Příloha č. 1

Očovská Z, Maříková M, Kočí J, Vlček J.

Drug-related Hospital Admissions via the Department of Emergency Medicine: A Cross-sectional Study from the Czech Republic.

Frontiers in Pharmacology. 2022; 13: 899151. doi: 10.3389/fphar.2022.899151

frontiers | Frontiers in Pharmacology

ORIGINAL RESEARCH
published: 13 June 2022
doi: 10.3389/fphar.2022.899151

Drug-Related Hospital Admissions *via* the Department of Emergency Medicine: A Cross-Sectional Study From the Czech Republic

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Specialty section:
This article was submitted to Drugs Outcomes Research and Policies, a section of the journal Frontiers in Pharmacology

Received: 18 March 2022
Accepted: 09 May 2022
Published: 13 June 2022

Citation:
Očovská Z, Mařík M, Kočí J and Vlček J (2022) Drug-Related Hospital Admissions via the Department of Emergency Medicine: A Cross-Sectional Study From the Czech Republic. Front. Pharmacol. 13:899151. doi: 10.3389/fphar.2022.899151

Background: Drug-related hospital admissions (DRAs) represent a significant problem affecting all countries worldwide. This study aimed to determine the prevalence and preventability of DRAs, identify the most common medications involved in DRAs, the most common clinical manifestations of DRAs and describe the preventability aspects of DRAs.

Methods: This cross-sectional study examined unplanned hospital admissions to the University Hospital Hradec Králové *via* the department of emergency medicine in August–November 2018. Data were obtained from electronic medical records. The methodology of DRA identification was adapted from the OPERAM DRA adjudication guide.

Results: Out of 1252 hospital admissions, 195 DRAs have been identified (145 related to treatment safety, 50 related to treatment effectiveness). The prevalence of DRAs was 15.6% (95% CI 13.6–17.6). The most common medication classes involved in DRAs related to treatment safety were Antithrombotic agents, Antineoplastic agents, Diuretics, Corticosteroids for systemic use, and Beta blocking agents. The most common medication classes involved in DRAs related to treatment effectiveness included Diuretics, Antithrombotic agents, Drugs used in diabetes, Agents acting on the renin-angiotensin system, and Lipid modifying agents. Gastrointestinal disorders were the leading causes of DRAs related to treatment safety, while Cardiac disorders were the leading causes of DRAs related to treatment effectiveness. The potential preventability of DRAs was 51%. The highest share of potential preventability in medication classes repeatedly involved in DRAs related to treatment safety was observed for Anti-inflammatory and antirheumatic products, Psycholeptics, and Drugs used in diabetes. Potentially preventable DRAs related to treatment safety were most commonly associated with inappropriate drug selection, inappropriate monitoring, inappropriate dose selection, and inappropriate lifestyle measures. On the contrary, DRAs related to treatment effectiveness were more commonly associated with medication nonadherence.

Conclusion: It should be emphasized that in most DRAs, medications were only a contributory reason of hospital admissions and that benefits and risks have to be carefully balanced. It is highlighted by the finding that the same medication classes (Antithrombotic agents and Diuretics) were among the most common medication classes involved in DRAs related to treatment safety and simultaneously in DRAs related to treatment effectiveness. The study highlighted that apart from problems related to prescribing, problems related to monitoring and patient-related problems represent significant preventability aspects.

Keywords: adverse drug event, drug-related problem, hospitalization, prevalence, preventability, Czech Republic

INTRODUCTION

Drug-related hospital admissions (DRAs) represent a significant problem affecting all countries over the world. Although many studies have focused on adverse drug reactions (ADRs) leading to hospital admissions, fewer studies have addressed broader concepts, such as adverse drug events (ADEs) and drug-related problems (DRPs).

Multiple terms and definitions are used to describe medication harm in research and clinical practice (Falconer et al., 2019). ADEs could be defined as injuries caused by drug use that encompass ADRs and harm resulting from medication errors—they are the targets of broader efforts to improve patient safety (Nebeker et al., 2004).

A DRP is an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes (Pharmaceutical Care Network Europe Association, 2020). DRPs are divided into two main domains—DRPs related to treatment effectiveness (problem with the effect of the pharmacotherapy) and DRPs related to treatment safety (patient suffers, or could suffer, from an ADE). The third domain ("Other") includes unnecessary drug treatment (Pharmaceutical Care Network Europe Association, 2020).

While on the one hand, the use of medications might lead to ADEs, their use reduces hospital admissions as well. For example, the following medication classes were found to reduce emergency hospitalizations: angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, aldosterone receptor antagonists, statins, long-acting muscarinic antagonists, and long-acting beta-2 adrenoceptor agonists (Bobrovitz et al., 2018). Therefore, DRPs related to treatment effectiveness should also be the focus when studing DRAs.

So far, only a few studies have examined the extent to which DRPs contribute to hospital admissions. Recently, new tools (Thevelin et al., 2018; Kempen et al., 2019) have also incorporated DRPs related to treatment effectiveness. These include omission of an evidence-based drug, inappropriate selection of a drug or a dosage form, inappropriate administration, subtherapeutic dose, too short duration of treatment, medication nonadherence, inappropriate monitoring, inappropriate discontinuation, drug-drug interaction and drug-food interactions.

The concern should not only be minimizing the risks of pharmacotherapy, but also maximizing the effectiveness of pharmacotherapy (ensuring that the goals of treatment are reached). DRPs can be prevented primarily by appropriate pharmacotherapy (selection of medications and their formulation, dosing scheme, and duration of treatment—both prescribed and over-the-counter medications), appropriate use and administration of medications, appropriate medication adherence, appropriate monitoring (whether treatment goals are reached, risk factors of complications of the disease, occurrence of ADR and risk factors of ADRs), and appropriate lifestyle measures (e.g., fluid and food intake, smoking, alcohol consumption, sunscreen use).

As indicated by the definition of DRP, a DRP can be either potential (possibly leading to real problems for the patient) or actual/manifest (the problem already impacts the patient and his therapy) (Westerlund, 2019). Admission to the hospital can be a measurable outcome of manifest DRP.

Numerous studies have been conducted on DRAs from high-income countries. However, there are fewer studies from low- and middle-income countries and central and eastern Europe. This is the first study from the Czech Republic that examines DRAs without any department or age limit. In previous studies from the Czech Republic, the population studied was either from the pediatric ward (Langerová et al., 2014) or the geriatric ward (Maříková et al., 2021).

Reducing avoidable medication-related harm remains a difficult global patient safety challenge. Studies measuring the scope and nature of preventable ADEs can provide essential knowledge for the development of risk minimization measures.

The study aimed to provide information on:

a) the prevalence of DRAs to the University Hospital Hradec Králové *via* the department of emergency medicine,
b) the most common medications involved in DRAs,
c) the most common clinical manifestations of DRAs,
d) the potential preventability of DRAs,
e) medications most frequently associated with potentially preventable DRAs,
f) the most common clinical manifestations of potentially preventable DRAs, and
g) preventability aspects most frequently associated with potentially preventable DRAs.

METHODS

Study Design and Setting

This observational cross-sectional study examined hospital admissions to the University Hospital Hradec Králové *via* the

department of emergency medicine in order to identify those which are drug-related. Hospital admissions were identified using a register of all hospital admissions to the University Hospital Hradec Králové *via* the department of emergency medicine. Most of the patients were admitted to the departments of internal medicine (49%), surgery (26%), neurology (10%), pneumology (4%), anesthesiology, resuscitation and intensive medicine (3%), oncology and radiotherapy (3%), orthopedics (2%), infectious diseases (1%), and psychiatry (1%). The number of hospital admissions *via* the department of emergency medicine of the University Hospital Hradec Králové is approximately 450 per month.

The study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement for the reporting of the study (von Elm et al., 2008).

Inclusion and Exclusion Criteria

The study included all patients who were admitted *via* the department of emergency medicine to any hospital ward of University Hospital Hradec Králové. Hospital admissions that took place between 12th August and 6th November 2018 were included. Visits to the department of emergency medicine without inpatient hospitalization were not included. Hospitalizations for diagnostic or elective surgical procedures for pre-existing conditions, hospitalizations with missing medical records, and hospitalizations taking less than 24 h were excluded. There were no exclusion criteria related to age or department. Patients hospitalized more than once were counted as separate cases.

Data Collection

The data collection process was retrospective. Data were obtained from electronic medical records and entered into a Microsoft Access database. The collected data included demographic characteristics, medication history, medical history, presenting complaint, admission diagnosis, laboratory values and results of clinical investigations, documented ADRs and information on medication adherence. Medications stated in medication history were counted as active substances.

Ethics Committee Approval

The study was approved by Ethics Committee of the University Hospital Hradec Králové and Ethics Committee of the Faculty of Pharmacy in Hradec Králové. Patient informed consent was not required due to the observational design of the study and the retrospective data collection process. No personal data that could identify the patients were collected.

Methods of Assessment

The methodology of DRA adjudication was adapted from the Drug-related admissions adjudication guide developed within the OPERAM project (Thevelin et al., 2018). The DRA identification process had the following steps: data abstraction, screening for potential ADEs causing or contributing to hospital admission, causality assessment, assessment of contribution to hospital admission, and the assessment of preventability.

Potential ADEs that caused or contributed to hospital admission were identified and the causality of each ADE was assessed using WHO-UMC criteria. The modified WHO-UMC causality criteria (Klopotowska et al., 2013) described in the Drug-related admissions adjudication guide (Thevelin et al., 2018) were used to assess causality due to underuse. In addition, dosage adjustments were taken into account. ADEs with certain causal relationships had to fulfill the following criteria: 1) plausible time relationship to drug intake/dose increase, 2) plausible response to withdrawal/dose decrease, 3) cannot be explained by any disease, 4) definitive pharmacologically or phenomenologically, and 5) satisfactory rechallenge. ADEs with probable causal relationship had to fulfill the following criteria: 1) reasonable time relationship to drug intake/dose increase, 2) clinically reasonable response to withdrawal/dose decrease, and 3) unlikely to be attributed to any disease. ADEs with possible causal relationships included events with a reasonable time relationship to drug intake/dose increase that could also be explained by disease or information on dechallenge was lacking or unclear. ADEs with certain, probable, or possible causal relationships were considered confirmed ADEs.

In case of a confirmed ADE, the ADE contribution to hospital admission was accessed. According to the definition of DRA, hospitalizations due to ADEs that were the main reason for admission, as well as ADEs that were a contributory reason for admission, were considered a DRA. The main reason for admission was the primary cause of admission and was usually documented in the admission or discharge letter. A contributory reason for admission was a clinically significant contributory factor to admission—an event that worsened the main reason for admission or played a substantial role in the admission, but other factors also contributed significantly to the admission.

Drug therapeutic failure without an evident cause, drug-related laboratory deviation without clinical manifestation, intentional intoxication, and ADE that was present at hospital admission but not related to the reason of admission were not considered a DRA.

The last step was the assessment of preventability. DRAs judged to be due to medication errors were deemed to be potentially preventable. Preventability was further assessed using Hallas criteria as definitely avoidable, possibly avoidable, not avoidable, and unevaluable (Hallas et al., 1990).

Preliminary screening for potential ADEs was performed by a PhD candidate in clinical pharmacy (ZO), and the consensus assessment was performed by three board-certified clinical pharmacists (MM, JV, PS).

Classification

The identified DRAs were classified into two groups—DRAs related to treatment safety and DRAs related to treatment effectiveness. The Anatomical Therapeutic and Chemical (ATC) classification was used to code medications and medication groups (WHOCC, 2022). Medications were coded up to the fifth level. Medical Dictionary for Regulatory Activities (MedDRA) was used to classify clinical manifestations (BioPortal, 2021). MedDRA® the Medical Dictionary for Regulatory Activities terminology is the international medical terminology developed under the auspices of the International Council for

Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH).

