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DRUG-RELATED PROBLEMS PRIOR TO HOSPITALIZATION ON INTERNAL MEDICINE WARDS

IVANA DRAGANOV[1], ANETA DRNDAREVIĆ[1], MILENA KOVAČEVIĆ[1]*, BRANISLAVA MILJKOVIĆ[1], MILJANKA VUKSANOVIĆ[2, 3], ALEKSANDAR JANKOVIĆ[2, 4], ANA KALABA[5], and SANDRA VEZMAR KOVAČEVIĆ[1]

[1]University of Belgrade – Faculty of Pharmacy,
Department of Pharmacokinetics and Clinical Pharmacy, Belgrade, Serbia
[2]University of Belgrade, School of Medicine, Belgrade, Serbia
[3]University Hospital Medical Center "Zvezdara",
Department of Endocrinology, Diabetes and Metabolic Disorders, Belgrade, Serbia
[4]University Hospital Medical Center "Zvezdara",
Department of Nephrology and Metabolic Disorders with Dialysis, Belgrade, Serbia
[5]University Hospital Medical Center "Zvezdara",
Department of Gastroenterology and Hepatology, Belgrade, Serbia

Abstract: Drug-related hospitalizations pose a significant burden to the health-care system. The aim was to investigate the prevalence of drug-related problems (DRPs) and their association with hospital admissions in five internal medicine wards. The study included patients admitted to the nephrology, cardiology, gastroenterology, endocrinology, and geriatric wards. The Pharmaceutical Care Network Europe classification V9.1 was used for identifying DRPs. In total, 535 patients participated in the study. We identified 954 DRPs (range 1-7) in 80.7% of patients. Most DRPs were identified on the endocrinology, cardiology, and geriatric wards, and they were associated with the efficacy of treatment (71.4%), adverse drug events (10.2%), and unnecessary drug treatment (18.4%). DRPs were associated with the cause of hospitalization in 74.4% of patients on the nephrology ward, 60.1% and 60.6% of patients on the cardiology and endocrinology wards, respectively, whereas this number was lower on the geriatric and gastroenterology wards (26.9% and 8.9%, respectively). Suboptimal drug treatment due to medication omissions was often associated with the potential cause of hospital admission. Focusing on patients with specific diseases and DRPs, rather than reducing the number of medications in primary care, may be potentially rational in an attempt to reduce drug-related hospitalizations.

Keywords: drug-related problems, internal medicine, hospital admission

A drug-related problem (DRP) is, by definition, an event or circumstance that actually or potentially interferes with desired health outcomes [1]. DRPs can be classified in several ways, but they are usually related to efficacy and/or safety of treatment [2]. Lack of treatment efficacy can occur for many reasons. A symptom or illness may not be treated at all, or the treatment may be inappropriate because of the patients' individual characteristics, such as older age or compromised renal/hepatic function, for example [3, 4]. Also, the treatment may be suboptimal if some medications that could be beneficiary to the patient are missing [5]. Treatment safety is usually associated with the (possible) occurrence of adverse drug events, defined as unfavorable medical events related to drug therapy or adverse drug reactions (ADRs) defined as "any response to a drug which is noxious and unintended, and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function." [6-8]. Another DRP that requires attention is the presence of medicines that may be unnecessary, which increases the cost-burden of the patient or/and the health-care system but also increases the risk of ADRs [8].

The relationship between DRPs, which occur in the primary care setting and hospitalizations, has been studied in various patient populations

* Corresponding author: e-mail: milenak@pharmacy.bg.ac.rs

[8-12]. The prevalence of drug-related admissions to hospital ranged between 10-30% and was influenced by age and type of morbidity of the patient [13, 14]. Drug-related hospitalizations pose a significant burden in terms of costs to the health-care system, and studies revealed that costs associated with drug-related morbidity and mortality are increasing rapidly [15-17]. However, these costs may be underestimated because most studies that investigated drug-related hospitalizations were limited to exploring the relationship of ADRs and hospital admissions, whereas only a small number of authors broadened the analysis by including DRPs related to treatment efficacy and overprescribing [8, 9]. Studies show that > 70% of drug-related hospitalizations may be preventable, but first DRPs associated with hospital admissions have to be accurately characterized [8]. The aim of this study was to investigate the prevalence of DRPs and their association with hospital admissions on five internal medicine wards. The findings of our study will help to identify the gaps of prescribing medicines to patients at risk for hospitalization.

