Interdisciplinary Research in Medical Sciences Specialty
ISSN: 3062-4401
2022, Volume 2, Issue 1, Page No: 97-104

Available online at: www.galaxypub.co/page/journals

Galaxy Publication

Perioperative Medication Patterns and Risk of Drug-Drug Interactions in General Surgery Patients: Insights from a Turkish Hospital

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Received: 12 February 2022; **Revised:** 14 April 2022; **Accepted:** 17 April 2022

ABSTRACT

Perioperative pharmacy services are designed to enhance medication safety and patient-oriented care during surgical procedures. This study set out to review drug use and identify potential drug–drug interactions (pDDIs) within a general surgery department. A prospective, descriptive study was performed in a general surgery service of a Turkish hospital. Individuals admitted for any surgical intervention and hospitalized for at least 24 hours were included. Information regarding chronic medication use, as well as drugs given before and after surgery, was recorded. pDDIs were determined through the Lexicomp database.

A total of 95 participants were evaluated, with a median age of 54 (range: 19–86). Among them, 66.3 % had one or more comorbid conditions. The mean number of drugs ordered postoperatively exceeded that of the preoperative period (5.7 vs. 4.5, $p < 0.0001$). Additionally, pDDIs were more frequently observed in postoperative medication orders than in those written before surgery ($p < 0.05$). Most surgical patients in this study presented with at least one chronic illness. The increased quantity of medications used following surgery may have contributed to the occurrence of pDDIs. Consequently, the integration of clinical pharmacy services is anticipated to promote safer and more rational pharmacotherapy in surgical settings.

Keywords: Drug interactions, Surgery, Medication, Preoperative, Postoperative, Pharmacy

How to Cite This Article: Martin J, Rousseau O, Lambert P. Perioperative Medication Patterns and Risk of Drug-Drug Interactions in General Surgery Patients: Insights from a Turkish Hospital. Interdiscip Res Med Sci Spec. 2022;2(1):97-104. https://doi.org/10.51847/qPZR17CYOc

Introduction

The American College of Clinical Pharmacy (ACCP) defines clinical pharmacy as the discipline focused on the science and application of appropriate medication use, while the European Society of Clinical Pharmacy (ESCP) describes the clinical pharmacist as a healthcare professional who delivers services aimed at promoting the safe and effective utilization of medical treatments and related products [1].

General surgery units accommodate patients hospitalized for many different diagnoses, resulting in a highly varied patient group. A large proportion of individuals undergoing surgery are already on long-term medication regimens. During the perioperative stage, additional therapeutic classes—such as anesthetics, antimicrobials, and analgesics—are commonly administered. When combined with chronic treatments, these drugs may lead to several medication-related concerns, including pDDIs; therefore, a comprehensive evaluation of patient therapy is essential [2].

Perioperative pharmacy represents a subspecialty within clinical pharmacy. Originating in the early 1980s, this role encompasses supplying drugs for operating room use, ensuring proper storage conditions, verifying expiration dates, monitoring controlled substances, and assessing medication-related costs [3]. Updated standards for perioperative pharmacy practice were issued by the American Society of Health-System Pharmacists (ASHP), with the initial version published in 1991 [4–6].

For pharmacists to function effectively within surgical environments, it is important to recognize key distinctions—for instance, the medication-use process differs significantly from that on typical inpatient wards, a substantial proportion of drugs are high-risk, and off-label prescribing is common [6]. Perioperative pharmacists

assess the appropriateness of prescribed drugs, provide recommendations to both patients and clinicians, and offer guidance supported by current evidence.

Past studies have emphasized the value of perioperative pharmacy services in general surgery departments [2, 7–10]. Findings include reductions in adverse drug events, lower rates of medication errors, and overall improvements in patient outcomes [2]. Other research has shown that the involvement of clinical pharmacists supports more rational antibiotic prescribing during the perioperative phase, prompting further investigation into pharmacist-led interventions [7, 11, 12].