Potentially preventable DRAs were classified according to the OPERAM DRA adjudication guide (Thevelin et al., 2018) into DRAs related to overuse, underuse, and misuse as well as the Pharmaceutical Care Network Europe Classification V 9.1 (Pharmaceutical Care Network Europe Association, 2020) into DRAs concerning the following DRPs: drug selection, dose selection, treatment duration, patient-related, patient transfer-related and other (No or inappropriate outcome monitoring). An additional category was added—inappropriate lifestyle measures.

Outcome Measures

The main outcome measure was the prevalence of DRAs (defined as the number of unplanned DRAs divided by the total number of unplanned hospital admissions). DRA was defined as a hospitalization due to an ADE, which is the main or contributory reason for hospital admission of a patient. The term ADE was defined as harm due to an ADR or a medication error related to overuse, underuse, or misuse of prescription and non-prescription medications (Thevelin et al., 2018).

The other outcomes included: the prevalence of potentially preventable DRAs (defined as the number of potentially preventable DRAs divided by the total number of DRAs), the most common medication classes implicated in DRAs, the most common clinical manifestations of DRAs, the most common medication classes implicated in potentially preventable DRAs, the most common clinical manifestations of potentially preventable DRAs and preventability aspects of potentially preventable DRAs.

Sample Size Calculation and Data Analysis

The following formula (Daniel and Cross, 2013) was used to calculate the sample size:

$$n = \frac{Z^2 P(1-P)}{d^2}$$

where p stands for the expected prevalence, Z for the standard normal variable corresponding to the confidence interval (CI), and d for precision.

A sample size of 1252 patients was required to estimate the prevalence of DRAs, based on 95% CI, precision level of 2%, and the prevalence of 15.4% [obtained from the latest systematic review (Ayalew et al., 2019)].

Categorical variables were expressed as absolute values and percentages. Continuous variables were expressed as medians with interquartile ranges.

RESULTS

Prevalence of Drug-Related Hospital Admissions and Sample Characteristics

The study included 1252 unplanned hospital admissions to University Hospital Hradec Králové *via* the department of emergency medicine. The number of patients admitted to the hospital was 1202, as some patients were admitted more than once. A total of 195 hospital admissions were identified to be drug-related. Of the 195 DRAs, 145 DRAs (74%) were related to treatment safety, and 50 DRAs (26%) were related to treatment effectiveness. The total prevalence of DRAs was 15.6% (95% CI 13.6–17.6). For the flow diagram, see **Figure 1**.

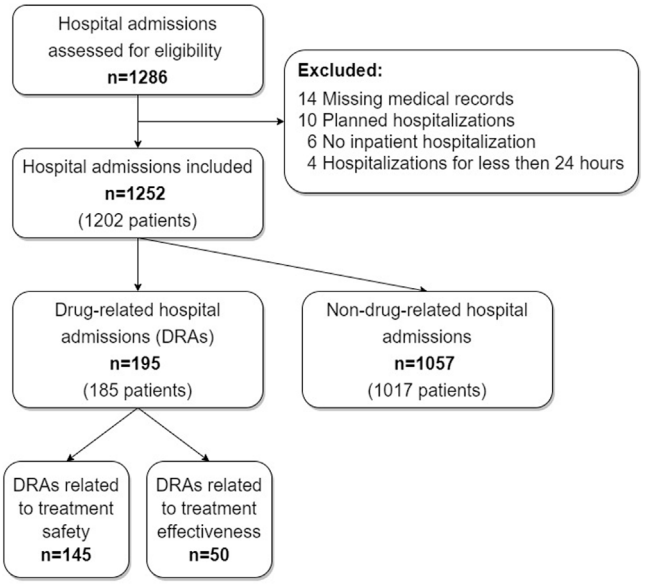

FIGURE 1 | A flow diagram depicting the number of hospital admissions at each step of the study.

The demographic and clinical characteristics of the study sample and the comparison of subgroups are shown in **Table 1**.

Table 2 shows the comorbidities of the study sample and the comparison of subgroups.

Table 3 shows the number of hospital admissions with corresponding medication classes in the patients' medication history and the comparison of subgroups.

Clinical Manifestation of Drug-Related Hospital Admissions

A total of 152 ADEs were related to treatment safety. More than one ADE was identified in 7 DRAs. **Table 4** shows the MedDRA classification of ADEs related to treatment safety.

Table 5 shows the classification of DRAs related to treatment effectiveness according to MedDRA.

Medications Involved in Drug-Related Hospital Admissions Related to Treatment Safety

Table 6 shows the ATC classification of medication classes involved in DRAs related to treatment safety. A total of 254 medications were involved in ADEs related to treatment safety. The medications classes most frequently concerned the

TABLE 1 | Demographic and clinical characteristics of the study sample and the comparison of subgroups.

Characteristic	Total N = 1252	DRAs *n* = 195	DRAs related to		Non-DRAs *n* = 1057	DRAs related to safety	
			Treatment effectiveness *n* = 50	Treatment safety *n* = 145		Preventable *n* = 50	Non-preventable *n* = 95
Age							
Median	71	75	68	77	70	82	76
IQR	58–82	66–84	59–78	70–85	56–81	71–86	69–83
Sex							
Female—No. (%)	570 (46%)	91 (47%)	19 (38%)	72 (50%)	479 (46%)	27 (54%)	45 (47%)
Male—No. (%)	682 (54%)	104 (53%)	31 (62%)	73 (50%)	578 (55%)	23 (46%)	50 (53%)
Number of medications in medication history							
Median	5	8	5	9	5	8	10
IQR	2–9	5–11	3–8	6–12	1–8	5–10	7–13
Charlson comorbidity index							
Median	4	5	5	6	4	6	6
IQR	2–6	4–7	2–6	4–7	2–6	4–7	4–7
Estimated glomerular filtration rate							
Median	66	55	65	54	69	54	54
IQR	44–88	34–81	41–90	32–74	46–89	34–76	31–74
Body mass index							
Median	26	26	26	26	26	26	26
IQR	23–31	23–29	24–29	23–31	23–31	23–28	24–31

DRA, Drug-related hospital admission; IQR, interquartile range.

Cardiovascular system (27%), Blood and blood forming organs (26%), Antineoplastic and immunomodulating agents (16%), and Nervous system (11%). More than one medication was involved in 70 (48%) DRAs related to treatment safety.

The most common medications involved in DRAs related to treatment safety included low dose acetylsalicylic acid (n = 23), warfarin (n = 22), prednisone (n = 8), hydrochlorothiazide (n = 8), clopidogrel (n = 7), furosemide (n = 7), perindopril (n = 6), insulin (n = 6), amiodarone (n = 5), bisoprolol (n = 5), ibuprofen (n = 5), nadroparin (n = 5), and spironolactone (n = 5).

Medications Involved in Drug-Related Hospital Admissions Related to Treatment Effectiveness

Table 7 shows the ATC classification of the medication classes involved in 50 DRAs related to treatment effectiveness (N = 62). There were 9 DRAs related to treatment effectiveness in which more than one medication class was involved.

Causality Assessment

Causality was assessed for every event separately. There were 7 DRAs, with more than 2 ADEs contributing to hospital admission. According to the causality assessment, 51% ADEs were probable, and 49% ADEs were possible. No ADE was certain, as no event was a recognized pharmacological phenomenon, and rechallenge was almost never performed. ADEs with probable causality were events unlikely to be attributed to disease, and the response to withdrawal (or drug initiation) was clinically reasonable, while ADEs with possible causality included events that could also be explained by disease or the information on withdrawal (or drug initiation) was lacking or unclear. **Table 8** shows the categories of causal relationships of ADEs involved in DRAs. Within DRAs related to treatment effectiveness, 46% of events had a probable causal relationship. Within DRAs related to treatment safety, 53% of events had a probable causal relationship.

Contribution to Hospital Admissions

In 55% of DRAs, ADEs only contributed to the admission, which means that ADE was one factor among others that together resulted in hospitalization. The most common other factors were heart failure decompensation and infection. **Table 9** shows the categories of contributions to hospital admissions.

Potentially Preventable Drug-Related Hospital Admissions

The overall potential preventability of DRAs was 51.3% (both definitely avoidable and possibly avoidable DRAs). We have identified 50 potentially preventable DRAs related to treatment safety and 50 potentially preventable DRAs related to treatment effectiveness. In addition, 83 (43%) DRAs were not avoidable, and 12 (6%) DRAs were unevaluable.

Table 10 shows the classification of preventable DRAs related to treatment safety. Regarding treatment safety, the most common preventability aspects included inappropriate drug selection, inappropriate monitoring, inappropriate dose selection, and inappropriate lifestyle measures.

Table 11 shows the classification of preventable DRAs related to treatment effectiveness. The most common preventability aspect of DRAs related treatment effectiveness was medication nonadherence.

Potentially preventable DRAs were also classified according to the Pharmaceutical Care Network Europe classification of DRPs (**Supplementary Tables S1, S2**).

TABLE 2 | Comorbidities of the study sample and inter-group differences.

Presence of comorbidity	Total *N* = 1252	DRAs *n* = 195	DRAs related to		Non-DRAs *n* = 1057	DRAs related to safety	
			Treatment effectiveness *n* = 50	Treatment safety *n* = 145		Preventable *n* = 50	Non-preventable *n* = 95
Arterial hypertension	60%	75%	70%	77%	57%	74%	79%
Dyslipidemia	34%	41%	28%	45%	33%	40%	47%
Diabetes	28%	38%	40%	37%	26%	34%	39%
Coronary artery disease	21%	29%	32%	28%	20%	28%	28%
Valvular heart disease	19%	33%	38%	32%	16%	22%	37%
Atrial fibrillation	17%	31%	22%	34%	15%	30%	37%
Vertebrogenic algic syndrome	17%	27%	14%	31%	16%	36%	28%
Tumors	17%	23%	6%	28%	16%	20%	33%
Heart failure	14%	26%	32%	24%	12%	24%	24%
Chronic kidney disease	13%	24%	10%	29%	11%	30%	28%
Hyperuricemia/gout	11%	13%	4%	16%	11%	16%	16%
Osteoarthrosis	11%	12%	8%	14%	11%	16%	13%
Benign prostatic hyperplasia	11%	16%	16%	16%	10%	18%	15%
Hypothyreosis	10%	13%	10%	14%	9%	16%	14%
Anemia	9%	17%	10%	19%	8%	16%	21%
Chronic venous insufficiency	9%	16%	16%	17%	8%	20%	15%
Dementia	9%	10%	6%	12%	8%	16%	9%
Venous thromboembolism	8%	13%	16%	12%	7%	16%	11%
Depression/anxiety	8%	11%	18%	9%	7%	10%	8%
Liver disease	8%	13%	18%	12%	7%	12%	12%
Peripheral artery disease	7%	11%	8%	12%	7%	14%	12%
Chronic obstructive pulmonary disease	7%	10%	14%	8%	7%	2%	12%
Osteoporosis	7%	10%	2%	13%	6%	10%	15%
Peptic ulcer	6%	9%	4%	11%	6%	20%	6%
Heart arrhythmia	6%	6%	6%	6%	6%	6%	5%
Gastroesophageal reflux disease	6%	8%	6%	9%	6%	8%	9%
Asthma	6%	6%	8%	5%	6%	4%	5%
Obesity	27%	22%	16%	24%	28%	18%	27%
Overweight	31%	35%	42%	33%	31%	32%	34%
Tobacco smoking	17%	15%	28%	11%	17%	16%	8%
Alcohol consumption	10%	11%	26%	6%	10%	8%	5%
Immobility	5%	7%	2%	9%	4%	12%	7%

DRA: Drug-related hospital admission.

Note: Comorbidities with <2% prevalence were omitted from this table for readability.

Medications Involved in Preventable Drug-Related Hospital Admissions

Medications associated with potentially preventable DRAs related to treatment safety are listed in **Table 12**.

The highest share of potential preventability in medication classes repeatedly involved in DRAs related to treatment safety was observed for Anti-inflammatory and antirheumatic products, Psycholeptics, and Drugs used in diabetes. For detailed information, see **Table 13**.

