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Research article

Medication use and potential drug-drug interactions in a general surgery clinic: A descriptive study

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ABSTRACT

Aim: Perioperative pharmacies optimize medication safety and patient-centered care during surgery. This research aims to assess medication usage and potential drug-drug interactions (pDDIs) in a general surgery clinic.
Methods: This prospective and descriptive research was carried out in a general surgery clinic at a hospital in Turkey. The patients who were admitted for any surgical procedure and stayed for a minimum of 24 h were included in the study. Information on prior medication use as well as pre- and post-operative medications was documented. pDDIs were assessed using the Lexicomp database.
Results: The study involved 95 patients, with a median age of 54 (ranging from 19 to 86). It was found that 66.3 % of the patients had at least one comorbidities. The average number of medications administered during the post-operative period was greater than during the preoperative period (5.7 vs 4.5, $p < 0.0001$). Furthermore, the incidence of pDDIs identified in doctors' orders after surgery was higher compared to before surgery ($p < 0.05$).
Conclusion: In this study, the majority of patients scheduled for surgery had at least one comorbidity. We suspect that the elevated number of medications administered postoperatively could have led to pDDIs Consequently, we expect that clinical pharmacy services will help ensure the safe and rational use of medications in surgical clinics.

Main points

This study is one of the first to evaluate drug use in general surgery clinics in Turkey.
In this study, medication use and potential drug-drug interactions (pDDIs) were examined.
This study will contribute to the development of perioperative pharmacy practices.

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1. Introduction

The American College of Clinical Pharmacy (ACCP) defines "Clinical Pharmacy" as 'the field of pharmacy that deals with the science and practice of rational drug use,' and the clinical pharmacist is defined by the European Society of Clinical Pharmacy (ESCP) as 'a healthcare professional who produces various services to ensure and disseminate the rational and appropriate use of medical products and equipment [1].

A general surgery clinic is a service where hospitalizations occur because of a wide variety of diagnoses; therefore, it has a diverse patient profile. Most patients undergoing surgery use one or more chronic medications. Additionally, during the perioperative period, patients were treated with different medication groups in the hospital, mainly anesthetics, antibiotics, and analgesics. Besides chronic medications from different pharmacological groups, medications used by patients in the perioperative period may cause various drug-related problems, especially pDDIs. Therefore, patients must evaluate treatments from different perspectives [2].

Perioperative pharmacy services are a specialty in clinical pharmacies. This service, which emerged in the early 1980s, includes providing drug stock for access by operating room personnel, monitoring appropriate storage conditions for drugs, checking expiration dates of drugs, calculating drug costs, and keeping track of controlled drugs [3]. However, guidelines defining "perioperative pharmacy" services have been updated by the American Society of Health-System Pharmacists (ASHP), which was first published in 1991 [4–6].

To understand and optimize the role of the pharmacist in the surgical clinic, important differences need to be recognized. For example, the medication use process in the perioperative environment is different from that in the patient care unit, the majority of drugs are high-risk, and off-label use of drugs [6]. The perioperative pharmacist evaluates the suitability of the medications in the patient's prescription, makes recommendations to the patient and healthcare professionals, and provides health consultancy with the current literature.

Many studies have revealed the importance of perioperative pharmacy in general surgery clinic [2,7–10]. In one of these studies, the positive effects of pharmacists in the perioperative environment include a reduction in adverse drug events, a decrease in medication error rates, and an overall improvement in patient outcomes [2]. Another study suggested that clinical pharmacists' participation in drug therapy effectively ensures the rational use of antibiotics in the perioperative period, and further research should be pioneered into how clinical pharmacists work [7,11,12].

Studies have shown that the use of appropriate medications increased significantly after perioperative pharmacist intervention, leading to a reduction in both the patient's length of stay and the cost of hospitalization. The effect of clinical pharmacists' participation in treatment on the appropriate use of antibiotics is also emphasized [9,11]. Clinical pharmacists, in collaboration with other healthcare professionals, support the delivery of treatment and pharmaceutical care at the highest level. To enhance treatment compliance for patients hospitalized during the treatment and discharge processes, clinical pharmacists ensure that treatment is completed with rational pharmacotherapy practices.

