

## RISK FACTORS FOR POTENTIAL DRUG-DRUG INTERACTIONS OF ANALGESICS IN HOSPITALIZED UROLOGICAL PATIENTS

Milovanović Ivan,<sup>1,2</sup> Pejčić Ana,<sup>3</sup> Kovačević Zoran,<sup>4</sup> Janićijević Katarina<sup>5</sup>

<sup>1</sup> University of Kragujevac, Faculty of Medical Sciences, Kragujevac, Serbia

<sup>2</sup> University Clinical Centre Kragujevac, Clinic of Urology, Kragujevac, Serbia

<sup>3</sup> University of Kragujevac, Faculty of Medical Sciences,

Department of Pharmacology and Toxicology, Kragujevac, Serbia

<sup>4</sup> University Clinical Centre Kragujevac, Clinic of Nephrology, Kragujevac, Serbia

<sup>5</sup> University of Kragujevac, Faculty of Medical Sciences, Department of Social Medicine, Kragujevac, Serbia

Primljen/Received: 04. 11. 2025.

Prihvaćen/Accepted: 28. 12. 2025.

Online First: January 2026.

**Abstract: Objective:** To evaluate potential drug–drug interactions (pDDIs) involving analgesics in hospitalized urological patients and identify risk factors influencing their number.

**Methods:** This study involved a post hoc analysis based on data obtained from a retrospective observational cohort clinical study conducted at the Clinic of Urology, University Clinical Centre Kragujevac, Serbia. Of the original 220 patients, 191 who received analgesics were included. Daily pharmacotherapy data, along with demographic and clinical characteristics, were collected, while pDDIs were identified and classified using the Lexicomp Interaction Checker. Descriptive statistics were used to summarize the data. Multiple linear regression with backward elimination was used to identify independent predictors of the number of pDDIs.

**Results:** Analgesic-related pDDIs were detected in 175 patients (91.6%). Non-steroidal anti-inflammatory drugs (NSAIDs) were prescribed to 173 patients (90.6%), opioids to 53 (27.7%), and paracetamol to 54 (28.3%). The mean number of pDDIs per patient was  $5.5 \pm 5.5$  (range 0–30). Category X interactions most frequently included NSAID combinations (diclofenac + ketorolac, ketorolac + metamizole), while category D interactions frequently involved enoxaparin + ketorolac and opioid–benzodiazepine pairs. Category C interactions were dominated by NSAID + potassium chloride and tramadol + ondansetron or atropine combinations. Multiple regression analysis identified diabetes, a higher number of prescribed drugs, and the use of NSAIDs or opioids as positive predictors of the number of pDDIs, whereas a cancer diagnosis was associated with a lower number.

**Conclusion:** Analgesic-related pDDIs affect the majority of hospitalized urological patients. Avoiding high-risk combinations, close monitoring, and multidisciplinary medication review in patients with risk factors may help reduce preventable harm.

**Keywords:** analgesics, drug–drug interactions, urology, hospitalized patients.

### INTRODUCTION

The safe and effective use of analgesics remains a major challenge in hospitalized patients, particularly in those with complex comorbidities, polypharmacy, and specialist-care needs (1). Drug–drug interactions (DDIs) occur when the response or exposure to one drug is altered by the concurrent administration of another drug, which may result in a change in the therapeutic effect or the development of adverse drug reactions, while the term potential DDI (pDDI) refers to the “co-prescription of two drugs known to interact” (2).

Within hospital settings, urological patients represent a subset of inpatients who may be particularly vulnerable to analgesic-related interactions (3, 4). These patients frequently undergo surgical procedures, often have renal impairment, and receive analgesics alongside diverse urologic and non-urologic pharmacotherapies (5). A recent retrospective cohort study in a urology clinic reported that 95% of patients had at least one pDDI during hospitalization, while risk factors included duration of hospitalization, surgical interventions, arrhythmias, dementia, renal failure, cancer, number of prescribed drugs, and various pharmacological drug classes, including some analgesics (3). Despite these findings, there is limited published

work focusing specifically on analgesic-related pDDIs in hospitalized urological populations.