Medications Involved in Non-preventable Drug-Related Hospital Admissions

The most common medication classes involved in non-preventable DRAs included Antithrombotic agents (24%), Antineoplastic agents (19%), Diuretics (11%), Corticosteroids for systemic use (8%), Immunosuppressants (6%), Antibacterials for systemic use (5%), Beta blocking agents (5%), and Agents acting on the renin-angiotensin system (5%).

Clinical Manifestations Associated With Potentially Preventable Drug-Related Hospital Admissions

The most common clinical manifestations associated with potentially preventable DRAs related to treatment safety were Hypoglycemia (6), Gastroduodenal hemorrhage (6), Depressed level of consciousness (5), and Bradycardia (4). The MedDRA classification is shown in **Table 14**.

DISCUSSION

The aims of the study (prevalence of DRAs, medications involved in DRAs, clinical manifestations of DRAs, preventability of DRAs, and preventability aspects) are discussed separately:

Prevalence of Drug-Related Hospital Admissions

Epidemiological studies demonstrate that the burden of ADRs in both inpatient and outpatient settings is substantial (Bouvy et al.,

TABLE 3 | Baseline medications grouped by ATC group and inter-group differences.

ATC group	Total *N* = 1252	DRAs *n* = 195	DRAs related to		non-DRAs *n* = 1057	DRAs related to safety	
			Treatment effectiveness *n* = 50	Treatment safety *n* = 145		Preventable *n* = 50	Non-preventable *n* = 95
Diuretics	58%	90%	92%	89%	52%	70%	99%
Antithrombotic agents	53%	78%	52%	88%	48%	84%	89%
Agents acting on the renin-angiotensin system	40%	43%	40%	44%	40%	44%	44%
Drugs used in diabetes	36%	51%	60%	48%	33%	46%	48%
Beta blocking agents	35%	44%	34%	48%	33%	42%	51%
Drugs for obstructive airway diseases	32%	32%	30%	32%	33%	16%	41%
Lipid modifying agents	32%	35%	28%	37%	32%	34%	39%
Drugs for acid related disorders	30%	46%	26%	52%	27%	48%	55%
Analgesics	23%	39%	8%	50%	20%	50%	51%
Calcium channel blockers	22%	25%	16%	28%	22%	32%	25%
Psychoanaleptics	22%	27%	28%	26%	21%	24%	27%
Psycholeptics	21%	27%	16%	30%	20%	44%	23%
Mineral supplements	16%	24%	10%	29%	15%	22%	33%
Antigout preparations	15%	19%	6%	24%	14%	20%	26%
Cardiac therapy	13%	26%	16%	29%	11%	16%	36%
Urologicals	13%	19%	14%	21%	11%	16%	23%
Thyroid therapy	12%	14%	4%	17%	12%	18%	17%
Vitamins	12%	18%	14%	19%	11%	12%	23%
Antiepileptics	8%	14%	6%	17%	7%	18%	16%
Vasoprotectives	7%	10%	6%	11%	7%	16%	8%
Anti-inflammatory and antirheumatic products	7%	14%	10%	16%	6%	32%	7%
Antihypertensives	6%	8%	4%	10%	5%	14%	7%
Antianemic preparations	6%	9%	10%	8%	5%	8%	8%
Drugs for functional gastrointestinal disorders	6%	11%	6%	12%	5%	10%	14%
Corticosteroids for systemic use	5%	13%	4%	16%	4%	4%	22%
Antineoplastic agents	5%	18%	0%	25%	2%	4%	36%
Antihistamines for systemic use	5%	8%	4%	9%	4%	4%	12%
Ophthalmologicals	5%	6%	0%	8%	4%	8%	7%
Laxatives	3%	4%	0%	6%	3%	6%	5%
Immunosuppressants	3%	7%	4%	8%	2%	2%	12%
Cough and cold preparations	3%	4%	0%	5%	2%	0%	7%
Anti-parkinson drugs	2%	5%	4%	6%	2%	6%	5%
Other nervous system drugs	2%	0%	0%	0%	3%	0%	0%
Antidiarrheals, intestinal antiinflammatory/ antiinfective agents	2%	6%	6%	6%	2%	4%	6%
Drugs for treatment of bone diseases	2%	2%	0%	2%	2%	4%	1%

DRA, Drug-related hospital admission; ATC: Anatomical Therapeutic Chemical.
Note: Medication classes with <2% prevalence were omitted from this table for readability.

2015). As the population is aging and multimorbidity and polypharmacy are increasing, one would expect the prevalence of DRAs to rise as well. However, at the same time, safer alternatives are being used in clinical practice, high-risk medications are being withdrawn from the market, and preventative measures are being implemented in clinical practice. The prevalence of DRAs differs due to inconsistencies in the definitions and methods of DRA identification (Leendertse et al., 2010; Linkens et al., 2020; Laatikainen et al., 2021), the selected threshold of causality assessment (Wallerstedt et al., 2021), patient population (Beijer and de Blaey, 2002; Leendertse et al., 2010; Laatikainen et al., 2021) and whether the denominator includes all admissions, only acute admissions, or specific wards (Leendertse et al., 2010). When comparing the prevalence of DRAs, one has to take all these things into account. Due to the current heterogeneity, it is practically impossible to compare the prevalences of DRAs among different studies. We found that 15.6% of acute hospital admissions were drug-related. The prevalence of DRAs related to treatment safety was found to be 11.6%. If we excluded the cases with possible causality, the prevalence would be 6%. If we limited the finding only to ADEs with a probable causal relationship which was the main reason for hospital admission related to treatment safety, the prevalence would be 3%. The results of the subgroup analysis can be found in **Supplementary Table S3**. A noteworthy difference is between different age groups. Among older patients (65 years or older), the prevalence of DRAs was 18.6% while the prevalence of DRAs among the rest of the patients was 10%. The prevalence of DRAs among patients aged 75 years or older was 20%.

This study followed the OPERAM DRA adjudication guide (Thevelin et al., 2018), which was interested in DRPs that cause harm. To differentiate between potential DRPs and manifest DRPs, the term ADEs was used for manifest DRPs. However, the term was

TABLE 4 | MedDRA classification of ADEs related to treatment safety (N = 152).

MedDRA system organ class (No., %)	MedDRA preferred term	No.
Gastrointestinal disorders (31, 20.4%)	Gastroduodenal hemorrhage	10
	Intestinal hemorrhage	7
	Diarrhea	3
	Gastric ulcer perforation	3
	Pancreatitis	1
	Gastrooesophageal reflux disease	1
	Gastritis	1
	Esophagitis	1
	Duodenal perforation	1
	Abdominal discomfort	1
	Dyspepsia	1
	Nausea	1
Metabolism and nutrition disorders (26, 17.1%)	Hyponatremia	12
	Hypoglycemia	6
	Hyperglycemia	3
	Dehydration	2
	Hyperkalemia	2
	Calciphylaxis	1
Blood and lymphatic system disorders (18, 11.8%)	Bone marrow toxicity	10
	Microcytic anemia	7
	Anemia folate deficiency	1
Nervous system disorders (17, 11.1%)	Cerebral hemorrhage	6
	Depressed level of consciousness	8
	Subdural hemorrhage	2
	Diplopia	1
Infections and infestations (14, 9.2%)	Infection susceptibility increased	10
	Clostridium difficile colitis	4
Cardiac disorders (12, 7.9%)	Bradycardia	7
	Atrioventricular block	3
	Hypertension	1
	Cardiomyopathy	1
Vascular disorders (10, 6.6%)	Hypotension	4
	Hematoma	3
	Syncope	2
	Hemorrhage	1
Renal and urinary disorders (8, 5.3%)	Hematuria	4
	Prerenal failure	4
Respiratory, thoracic, and mediastinal disorders (7, 4.6%)	Hemoptysis	3
	Pulmonary embolism	1
	Pulmonary alveolar hemorrhage	1
	Interstitial lung disease	1
	Epistaxis	1
Immune system disorders (4, 2.6%)	Drug hypersensitivity	4
Psychiatric disorders (2, 1.3%)	Confusional state	1
	Disorientation	1
Endocrine disorders (1, 0.7%)	Sec. adrenocortical insufficiency	1
General disorders and administration site conditions (1, 0.7%)	Fatigue	1
Injury, poisoning, and procedural complications (1, 0.7%)	Fall	1

ADE, Adverse Drug Event; MedDRA, Medical Dictionary for Regulatory Activities.

also applied to DRP related to treatment effectiveness. One could argue that manifest DRPs related to treatment effectiveness should not be called ADEs, since ADE is mostly defined as an injury resulting from the use of a drug, and the term ADE does not include failure to use a drug (Nebeker et al., 2004). Another confusion comes when comparing ADRs and ADEs. Some studies use the definition of ADR as a noxious and unintended response to a drug, which occurs at doses normally used, while others drop the part about normally used doses or use other definitions. Therefore, one must be cautious even when comparing studies with the same outcomes, as they might be using different definitions. There is a pressing need for further discussion and international consensus on this topic (Falconer et al., 2019).

Medications Implicated in Drug-Related Hospital Admissions

Several studies have revealed that DRAs are caused by commonly used medications. In our study, the most common medication

TABLE 5 | MedDRA classification of DRAs related to treatment effectiveness (N = 50).

MedDRA system organ class	No.	%	MedDRA preferred term	No.
Cardiac disorders	16	32	Heart failure signs and symptoms	14
			Myocardial infarction	2
Nervous system disorders	9	18	Ischemic stroke	9
Metabolism and nutrition disorders	9	18	Diabetic complication	9
Vascular disorders	6	12	Venous thrombosis	3
			Hypertension	2
			Granulomatosis with polyangiitis	1
Blood and lymphatic system disorders	3	6	Anemia	3
Infections and infestations	2	4	Infection	2
Immune system disorders	2	4	Crohn's disease	2
Psychiatric disorders	2	4	Depression	1
			Bipolar disorder	1
Endocrine disorders	1	2	Thyrotoxic crisis	1

DRA, Drug-related hospital admission; MedDRA, Medical Dictionary for Regulatory Activities.

TABLE 6 | ATC classification of medication classes involved in DRAs related to treatment safety (N = 254).

ATC code	ATC group	No.	%
B01	Antithrombotic agents	65	25.6
L01	Antineoplastic agents	30	11.8
C03	Diuretics	28	11.0
H02	Corticosteroids for systemic use	14	5.5
C07	Beta blocking agents	14	5.5
M01	Anti-inflammatory and antirheumatic products	13	5.1
C09	Agents acting on the renin-angiotensin system	13	5.1
N02	Analgesics	11	4.3
L04	Immunosuppressants	10	3.9
J01	Antibacterials for systemic use	9	3.5
A10	Drugs used in diabetes	8	3.1
C01	Cardiac therapy	8	3.1
N03	Antiepileptics	5	2.0
N06	Psychoanaleptics	5	2.0
N05	Psycholeptics	5	2.0
C08	Calcium channel blockers	3	1.2
R03	Drugs for obstructive airway diseases	2	0.8
C02	Antihypertensives	2	0.8
M03	Muscle relaxants	2	0.8
A12	Mineral supplements	1	0.4
A07	Antidiarrheals, intestinal anti-inflammatory/antiinfective agents	1	0.4
H01	Pituitary and hypothalamic hormones and analogues	1	0.4
R05	Cough and cold preparations	1	0.4
N04	Anti-parkinson drugs	1	0.4
G03	Sex hormones and modulators of the genital system	1	0.4
G04	Urologicals	1	0.4

DRA, Drug-related hospital admission; ATC, Anatomical Therapeutic Chemical.

classes involved in DRAs related to treatment safety were Antithrombotic agents, Antineoplastic agents, Diuretics, Corticosteroids for systemic use, Beta blocking agents, Anti-inflammatory and antirheumatic products, and Agents acting on the renin-angiotensin system. The OPERAM trial has found Diuretics and Antithrombotic agents to be the most frequently involved or omitted medication classes in DRAs (Blum et al., 2021). Summarizing our findings on DRAs related to treatment effectiveness and DRAs related to safety, we have found the same medication classes (Antithrombotic agents and Diuretics) to be most frequently involved in DRAs.