Evidence also indicates that appropriate medication use improves significantly when perioperative pharmacists participate, contributing to shorter hospital stays and reduced costs. Their role in ensuring optimal antibiotic use is repeatedly highlighted [9, 11]. Working together with multidisciplinary teams, clinical pharmacists help deliver high-quality therapeutic management and pharmaceutical care. They also guide patients throughout hospitalization and discharge to promote adherence to rational pharmacotherapy.

Despite existing international recommendations, current perioperative pharmacy practice guidelines offer limited detail on designing and implementing comprehensive clinical pharmacy programs across surgical care settings [2]. Although numerous international studies support the role of clinical pharmacists in surgical units, research within Turkey is scarce. This investigation, therefore, aimed to assess medication use and pDDIs in a general surgery clinic.

Materials and Methods

This research was performed in the General Surgery Clinic of Istanbul, Turkey, between January 01, 2022, and July 01, 2022 (a 6-month period).

Study objects

This research involved individuals aged 18 years or older who were admitted to a general surgery ward and expected to remain hospitalized for more than 48 hours. Patients documented as pregnant or diagnosed with dementia or cognitive deficits were excluded. Written informed consent was obtained from every participant.

Sample size

Sample size calculations were performed using the Raosoft software, assuming a 95 % confidence level and a 5 % margin of error. The minimum required sample was estimated at 87, and ultimately, 95 subjects were enrolled. The response distribution was set at 50 % as recommended by the Raosoft program.

Evaluation of medication use

Information regarding demographics, chronic illnesses, and drugs administered during hospitalization was retrieved from medical files. Physician orders from the day immediately preceding surgery and the first postoperative day were reviewed.

Definition and classification of potential pDDIs

The Lexicomp interaction database served as the primary tool for identifying drug interactions. Prior studies indicate that Lexicomp provides highly specific and reliable information when compared with other interaction resources [13–15]. Lexicomp sorts interactions into five categories:

- X: avoid concomitant use—evidence shows clinically significant interactions and combinations are usually inappropriate;
- D: consider adjusting therapy—interactions are meaningful and require individualized evaluation of risks and benefits;
- C: monitor therapy—interactions may be substantial and require a monitoring strategy;
- B: no intervention needed—interactions are possible but rarely clinically relevant;
- A: no identified interaction.

For this study, only interactions labeled D and X were classified as pDDIs.

Statistical analysis

Analyses were performed using SPSS version 15.0. Percentages were used to summarize sociodemographic data and pDDI frequencies. For continuous variables, descriptive metrics included mean, median, standard deviation, and interquartile ranges or percentages. Categorical variables were reported as counts and percentages. The Kolmogorov–Smirnov and Shapiro–Wilk tests were used to evaluate distribution assumptions. Chi-square tests (Pearson or Fisher's exact) were applied to categorical variables. Statistical significance was defined as $p < 0.05$ at a 95 % confidence level.

Results and Discussion

The median age of the 95 participants was 54 years (range: 19–86), and 56.8 % were women. Seventy-five percent had at least one chronic condition, and 72 % reported previous surgical history. **Table 1** presents the demographic and clinical characteristics of the sample. Additionally, 43 % of all admissions were related to cancer surgery **(Figure 1)**.