Prescribing practices in analgesic therapy can also influence DDI risk (6, 7, 8). In a study from a tertiary hospital in Pakistan, analgesics were often prescribed without formal pain-intensity assessment, and every prescription was found to include at least one pDDI, with 60% of interactions rated as major (6). These findings emphasize that prescribing context, analgesic selection, monitoring, and patient-level characteristics may all contribute to pDDI development (6,7). Comparable patterns have been observed in outpatient settings (9, 10, 11). Several population-based studies conducted in primary care and community pharmacy practice have reported that analgesics are among the drug groups most frequently implicated in pDDIs in ambulatory patients, particularly non-steroidal anti-inflammatory drugs (NSAIDs) co-prescribed with anti-hypertensives, antithrombotics, or other nephrotoxic agents (9, 10, 11). For example, in a national cohort study from Poland, analgesic-related pDDIs affected 6.47% of the entire population, with the most common combinations involving NSAIDs and antihypertensive therapy (9). In family medicine clinics in Mexico City, approximately 80% of ambulatory adults aged  $\geq 50$  years receiving non-opioid analgesics had at least one pDDI, while older age, cardiovascular disease, and the use of  $\geq 5$  medications were significant predictors (10). A more recent community-pharmacy study similarly identified clinically relevant interactions between NSAIDs and antithrombotics, reinforcing that polypharmacy and long-term analgesic use also drive pDDI risk in non-hospital settings (11).

## AIM

The aim of this study was to evaluate pDDIs involving analgesics in hospitalized urological patients and to identify independent risk factors influencing their number. By focusing on this specialized inpatient population, we aim to generate evidence to support safer analgesic prescribing, strengthen interdisciplinary collaboration across urology, pharmacy, and pain management, and ultimately reduce preventable harm associated with pDDIs.

## MATERIAL AND METHODS

### Study design

This study involved a post hoc analysis based on data obtained from a retrospective observational cohort clinical study conducted at the Clinic of Urology of the University Clinical Centre Kragujevac, a public tertiary care hospital in Kragujevac, Serbia (3). The primary aim of the original study was to evaluate pD-

DIs and the factors influencing their number among hospitalized urological patients (3), while this post hoc analysis focused on pDDIs involving analgesics. Ethical approval was granted by the Ethics Committee of the University Clinical Centre Kragujevac prior to the initiation of the study (3).

### Selection criteria and study sample

The original cohort included all consecutive patients admitted to the Clinic of Urology between January 1 and December 28, 2023, who had urological conditions, including but not limited to urinary tract infections, male genital tract infections, urinary tract tumors, male genital tract tumors, benign prostatic hyperplasia, and urinary stones (3). Eligible patients were those aged over 18 years who received at least two medications during a hospital stay lasting at least 48 hours, while patients hospitalized for organizational reasons, pregnant patients, and those with incomplete medical documentation were excluded (3). The original study population consisted of 220 patients (3), and for this post hoc analysis aimed at evaluating pDDIs involving analgesics, 191 patients who received analgesic therapy during hospitalization were identified and included in the analysis.

### Data collection

Data were collected from the patients' medical records. Pharmacotherapy data for each day of hospitalization (all drugs prescribed to the patient during each day of hospital treatment), along with demographic and clinical characteristics, were collected. The following variables were considered: age, gender, length of hospital stay (in days), primary urological pathology (reason for admission), comorbidities, Charlson Comorbidity Index, occurrence of infection during hospitalization, surgery during hospitalization, endoscopic procedure during hospitalization, transfusion of blood or blood products during hospitalization, documented drug allergies, pharmacotherapy data (number of prescribed drugs as a continuous variable, number of prescribed therapeutic subgroups [Anatomical Therapeutic Chemical (ATC) Classification level 2], prescribed pharmacological drug classes, and number of physicians prescribing drugs during hospitalization), and interaction-checker data (number and description of pDDIs). The pDDI, which served as the outcome variable, was defined as the co-prescription of two drugs known to interact (2, 3). Identification and classification of pDDIs were performed using the Lexicomp Interaction Checker, a commercial drug-interaction database with a paid subscription, which categorizes interactions according to the following risk

ratings: X (Avoid combination), D (Consider therapy modification), C (Monitor therapy), B (No action needed), and A (No known interaction) (3).