Regarding preventable DRAs related to treatment safety, the most common medication classes identified in our study were Anti-inflammatory and antirheumatic products, Antithrombotic agents, Drugs used in diabetes, Diuretics, Cardiac therapy, Psycholeptics, Analgesics, and Beta blocking agents. Similar findings were reported in a systematic review (Howard et al., 2007), which identified antiplatelets, diuretics, non-steroidal anti-inflammatory drugs (NSAIDs), anticoagulants, opioid analgesics, drugs affecting the renin-angiotensin system, and beta-blockers as the medication classes most commonly involved in preventable DRAs related to ADRs and overtreatment.

TABLE 7 | ATC classification of medication classes involved in DRAs related to treatment effectiveness (N = 62).

ATC code	ATC group	No.	%
C03	Diuretics	14	22.6
B01	Antithrombotic agents	12	19.4
A10	Drugs used in diabetes	8	12.9
C09	Agents acting on the renin-angiotensin system	7	11.3
C10	Lipid modifying agents	5	8.1
C07	Beta blocking agents	3	4.8
J01	Antibacterials for systemic use	3	4.8
B03	Antianemic preparations	3	4.8
L04	Immunosuppressants	2	3.2
C08	Calcium channel blockers	1	1.6
A07	Intestinal antiinflammatory agents	1	1.6
H03	Thyroid therapy	1	1.6
N06	Psychoanaleptics	1	1.6
N05	Psycholeptics	1	1.6

DRA, Drug-related hospital admission; ATC, Anatomical Therapeutic Chemical.

Regarding preventable DRAs related to treatment effectiveness, the systematic review by Howard et al. identified diuretics, antiepileptics, drugs used in diabetes, and beta-blockers to be most commonly involved in DRAs. A systematic review of prospective observational studies (Mongkhon et al., 2018) identified medications targeting the cardiovascular system, respiratory system, central nervous system, endocrine system, and medication used to treat infections to be most commonly associated with hospital admissions due to medication nonadherence. In our study, the most common medication classes were Diuretics, Antithrombotic agents, Drugs used in diabetes, and Agents acting on the renin-angiotensin system.

Comparison With Other Countries

Compared to lower-income countries, we have observed a lower prevalence of DRAs related to Antiinfectives for systemic use. Antiinfectives for systemic use were frequently involved in DRAs in Ethiopia (Angamo et al., 2017; Demessie and Berha, 2022), South Africa (Mouton et al., 2016), Nigeria (Adedapo et al., 2021), and India (Geer et al., 2016). Antiinfectives for systemic use were also frequently implicated in DRAs in Brazil (de Paula et al., 2012) during the time when the requirement to be prescription only was not met. In higher-income countries, Antiinfectives for systemic use are among the top medication classes among the pediatric population. A review comparing ADR-related hospitalizations in developed and developing countries (Angamo et al., 2016) found that antiinfectives were more commonly reported to be associated with ADR-related admissions in developing countries than in developed countries.

Compared to certain higher-income countries, Opioids were not among the most common medication classes involved in DRAs related to treatment safety. Opioids appear to be frequently involved in the United States (Budnitz et al., 2011; Poudel et al., 2017), Australia (Zhang et al., 2019), Canada (Bayoumi et al., 2014). A possible explanation could be that strong opioids are not yet widely prescribed in the Czech Republic compared to these countries. However, hospital admissions due to tramadol were also present in our setting. Otherwise, the same medication classes continue to be involved in DRAs in different countries.

Clinical Manifestations of Drug-Related Hospital Admissions

Clinical manifestations of DRAs related to treatment safety most frequently concerned Gastrointestinal disorders (especially Gastrointestinal hemorrhage), Metabolism and nutrition disorders (especially Hyponatremia, Hypoglycemia) and Blood and lymphatic system disorders (Bone marrow toxicity, Microcytic anemia), Nervous system disorders (Depressed level of consciousness), Infections and infestations (Increased infection susceptibility) and Cardiac disorders (Bradycardia). Gastrointestinal disorders and Microcytic anemia were associated with anticoagulants, antiplatelets, and NSAIDs. Hyponatremia was associated with the use of thiazide diuretics. Hypoglycemia was associated with the use of insulin and sulfonylureas. Bone marrow toxicity was associated with the use of antineoplastic agents. A depressed level of consciousness was associated with opioid analgetics. Increased susceptibility to infection was associated with immunosuppressants. Bradycardia was associated with beta-blockers, amiodarone, and digoxin.

TABLE 8 | Causality assessment of ADEs.

Causality category	All ADEs *N* = 202	Treatment safety *n* = 152	Treatment effectiveness *n* = 50
probable	104	81	23
possible	98	71	27

ADE, Adverse drug events.

TABLE 9 | Classification of DRAs—contribution to hospital admissions.

Contribution to hospital admission	All DRAs *N* = 195	Treatment safety *n* = 145	Treatment effectiveness *n* = 50
main reason	88	55	33
contributory reason	107	90	17

DRA, Drug-related hospital admission.

TABLE 10 | Classification of potentially preventable DRAs related to treatment safety (N = 50).

Categories of preventable DRAs related to treatment safety	No.	Medication involved
OVERUSE		
Drug without an indication	4	low-dose acetylsalicylic acid (3), levodopa
UNDERUSE		
Omission of an indicated drug	3	omission of gastric acid suppressants despite prior gastritis or gastrointestinal ulcer naproxen, ibuprofen, ibuprofen (+rivaroxaban)
MISUSE		
Wrong drug	13	
• inappropriate according to guidelines		nimesulide, furosemide
• contraindication or precaution for a certain condition with increased risk of toxicity		diclofenac (2), meloxicam (2), ibuprofen (2), nimesulide, amiodarone, bisoprolol, dosulepin, doxazosin
Wrong dose	9	
• the dose was too high		glimepiride, tramadol
• the dose was not adapted to the patient characteristics (age, renal function, weight)		diclofenac, tiapride, nadroparin
• the dose was given too frequently		metoprolol
• accidentally ingesting a toxic amount of drug		tramadol + zolpidem, tiapride, insulin
Inappropriate monitoring	11	
• symptoms of bradycardia, heart rate		amiodarone (+bisoprolol), verapamil, digoxin (+nebivolol)
• symptoms of bleeding, INR		warfarin (5)
• blood glucose		insulin (2)
• blood potassium		potassium chloride
Drug-drug interactions	1	haloperidol (+morphine, fentanyl)
OTHER		
Inappropriate lifestyle measures	9	
• food intake		glimepiride, insulin
• fluid intake		furosemide (2), digoxin, amiloride (+telmisartan), perindopril
• smoking		hormonal contraceptives
• heavy episodic alcohol consumption		warfarin

DRA, Drug-related hospital admission; INR, International Normalized Ratio.

TABLE 11 | Classification of potentially preventable DRAs related to treatment effectiveness (N = 50).

Categories of preventable DRAs related to treatment effectiveness	No.	Medication classes involved
UNDERUSE		
Omission of the indicated drug	8	Antithrombotic agents (2), Antithrombotic agents + Lipid modifying agents (2), Agents acting on the renin-angiotensin system (1), Antianemic preparations (1), Thyroid therapy (1), Diuretics + Agents acting on the renin-angiotensin system (1)
The duration of therapy is too short	1	Antithrombotic agents (1)
Adherence concerns	35	Diuretics (7), Drugs used in diabetes (6), Agents acting on the renin-angiotensin system (4), Antibacterials for systemic use (3), Antithrombotic agents (3), Antianemic preparations (2), Immunosuppressants (2), Antithrombotic agents + Lipid modifying agents (1), Calcium channel blockers + Antithrombotic agents (1), Calcium channel blockers + Beta blocking agents + Diuretics + Lipid modifying agents (1), Diuretics + Agents acting on the renin-angiotensin system + Antithrombotic agents + Lipid modifying agents (1), Diuretics + Beta blocking agents (1), Intestinal antiinflammatory agents (1), Psychoanaleptics (1), Psycholeptics (1)
MISUSE		
Inappropriate monitoring	5	Drugs used in diabetes (2), Diuretics (2), Antithrombotic agents (1)
Inappropriate discontinuation or dose decrease	1	Diuretics + Beta blocking agents (1)

DRA, Drug-related hospital admission.

Clinical manifestation of DRAs related to treatment effectiveness most frequently concerned Cardiac disorders (particularly Heart failure symptoms), followed by Nervous system disorders (Ischemic stroke) and Metabolism and nutrition disorders (Diabetic complications). Heart failure symptoms were associated with the underuse of diuretics. Ischemic stroke due to cardioembolism was associated with the underuse of anticoagulants, while ischemic stroke due to atherosclerosis was associated with the underuse of antiplatelet agents, statins, and antihypertensive therapy. Diabetic complications were associated with nonadherence to antidiabetics.

TABLE 12 | Medication classes involved in potentially preventable DRAs related to treatment safety (N = 51).

Medication classes	No.	Medications
Anti-inflammatory and antirheumatic products	12	ibuprofen (4), diclofenac (3), meloxicam (2), nimesulide (2), naproxen (1)
Antithrombotic agents	10	warfarin (6), acetylsalicylic acid (3), nadroparin (1)
Drugs used in diabetes	6	insulin (4), glimepiride (2)
Cardiac therapy	4	digoxin (2), amiodarone (2)
Diuretics	4	furosemide (3), amiloride (1)
Psycholeptics	4	tiapride (2), haloperidol (1), zolpidem (1)
Analgesics	2	tramadol (2)
Beta blocking agents	2	metoprolol (1), bisoprolol (1)
Agents acting on the renin-angiotensin system	1	perindopril
Antihypertensives	1	doxazosin
Anti-parkinson drugs	1	levodopa
Calcium channel blockers	1	verapamil
Mineral supplements	1	potassium chloride
Psychoanaleptics	1	dosulepin
Sex hormones and modulators of the genital system	1	hormonal contraceptive

DRA, Drug-related hospital admission.

TABLE 13 | Medication classes and corresponding share of preventability of DRAs related to treatment safety.

Medication classes repeatedly involved in DRAs related to treatment safety	DRAs related to treatment safety (No.)	Preventable DRAs related to treatment safety (No.)	Share (%)
Anti-inflammatory and antirheumatic products	13	12	92
Psycholeptics	5	4	80
Drugs used in diabetes	8	6	75
Antihypertensives	2	1	50
Cardiac therapy	8	4	50
Calcium channel blockers	3	1	33
Psychoanaleptics	5	1	20
Analgesics	11	2	18
Antithrombotic agents	65	10	15
Diuretics	28	4	14
Beta blocking agents	14	2	14
Agents acting on the renin-angiotensin system	13	1	8

DRA, Drug-related hospital admission.
Note: Medication classes involved only once in DRAs and medication classes that were not involved in preventable DRAs related to treatment safety were excluded.

TABLE 14 | MedDRA categories of preventable DRAs related to treatment safety (N = 50).

MedDRA system organ class	No.	%	MedDRA preferred term
Gastrointestinal disorders	14	28	Gastroduodenal hemorrhage (6), Gastric ulcer perforation (2), Intestinal hemorrhage (2), Esophagitis (1), Diarrhea (1), Gastritis (1), Nausea (1)
Metabolism and nutrition disorders	10	20	Hypoglycemia (6), Hyperkalemia (2), Dehydration (2)
Nervous system disorders	9	18	Cerebral hemorrhage (2), Subdural hemorrhage (2), Depressed level of consciousness (5)
Cardiac disorders	5	10	Bradycardia (4), Atrioventricular block (1)
Vascular disorders	3	6	Hematoma (2), Syncope (1)
Respiratory, thoracic, and mediastinal disorders	3	6	Pulmonary embolism (1), Pulmonary alveolar hemorrhage (1), Hemoptysis (1)
Renal and urinary disorders	2	4	Prerenal failure (2)
Blood and lymphatic system disorders	2	4	Microcytic anemia (2)
Psychiatric disorders	1	2	Disorientation (1)
General disorders and administration site conditions	1	2	Fatigue (1)

MedDRA, Medical Dictionary for Regulatory Activities; DRA, Drug-related hospital admission.