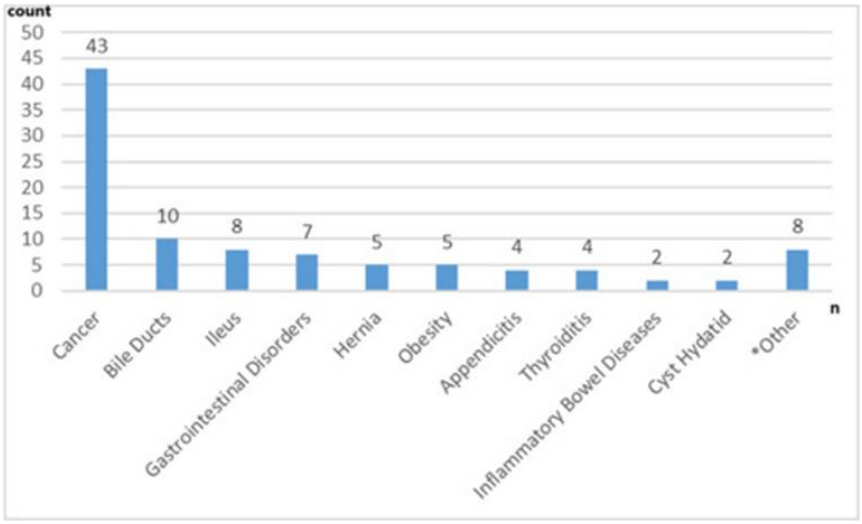

Figure 1. Distribution of diagnoses of the study population (Other ∗: Organ transplantation 2 patients, Retroperitoneal lymph node dissection 1 patient, Stabbing thorax injury 1 patient, Vascular repair 1 patient, Chronic pancreatitis 1 patient, Necrotizing fasciitis 1 patient, etc.).

Table 1. Sociodemographic characteristics of patients.

Characteristic	Category	n	%
Gender	Female	54	56.8
	Male	41	43.2
Alcohol use	No	90	94.7
	Yes	5	5.3
Smoking	No	76	80.0
	Yes	19	20.0
Education level	Low*	63	66.4
	High**	22	33.6
Number of comorbid diseases	None	25	26.3
	One	27	28.4
	Two	24	25.3
	Three or more	14	14.7
Drug or other allergy	No	82	86.3
	Yes	13	13.7
History of previous surgery	No	27	28.4
	Yes	68	71.6

N: number of patients; ∗ illiterate, primary or secondary school; ∗∗ high school, university graduate.

Before surgery, antibacterials constituted the most frequently prescribed drug group (29.6 %), whereas after surgery, proton pump inhibitors (PPIs) were most common (17.2 %), as illustrated in **Figures 2 and 3**. A statistically significant positive correlation was observed between age and total number of medications (Spearman's rho = 0.337, p = 0.001).

Seven pDDIs were identified in preoperative medication orders, with enoxaparin appearing most often **(Table 2)**. Postoperatively, 18 pDDIs were noted, with enoxaparin and tramadol being the most common interacting agents **(Table 3)**. Altogether, 25 pDDIs in categories D and X were recorded. Drugs most frequently implicated included enoxaparin (n = 15), diclofenac (n = 6), and tramadol (n = 6).

Category D interactions occurred significantly more often in postoperative orders compared with preoperative orders ($p < 0.05$). The same trend was seen for the total number of pDDIs **(Table 4)**.

A weak but significant correlation existed between the amount of pDDIs and the total number of medications used both before and after surgery (Spearman's rho: 0.280, p = 0.007).

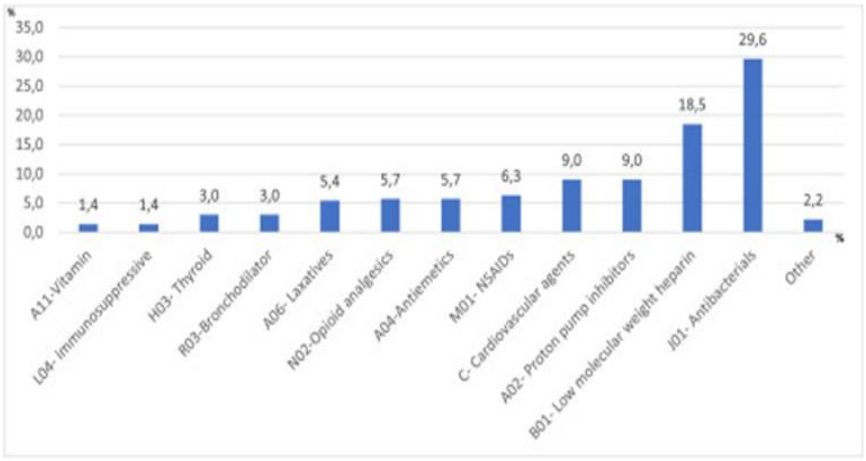

Figure 2. ATC classification of medications prescribed before surgery (percentages shown; NSAIDs: non-steroidal anti-inflammatory drugs).