EXPERIMENTAL

All patients admitted to the nephrology, cardiology, gastroenterology, endocrinology, and geriatric wards of the University Clinical Hospital Center "Zvezdara" during 2019 were included in the study. The Ethics Committee of the Clinical Hospital Center "Zvezdara", a tertiary care center, approved the research (No. IRB00009457 on April 7th, 2016).

On hospital admission, two clinical pharmacists performed a medication review of all the patients, which consisted of analyses of the patients' medical reports and the complete list of prescribed medicines prior to hospitalization. We used the Medication Appropriateness Index (MAI) for the evaluation of the benefits and risks of each prescribed medicine [18]. Moreover, the European treatment guidelines for each disease, classified by using the International Classification of Diseases-10th Revision (ICD-10) [19], were used to establish the appropriateness of treatment.

For the identification of DRPs we used the PCNE classification for DRPs V9.1 [1], which consists of three primary problem domains: treatment effectiveness, treatment safety, and other. Treatment effectiveness was further classified as: no effect of drug treatment despite correct use (P1.1), effect of drug treatment not optimal (P1.2), and untreated symptom or indication (P1.3). Treatment safety was an issue if an adverse drug event (possibly) occurred (P2.1). Other DRPs included unnecessary drug-treatment (P3.1).

Following the identification of DRPs, we categorized the cause of hospital admission as possibly related or not related with the previous treatment. For example, if a patient with a history of myocardial infarction was admitted to the hospital because of reinfarction, the absence of antithrombotic medicines, beta-blockers, and/or statins in the previous treatment could have been associated with the outcome. Moreover, if a patient was admitted because of worsening of heart failure, but previous treatment lacked inhibitors of the angiotensin-converting enzyme (ACEI) or beta-blockers, this was also categorized as a possible relationship. On the other hand, if the aforementioned patients were admitted to the hospital but the previous treatment was in accordance with the guideline recommendations then, the cause of hospitalization was not associated with DRPs. Moreover, some patients were admitted to the hospital because of acute infections, diagnostic procedures, etc., which was clearly unrelated to their previous treatment. The decision to categorize the cause of hospital admission as possibly related or not related to the previous treatment was made after a discussion and consensus between the clinical pharmacists performing the review and the medical doctors attending the patient on the ward. We used PASW software, version 18.0 (SPSS Inc., Chicago, Illinois) for statistical analysis. Continuous variables in the text and tables are expressed as the median and standard deviation (SD) with a range, whereas categorical data is shown in absolute numbers and percentages. The non-parametric Kruskal-Wallis and the Mann-Whitney U tests were used to compare the number of DRPs among and between the wards. Chi-square or Fisher's exact test for independence was used to associate demographic and clinical variables with DRPs. Binary logistic regression was used to investigate the variables associated with the cause of hospital admission (crude odds ratios). Independent variables that showed statistically significant association with hospitalization in the univariate analysis were entered into the next step. A multivariate logistic regression (method enter) was applied to evaluate the association between the variables and the cause of hospitalization when adjusted for potential confounders (such as the total number of DRPs, number of diagnoses, or the total number of drugs). Results are presented as odds ratio (OR) and their 95% confidence intervals (CI). P-value of < 0.05 was considered statistically significant.

RESULTS

A medication review at hospital admission was performed for 535 patients of whom 55.0% were male and the median age was 70 years. The demographic and clinical characteristics of the cohort are presented in Table 1.