Similarly, a study in the United Kingdom (Rogers et al., 2009) identified heart failure and stroke to be the most frequent manifestations of DRAs due to undertreatment. In a study in Belgium (Somers et al., 2010), the most common symptom associated with drug therapy failures was dyspnea. A study from Australia (Kalisch Ellett et al., 2021) identified that chronic heart failure and osteoporosis were most frequently associated with potentially suboptimal medication-related processes of care related to the underuse of medications. However, there are not many studies that focus not only on DRAs related to treatment safety but also on DRAs related to treatment effectiveness.

Preventability of Drug-Related Hospital Admissions

We have found that half of DRAs were potentially preventable. However, in the subgroup of DRAs related to treatment safety, only 34% of DRAs were found to be preventable. Meta-analysis on the preventability of ADRs (Hakkarainen et al., 2012) found that half of ADRs among adult outpatients can be prevented.

Recent studies have also observed higher preventability: 60.9% (Li et al., 2021) 42.9% (Dechanont et al., 2021), 53.5% (Maříková et al., 2021), 46% (Kalisch Ellett et al., 2021) 47% (Lombardi et al., 2020), 76.4% (Cabre et al., 2018) 69% (Giardina et al., 2018). However, most of them were limited to older patients, in whom the preventability is higher than in the general population.

Like the prevalence of DRAs, the prevalence of preventable DRAs varies according to many factors. The inclusion of indirect drug-related causes for patient morbidity (errors of omission) and average sample age is associated with a higher prevalence of preventable DRAs (Winterstein et al., 2002). Variations can also be explained by differences in study populations and data collection methods (Patel et al., 2017).

Preventability Aspects

A systematic review (Howard et al., 2007) identified problems with patient adherence to medication (33.3%) and prescribing problems (30.6%) as the most common underlying causes of preventable DRAs, followed by monitoring problems (22.2%).

Taking the results of DRAs related to treatment safety and treatment effectiveness together, our study confirms these findings. In our study, 38% of preventable DRAs concerned medication adherence problems, 35% concerned prescribing problems (drug selection, dosage selection, treatment duration) 17% inappropriate monitoring. Furthermore, 1% were related to medication reconciliation problems and 9% were related to inappropriate lifestyle measures (fluid intake, food intake, alcohol consumption, and smoking).

Similar underlying causes were also observed in a recent study on medication-related hospital readmissions (Uitvlugt et al., 2021), which found that 35% of preventable readmissions were due to prescribing errors, and 35% of preventable readmissions were due to nonadherence. Uitvlught et al. had pointed out that if patients present at the emergency department due to nonadherence, this will typically manifest itself as a worsening of their underlying disease, and only if the patient indicates that they are not adherent, this will be recognized as an ADE. Additionally, Uitvlugt et al. had found that 30% of preventable readmissions were due to transition errors. In this study, only one transition error was identified. However, our study did not assess readmissions. The explanation could be that not all transition errors have been revealed. Pharmacists could play a role in managing patient electronic medication records both in the hospital (medication reconciliation, discharge list) and in the pharmacy (over-the-counter medications) and potentially reduce the discrepancies in the medication history.

Howard et al. suggested concentrating interventions on the drug groups that accounted for more than half of the drug groups associated with preventable DRAs (antiplatelets, diuretics, NSAIDs, and anticoagulants). In our study, Anti-inflammatory and antirheumatic products, Antithrombotic agents, Drugs used in diabetes were the medication classes that accounted for more than half of the medication classes associated with preventable DRAs related to treatment safety. Diuretics, Antithrombotic agents, Drugs used in diabetes, and Agents acting on the renin-angiotensin system were the medication classes, which accounted for more than half of the medication classes associated with preventable DRAs related to treatment effectiveness.

Similarly, (Schmiedl et al., 2018), suggested regular individualized medication reviews of the most commonly implicated drugs in preventable DRAs. In this prospective multicenter, long-term study conducted in Germany (Schmiedl et al., 2018), the most frequently implicated drugs included digitoxin, low-dose acetylsalicylic acid, phenprocoumon, diclofenac, fast-acting insulin, glyburide (glibenclamide), spironolactone, torasemide, and intermediate-acting combined with fast-acting insulin. The most common preventability aspects included missing prevention strategies, relevant drug-drug interactions, and inappropriate drugs for age, body weight, and comorbidities.

In the prospective multicenter study from the Netherlands (Leendertse et al., 2008), medication classes associated most often with potentially preventable DRAs included antiplatelet drugs, oral anticoagulants, NSAIDs, and their combinations, antidiabetic drugs, and medications that act on the central nervous system. The most common medication errors associated with potentially preventable DRAs in the HARM study (Leendertse et al., 2008) included lack of a clear indication for the medication, nonadherence to the medication regimen, inadequate monitoring, and drug-drug interactions.

Epidemiological studies on preventable DRAs are constantly needed since clinical practice is changing as new preventive measures are being implemented. Compared to the past, lower target serum digoxin concentrations are recommended. Digoxin concentrations ≥1.2 ng/ml are avoided, since it has been shown to increase cardiovascular mortality (Rathore et al., 2003) and other ADEs. Lower doses of spironolactone are used in practice, and potassium levels and renal function are monitored following the publication that identified increased hyperkalemia-associated morbidity and mortality among patients treated with angiotensin-converting enzyme inhibitors and spironolactone (Juurlink et al., 2004). In the geriatric population, the goal is

not too tight glycemic control, and sulfonylureas (especially glibenclamide) are prescribed less often.

Academicians should assess potential options that exceed the obligatory demands. Additional efforts are still needed to identify evidence-based interventions during sick days. Recently, the absence of a sick day management plan was identified to be among the root causes of preventable ADEs (de Lemos et al., 2021). Similarly, in our study, DRAs were related to acute illness accompanied by dehydration. However, randomized controlled trials that access the risks and benefits of temporarily stopping angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers are still needed.

In addition, there is a need for the development of safe and effective medications for chronic pain. On the one hand, NSAIDs contribute to DRAs related to the gastrointestinal tract. On the other hand, opioids pose a risk of opioid dependence and addiction and other ADEs.

In the same way, the preventability aspects of DRAs related to treatment effectiveness will also change over time. There is still a huge burden of diseases affecting the cardiovascular system on hospital admissions. Recently, SGLT2 inhibitors (empagliflozin or dapagliflozin) have been recommended in certain patients with heart failure. Underuse of these medications could become a new DRP that contributes to hospital admissions of patients with heart failure with reduced ejection fraction. In addition, target low-density lipoprotein cholesterol levels for cardiovascular disease prevention have been modified. Last but not least, addressing medication nonadherence might get a greater awareness in the future.

Interpretation

Recently, it was suggested that the widespread use of a signal detection cut-off in descriptive prevalence studies may have contributed to the perception that harmful drug treatment is the major problem of health care (Wallerstedt et al., 2021). Therefore, it should be underlined that medications often pose a risk in certain situations and many ADEs are multifactorial in nature. The underlying causes are also related to the behavior of the patients (medication nonadherence and inappropriate lifestyle measures).

Wallerstedt et al. have another excellent point in stating that studies on DRAs in which the benefits of treatment are not captured may bring about the risk of unjustly discrediting pharmacotherapy. This view is supported by our finding that Antithrombotic agents and Diuretics were the common cause of DRAs related to treatment safety and simultaneously the most common cause of DRAs related to treatment effectiveness. Had we only included DRAs related to treatment safety, a layman not taking the benefit-risk balance into account could assume that these medications are rather harmful. On the one hand, the use of Antithrombotic agents was associated with bleeding events, but on the other hand, their underuse was associated with cases of thromboembolic stroke due to atrial fibrillation. Similarly, on the one hand, Diuretics were involved in electrolyte imbalances and prerenal failure. On the other hand, withdrawal of Diuretics was associated with decompensation of heart failure.

Wallerstedt et al. point out that an adverse event can be the consequence of a prudent benefit-risk evaluation and correct drug treatment. These observations are confirmed by our finding that only a minority of DRAs related to treatment safety were preventable. We agree with Wallerstedt's statement that medication error would probably be the primary interest from a health care perspective as these events could possibly be prevented. However, we think that the information on non-preventable ADRs might also be valuable as it could prompt pharmaceutical companies to invest in the development of safer alternatives.

Wallerstedt et al. have also emphasized that problems that may just as well have been caused by the disease may be less relevant when quantifying a health care problem for health care decision making and suggested restricting the reported events to those with at least a probable causal relationship with drug treatment. Therefore, it should be emphasized that the prevalence of DRAs identified in this study (15.6%) included events with possible causality, contributory reasons of admission, and ADRs, which were not preventable as well. Our definition of DRA covered all manifest DRPs that were the main reason or contributed to hospital admission. If we took into account only manifest DRPs that were the main reason for hospital admissions, the prevalence of DRAs would be 7%. If we took only manifest DRPs with a certain or probable causal relationship into account, the prevalence of DRAs would be 6%.

Strengths

The first strength of the study is that electronic medical records were used as a data source for DRA identification. It has been noted that spontaneous reporting or database methods of data collection underreport ADEs and ADRs compared to medical chart screening (Leendertse et al., 2010). Another advantage of using medical records is the possibility to detect some cases of DRAs related to treatment effectiveness. Electronic medical records capture important health information (e.g., presenting complaint, laboratory data, documented ADRs, previous falls, smoking status, smoking history, alcohol consumption) compared to administrative claims databases.

The second strength of the study is the method of DRA identification. Own definitions and assessments hinder the interpretation and comparison of different studies. This study followed a comprehensive guide, and both causality assessment and assessment of contribution to the hospital admissions were performed. We have not limited the identification of DRAs to the trigger list since trigger lists require constant updates whenever official guidelines are updated (Hedman, 2020). As described in the DRA adjudication guide (Thevelin et al., 2018), only manifest DRPs (DRPs that caused harm) that were the main reason or contributory reason for hospital admission were considered DRA. Drug-related laboratory deviations and ADEs that were present at admission but did not contribute to hospital admission were not included in the definition of DRA. However, they can be found in **Supplementary Tables S4, S5**.

The third strength is that the study assessed potential preventability and identified medication classes involved in potentially preventable DRAs as well as preventability aspects.

As suggested by Wallerstedt et al., preventable DRAs should be the main concern of research, as DRAs, which can potentially be avoided, are of interest for clinical practice.

The fourth strength is the generalizability of the study. Most studies focus on specific departments. In this study, no exclusion criteria related to department were applied.

Additional strength could be the categorization of DRAs on DRAs related to treatment safety and DRAs related to treatment effectiveness. Although the latest guidelines focused on manifest DRPs, they have not suggested differentiating between problems and causes. Perhaps it could be useful to classify DRAs in a hierarchical manner, separate causes from problems, as was suggested for DRPs (van Mil et al., 2004).

Limitations

The main limitation of this study is the retrospective data collection process. The gold standard method is a prospective evaluation of patient medical records, laboratory tests, and interviews with patients and care providers (Parameswaran Nair et al., 2018). The limitation related to retrospective data collection includes the absence of medication reconciliation, patient interview, medication adherence confirmation. Therefore, the finding that the prevalence of DRAs related to treatment effectiveness was not as high as the prevalence of DRAs related to treatment safety could be skewed since no patient interview was conducted, and medication nonadherence was only taken into account when explicitly stated in electronic medical records.