Current guidelines for perioperative pharmacy practice have limited information on developing and implementing an appropriate clinical pharmacy program throughout the surgical care continuum for patients [2]. Many studies highlight the importance of clinical pharmacy in international general surgery clinics; however, there are very few studies in our country. This study aimed to evaluate the medication use and pDDIs in a general surgery clinic.

2. Materials and methods

This study was conducted at the General Surgery Clinic of Istanbul (Turkey) between January 01, 2022 and July 1, 2022 (6 months).

2.1. Study objects

The study included patients over 18 years old who were admitted to a general surgery clinic with an anticipated hospital stay of over 48 h. Exclusions were made for patients with conditions listed in their medical records, such as pregnancy, dementia, or cognitive impairment. Written informed consent was secured from all participants.

2.2. Sample size

The sample size of the study was determined according to the Raosoft program, with a margin of error of 95 % in a confidence interval of 5 %; the sample size was calculated as 87, and 95 patients were included in the study. Response distribution was calculated as 50 %, according to the raosoft program recommendation.

2.3. Evaluation of medication use

Sociodemographic information, chronic diseases, and drug use during the hospital stay were obtained from hospital records. Doctor's orders, including the first day before surgery and the first day after surgery, were examined.

2.4. Definition and classification of potential pDDIs

Lexicomp drug interaction database was used in this study. According to existing literature, the Lexicomp drug interaction database provides more precise and selective interaction information compared to other interaction checkers [13–15]. Lexicomp database classifies interactions into five levels: X (avoid combination: evidence indicates that these drugs can interact in a clinically significant way and are generally contraindicated), D (consider treatment modification: evidence suggests that the drugs can interact significantly, requiring a patient-specific evaluation to weigh the benefits and risks of concurrent use), C (monitor treatment: evidence shows potential significant interactions, necessitating a monitoring plan to identify any adverse effects), B (no action required: evidence suggests possible interactions but with minimal or no clinical concern), and A (no known interaction: no interactions identified). In this study, interactions categorized as D and X were reviewed as pDDIs.

2.5. Statistical analysis

The analysis was conducted using the SPSS 15.0 statistical software. Data on patients' sociodemographic characteristics and pDDIs were presented as percentages. Descriptive statistics for continuous variables included measures such as mean, median, standard deviation, and interquartile ranges or percentages. Categorical variables were reported as frequencies and percentages. The distribution characteristics of continuous variables were assessed using the Kolmogorov-Smirnov and Shapiro-Wilk tests. Categorical data were analyzed using the Chi-Square test (Pearson's and Fisher's exact test). Results were considered statistically significant at a 95 % confidence level ($p < 0.05$).

3. Results

The median age of the ninety-five patients participating in the study was 54, with a range from 19 to 86, and 56.8 % were female. Seventy-five percent of the patients had at least one comorbidity, while seventy-two percent had a history of previous surgery. Table 1 details the sociodemographic characteristics of the patients. Additionally, we noted that 43 % of the patients were admitted for surgical procedures related to cancer, as illustrated in Fig. 1.

The most commonly prescribed medications prior to surgery were antibacterials (29.6 %), while proton pump inhibitors (PPIs) (17.2 %) were the most frequently used medications after surgery (see Figs. 2 and 3). A significant positive correlation was found between the total number of medications and age (Spearman's rho = 0.337, $p = 0.001$).

A total of 7 pDDIs were detected in the preoperative orders and the most frequently interacting drug was enoxaparin (Table 2). A total of 18 pDDIs were detected in the postoperative orders and the most frequently interacting drugs were enoxaparin and tramadol (Table 3). A total of 25 potential interactions in the D and X categories were identified. The drugs most frequently involved in interactions were enoxaparin (n = 15), diclofenac (n = 6), and tramadol (n = 6).

The number of pDDIs in category D was significantly higher in postoperative physician orders compared to preoperative orders ($p < 0.05$). A similar pattern was observed for the overall number of pDDIs (see Table 4).