We identified 954 DRPs (median 2.00 (1.41), range 1-7) in 80.7% of patients. There was a significant difference in the number of identified DRPs among the wards. Patients on the gastroenterology ward were associated with significantly lower median number of DRPs prior to admission compared with the other wards ($p < 0.001$). Moreover, the number of DRPs was significantly lower on the nephrology ward compared with endocrinology and geriatrics ($p < 0.05$). In contrast, there was no statistical difference in the number of DRPs among the endocrinology, cardiology, and geriatric wards. Most DRPs were associated with the efficacy of treatment (71.4%), adverse drug events accounted for 10.2% DRPs, and 18.4% unnecessary drug treatment. DRPs and their distribution among the wards are presented in Table 2.

The lack of efficacy of treatment could mostly be associated with the absence of necessary

Table 1. Demographic characteristics and comorbidities of the patients (N = 535).

Characteristic	Value
Age, years, median (range)	70 (20-95)
Sex: male, number (%)	294 (55.0)
The number of medications on admission per patient, mean (SD) (range)	5.0 (3.4) (0-18)
The number of comorbidities per patient, mean (SD) (range)	4.0 (2.1) (1-13)
Most prevalent conditions for hospital admission, number (%)	
Acute ischemic disease	89 (16.6)
Worsening of diabetes	84 (15.7)
Worsening of renal function	55 (10.3)
Worsening of heart failure	37 (6.9)
Infection	28 (5.2)
Bleeding	19 (3.6)
Angina pectoris (stable)	17 (3.2)
Carcinoma	17 (3.2)
Pain	15 (2.8)
Most prevalent comorbidities, number (%)	
Arterial hypertension	308 (57.6)
Diabetes mellitus	203 (37.9)
Angina pectoris	162 (30.3)
Myocardial infarction (history or acute)	152 (28.4)
Renal failure	105 (19.6)
Atrial fibrillation	82 (15.3)
Heart failure	79 (14.8)
Asthma/COPD	71 (13.3)
Anemia	64 (12.0)
Dyslipidemia	53 (9.9)
BPH	39 (7.3)
Crohn's disease	34 (6.4)
Hypothyroidism	32 (6.0)
Dyspepsia	31 (5.8)
Gout	27 (5.0)

BPH – benign prostatic hyperplasia; COPD – chronic obstructive pulmonary disease; SD - standard deviation.

Table 2. Drug-related problems associated with treatment prior to hospital admission.

	Endocrinology N = 94	Gastroenterology N = 90	Geriatrics N = 130	Cardiology N = 143	Nephrology N = 78	Total N = 535
	number (%)					
Effect of drug treatment not optimal	152 (78.8)	41 (46.6)	189 (68.5)	205 (75.6)	72 (57.1)	659 (69.1)
Untreated symptoms or indication	7 (3.6)	4 (4.5)	7 (2.5)	3 (1.1)	1 (0.8)	22 (2.3)
Adverse drug event (possibly) occurring	14 (7.2)	17 (19.3)	27 (9.8)	27 (10.0)	12 (9.5)	97 (10.2)
Unnecessary drug treatment	20 (10.4)	26 (29.5)	53 (19.2)	36 (13.3)	41 (32.5)	176 (18.4)
Total number of DRPs	193	88	276	271	126	954
Number of DRPs per patient, median (SD)	2.00 (1.35)	1.00 (1.15)	2.00 (1.53)	2.00 (1.37)	2.00 (1.29)	2.00 (1.41)
	<0.001	reference	<0.001	<0.001	<0.001	

DRP – drug-related problem; SD – standard deviation.

medication. We identified 630 missing medicines such as statins, ACEI, beta-blockers, aspirin, and others (see Figure 1). In contrast, 233 prescribed medicines could be omitted or substituted with more appropriate medicines.

Patients with diabetes could be associated with the lack of: a statin in the presence of dyslipidemia or age > 40 years (42.9%), an ACEI in the presence of hypertension or increased albumin/creatinine ratio (34.5%), and an antidiabetic drug (17.7%). In patients with a history of myocardial infarction, we observed the absence of statins (37.5%), beta blockers (32.2%), and antithrombotic agents (19.1%). In contrast, in patients with renal failure we observed more medications that could have been omitted such as: benzodiazepines (10.5%), trimetazidine (7.6%), and NSAIDs (3.8%).