The second limitation is the inclusion of cases with a possible causal relationship. Recently, Wallerstedt et al. suggested restricting reported events to those with at least a probable causal relationship with drug treatment (Wallerstedt et al., 2021). Although this suggestion differs from the OPERAM DRA adjudication guide (Thevelin et al., 2018) and AT-HARM10 tool (Kempen et al., 2019), we have provided these results in **Supplementary Tables S6–S10**. The essential distinctions between probable causal relationship and possible causal relationship are that in the latter case, there may be another equally likely explanation for the event, and/or there is no information or uncertainty with regard to what has happened after stopping. Therefore, the case is classified as possible, not only when the event could also be explained by disease but also when the information on withdrawal is lacking. There are cases when a dechallenge cannot be performed (e.g., when the benefit of the medication is greater than the risks or patient death). However, with the inclusion of a possible causal relationship, there is a possibility of a non-drug-related explanation of the symptoms being classified as ADE. In our study, there were cases of hyperkalemia associated with a reduction in kidney function due to dehydration and events that were multifactorial (hyponatremia, fall, syncope). Coppes et al. (2021) have highlighted that the tools to identify DRAs have no scale to assess the medication-relatedness of hospital admission, so some cases might be identified as drug-related, but disease progression may play a larger role. Wallerstedt et al. indicated that medical doctors are more likely to attribute the hospital admission to exacerbation of disease while pharmacists tend to attribute the event to ADEs (Wallerstedt et al., 2021). Therefore, there is a possibility of over-attribution of conditions to ADEs. Several other issues arise in applying causality assessment algorithms to adverse drug events. There is a need to update the algorithmic methods to allow perfect applicability in all possible clinical scenarios accordingly or not with the terms of marketing authorization (Mascolo et al., 2017).

The third limitation is the heterogeneity of electronic medical records. Variability of the completeness of electronic medical records between departments might affect the results. In our study, the share of falls on DRAs might be underestimated as the electronic medical records from the department of surgery were insufficient to evaluate the causality of falls.

The last limitation is the assessment of inter-rater reliability. Fleiss cappa indicated slight agreement (0.09) between the raters. However, only the cases preselected by the main investigator have undergone consensus assessment, as the consensus assessment of each case would be time-consuming. However, given the fact that pharmacists tend to attribute adverse events rather to the medications than the disease, the risk of a potential miss will likely be small.

CONCLUSION

The total prevalence of DRAs to University Hospital Hradec Králové *via* the emergency department was 15.6%. Of 195 DRAs, 74% DRAs were related to treatment safety, and 26% DRAs were related to treatment effectiveness. If we took only manifest DRPs that were the main reason for hospital admissions into account, the prevalence of DRAs would be 7%.

ADEs affecting Gastrointestinal disorders and Metabolism and nutrition disorders accounted for 38% of DRAs related to treatment safety. Cardiac disorders accounted for 32% of all DRAs related to treatment effectiveness.

DRAs related to treatment safety most frequently involved Antithrombotic agents, Antineoplastic agents, Diuretics, Corticosteroids for systemic use, and Beta blocking agents, while DRAs related to treatment effectiveness most frequently involved Diuretics, Antithrombotic agents, Drugs used in diabetes, Agents acting on the renin-angiotensin system, and Lipid modifying agents.

The potential preventability of DRAs was 51%. Anti-inflammatory and antirheumatic products, Antithrombotic agents, and Drugs used in diabetes represented were most frequently associated with preventable DRAs related to treatment safety. The medication classes with the highest of preventability included Anti-inflammatory and antirheumatic products, Psycholeptics, and Drugs used in diabetes. The most common preventable ADEs included gastroduodenal hemorrhage, hypoglycemia, and a depressed level of consciousness.

The preventability aspects involved in potentially preventable DRAs related to treatment safety included primarily problems with drug selection, inappropriate monitoring and problems with dose selection, and inappropriate lifestyle measures. On the contrary, medication nonadherence was the most common preventability aspect of potentially preventable DRAs related to treatment effectiveness.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusion of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of the University Hospital Hradec Králové and Ethics Committee of the Faculty of Pharmacy in Hradec Králové.

AUTHOR CONTRIBUTIONS

ZO, MM, and JV conceived and designed the study. JK created the registry of patients admitted to University Hospital Hradec Králové *via* the department of emergency medicine. ZO designed a Microsoft Access database for data collection. ZO collected and analyzed the data. ZO, MM, and JV were involved in the interpretation of data. JV supervised the study and critically revised the manuscript for important intellectual content. ZO drafted the manuscript, and all co-authors contributed to and approved the final manuscript.

FUNDING

This work was supported by the EFSA-CDN project (Reg. No. CZ.02.1.01/0.0/0.0/16_019/0000841) co-funded by the European Union, by Charles University (project SVV 260 551), by Charles University Grant Agency (project GA UK 14120).

ACKNOWLEDGMENTS

We are grateful to PharmDr. Petra Šubrtová (board-certified clinical pharmacist) for participation in the consensus assessment.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2022.899151/full#supplementary-material

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Supplementary Material

Supplement to: Očovská Z, Maříková M, Kočí J, Vlček J. Drug-related Hospital Admissions via the Department of Emergency Medicine: A Cross-sectional Study from the Czech Republic. *Front Pharmacol*. 2022; 13: 899151. doi: 10.3389/fphar.2022.899151

This supplementary material has been provided by the authors to give readers additional information about their work.

Table of Contents

1 Potentially preventable DRAs

Supplementary Table 1: Drug-related problems involved in DRAs related to treatment safety

Drug-related problems related to treatment safety	No.	Description
Drug selection	21	
• Inappropriate drug according to guidelines	13	nimesulide (for long-term treatment) furosemide (for arterial hypertension) doxazosin (safer alternative for benign prostatic hyperplasia exists) nimesulide + ASA (history of GIT ulceration) ibuprofen + warfarin (history of GIT ulceration) amiodarone (history of syncope) meloxicam + dabigatran (history of microcytic anemia) bisoprolol (history of bradycardia) dosulepin (inappropriate for older patients) diclofenac (history of microcytic anemia) diclofenac (history of microcytic anemia) meloxicam (history of gastritis) ibuprofen (history of GIT bleeding)
• No indication for the drug	4	low-dose acetylsalicylic acid (3), levodopa
• Inappropriate combination of drugs	1	haloperidol (+ morphine, fentanyl)
• No or incomplete drug treatment in spite of existing indication	3	omission of gastric acid suppressants despite prior gastritis or gastrointestinal ulcer: naproxen, ibuprofen, ibuprofen (+ rivaroxaban)
Dose selection	6	
• Drug dose too high	5	glimepiride (8 mg per day) tramadol (450 mg per day) diclofenac (100 mg in older patient) tiapride (300 mg in renal impairment) nadroparin (inappropriate dose per weight)
• Dosage regimen too frequent enough	1	metoprolol (100 mg four times a day)
Patient-related	3	
• Patient takes more drugs than prescribed	1	tramadol + zolpidem (overdose)
• Patient unable to use the drug as directed	2	tiapride, insulin (patients with dementia)
Other	20	
• **No or inappropriate outcome monitoring**	11	
○ symptoms of bradycardia, heart rate		amiodarone (+ bisoprolol), verapamil, digoxin (+ nebivolol)
○ symptoms of bleeding, INR		warfarin (5)
○ blood glucose		insulin (2)
○ blood potassium		potassium chloride
• **Inappropriate lifestyle measures**	9	
○ food intake		glimepiride, insulin
○ fluid intake		furosemide (2), digoxin, perindopril, amiloride (+ telmisartan)
○ smoking		hormonal contraceptives
○ heavy episodic alcohol consumption		warfarin
Total	**50**	

ASA: Acetylsalicylic acid (low-dose), GIT: Gastrointestinal, INR: International Normalized Ratio

Supplementary Table 2. Drug-related problems involved in DRAs related to treatment effectiveness

Drug-related problems related to treatment effectiveness	No.	Medication classes involved	No.
Drug selection			
• No or incomplete drug treatment in spite of existing indication	7	Antithrombotic agents	2
		Antithrombotic agents + Lipid modifying agents	2
		Agents acting on the renin-angiotensin system	1
		Antianemic preparations	1
		Thyroid therapy	1
Treatment duration			
• Duration of treatment too short	1	Antithrombotic agents	1
Patient-related			
• Patient takes less drug than prescribed or does not take the drug at all	35	Diuretics	7
		Drugs used in diabetes	6
		Agents acting on the renin-angiotensin system	4
		Antibacterials for systemic use	3
		Antithrombotic agents	3
		Antianemic preparations	2
		Immunosuppressants	2
		Antithrombotic agents + Lipid modifying agents	1
		Calcium channel blockers + Antithrombotic agents	1
		Calcium channel blockers + Beta blocking agents + Diuretics + Lipid modifying agents	1
		Diuretics + Agents acting on the renin-angiotensin system + Antithrombotic agents + Lipid modifying agents	1
		Diuretics + Beta blocking agents	1
		Intestinal antiinflammatory agents	1
		Psychoanaleptics	1
		Psycholeptics	1
Patient transfer related			
• Medication reconciliation problem	1	Diuretics + Agents acting on the renin-angiotensin system	1
Other			
• No or inappropriate outcome monitoring	6	Drugs used in diabetes	2
		Diuretics	2
		Antithrombotic agents	1
		Diuretics + Beta blocking agents	1
Total	**50**		

DRA: Drug-related hospital admission

2 Subgroup analysis

Supplementary Table 3 depicts how results change when looking at subgroups of patients.

Supplementary Table 3: Subgroup analysis

Subgroups	All Hospital admissions	DRAs	DRAs related to treatment safety	DRAs related to treatment effectiveness	Prevalence of DRAs	Preventable DRAs	Preventable DRAs related to treatment safety
Whole sample	*1252*	*195*	*145*	*50*	*15.6%*	*100 (51%)*	*50 (34%)*
Age							
< 18	24	0	-	-	-	-	-
18-64	416	44	22	22	10.6%	29 (66%)	7 (32%)
≥ 65	812	151	123	28	18.6%	71 (47%)	43 (35%)
Sex							
female	570	91	72	19	16.0%	46 (51%)	27 (38%)
male	682	104	73	31	15.2%	54 (52%)	23 (32%)
Department							
internal medicine	610	134	101	33	22.0%	68 (51%)	35 (35%)
surgery	320	18	14	4	5.6%	10 (56%)	6 (43%)
neurology	126	13	6	7	10.3%	10 (77%)	3 (50%)
pulmology	47	12	10	2	25.5%	3 (25%)	1 (10%)
oncology	33	8	8	0	24.2%	1 (13%)	1 (13%)
anestesiology	42	6	4	2	14.3%	5 (83%)	3 (75%)
psychiatry	12	3	1	2	25.0%	3 (100%)	1 (100%)
dermatology	2	1	1	0	50.0%	0	0
other	60	0	-	-	-	-	-
Charlson Comorbidity Index							
< 5	684	74	50	24	10.8%	44 (59%)	20 (40%)
≥ 5	568	121	95	26	21.3%	56 (46%)	30 (32%)

DRA: Drug-related hospital admission

3 Events that did not fulfill the definition of DRA

Supplementary Table 4 lists Drug-related laboratory deviations without clinical manifestation (n=42).