### Statistical analysis

All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS), version 18. Descriptive statistics were used to summarize the data. Measures of central tendency (mean, median) and dispersion (standard deviation and range) were calculated for continuous variables, while categorical variables were expressed as frequencies and percentages. The influence of potential risk factors on the number of analgesic-related pDDIs per patient was assessed using univariate linear regression and multiple linear regression with backward elimination, applying a probability of  $F \leq 0.1$  for variable removal. In this procedure, all potential predictor variables were initially included in the model and subsequently removed one at a time, beginning with the variable showing the highest p value, until only predictors with  $p \leq 0.1$  remained. Dichotomous categorical variables were coded as 0 and 1, where 0 indicated the absence of a qualitative attribute and 1 indicated its presence, except for gender, where 0 represented female and 1 represented male. The statistical validity of the regression model was evaluated using analysis of variance (F value) and the coefficient of determination ( $R^2$ ), which indicated the percentage of variance in the outcome (number of pDDIs per patient) explained by the model. The effects of individual risk factors were interpreted using their regression coefficients (B) with

corresponding 95% confidence intervals. A p value of less than 0.05 was considered statistically significant.

## RESULTS

Characteristics of the study population are shown in Table 1. Some form of urological cancer was the main pathology in 77 patients (40.3%), including bladder cancer ( $n = 46$ ; 24.1%), prostate cancer ( $n = 15$ ; 7.9%), kidney cancer ( $n = 15$ ; 7.9%), and testicular cancer ( $n = 3$ ; 1.6%); two patients had cancer in two organs. The remaining urological diagnoses were distributed as follows: benign prostatic hyperplasia ( $n = 55$ ; 28.8%), infections ( $n = 32$ ; 16.8%), hematuria ( $n = 22$ ; 11.5%), calculosis ( $n = 23$ ; 12.0%), hydronephrosis ( $n = 17$ ; 8.9%), urinary retention ( $n = 11$ ; 5.8%), hydrocele ( $n = 8$ ; 4.2%), urethral stricture ( $n = 5$ ; 2.6%), renal colic ( $n = 5$ ; 2.6%), and other diagnoses ( $n = 8$ ; 4.2%). Additionally, eight patients (4.2%) had non-urological cancers, bringing the total number of patients with any form of cancer to 85 (44.5%).

NSAIDs were prescribed to 173 patients (90.6%), paracetamol to 54 patients (28.3%), and opioid analgesics to 53 patients (27.7%). Analgesic-related pDDIs were detected in 175 patients (91.6%). By category, X pDDIs occurred in 30 patients (15.7%), D in 62 (32.5%), C in 167 (87.4%), and B in 67 (35.1%). The overall mean  $\pm$  standard deviation (range) number of analgesic-related pDDIs per patient was  $5.5 \pm 5.5$  (0–30), with category-specific means of  $0.3 \pm 0.6$  (0–3) for X,  $0.8 \pm 1.6$  (0–9) for D,  $3.7 \pm 3.7$  (0–21) for C, and  $0.6 \pm 1.1$  (0–9) for B.

**Table 1.** Characteristics of the study population ( $n = 191$ )

Variable	Mean $\pm$ standard deviation; median (range) or number (%)
<b>Age (years)</b>	$65.8 \pm 12.4$ ; 68.0 (23–90)
<b>Gender (male/female)</b>	145 (75.9%)/46 (24.1%)
<b>Duration of hospitalization (days)</b>	$7.7 \pm 6.1$ ; 6.0 (2–31)
<b>Comorbidities</b>	
Charlson Comorbidity Index	$1.4 \pm 1.3$ ; 2.0 (0–6)
Hypertension	116 (60.7%)
Renal failure	47 (24.6%)
Diabetes	49 (25.7%)
Hyperlipidemia	33 (17.3%)
Arrhythmias	18 (9.4%)
Psychiatric disorders	13 (6.8%)
Ischemic heart disease	13 (6.8%)
Chronic obstructive pulmonary disease	10 (5.2%)
Non-urological cancer	8 (4.2%)