DRPs on hospital admission could be associated with the cause of hospitalization in almost half (45.2%) of the patients included in the study. Nevertheless, we observed variability among the wards. On the nephrology ward, 74.4% of patients had a DRP that was characterized as a possible cause of the hospitalization. Similarly, 60.1% and 60.6% of patients may have been hospitalized because of DRPs on the cardiology and endocrinology wards, respectively. Whereas, this number was lower on the geriatric and gastroenterology wards (26.9% and 8.9%, respectively).

Acute ischemic heart disease was the most prevalent (89 patients) cause of admission to the hospital, and the majority of patients (66.3%) were not treated adequately prior to the attack. Poor control or worsening of diabetes was the cause of hospital admission of 84 patients and suboptimal treatment of the disease prior to hospitalization was observed in 72.6% of patients. Worsening of renal failure, heart failure, or angina pectoris were associated with DRPs prior to admission in 80%, 76%, and 65% of patients, respectively. In contrast, infection, bleeding, carcinoma, and pain were causes of hospitalization not frequently (5-31%) associated with DRPs prior to admission.

The cause of hospital admission may be associated with several patient characteristics as shown in Table 3. However, predictors of hospitalization were the ward of admission, suboptimal effect of drug treatment, and the presence of diabetes, history of myocardial infarction and renal failure prior to admission. The number of diagnoses showed a positive association with hospitalization (OR above 1); however, when entered

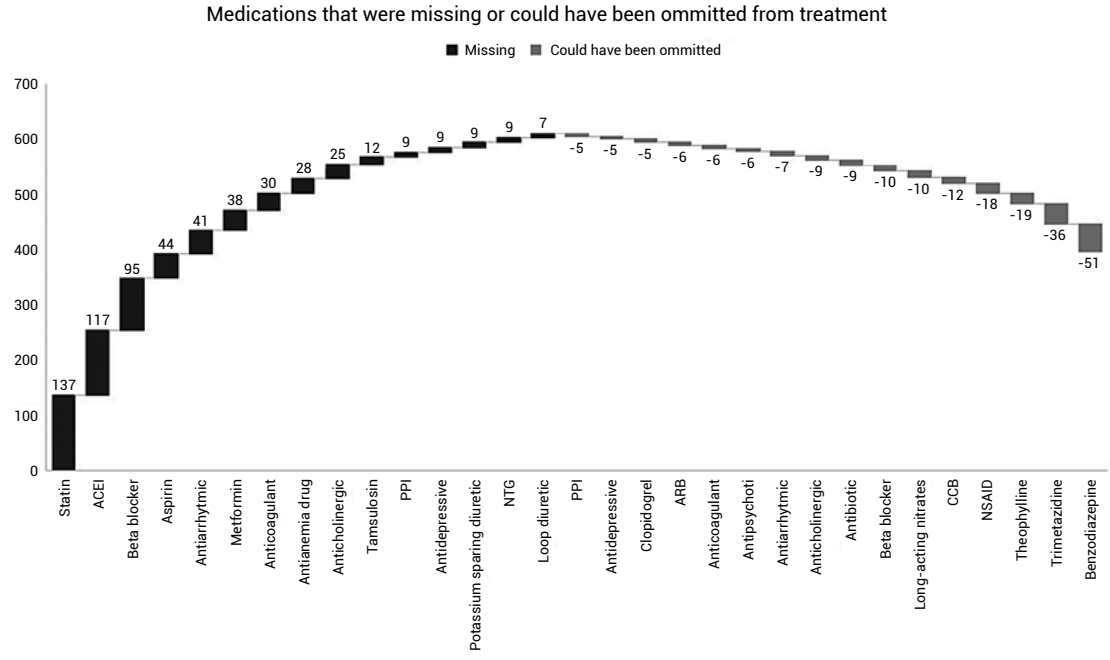

Figure 1. Frequency of medications that were missing or could have been omitted from treatment.

along with other clinical and therapy variables, the adjusted odds ratio was below 1, showing that it was a possible confounder.