Table 1
Sociodemographic characteristics of patients.

	n	%
Gender		
Female	54	56.8
Male	41	43.2
Alcohol Use		
No	90	94.7
Yes	5	5.3
Smoking		
No	76	80
Yes	19	20
Education status		
*Low	63	66.4
**High	22	33.6
Number of comorbid diseases		
None	25	26.3
Only one	27	28.4
Only two	24	25.3
3 and more	14	14.7
Allergy status		
No	82	86.3
Yes	13	13.7
History of previous surgery		
No	27	28
Yes	68	72

N: number of the patients; * illiterate, graduation from primary and secondary school, ** high school, graduation from university and.

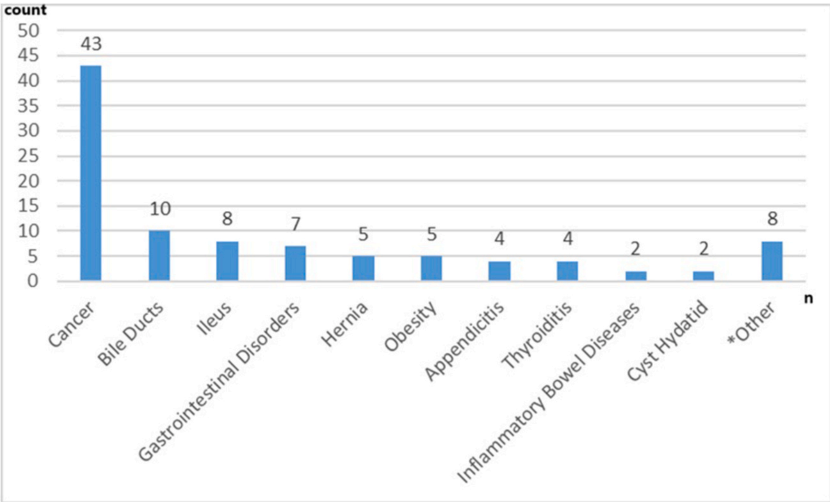

Fig. 1. Distribution of diagnoses of patients included in the study (Other *: Organ transplantation 2 patients, Retroperitoneal lymph gland dissection 1 patient, Stabbing thorax injury 1 patient, Vascular repair 1 patient, Chronic pancreatitis 1 patient, etc, Necrotizing fasciitis 1 patient).

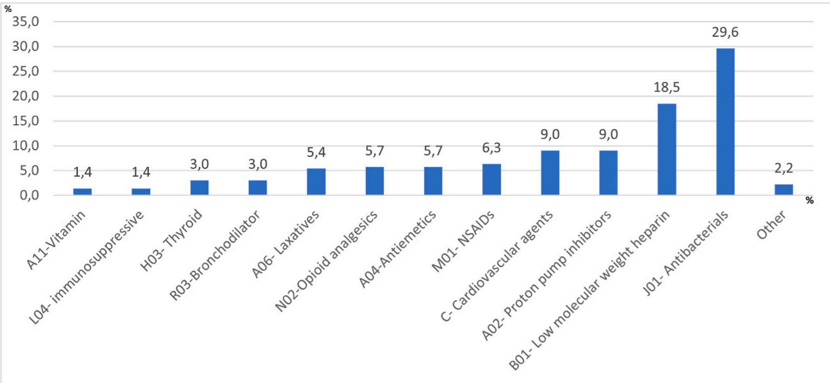

Fig. 2. The Anatomical Therapeutic Chemical (ATC) classification of drugs included in doctor's orders before surgery (percentage value was shown, NSAIDs: non-steroidal anti-inflammatory drugs).