Dementia	3 (1.6%)
Asthma	1 (0.5%)
Cerebrovascular diseases	1 (0.5%)
Heart failure	1 (0.5%)
<b>Development of infection during hospitalization</b>	30 (15.7%)
<b>Endoscopic procedure during hospitalization</b>	10 (5.2%)
<b>Surgery during hospitalization</b>	148 (77.5%)
<b>Transfusion of blood or blood products during hospitalization</b>	52 (27.2%)
<b>Number of physicians prescribing drugs to the patient during hospitalization</b>	$2.5 \pm 1.1$ ; 2.0 (1–6)
<b>Information about drug allergy in the medical documentation</b>	19 (9.9%)
<b>Number of prescribed drugs</b>	$13.1 \pm 5.6$ ; 12.0 (3–33)
<b>Number of different therapeutic subgroups prescribed (2<sup>nd</sup> level of ATC classification)</b>	$9.0 \pm 3.4$ ; 9.0 (3–20)
<b>Pharmacological drug classes</b>	
5-alpha-reductase inhibitors	9 (4.7%)
Angiotensin-converting enzyme inhibitors	79 (41.4%)
Acetylcholinesterase inhibitors	85 (44.5%)
Alpha-blockers	25 (13.1%)
Antiarrhythmic drugs	17 (8.9%)
Antibiotics	190 (99.5%)
Anticoagulants	61 (31.9%)
Antidepressants	8 (4.2%)
Antidiabetics	59 (30.9%)
Antiemetics	84 (44.0%)
Antiepileptics	6 (3.1%)
Antiplatelets	11 (5.8%)
Antipsychotics	6 (3.1%)
Beta-blockers	88 (46.1%)
Benzodiazepines	34 (17.8%)
Bronchodilators	24 (12.6%)
Calcium channel blockers	45 (23.6%)
Corticosteroids	23 (12.0%)
Diuretics	72 (37.7%)
Hypouricemics	25 (13.1%)
Iron preparations	7 (3.7%)
Nitrates	10 (5.2%)
Proton pump inhibitors	128 (67.0%)
Products containing calcium	55 (28.8%)
Products containing potassium	149 (78.0%)
Statins	31 (16.2%)

Table 2 shows the most frequently detected NSAID-related pDDIs, while Table 3 shows the most frequently detected opioid-related pDDIs. The most common category X NSAID-related pDDIs involved co-administra-

tion of NSAIDs, particularly diclofenac + ketorolac and ketorolac + metamizole, both associated with an increased risk of bleeding and serious NSAID-related adverse effects. There were no opioid-related category X pDDIs.

**Table 2.** Description and frequency of most frequently detected potential drug-drug interactions of nonsteroidal anti-inflammatory drugs

Combination	Possible clinical outcome	Number (%)
<b>X (Avoid combination)</b>		
Diclofenac + ketorolac	Enhanced adverse/toxic effects (additive risk of bleeding and serious NSAID-related adverse effects).	20 (10.5%)
Ketorolac + metamizole	Enhanced adverse/toxic effects (additive risk of bleeding and serious NSAID-related adverse effects).	17 (8.9%)
<b>D (Consider therapy modification)</b>		
Enoxaparin + ketorolac	Enhanced anticoagulant effect of enoxaparin.	25 (13.1%)
Furosemide + ketorolac	Reduced diuretic effect of furosemide and enhanced nephrotoxic effect of ketorolac.	17 (8.9%)
<b>C (Monitor therapy)</b>		
Ketorolac + potassium chloride	Enhanced hyperkalemic effect of potassium salts.	81 (42.4%)
Diclofenac + potassium chloride	Enhanced hyperkalemic effect of potassium salts.	44 (23.0%)
<b>B (No action needed)</b>		
Amlodipine + ketorolac	Reduced antihypertensive effect of amlodipine.	24 (12.6%)
Amlodipine + diclofenac	Reduced antihypertensive effect of amlodipine.	13 (6.8%)