DISCUSSION AND CONCLUSION

Although many studies reported a high prevalence of DRPs among patients in primary care or patients admitted to medical wards, not many investigated the potential relationship between the DRPs and the cause of hospital admission. To our best knowledge this is the first study to characterize DRPs and their potential association with hospital admission on five different wards of internal medicine. DRPs on admission to hospital were common among patients in our patient population (80.7%), which is in accordance with previous findings (66-94%) [20-22]. Nevertheless, nearly in the half of the patient population (45.2%) DRPs may have been the reason for hospitalization. Other authors reported somewhat lower and variable (9.1-40%) frequency of DRPs and possibly related hospitalizations [8, 9, 23, 24]. The reason for such discrepancies may be associated with the definition and classification of DRPs, as well as the method used to assess causality of DRPs and hospitalization [23, 25].

In our study, suboptimal drug treatment was the most common DRP (69.1% of patients) and predictive of possible hospitalization cause. This is a unique finding, since other authors reported adverse drug reactions and adherence issues as major risk factors for drug-related hospitalizations [9, 23, 26]. Previous studies usually investigated ADRs as a possible cause of drug-related hospitalization [27]. Some studies included inappropriate drug choice, untreated indications, drug use without indication, non-adherence, drug-drug interactions, and similar DRPs, but only a few studies used the PCNE classification system for DRPs and related it to the possible cause of hospital admission [24, 27-29]. This can partly explain why other authors did not assess the suboptimal effect of drug treatment on hospital admission. The drawback of this approach is that it is debatable if the suboptimal effect of drug treatment is the true cause of hospitalization.

Nevertheless, when we analyzed the causes of the suboptimal effect of drug treatment, they were mainly driven by the lack of presence of medications that could have been beneficial to the patients. We predominantly observed a lack of statins, ACEIs, beta-blockers, and aspirin in our population. This is partly in accordance with other authors who reported antithrombotic agents, drugs used in diabetes, beta-blockers, antiepileptics and diuretics to be involved in DRPs related to treatment efficacy [24, 30, 31]. Moreover, medications that target the cardiovascular, respiratory, central nervous, and endocrine systems, and anti-infectives, were associated with hospital admission due to non-adherence [32]. Drug omissions are recognized as inappropriate drug prescribing in

Table 3. Predictors of hospitalization associated with inadequate treatment in primary care.

	Crude OR (95% CI) a	p-value	Adjusted OR (95% CI) b	p-value
Total number of DRPs	1.75 (1.52-2.02)	<0.001	1.70 (1.44-2.00)	<0.001
Effect of drug treatment not optimal	1.94 (1.64-2.29)	<0.001	1.56 (1.18-2.07)	0.002
Untreated symptoms or indication	1.16 (0.53-2.55)	0.705		
Adverse drug event	1.28 (0.90-1.82)	0.172		
Unnecessary drug treatment	0.97 (0.72-1.30)	0.833		
Ward	1.37 (1.20-1.57)	<0.001	1.48 (1.21-1.80)	<0.001
Age	1.00 (0.99-1.01)	0.916		
Sex	1.10 (0.78-1.55)	0.586		
Number of diagnoses	1.10 (1.01-1.19)	0.022	0.77 (0.68-0.86)	<0.001
Number of medications	1.02 (0.97-1.08)	0.379		
Hypertension	1.35 (0.96-1.91)	0.088		
Heart failure	1.60 (0.99-2.59)	0.055		
Diabetes	2.50 (1.74-3.57)	<0.001	3.80 (2.32-6.21)	<0.001
Renal failure	2.51 (1.61-3.91)	<0.001	3.71 (1.99-6.95)	<0.001
Atrial fibrillation	3.03 (1.83-4.99)	<0.001	3.35 (1.78-6.29)	<0.001
Myocardial infarction	2.51 (1.70-3.69)	<0.001	2.16 (1.33-3.52)	0.002
Asthma/COPD	0.91 (0.55-1.51)	0.712		
Angina pectoris	1.19 (0.83-1.73)	0.347		
Hypothyroidism	0.92 (0.45-1.89)	0.820		
Anemia	1.02 (0.60-1.72)	0.954		
Dyslipidemia	1.16 (0.66-2.05)	0.605		
BPH	0.65 (0.33-1.27)	0.205		
Crohn's disease	0.14 (0.05-0.42)	<0.001	0.25 (0.07-0.88)	<0.001
Gout	0.81 (0.36-7.78)	0.597		
Dyspepsia	0.64 (0.30-1.36)	0.243		