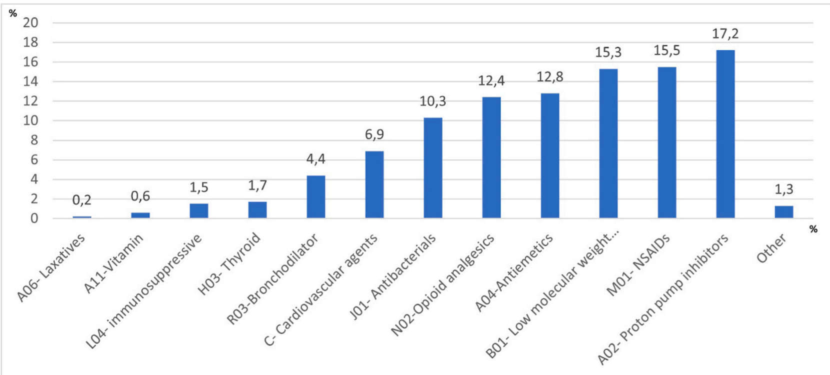

Fig. 3. The Anatomical Therapeutic Chemical (ATC) classification of drugs included in doctor's orders after surgery (percentage value was shown, NSAIDs: non-steroidal anti-inflammatory drugs).

Table 2
Potential drug-drug interactions (pDDIs) in doctor's order before surgery.

Category of pDDIs	Outcome of the pDDIs
D (n = 6)	Enoxaparin + etodolac: Etodolac may increase the anticoagulant effects of enoxaparin (n = 1). Enoxaparin + diclofenac: Diclofenac may increase the anticoagulant effects of enoxaparin (n = 1). Ryzodeg (insulin degludec + insulin aspart) + empagliflozin: SGLT2 inhibitors may increase the hypoglycemic effects of insulin (n = 1). Enoxaparin + escitalopram: Escitalopram may increase the anticoagulant effects of enoxaparin (n = 2). Enoxaparin + aspirin: Antiplatelet medications may increase the anticoagulant effects of enoxaparin (n = 1).
X (n = 1)	Salbutamol + propranolol: Beta-Blockers (Non-selective) may reduce the bronchodilator effect of Beta2-Agonists. Avoid the use of non-selective beta-blockers in patients treated with beta2-agonists. If used concomitantly, closely monitor the decreased bronchodilator effects of the beta2-agonist. (n = 1)

n: number of patients; X: avoid combination; D: consider treatment modification;: Nonsteroidal anti-inflammatory drug; SGLT2: Sodium-glucose co-transporter 2.

Table 3
Potential drug-drug interactions (pDDIs) in doctor's order after surgery.

Category of pDDIs	Outcome of the pDDIs
D (n = 16)	Pheniramine + tramadol: Pheniramine may increase the CNS depressant effect of tramadol. (n = 1) Enoxaparin + sertraline: Sertraline may increase the anticoagulant effect of enoxaparin. (n = 1) Tramadol + lamotrigine: Lamotrigine may increase the CNS depressant effect of tramodol. (n = 1) Enoxaparin + diclofenac: Diclofenac may increase the anticoagulant effect of enoxaparin. (n = 4) Furosemide + diclofenac: Diclofenac may reduce the effect of furosemide. Furosemide may increase the nephrotoxic effect of diclofenac. (n = 1) Tramadol + hyosine: Hyosin may increase the CNS depressant effect of tramadol. (n = 1) Tramadol + petidine: Pethidine may increase the serotonergic effect of tramadol and cause serotonin syndrome. (n = 2) Enoxaparin + escitalopram: Escitalopram may increase the anticoagulant effect of enoxaparin. (n = 2) Enoxaparin + silastazole: Cilastazole may increase the anticoagulant effect of enoxaparin. (n = 1) Tramadol + fentanyl: Fentanyl may increase the CNS depressant effect of tramadol. Fentanyl may increase the serotonergic effect of tramadol. (n = 1) Enoxaparin + etodorac: Etodolac may increase the anticoagulant effects of enoxaparin. (n = 1)
X (n = 2)	Enoxaparin + apixaban: Apixaban may increase the anticoagulant effect of anticoagulants. (n = 1) Trimetazidine + metoclopramide: Metoclopramide may increase the negative/toxic effect of trimetazidine. Specifically, the risk of extrapyramidal symptoms may increase. (n = 1)

n: number of patients; X: avoid combination; D: consider treatment modification; CNS: Central nervous system; NSAIDs: Nonsteroidal anti-inflammatory drug.

Table 4
Evaluation of potential drug-drug interactions (pDDIs).