**Abbreviations:** NSAID – Nonsteroidal anti-inflammatory drug(s)

**Table 3.** Description and frequency of most frequently detected potential drug-drug interactions of opioids

Combination	Possible clinical outcome	Number (%)
<b>D (Consider therapy modification)</b>		
Diazepam + tramadol	Increased risk of central nervous system depression	3 (1.6%)
Bromazepam + tramadol	Increased risk of central nervous system depression	2 (1.0%)
Lorazepam + tramadol	Increased risk of central nervous system depression	2 (1.0%)
Clobazam + tramadol	Increased risk of central nervous system depression	1 (0.5%)
Diazepam + fentanyl	Increased risk of central nervous system depression	1 (0.5%)
<b>C (Monitor therapy)</b>		
Ondansetron + tramadol	Ondansetron may enhance the serotonergic effect of tramadol (it could result in serotonin syndrome) and may diminish the therapeutic effect of tramadol.	40 (20.9%)
Atropine + tramadol	Enhanced adverse/toxic effect of tramadol (increased risk for constipation and urinary retention).	40 (20.9%)
<b>B (No action needed)</b>		
paracetamol + tramadol	Decreased absorption of paracetamol.	7 (3.7%)

Significant predictors from univariate linear regression and from the final step of multiple linear regression evaluating the number of pDDIs involving analgesics are shown in Table 4. In the multiple linear regression model, positive predictors of

the number of analgesic pDDIs, i.e., factors which may increase their rate, were diabetes, number of prescribed drugs, NSAIDs and opioid analgesics. In contrast, cancer was identified as a negative predictor.

**Table 4.** Significant predictors from univariate linear regression and from the final step of multiple linear regression evaluating the number of potential drug-drug interactions involving analgesics

Variable	B	95% CI	p
<b>Univariate linear regression</b>			
Charlson Comorbidity Index	0.816	0.230; 1.402	0.007*
Hypertension	3.370	1.850; 4.891	< 0.001*
Diabetes	2.420	0.669; 4.170	0.007*
Length of hospitalization	0.387	0.270; 0.503	< 0.001*
Surgery during hospitalization	3.750	1.963; 5.536	< 0.001*
Number of physicians who prescribed drugs to the patient during hospitalization	1.368	0.682; 2.055	< 0.001*
Number of prescribed drugs	0.687	0.587; 0.787	< 0.001*
Calcium channel blockers	3.055	1.272; 4.838	0.001*
Diuretics	2.919	1.367; 4.471	< 0.001*
Non-steroidal anti-inflammatory drugs	4.156	1.557; 6.756	0.002*
Opioid analgesics	6.664	5.210; 8.118	< 0.001*
Paracetamol	1.929	0.221; 3.637	0.027*
<b>Final step of multiple linear regression</b>			
Constant	-6.742	-8.613; -4.872	<0.001*
Diabetes	1.672	0.573; 2.771	0.003*
Cancer	-1.049	-2.024; -0.073	0.035*
Number of prescribed drugs	0.514	0.416; 0.612	< 0.001*
Non-steroidal anti-inflammatory drugs	4.724	3.100; 6.349	< 0.001*
Opioid analgesics	4.544	3.330; 5.757	< 0.001*
R <sup>2</sup> ; F (p)	0.646; 67.599 (< 0.001*)		

**Abbreviations:** pDDIs – potential drug-drug interactions, B – Unstandardized coefficient; CI – Confidence interval; Constant – model intercept (predicted value of the outcome when all predictors equal zero); F (p) – F-statistic (test statistic used to assess whether the overall regression model is statistically significant) and the probability value associated with it; p – Statistical significance; R<sup>2</sup> – Coefficient of determination (indicates the percentage of variance in the outcome); \*Statistically significant ( $p < 0.05$ ). List of variables entered in multiple linear regression analysis: age, gender, drug allergy noted in the medical documentation, Charlson Comorbidity Index, renal colic, hypertension, diabetes, cancer, length of hospitalization, surgery during hospitalization, development of infection during hospitalization, number of physicians who prescribed drugs to the patient during hospitalization, number of prescribed drugs, calcium channel blockers, diuretics, non-steroidal anti-inflammatory drugs, opioid analgesics, paracetamol.