a – results obtained using univariate binary logistic regression; b – results obtained using mutivariate binary logistic regression; DRP – drug-related problem; COPD – chronic obstructive pulmonary disease; BPH – benign prostatic hyperplasia; OR – odds ratio; CI – confidence interval.

the STOPP/START criteria, in particular START which represents the Screening Tool to Alert to Right Treatment in elderly patients, as well as in the PCNE classification system [1, 33]. It can be argued that the lack of presence of medications such as statins in patients with diabetes, or appropriate cardiovascular drugs in patients with cardiovascular diseases may be associated with worsening of the disease or the onset of cardiovascular events [34-36].

However, the reason for the high prevalence of suboptimal treatment in our patients remains unclear. It can be partly explained by the national reimbursement system, which does not follow treatment guidelines accurately, i.e. statins are not reimbursed if used for the primary prevention of cardiovascular events in patients with diabetes. However, the absence of antidiabetic drugs in patients with diabetes, or beta-blockers, statins, and antithrombotic agents in patients with a history of myocardial infarction are difficult to explain and may be related to intentional lack of adherence rather than a lack of prescription. Nevertheless, there are probably many reasons that can contribute to the fact that many patients receive suboptimal treatment in primary care possibly leading to a higher incidence of hospital admissions.

Although many studies associated age, multimorbidity, and/or the number of medications with the prevalence of DRPs, they were not predictors

for potential causes of hospitalization in our study [9, 23, 37, 38]. Our findings were in line with Lea et al., who reported that the number of medications and a higher Charlson Comorbidity Index were not associated with increased odds for drug-related hospitalization [9]. Moreover, we found that the geriatric ward, where comorbidity is mostly prevalent, was among the wards with the lowest drug-related hospitalizations. Such findings are supported by the study of Sommers et al., who found that drug-related hospital admissions were more frequent in somewhat younger patients [23]. This is also consistent with our finding that the number of diagnoses was inversely associated with the risk of drug-related hospitalization.

Furthermore, the association between the wards or diagnoses with the hospitalization was confirmed when controlled for the potential confounders, such as the total number of DRPs or the number of diagnoses. Nevertheless, when we look at the number of DRPs on admission on the geriatric ward, it was among the highest, but the patients were often hospitalized because of pain, bleeding, infections, and other causes that were not associated with previous treatment. In contrast to the geriatric ward, nephrology was associated with a lower overall number of DRPs but the highest prevalence of possibly drug-related hospitalizations. Other studies found prevalent DRPs in hospitalized patients with chronic kidney disease, but the relationship of DRPs with hospitalization causes were not adequately addressed [39-41]. As opposed to other diseases, patients with renal failure were associated with inappropriate drug selection rather than the suboptimal effect of drug treatment. The lower prevalence of DRPs and drug-related hospitalizations in patients on the gastroenterology ward was expected, since these patients were mainly admitted to the hospital because of acute onset of pain in the gastrointestinal tract, caused by infections or ulcerative colitis/Crohn's disease.