Category of pDDIs	D (mean ± SE)	X (mean ± SE)	Total (D + X) (mean ± SE)
Before Surgery	0.06 ± 0.03	0.01 ± 0.01	0.07 ± 0.03
After Surgery	0.17 ± 0.05	0.02 ± 0.01	0.19 ± 0.06
p	0.032*	0.566	0.034*

SE: standard error, X: avoid combination; D: consider treatment modification, *: statistical significance (Wilcoxon analysis).

A weak correlation was noted between the number of pDDIs and the total number of drugs administered before and after surgery (Spearman's rho: 0.280, p = 0.007).

4. Discussion

One of the most basic tasks of a clinical pharmacist is the detection, resolution, or prevention of possible and existing problems in drug treatment. Clinical pharmacists make positive contributions to improving rational drug use in various clinics using a multidisciplinary and patient-oriented approach [16]. Pharmacists in the general surgical clinic evaluate the patients' regular medications, list of drugs used during the surgical procedure, and discharge medications together to assess the suitability of the drug indication, dose, etc. They can provide side-effect tracking and answer questions by following up with the patient after discharge [17–19].

Pharmacists in charge of perioperative services know the process of drug use, legal requirements, and drugs used in the perioperative period. With these features, pharmacists optimize perioperative medication use processes and safety, especially with operating room staff. Pharmacists are also well-equipped health personnel to perform other useful activities, from managing medicine supply to taking a medication history and providing consultation during discharge [2].

The duties of the perioperative pharmacists in the guidelines issued by the Australian Hospital Pharmacists Association (Society of

Hospital Pharmacists of Australia, SHPA) include obtaining an accurate history of drugs, ensuring drug treatment consensus, perioperative management of drugs, perioperative management, guiding surgical antimicrobial prophylaxis, and drug optimization, to ensure control of the use of high-risk drugs, to implement drug safety principles, and to ensure quality control and cost-effective maintenance [20].

The presentation of pharmacist information services in a study investigating the development of rational drug use in the general surgical clinic, to ensure rational drug use, and to increase the work efficiency of clinical pharmacists, the effects of the clinical pharmacy management system'' were examined. The results showed that the quality of prescriptions in the general surgical clinic increased, and the rate of antibiotic use decreased by at least 50 %. Thus, it was concluded that the clinical pharmacy management system increased work efficiency and established standards for rational drug use [21].

In a study conducted on patients undergoing obesity surgery, post-surgical pharmacist consultations and physician orders were examined. The need for changes in the formulation and dosage of drugs included in the prescriptions of these patients and 98 % of the recommendations of perioperative pharmacists were accepted [22].

In this study, more than half (56.8 %) of the patients were female, and the median age of the patients was 54 years. In studies conducted in different surgical clinics (orthopedics and cardiovascular surgery), it has been determined that the average age is between 40 and 70 years and 30–60 % of the patient population consists of female patients [23–27]. The population of this study is similar to these studies.

It was determined that 72 % of the patients included in this study had a history of at least one operation, and the prevalence of comorbidities was 73 %. In a study conducted in the surgical clinic, it was determined that 18 % of the patients had a history of operation and the prevalence of comorbidities was 44 % [24]. In the light of these data, it can be thought that the prevalence of comorbidities may be high in patients treated in the surgical clinic. This emphasizes the importance of drug consensus.

When the surgical procedures applied to the patients included in this study were evaluated, it was determined that procedures applied for cancer treatment, especially colorectal cancer, were frequently performed. In a study conducted by Tefera et al. [24] in a general surgery clinic, it was determined that the most common surgical procedure applied to patients was gastrointestinal intervention. This finding is similar to the results of this study.

An analysis of the prescriptions for patients included in this study revealed that the use of antibacterial drugs was 30 % during the preoperative period, while the most commonly prescribed medication after surgery was PPIs (17 %). In the study conducted by Spanakis et al. [27] in the cardiovascular surgery clinic, it was determined that cardiovascular system drugs were frequently used before and after surgery in the surgical clinic. Owing to the variety of drug profiles used in different surgical clinics, prescription examinations by pharmacists will contribute positively to rational drug use.