## DISCUSSION

Analgesic-related pDDIs occurred in more than 90% of patients, indicating that interaction-relevant co-prescribing is not occasional but rather a routine pharmacotherapeutic reality in this clinical setting. Although most interactions were classified as category C (Monitor therapy), clinically relevant category X (Avoid combination) and category D (Consider therapy modification) interactions were also recorded. These latter categories represent combinations for which therapy modification or complete avoidance is recommended, carrying more direct implications for clinical decision-making. Notably, many of the highest-frequency category X and D pDDIs involved combinations of ketorolac with other NSAIDs or with

drugs associated with bleeding risk or nephrotoxicity, while category C interactions were dominated by NSAID–potassium chloride combinations, consistent with potential hyperkalaemia risk. Multiple regression analysis showed that diabetes, a higher number of prescribed drugs, NSAID use, and opioid use independently predicted higher pDDI counts, whereas cancer diagnosis was associated with lower counts.

The findings of this study highlight several critical prescribing considerations that physicians should observe to minimize the risk of clinically significant pDDIs. NSAID co-administration represents the highest-risk interactions (category X) and should be strictly avoided due to the additive potential for gastrointestinal bleeding, renal injury, and other serious NSAID-related adverse effects (12, 13). Concomitant

use of two NSAIDs magnifies cyclooxygenase inhibition, leading to a more profound reduction in protective gastrointestinal prostaglandins, which play a crucial role in maintaining mucosal blood flow, stimulating mucus and bicarbonate secretion, and promoting epithelial repair (14). When prostaglandin synthesis is markedly suppressed by the concurrent use of two NSAIDs, the gastric and duodenal mucosa becomes significantly more susceptible to injury, thereby increasing the risk of serious gastrointestinal complications, including ulceration, bleeding, and perforation (14). Large observational studies and systematic reviews have shown markedly elevated upper gastrointestinal bleeding risk with NSAID exposure, with ketorolac among the agents carrying particularly high gastrototoxicity (15, 16). Furthermore, NSAIDs inhibit cyclooxygenase and reduce the synthesis of key renal prostaglandins, which are essential for maintaining renal blood flow and glomerular filtration (17). By disrupting this prostaglandin-mediated autoregulatory mechanism, NSAIDs diminish the kidney's ability to preserve adequate filtration pressure, thereby increasing susceptibility to reduced renal perfusion and precipitating acute kidney injury (17).

Similarly, combinations of anticoagulants and NSAIDs and loop diuretics, such as enoxaparin + ketorolac and furosemide + ketorolac (category D), warrant careful evaluation and, where possible, therapy modification, given the potential risk of bleeding or nephrotoxicity and reduced diuretic efficacy (18, 19). Concurrent use of anticoagulants and NSAIDs significantly increases bleeding risk because NSAIDs impair gastrointestinal mucosal protection while anti-coagulants inhibit clot formation, so even minor mucosal lesions may lead to serious bleeding (18). Loop diuretics such as furosemide reduce intravascular volume by promoting natriuresis and diuresis, rendering the kidney more dependent on prostaglandin-mediated vasodilation to maintain glomerular filtration (20). The addition of ketorolac (or other NSAIDs) removes this compensatory mechanism, increases the risk of renal injury, and compromises diuretic efficacy (20). Beyond that, NSAIDs can decrease the natriuretic and diuretic effects of loop diuretics by reducing renal prostaglandin-mediated afferent arteriolar dilation and impairing sodium and water excretion (21).