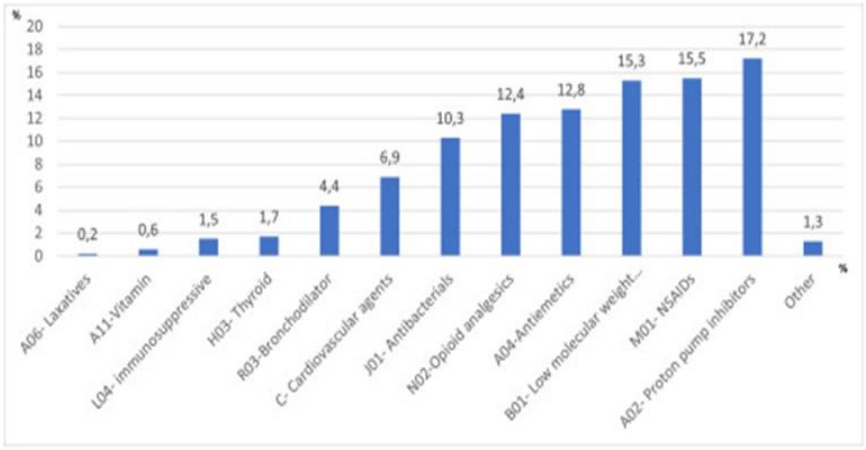

Figure 3. ATC classification of medications prescribed after surgery (percentages shown; NSAIDs: non-steroidal anti-inflammatory drugs).

Table 2. Potential drug–drug interactions (pDDIs) in preoperative physician orders.

pDDI Risk Category	Number of Occurrences	Specific Drug-Drug Interactions and Clinical Effects
Category D (Consider therapy modification)	**n = 6**	- Enoxaparin + etodolac: Etodolac may enhance the anticoagulant effect of enoxaparin (n = 1) - Enoxaparin + diclofenac: Diclofenac may enhance the anticoagulant effect of enoxaparin (n = 1) - Ryzodeg (insulin degludec + insulin aspart) + empagliflozin: Empagliflozin may increase the hypoglycemic effect of insulin (n = 1) - Enoxaparin + escitalopram: Escitalopram may enhance the anticoagulant effect of enoxaparin (n = 2)

		- Enoxaparin + aspirin: Aspirin may enhance the anticoagulant effect of enoxaparin (n = 1)
Category X (Avoid combination)	**n = 1**	- Salbutamol + propranolol: Non-selective beta-blockers may diminish the bronchodilator effect of beta$_2$-agonists. Avoid concomitant use; if unavoidable, closely monitor for reduced bronchodilator response (n = 1)

n: total patient count; X: combination should be avoided; D: treatment adjustment advised; NSAID: Nonsteroidal anti-inflammatory agent; SGLT2: Sodium–glucose co-transporter 2.

Table 3. Possible drug–drug interactions (pDDIs) identified in postoperative physician orders.