In this study, the number of drugs used in the postoperative period was higher than that used before surgery. A similar result was observed by Spanakis et al. [27]. In a study conducted in the surgical clinic, it was stated that pDDIs are one of the most important drug-related problems that may arise with an increase in the number of drugs [23]. When the results of this study and the literature data are evaluated, it is thought that an increase in the number of drugs may lead to an increase in the number of pDDIs.

The pDDIs of the drugs in the doctor's order of the patients were evaluated using the Lexicomp database, and 25 pDDIs in the D and X categories were identified. In a study conducted in a surgical clinic, the drugs prescribed by 300 patients were evaluated using the Medscape database, and one contraindicated and seven serious pDDIs were determined [24]. In a study conducted by Rabba et al. [20] with 502 patients in the surgical clinic, pDDIs in patients' prescriptions were examined using the Micromedex database, and at least one pDDIs was detected in 56 % of the patients. It was observed that 53 % of these pDDIs were in the major category, and 0.5 % were in the contraindicated category. In a study conducted by Rodriguez et al. [26] with 370 patients in the surgical clinic, 385 pDDIs were detected in 46 % of prescriptions using the Micromedex database, and approximately half of these interactions (46 %) were in the major interaction category. When the data from this study and other studies in the literature are evaluated, it can be thought that pDDIs rates are high in the surgical clinic.

In this study, the most interacting drugs were enoxaparin, NSAIDs, and tramadol. In the study conducted by Rabba et al. [25], it was determined that the drugs with significant pDDIs were ranitidine, meperidine, bisoprolol and aspirin. As a result of this study, it was stated that antibiotics (metronidazole and ciprofloxacin) and analgesics such as meperidine have the potential to cause pDDIs in surgical patients [25]. In a study by Rodriguez et al. [26], it was determined that the drugs that most involved pDDIs were metronidazole, fluoroquinolone, enoxaparin, NSAIDs and phenytoin. In another study conducted in the general surgery clinic, it was observed that drugs that frequently interact with paracetamol and phenytoin [28]. According to the results of this study and the data of other studies, it can be concluded that the use of antibiotics, LMWH, and NSAIDs in the surgical clinic may cause pDDIs.

Based on the data from this study and existing literature, the importance of clinical pharmacy services in surgical clinics has been highlighted in numerous recent studies. Clinical pharmacists contribute significantly to improving clinical outcomes, particularly through prescription reviews and drug reconciliation. We advocate for prioritizing the training of more pharmacists to work in surgical clinics, as this could enhance patient care globally, particularly in low- and middle-income countries. To encourage pharmacists to pursue advanced clinical training, we believe it would be advantageous to establish a career framework that supports specialization in surgical practice, as well as to integrate more clinical practice opportunities into the pharmacy undergraduate curriculum. Expanding clinical pharmacy practices and education programs to include perioperative pharmacy services would contribute positively to improving patient treatment outcomes. To further develop perioperative pharmacy, we propose organizing educational content at both the undergraduate and graduate levels, ensuring its continuity through in-service training.

Limitations of the study: As this study was conducted during the pandemic period, the interaction with the patient was very limited, and the data were obtained from the patient file and computer. For this reason, there are incomplete data, particularly laboratory data. Second limitation is that the evaluation of drug use was performed only before and after surgery, and the drugs used during the surgical procedure were not included in the evaluation. The third limitation was that, although the use of multiple databases would have enhanced the analysis, time constraints required the use of a single database. Since this study was conducted at a single center, more studies are needed to generalize the results.

CRediT authorship contribution statement

Sevgi Teker Yıldırım: Writing – review & editing, Writing – original draft, Resources, Investigation, Formal analysis, Conceptualization. **Şevket Cumhur Yeğen:** Writing – review & editing, Writing – original draft, Investigation, Conceptualization. **Songül Tezcan:** Writing – review & editing, Writing – original draft, Supervision, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Ethical approval statement

The local ethics committee (Marmara University Clinical Research Ethics Committee-Istanbul/Turkey) approved this prospective and descriptive study (protocol number: 09.2021.1103, Date: October 08, 2021).

Data availability statement

The data that support the findings of this study are available from the corresponding author, [S.T.], upon reasonable request.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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