Supplementary Table 4: List of drug-related laboratory deviations

Medications involved	Value (upper limit)	No.
Supratherapeutic INR		20
• warfarin	INR 8.7	
• warfarin	INR 11	
• warfarin	INR 4	
• warfarin	INR 4.58	
• warfarin	INR 3.9	
• warfarin	INR 4.06	
• warfarin	INR 11.14	
• warfarin	INR 3.96	
• warfarin	INR 3.63	
• warfarin	INR 6.9	
• warfarin	INR 3.91	
• warfarin	INR 3.91	
• warfarin	INR 5.08	
• warfarin	INR 11.7	
• warfarin	INR 3.69	
• warfarin	INR 3.84	
• warfarin	INR 4.2	
• warfarin	INR 5.3	
• warfarin	INR 7.1	
• warfarin	INR 3.96	
Hyperkalemia		10
• ramipril + irbesartan	K 5.2 mmol/L	
• ramipril	K 5.6 mmol/L	
• perindopril	K 5.9 mmol/L	
• spironolactone + telmisartan	K 7.5 mmol/L	
• spironolactone + perindopril	K 5.4 mmol/L	
• spironolactone + amiloride + perindopril	K 9.0 mmol/L	
• losartan	K 6.5 mmol/L	
• telmisartan	K 5.7 mmol/L	
• spironolactone	K 7.1 mmol/L	
• ramipril	K 5.7 mmol/L	
Hypokalemia		4
• hydrochlorothiazide + indapamide	K 2.8 mmol/L	
• hydrochlorothiazide	K 2.4 mmol/L	
• metipamide	K 2.8 mmol/L	
• furosemide + hydrochlorothiazide	K 2.9 mmol/L	
Increased drug level		4
• valproic acid	839.4 (693 µmol/L)	
• levetiracetam	285.3 (217 µmol/L)	
• digoxin	3.34 nmol/l (1.54 nmol/L)	
• digoxin	2.16 nmol/L (1.54 nmol/L)	
Tachycardia		2
• formoterol + fenoterol + ipratropium + tiotropium	128 beats per minute	
• fenoterol + vilanterol + umeclidinium + ipratropium + theophylline	147 beats per minute	
Hyponatremia		2
• losartan	Na 127 mmol/L	
• hydrochlorothiazide + amiloride	Na 119 mmol/L	

CK: Creatine kinase, INR: International Normalized Ratio

Supplementary Table 5 provides overview of adverse drug events that were present at admission, but did not contribute to hospital admissions (n=7).

Supplementary Table 5: List of adverse drug events that were present at hospital admission

Sex	Age	Clinical Manifestation	Medications involved	Causality	Reason of hospital admission
male	68	Gastroduodenal hemorrhage	ASA + rivaroxaban	possible	Peripheral artery disease
female	87	Confusion	tramadol + zolpidem	possible	Microcytic anemia
male	85	Abnormal dreams	zolpidem + trazodone	probable	Decompensated heart failure
male	81	Somnolence	pregabalin	possible	Aspiration pneumonia
female	70	Constipation	olanzapine	possible	Myopericarditis
female	71	Nausea	theophylline	possible	Acute Kidney Injury
male	79	Somnolence	trazodone + quetiapine	possible	Clostridium difficile colitis

ASA: Acetylsalicylic acid (low-dose)

In addition, there were six cases of drug therapeutic failure with no obvious cause associated with warfarin and five cases of intentional intoxications associated with medications acting on central nervous system.

4 Characteristics of DRAs with a probable causal relationship

Supplementary Table 6: Medication classes involved in DRAs related to treatment safety with a probable causal relationship

ATC group code	ATC group name	No.	%
B01	Antithrombotic agents	46	34.1
L01	Antineoplastic agents	19	14.1
M01	Antiinflammatory and antirheumatic products	11	8.1
C03	Diuretics	9	6.7
A10	Drugs used in diabetes	8	5.9
N02	Analgesics	6	4.4
C07	Beta blocking agents	5	3.7
C09	Agents acting on the renin-angiotensin system	5	3.7
N05	Psycholeptics	5	3.7
J01	Antibacterials for systemic use	4	3.0
H02	Corticosteroids for systemic use	3	1.5
L04	Immunosuppressants	3	2.2
C01	Cardiac therapy	2	2.2
C08	Calcium channel blockers	2	1.5
A12	Mineral supplements	1	0.7
C02	Antihypertensives	1	0.7
G03	Sex hormones and modulators of the genital system	1	0.7
N03	Antiepileptics	1	0.7
N04	Anti-parkinson drugs	1	0.7
N06	Psychoanaleptics	1	0.7
R03	Drugs for obstructive airway diseases	1	0.7
	Total	**135**	**100**

DRA: Drug-related hospital admission, ATC: Anatomical Therapeutic Chemical

Supplementary Table 7: Medication classes involved in DRAs related to treatment effectiveness with a probable causal relationship

ATC group code	ATC group name	No.	%
C03	Diuretics	7	26.9
A10	Drugs used in diabetes	5	19.2
J01	Antibacterials for systemic use	3	11.5
B01	Antithrombotic agents	2	7.7
C09	Agents acting on the renin-angiotensin system	2	7.7
C07	Beta blocking agents	2	7.7
C10	Lipid modifying agents	1	3.8
B03	Antianemic preparations	1	3.8
L04	Immunosuppressants	1	3.8
A07	Intestinal antiinflammatory agents	1	3.8
H03	Thyroid therapy	1	3.8
	Total	**26**	**100**

DRA: Drug-related hospital admission, ATC: Anatomical Therapeutic Chemical

Supplementary Table 8: Medication classes involved in potentially preventable DRAs related to treatment safety with a probable causal relationship

ATC group code	ATC group name	No.	%
M01	Antiinflammatory and antirheumatic products	11	28.9
B01	Antithrombotic agents	8	21.1
A10	Drugs used in diabetes	6	15.8
N05	Psycholeptics	4	10.5
C01	Beta blocking agents	2	5.3
A12	Analgesics	1	2.6
C03	Anti-parkinson drugs	1	2.6
C07	Cardiac therapy	1	2.6
G03	Diuretics	1	2.6
N02	Mineral supplements	1	2.6
N04	Psychoanaleptics	1	2.6
N06	Sex hormones and modulators of the genital system	1	2.6
	Total	**38**	**100**

DRA: Drug-related hospital admission, ATC: Anatomical Therapeutic Chemical

Supplementary Table 9: Clinical manifestations of DRAs related to treatment safety with a probable causal relationship

MedDRA System Organ Class	No.	%	MedDRA Preferred Term	No.
Gastrointestinal disorders	21	26.6	Gastroduodenal hemorrhage	10
			Intestinal hemorrhage	4
			Diarrhea	2
			Gastric ulcer perforation	2
			Esophagitis	1
			Nausea	1
			Abdominal discomfort	1
Metabolism and nutrition disorders	11	13.9	Hypoglycemia	6
			Hyperkalemia	2
			Hyperglycemia	1
			Calciphylaxis	1
			Hyponatremia	1
Blood and lymphatic system disorders	10	12.7	Bone marrow toxicity	8
			Microcytic anemia	2
Nervous system disorders	9	11.4	Cerebral hemorrhage	4
			Depressed level of consciousness	5
Vascular disorders	7	8.9	Hypotension	3
			Hematoma	3
			Hemorrhage	1
Respiratory, thoracic, and mediastinal disorders	6	7.6	Hemoptysis	2
			Pulmonary embolism	1
			Pulmonary alveolar hemorrhage	1
			Interstitial lung disease	1
			Epistaxis	1
Immune system disorders	4	5.1	Drug hypersensitivity	4
Renal and urinary disorders	4	5.1	Hematuria	4
Cardiac disorders	2	2.5	Bradycardia	1
			Cardiomyopathy	1
Psychiatric disorders	2	2.5	Confusional state	1
			Disorientation	1
Infections and infestations	2	2.5	Infection susceptibility increased	2
General disorders and administration site conditions	1	1.3	Fatigue	1
Total	**79**	**100**		

DRA: Drug-related hospital admission, MedDRA: Medical Dictionary for Regulatory Activities

Supplementary Table 10: Clinical manifestations of potentially preventable DRAs related to treatment safety with a probable causal relationship and associated medications

MedDRA System Organ Class category	No.	MedDRA Preferred Term	No.	Associated Medication
Gastrointestinal disorders	13	Gastroduodenal hemorrhage	6	ibuprofen (2) meloxicam nimesulide warfarin nadroparin
		Intestinal haemorrhage	2	nimesulide meloxicam
		Gastric ulcer perforation	2	ibuprofen naproxen
		Diarrhea	1	levodopa
		Esophagitis	1	diclofenac
		Nausea	1	digoxin
Metabolism and nutrition disorders	8	Hypoglycemia	6	glimepiride (2) insulin human (2) insulin glargine insulin lispro
		Hyperkalemia	2	amiloride potassium chloride
Nervous system disorders	6	Depressed level of consciousness	4	haloperidol tiapride dosulepin tramadol + zolpidem
		Cerebral hemorrhage	2	warfarin acetylsalicylic acid
Respiratory, thoracic and mediastinal disorders	3	Hemoptysis	1	warfarin
		Pulmonary embolism	1	hormonal contraceptives
		Pulmonary alveolar hemorrhage	1	warfarin
Blood and lymphatic system disorders	2	Microcytic anemia	2	ibuprofen diclofenac
Vascular disorders	2	Hematoma	2	warfarin (2)
Psychiatric disorders	1	Disorientation	1	tiapride
Cardiac disorders	1	Bradycardia	1	bisoprolol
General disorders and administration site conditions	1	Fatigue	1	metoprolol
Total	**37**			

DRA: Drug-related hospital admission, MedDRA: Medical Dictionary for Regulatory Activities

Příloha č. 2

Očovská Z, Maříková M, Vlček J.

Potentially Clinically Significant Drug-Drug Interactions in Older Patients Admitted to the Hospital: A Cross-sectional Study.

Frontiers in Pharmacology. 2023;14: 1088900. doi: 10.3389/fphar.2023.1088900

frontiers | Frontiers in Pharmacology

TYPE Original Research
PUBLISHED 02 February 2023
DOI 10.3389/fphar.2023.1088900

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Drugs Outcomes Research and Policies, a section of the journal Frontiers in Pharmacology

RECEIVED 03 November 2022
ACCEPTED 19 January 2023
PUBLISHED 02 February 2023

CITATION
Očovská Z, Mařík ová M and Vlček J (2023), Potentially clinically significant drug-drug interactions in older patients admitted to the hospital: A cross-sectional study. *Front. Pharmacol.* 14:1088900. doi: 10.3389/fphar.2023.1088900

Potentially clinically significant drug-drug interactions in older patients admitted to the hospital: A cross-sectional study

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Background: An international consensus list of potentially clinically significant drug-drug interactions (DDIs) in older people has been recently validated. Our objective was to describe the prevalence and characteristics of drug combinations potentially causing clinically significant DDIs identified in the medication history of older patients admitted to the hospital and the prevalence and characteristics of manifest DDIs—DDIs involved in adverse drug events present at hospital admission, DDIs that contributed to ADE-related hospital admissions, and DDIs involved in drug-related laboratory deviations.

Methods: The data were obtained from our previous study that examined the drug-relatedness of hospital admissions to University Hospital Hradec Králové *via* the department of emergency medicine in the Czech Republic. Patients ≥ 65 years old were included. Drug combinations potentially causing clinically significant DDIs were identified using the international consensus list of potentially clinically significant DDIs in older people.

Results: Of the 812 older patients admitted to the hospital, 46% were exposed to drug combinations potentially causing clinically significant DDIs. A combination of medications that affect potassium concentrations accounted for 47% of all drug combinations potentially causing clinically significant DDIs. In 27 cases, potentially clinically significant DDIs were associated with drug-related hospital admissions. In 4 cases, potentially clinically significant DDIs were associated with ADEs that were present at admissions. In 4 cases, the potentially clinically significant DDIs were associated with laboratory deviations. Manifest DDIs that contributed to drug-related hospital admissions most frequently involved antithrombotic agents and central nervous system depressants.

Conclusion: The results confirm the findings from the European OPERAM trial, which found that drug combinations potentially causing clinically significant DDIs are very common in older patients. Manifest DDIs were present in 4.3% of older patients admitted to the hospital. In 3.3%, manifest DDIs contributed to drug-related hospital admissions. The difference in the rates of potential and manifest DDIs suggests that if a computerized decision support system is used for alerting potentially clinically significant DDIs in older patients, it needs to be contextualized (e.g., take concomitant medications, doses of medications, laboratory values, and patients' comorbidities into account).

Abbreviations: ACE; Angiotensin-converting enzyme, ADE; Adverse drug event, ADR; Adverse drug reaction, ARB; Angiotensin II receptor blockers (AT1 receptor antagonists), ASA; Acetylsalicylic acid, CNS; Central nervous system, DDI; Drug-drug interaction, NSAID; Non-steroidal anti-inflammatory drug, OR; Odds ratio, SSRI; Selective serotonin reuptake inhibitors, SNRI; Serotonin and norepinephrine reuptake inhibitors, SRI; Serotonin reuptake inhibitors.