Physicians should also monitor for category C interactions, including NSAIDs with potassium chloride, which can exacerbate hyperkalemia (22, 23). NSAIDs reduce renal prostaglandin synthesis, impairing renal blood flow and decreasing potassium excretion in the distal nephron (23). When potassium chloride is administered concurrently, the reduced ability to excrete potassium can amplify potassium accumulation, there-

by increasing the risk of hyperkalemia (23). Opioid-benzodiazepine combinations likewise require attention because of the risk of enhanced central nervous system depression (18). Co-administration of these agents can lead to profound sedation, respiratory depression, and impaired cognitive or motor function, increasing the risk of falls, accidents, and other adverse events (24, 25). Overall, these results underscore the importance of avoiding high-risk combinations, adjusting or substituting medications when necessary, and closely monitoring patients for signs of adverse effects, particularly in settings of polypharmacy or co-existing comorbidities.

The identification of diabetes, a higher number of prescribed drugs, NSAID use, and opioid use as independent predictors of higher pDDI counts is consistent with previously published inpatient and outpatient studies (3, 26–30). Diabetes is a multidrug state, and diabetic patients are more frequently prescribed drugs that can alter renal hemodynamic autoregulation, such as angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and diuretics, all of which have well-known interaction potential with NSAIDs (19, 31). The number of prescribed drugs has repeatedly been identified as the strongest predictor of pDDIs across clinical settings, and this was also confirmed here, suggesting that medication burden, rather than any single pharmacological class, remains the core system-level driver of interaction exposure (3, 26, 28, 29). Opioid use as a predictor likely reflects the fact that opioid recipients are those with more severe pain syndromes or postoperative recovery, which is often accompanied by multimodal analgesic strategies and co-prescription of sedatives and antiemetics (7, 8, 30).

Interestingly, cancer diagnosis was a negative predictor. This finding may relate to more standardized analgesic protocols in oncology patients, as well as stricter multidisciplinary pharmacovigilance practices among physicians prescribing drugs to these patients. In the outpatient literature, oncological cohorts show higher pDDI risk in primary care because of polypharmacy (32), but in inpatient surgical oncology cohorts, a more streamlined, protocolized analgesic approach has been reported (33), which may align with our finding. This result suggests that oncology-type prescribing may represent an unintended “best practice” model for safer analgesic stewardship even within general urology.

This study has several limitations. First, it was conducted at a single center, which may limit generalizability and reflect center-specific prescribing practices and training characteristics. Second, we evaluated only pDDIs and did not assess clinical outcomes associated with the identified combinations. This is an

inherent limitation, as attribution of actual DDI events in real-world hospital settings is complex and notoriously difficult to ascertain.

## CONCLUSION

In conclusion, analgesic-related pDDIs occurred in the majority of hospitalized urological patients, with NSAIDs and opioids contributing most to clinically relevant interactions. Diabetes, a higher number of prescribed drugs, and the use of NSAIDs or opioids independently increased pDDI risk, whereas cancer diagnosis was associated with lower risk. Careful avoidance of high-risk combinations, regular monitoring, and multidisciplinary medication review may help reduce preventable harm.

## Abbreviations

**DDI(s)** – drug–drug interaction(s)

**pDDI(s)** – potential drug–drug interaction(s)

**NSAID(s)** – non-steroidal anti-inflammatory drug(s)

## Acknowledgments

This research was partially supported by the Ministry of Science, Technological Development and Innovations of the Republic of Serbia, through Grant Agreements with the Faculty of Medical Sciences, University of Kragujevac [contract no. 451-03-65/2024-03/200111, 451-03-136/2025-03/200111, and

451-03-137/2025-03/200111]. The funder had no role in the design, data collection, data analysis, or reporting of this study.

**Conflict of Interest Statement:** The authors declare that there is no conflict of interest related to this paper.

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**Data Availability Statement:** Requests to access the datasets should be directed to the corresponding author.