pDDI Risk Category	Number of Occurrences	Specific Drug-Drug Interactions and Clinical Effects
Category D (Consider therapy modification)	**n = 16**	• Pheniramine + tramadol: Pheniramine may enhance the CNS depressant effect of tramadol (n = 1) • Enoxaparin + sertraline: Sertraline may enhance the anticoagulant effect of enoxaparin (n = 1) • Tramadol + lamotrigine: Lamotrigine may enhance the CNS depressant effect of tramadol (n = 1) • Enoxaparin + diclofenac: Diclofenac may enhance the anticoagulant effect of enoxaparin (n = 4) • Furosemide + diclofenac: Diclofenac may reduce the diuretic effect of furosemide and increase its nephrotoxic potential (n = 1) • Tramadol + hyoscine: Hyoscine may enhance the CNS depressant effect of tramadol (n = 1) • Tramadol + pethidine: Pethidine may enhance the serotonergic effect of tramadol, increasing the risk of serotonin syndrome (n = 2) • Enoxaparin + escitalopram: Escitalopram may enhance the anticoagulant effect of enoxaparin (n = 2) • Enoxaparin + cilostazol: Cilostazol may enhance the anticoagulant effect of enoxaparin (n = 1) • Tramadol + fentanyl: Fentanyl may enhance both the CNS depressant and serotonergic effects of tramadol (n = 1) • Enoxaparin + etodolac: Etodolac may enhance the anticoagulant effect of enoxaparin (n = 1)
Category X (Avoid combination)	**n = 2**	• Enoxaparin + apixaban: Apixaban may significantly increase the anticoagulant effect of enoxaparin (n = 1) • Trimetazidine + metoclopramide: Metoclopramide may increase the risk of extrapyramidal symptoms and parkinsonian-like effects of trimetazidine (n = 1)

n: total patient count; X: do not combine; D: consider altering therapy; CNS: central nervous system; NSAIDs: Nonsteroidal anti-inflammatory agents.

Table 4. Assessment of potential drug–drug interactions (pDDIs).

Period	Category D (Consider therapy modification)	Category X (Avoid combination)	Total pDDIs (D + X)
	Mean ± SE	Mean ± SE	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-value	0.032*	0.566	0.034*

SE: standard error; X: avoid using together; D: modification recommended; ∗: significant finding based on Wilcoxon testing.

A central responsibility of clinical pharmacists is to detect, correct, and prevent actual or anticipated medication-related issues. Their involvement—grounded in multidisciplinary and patient-focused practice—supports appropriate pharmacotherapy across clinical settings [16]. Within general surgical units, pharmacists review chronic therapies, intraoperative medications, and discharge treatments collectively to verify indication accuracy, dosage suitability, and other key parameters. They also monitor adverse effects and provide answers to patient inquiries following discharge [17–19].

Pharmacists working in perioperative care are familiar with medication workflows, regulatory considerations, and drugs used before, during, and after surgery. These competencies allow them to enhance safety and streamline medication processes in collaboration with operating room teams. Their role additionally includes supply management, obtaining medication histories, and providing discharge counseling [2].

According to the guidance published by the Society of Hospital Pharmacists of Australia (SHPA), perioperative pharmacists are responsible for accurate medication histories, ensuring agreement on drug therapy, coordinating perioperative drug management, guiding antimicrobial prophylaxis for surgery, optimizing therapy, overseeing high-risk medication use, applying safety standards, and promoting cost-effective and quality-controlled care [20].

In research focused on rational drug use within a general surgery ward, the impact of implementing a clinical pharmacy management system on pharmacists' efficiency and prescribing quality was examined. The findings

demonstrated improved prescription quality and a reduction of at least 50 % in antibiotic utilization. The study concluded that such systems enhance workflow and establish structured approaches to rational pharmacotherapy [21].

A separate investigation involving individuals who underwent obesity-related operations evaluated postoperative pharmacist reviews and physician orders. The study found that nearly all (98 %) of perioperative pharmacist recommendations—concerning dosage alterations or formulation changes—were incorporated into patient prescriptions [22].

In the present study population, females represented 56.8 %, and the median age was 54 years. Research conducted in other surgical disciplines (orthopedic and cardiovascular settings) reports age ranges of 40–70 years and female proportions of 30–60 % [23–27], showing demographic consistency with our sample.

Here, 72 % of patients reported at least one prior surgical procedure, and 73 % had comorbid conditions. Another study from a surgical unit noted previous operations in 18 % of patients and comorbidities in 44 % [24]. These comparisons suggest that individuals in surgical settings may exhibit higher comorbidity burdens, underscoring the importance of aligning medication plans.

