specify such a DRP [6]. It is important to use medications at the appropriate time for maximum effect. This DRP may have been caused by lack of knowledge and workload. Studies have reported various rates since there is insufficient consistency in the systems used to classify DRPs, which can affect the detection of DRPs [7].

Several factors can influence the number and type of DRPs, such as modifiable factors like length of hospital stay and polypharmacy, and non-modifiable factors such as age, diagnosis, and comorbidities. This study found that patient's age, gender, renal status, and hepatic status did not have an impact on the presence of DRPs. Similar to the study by Blix et al., this study also found that age and gender did not affect the existence of DRPs [22]. However, most studies have shown that polypharmacy is a risk factor that affects DRPs. This study also found a positive correlation between the number of DRPs and length of hospital stay, the number of medications at admission, the number of medications at discharge, and number of multiple comorbidities [6,18,22,26]. Extended hospitalization and various comorbidities, which are known to affect DRPs, are risk factors that lead to polypharmacy, ultimately resulting in an increase in DRPs.

A clinical pharmacist working in hospital wards can provide services such as consulting with physicians, reviewing prescriptions, and preventing DRPs [27,28]. Furthermore, a clinical pharmacist's participation in patient rounds can detect and control most DRPs [28]. Consulting with doctors and

nurses provided by clinical pharmacists can decrease cost, length of hospital stay, and mortality rate [27,29,30].

This study highlights the role of the CPR in detecting and resolving DRPs in internal medicine wards during the ongoing residency rotation in a hospital where clinical pharmacy services were not routinely offered before. The limitations of this study include its short duration and the limited number of patients. Additionally, the absence of a staff clinical pharmacist in the hospital for the CPR to consult during training is a significant limitation. Conducting such studies with a larger number of residents, for a longer period and in the presence of a clinical pharmacy specialist would better reflect the impact of solution proposals and clinical pharmacy activities for DRPs in the rotation process. Since this study was conducted in a single center, the findings cannot be generalized to other internal medicine wards.

This study found that at least one DRP was detected in over half of the patients hospitalized in the internal medicine wards. The most common causes of DRPs were inappropriate drug selection and dose selection. The study also found that DRPs were influenced by the number of medications at admission and discharge, the number of comorbidities, and length of hospital stay. The healthcare team's acceptance rate of these interventions was lower than what has been reported in literature. However, considering that clinical pharmacy services were not routinely provided in this hospital, this acceptance rate can be considered successful as a starting point. Clinical pharmacists and other healthcare professionals should work collaboratively to minimize DRPs while delivering pharmaceutical care. Pharmaceutical care programs integrating CPR into multidisciplinary patient care teams will increase therapeutic success. This research has taken its place among the limited number of studies conducted by CPR in the literature on the identification, resolution, and prevention of DRPs in the internal medicine wards.

## **AUTHOR CONTRIBUTIONS**

Concept: Y.E.A., M.S.; Design: Y.E.A., M.S.; Control: Y.E.A., M.S.; Sources: - ; Materials: Y.E.A., M.S.; Data Collection and/or Processing: Y.E.A., M.S.; Analysis and/or Interpretation: Y.E.A., M.S.; Literature Review: Y.E.A., M.S.; Manuscript Writing: Y.E.A., M.S.; Critical Review: Y.E.A., M.S.; Other: -

# **CONFLICT OF INTEREST**

The authors declare that there is no real, potential, or perceived conflict of interest for this article.

## ETHICS COMMITTEE APPROVAL

The ethics committee approval has been received from Marmara University non-interventional clinical research ethics committee (No: 09.2022.272, Date: 11.02.2022).

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