**Note:** Artificial intelligence was not utilized as a tool in this study.

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## Sažetak

# FAKTORI RIZIKA ZA POTENCIJALNE INTERAKCIJE ANALGETIKA KOD HOSPITALIZOVANIH UROLOŠKIH BOLESNIKA

Milovanović Ivan,<sup>1,2</sup> Pejčić Ana,<sup>3</sup> Kovačević Zoran,<sup>4</sup> Janićijević Katarina<sup>5</sup>

<sup>1</sup> Univerzitet u Kragujevcu, Fakultet medicinskih nauka, Kragujevac, Srbija

<sup>2</sup> Univerzitetski klinički centar Kragujevac, Klinika za urologiju, Kragujevac, Srbija

<sup>3</sup> Univerzitet u Kragujevcu, Fakultet medicinskih nauka, Katedra za farmakologiju i toksikologiju, Kragujevac, Srbija

<sup>4</sup> Univerzitetski klinički centar Kragujevac, Klinika za nefrologiju, Kragujevac, Srbija

<sup>5</sup> Univerzitet u Kragujevcu, Fakultet medicinskih nauka, Katedra za socijalnu medicinu, Kragujevac, Srbija

**Cilj:** Izvršiti evaluaciju potencijalnih interakcija između lekova (PIL) koje uključuju analgetike kod hospitalizovanih uroloških bolesnika i identifikovati faktore koji utiču na njihov broj.

**Metode:** Studija je predstavljala *post hoc* analizu podataka prikupljenih u retrospektivnoj opservacionoj kohortnoj studiji sprovedenoj na Klinici za urologiju Univerzitetskog kliničkog centra Kragujevac, Srbija. Od originalnih 220 bolesnika, u analizu je uključen 191 bolesnik sa propisanim analgeticima. Prikupljeni su podaci o propisanim lekovima, demografskim i

kliničkim karakteristikama, dok su PIL identifikovane i klasifikovane pomoću *Lexicomp* baze. Podaci su obrađeni metodama deskriptivne statistike. Nezavisni prediktori broja PIL identifikovani su pomoću multiple linearne regresije koristeći metodu eliminacije varijabli „unazad“.

**Rezultati:** Potencijalne interakcije analgetika identifikovane su kod 175 bolesnika (91,6%). Nesteroidni antiinflamatorni lekovi (NSAIL) su bili propisani kod 173 bolesnika (90,6%), opioidi kod 53 (27,7%), a paracetamol kod 54 (28,3%). Prosečan broj PIL

po bolesniku bio je  $5,5 \pm 5,5$  (opseg 0–30). Najčešće interakcije kategorije X uključivale su kombinacije NSAIL (diklofenak + ketorolak, ketorolak + metamizol), dok su interakcije kategorije D često uključivale enoksaparin + ketorolak i kombinacije opioid + benzodiazepin. Među interakcijama kategorije C dominirale su kombinacije NSAIL + kalijum-hlorid i tramadol + ondansetron ili atropin. Multiplaregresiona analiza je identifikovala dijabetes, veći broj propisanih lekova i upotrebu NSAIL ili opioida kao pozitivne prediktore

broja PIL, dok je dijagnoza karcinoma bila povezana sa manjim brojem PIL.

**Zaključak:** Potencijalne interakcije analgetika javljaju se kod većine hospitalizovanih uroloških bolesnika. Izbegavanje kombinacija visokog rizika, pažljivo praćenje i multidisciplinarni pregled terapije kod pacijenata sa faktorima rizika mogu pomoći u smanjenju preventabilnih neželjenih ishoda.

**Ključne reči:** analgetici, interakcije između lekova, urologija, hospitalizovani bolesnici.

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**How to cite this article:** Milovanović I, Pejčić A, Kovačević Z, Janićijević K. Risk factors for potential drug-drug interactions of analgesics in hospitalized urological patients. Sanamed. Online First, January 2026. doi: 10.5937/sanamed0-62550

### Correspondence to/Autor za korespondenciju

Ana Pejčić,

Department of Pharmacology and Toxicology, Faculty of Medical Sciences, University of Kragujevac,

Svetozara Markovića 69, 34000 Kragujevac, Serbia,

Email: anapejcić201502@yahoo.com

Phone: +38134306800

### ORCID:

Ivan Milovanović: 0009-0007-0724-9211

Ana Pejčić: 0000-0003-1741-0025

Zoran Kovačević: 0009-0008-8637-1692

Katarina Janićijević: 0000-0001-9815-7716