The review of procedures performed in this study highlighted frequent interventions related to malignancy treatment, especially colorectal surgery. Tefera *et al*. [24] similarly reported gastrointestinal operations as the predominant procedures within general surgery, which aligns with the pattern observed here.

Prescription analysis indicated that antibacterial agents constituted 30 % of medications used preoperatively, whereas PPIs accounted for 17 % of postoperative prescriptions. In the cardiovascular setting, Spanakis *et al*. [27] reported that cardiovascular drugs were the most frequently prescribed both before and after surgery. Given the variability in drug regimens across surgical specialties, pharmacist review of orders remains a crucial contributor to rational medication use.

In this study, the quantity of medications administered after surgery exceeded the amount used beforehand. Spanakis *et al*. [27] reported a comparable pattern. Another investigation conducted in a surgical unit described pDDIs as one of the main medication-related challenges arising when the total number of prescribed agents increases [23]. When considering both the current findings and previous reports, it appears likely that a higher medication count contributes to a rise in pDDIs.

For patients in this study, potential interactions in postoperative medication orders were assessed via the Lexicomp database, which identified 25 pDDIs classified within categories D and X. In a separate surgical-clinic study, prescriptions from 300 individuals were screened using Medscape, revealing one contraindicated interaction and seven serious ones [24]. Rabba *et al*. [20] analyzed prescriptions from 502 surgical patients using Micromedex and found at least one pDDI in 56 % of cases; of these, 53 % were considered major and 0.5 % were contraindicated. Rodriguez *et al*. [26] evaluated 370 surgical-clinic patients using the Micromedex system and detected 385 pDDIs in 46 % of the prescriptions, with roughly 46 % of these categorized as major. Synthesizing this study with broader literature suggests that pDDI prevalence tends to be substantial within surgical settings.

The agents most frequently associated with interactions in this study were enoxaparin, NSAIDs, and tramadol. Rabba *et al*. [25] noted that ranitidine, meperidine, bisoprolol, and aspirin were commonly involved in clinically relevant interactions. Their findings also indicated that antibiotics such as metronidazole and ciprofloxacin, along with analgesics like meperidine, may predispose surgical patients to pDDIs [25]. Rodriguez *et al*. [26] reported metronidazole, fluoroquinolones, enoxaparin, NSAIDs, and phenytoin as the principal contributors to pDDIs. Another general-surgery study found that paracetamol and phenytoin frequently participated in interactions [28]. When this study's results are viewed alongside other reports, it appears that antibiotics, LMWH, and NSAIDs commonly contribute to pDDIs in surgical care.

Drawing from both the present findings and previously published work, many recent analyses emphasize the critical role of clinical pharmacists in surgical environments. Their involvement—particularly through medication review and reconciliation—has shown meaningful improvements in patient outcomes. We recommend expanding the number of pharmacists trained specifically for surgical settings, as this may bolster care quality worldwide, especially in low- and middle-income regions. Establishing a career development pathway focused on surgical specialization, supplemented by expanded hands-on training opportunities during pharmacy education, may help cultivate greater clinical expertise. Incorporating perioperative pharmacy into both educational programs and ongoing professional development would further strengthen treatment results. To promote continued growth in perioperative practice, we suggest structuring relevant training at undergraduate, postgraduate, and in-service levels.

Study limitations

Because this research was performed during the pandemic, direct patient engagement was minimal, and information was collected solely from electronic records, resulting in missing data, including laboratory parameters. A second limitation is that medication assessment covered only preoperative and postoperative use, excluding intraoperative agents. A third constraint was the reliance on a single database due to time limitations, even though using multiple sources would have enhanced evaluation. As the study was conducted in a single institution, additional research is required to confirm the generalizability of the findings.

Acknowledgments: We thank all the patients, doctors and nurses who helped us with this study.

Conflict of Interest: None

Financial Support: None

Ethics 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).

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