Our results indicate that specific DRPs may be related to hospital admission regardless of the number of DRPs in a patient or patient population. DRPs possibly associated with hospitalizations were prevalent on the endocrinology and cardiology wards. This finding is in accordance with other studies, which associated cardiovascular diseases and diabetes with increased risk of DRPs and drug-related hospitalizations [13, 31]. This is not surprising since diabetes, a history of myocardial infarction, and/or atrial fibrillation are associated with complex treatment that requires multiple medications, which increases the risk of DRPs of which some may be related to hospitalization. Interestingly, the number of diagnoses was identified as a confounder in our study, being associated with diseases such as diabetes, renal failure, atrial fibrillation, or myocardial infarction. The listed diagnoses were accompanied with other comorbidities, causing either further complications and new diseases, or were a complication of a previous disease (e.g. diabetes and renal failure; or myocardial infarction occurring in a patient with hypertension, coronary heart disease, dyslipidemia, or diabetes).

The main strength of this study is the accurate evaluation of drugs used prior to admission in every patient and the use of the validated DRP classification system (PCNE) and MAI. Moreover, the assessment of the relationship between the DRP and hospitalization was performed by a multidisciplinary team by consensus. Nevertheless, this can also represent the main limitation of our study since we had no validated tools to assess, with higher certainty, the relationship between a DRP and drug-related hospitalization. Another limitation is the absence of adherence data, as we did not assess adherence level at admission. However, a hospital admission as a stressful event could impact the patient's self-assessment of adherence. Therefore, it would be more precise to use data on adherence level from primary care in future research, using medication possession ratio or proportion of days covered, for instance. An additional important aspect are potential interactions of prescribed therapy with OTC medications, herbal or dietary supplements, which could impact therapy efficacy or safety. Our results may have overestimated the problem of drug-related hospitalization, but still we observed a high frequency of DRPs prior to hospital admission and this deserves further investigation since it could be related to the cause of hospitalization. However, using an appropriate statistical method such as multivariate logistic regression analysis, the statistically significant predictors for hospitalization were identified and measured, adjusted for potential confounders. The results of our study provide the frame for effective therapy optimization both in primary care and at the patient's admission to the hospital. Nonetheless, the findings are based on a single clinical center, which may limit the generalizability of the results to other settings or populations. Future directions of research include incorporating objective longitudinal data on medication adherence, expanding the study setting on different hospital settings (hospital admission through emergency vs. non-emergency department), and implementing validated tools for assessing the relationship between DRPs and hospital admissions to strengthen the study's conclusions.

This study indicates that DRPs, which can be associated with the reason for patient hospitalization, are prevalent in patients on different wards of internal medicine. Possibly drug-related hospitalizations were more frequent in patients with diabetes, renal failure, atrial fibrillation, and/or myocardial infarction. Suboptimal drug treatment, which included medication omissions that could have been beneficial for the patient, was often associated with the potential cause of hospital admission. The results indicate the necessity of a thorough investigation of DRPs in primary care patients with a focus on cardiovascular, renal, and endocrine diseases. According to our results, focusing on patients with specific diseases and DRPs in primary care may be potentially rational in the attempt to reduce drug-related hospitalizations, rather than reducing the number of medications. Our study highlighted the importance of assessment and prevention of DRPs as a frequent preventable cause of hospital admission. Due to the high burden of cardiovascular disease and diabetes worldwide, which if uncontrolled cause further renal complications, a proactive role of health-care professionals in DRPs screening and therapy optimization in primary care is necessary. A collaborative practice model between general practitioners and community pharmacists could prevent drug-related hospitalizations, improve therapy outcomes, and reduce costs in health-care systems.

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Conflict of Interest

The authors declare that there is no conflict of interest.

Authors' Contributions

Conceptualization, S.V.K., M.V., A.J., A.K.; Methodology, M.K., S.V.K.; Software, S.V.K.; Validation, M.K., S.V.K., M.V., A.J., A.K.; Formal Analysis, I.D., A.D., M.K., S.V.K.; Investigation, I.D., A.D., M.K., S.V.K.; Resources, S.V.K.; Data Curation, I.D., A.D.; Writing – Original Draft Preparation, I.D., S.V.K.; Writing – Review & Editing, A.D., M.K., M.V., A.J., A.K., B.M.; Visualization, S.V.K.; Supervision, S.V.K., B.M.; Project Administration, S.V.K.; Funding Acquisition, S.V.K, B.M.

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