KEYWORDS

hospitalization, Czech Republic, adverse drug event, drug drug interaction, older patients

Introduction

Multimorbidity is highly prevalent in our aging societies, and it often leads to the use of multiple medications in older patients. Following recommendations for prescription in clinical guidelines will result in several potentially serious drug-drug interactions (DDIs) (Dumbreck et al., 2015). Drug regimens are increasingly complex and potentially harmful, and people with polypharmacy need regular review and prescribing optimization (Guthrie et al., 2015). Polypharmacy might represent either appropriate polypharmacy or problematic polypharmacy. Appropriate polypharmacy is the concurrent use of multiple medications by one individual when medication use has been optimized and when the medications are prescribed according to the best evidence. Problematic polypharmacy is the concurrent use of multiple medications by one individual when medications are prescribed inappropriately or when the intended benefit of the medication is not realized (McCarthy et al., 2019).

Older patients are at higher risk of adverse drug events (ADEs) from DDIs due to age-related changes in pharmacokinetics and pharmacodynamics and a higher number of comorbidities and medications. Several population-based studies have reported significant harm associated with DDIs in older patients (Hines and Murphy, 2011).

Our findings suggest that more than two-thirds of patients admitted to the hospital *via* the emergency department have at least one potential DDI in their medication history (Očovská et al., 2021). Fortunately, only a few of these combinations potentially causing DDIs are contraindicated or require drug dosage adjustments (Očovská et al., 2022b). The most common management strategies suggested by DDI databases all concern monitoring (Očovská et al., 2022b). Moreover, for many potential DDIs, there is a theoretical potential for an adverse interaction to occur based on the known pharmacological properties of the administered drugs, but no clinically relevant adverse effect (Pirmohamed, 2010). As a consequence, potential DDIs far outnumber actual DDIs (Pirmohamed, 2010; Magro et al., 2012; Očovská et al., 2021). Concerns about DDIs for which no clinical outcome evidence exists might lead to the underuse of safe and effective medications (Bykov and Gagne, 2017). It would mean that the evidence-based benefits of the medications are ignored in the face of a theoretical potential for harm (Pirmohamed, 2010). Just as harm associated with DDIs is usually avoidable, suboptimal patient outcomes due to the underuse of evidence-based medications are also usually avoidable (Bykov and Gagne, 2017). The omission of recommended drug therapy is associated with negative health outcomes, including reduced quality of life and a greater risk of hospitalizations or death. In comparison to younger populations, older patients are more likely to suffer adverse consequences from both action and inaction (Sloane and Niznik, 2022).

Tukukino et al. have shown that interaction alerts are of questionable value as indicators of problematic prescribing. Most alerts are either already being addressed or are not relevant in the clinical setting. The identification of DDIs using DDI databases thus results in many DDIs which might not be clinically significant (Tukukino et al., 2022). Recently, an international consensus list of potentially clinically significant DDIs in older people has been validated (Anrys et al., 2021). However, the association of DDIs listed in the international consensus list with clinical manifestations has never been examined.

Therefore, our objective was not only to describe the prevalence and characteristics of potentially clinically significant DDIs recorded in medication history but also to describe the prevalence and characteristics of manifest/actual DDIs (DDIs associated with ADE-related hospital admissions, ADEs that were present at hospital admissions and laboratory deviations).

Methods

This is a sub-study of our previous observational study, which has been described earlier (Očovská et al., 2022a). The study examined the drug-relatedness of hospital admissions to the University Hospital Hradec Králové *via* the department of emergency medicine in August–November 2018. The number of hospital admissions *via* the department of emergency medicine of the University Hospital Hradec Králové is approximately 450 per month. The exclusion criteria included visits to the department of emergency medicine without inpatient hospitalization, hospitalizations for diagnostic or elective surgical procedures for pre-existing conditions, hospitalizations with missing medical records, and hospitalizations taking less than 24 h. We have not applied any exclusion criteria related to the type of medical ward. Most of the patients were admitted to the departments of internal medicine (49%), surgery (26%), neurology (10%), pneumology (4%), anesthesiology, resuscitation and intensive medicine (3%), oncology and radiotherapy (3%), orthopedics (2%), infectious diseases (1%), and psychiatry (1%). In this sub-study, we analyzed only hospital admissions of older patients (≥ 65 years old).

The design of the original study was cross-sectional–we have examined each patient's medical record only at one point in time (we have not followed the patients in time). The data collection was performed retrospectively during 2018–2021. Data were obtained from electronic medical records and entered into a Microsoft Access database. The collected data included demographic characteristics, medication history, medical history, presenting complaint, admission diagnosis, laboratory values, results of clinical investigations, documented ADRs and information on medication adherence. Medications stated in medication history were counted as active substances.

Identification of potentially clinically significant DDIs

Potentially clinically significant DDIs were identified using the international consensus list of potentially clinically significant DDIs in older people (Anrys et al., 2021). Potential harms resulting from these DDIs were classified according to Zerah et al. (2021) into the following categories: serious cardiovascular adverse effects; serious neurological adverse effects; bleeding; deterioration of renal function and/or hyperkalemia (including severe myopathy and rhabdomyolysis, which may lead to acute renal failure); hematologic toxicity; and miscellaneous others.

Potentially clinically significant DDIs should be interpreted as drug combinations potentially causing clinically significant DDIs.

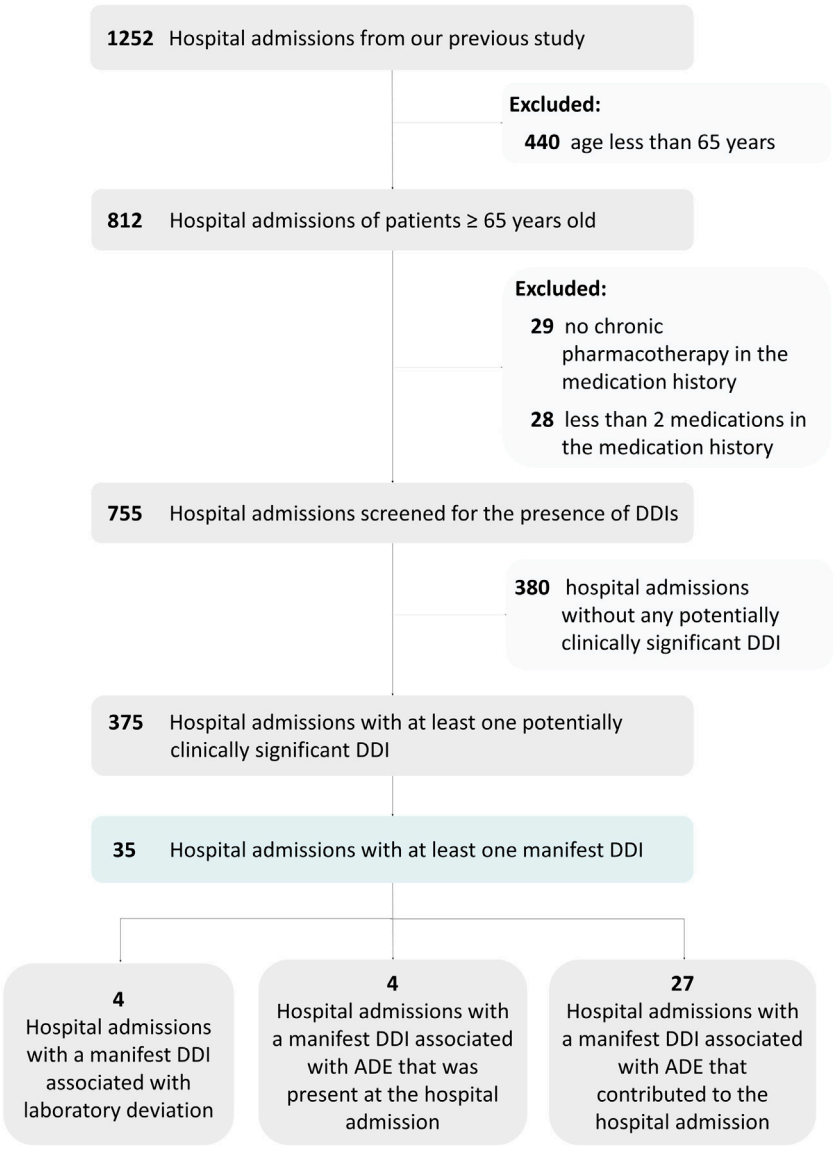

FIGURE 1
Flow chart showing the number of hospital admissions in each step.

Outcome measures

The prevalence of hospital admissions with a potentially clinically significant DDI was calculated as the number of hospital admissions with at least one potentially clinically significant DDI according to the international consensus list (Anrys et al., 2021) divided by the total number of hospital admissions of older patients.

The prevalence of hospital admissions with a manifest DDI was calculated as the number of hospital admissions with at least one DDI according to the international consensus list (Anrys et al., 2021) that was associated with laboratory deviation, ADE that was present at hospital admission, or drug-related hospital admissions divided by the total number of hospital admissions of older patients.

Manifest DDIs included potentially clinically significant DDIs with potential harms that corresponded with observed clinical manifestations of ADE or laboratory deviations. The clinical adjudication process of drug-related hospital admissions has already been described in detail in our previous study (Očovská et al., 2022a). Drug-related hospital admissions were identified using the OPERAM drug-related hospital admissions adjudication guide (Thevelin et al., 2018). The process of drug-related hospital admissions identification consisted of data abstraction, screening for potential ADEs causing or contributing to hospital admission, causality assessment (using modified WHO-UMC criteria) and assessment of contribution to hospital admission.

Statistical analysis

Data were analyzed using Microsoft Excel and IBM SPSS Statistics version 28. Descriptive statistics was performed in Microsoft Excel and multiple logistic regression was performed in IBM SPSS Statistics. We considered a *p*-value less than 0.05 as statistically significant.

Results

Figure 1 shows the number of hospital admissions in each step of the study. Of 812 older patients admitted to the hospital, 375 patients (46%) had at least one drug combination potentially causing clinically significant DDI according to the international consensus list (Anrys et al., 2021) in the medication history. In 35 cases, potentially clinically significant DDIs were associated with clinical manifestations. The prevalence of hospital admissions with at least one manifest clinically significant DDI according to the international consensus list was 4.3%.

Descriptive characteristics of the study sample can be found in Supplementary Tables S1–S3. Polypharmacy (≥5 medications) was present in 597 (74%) patients and hyperpolypharmacy (≥ 10 medications) was present in 228 (28%) patients.

Drug combinations potentially causing clinically significant DDIs

The most common medications involved in potentially clinically significant DDIs according to the international consensus list (Anrys et al., 2021) included furosemide, hydrochlorothiazide, fenoterol, amiodarone, acetylsalicylic acid, warfarin, amiloride, formoterol, spironolactone, ramipril, perindopril, potassium chloride, escitalopram, theophylline, atorvastatin, citalopram, tramadol, sertraline, ibuprofen, digoxin, diclofenac, and meloxicam. Supplementary Table S4 shows the most common potentially clinically significant DDIs according to the international consensus list (Anrys et al., 2021) that were listed in the medication history of older patients. Supplementary Table S5 shows medication classes involved in potentially clinically significant DDIs according to the international consensus list (Anrys et al., 2021). The most common medication classes involved in potentially clinically significant DDIs included Diuretics (C03), Drugs for obstructive airway diseases (R03), Antithrombotic agents (B01), Agents acting on the renin-angiotensin system (C09), Antiinflammatory and antirheumatic products (M01), Cardiac therapy (C01) and Psychoanaleptics (N06).

Potential harms of potentially clinically significant DDI according to the international consensus list (Anrys et al., 2021) included hypokalemia (n = 240), bleeding (n = 148), hyperkalemia (n = 139), CNS depression (n = 63), additive adverse effects on renal function (n = 52), hyponatremia (n = 45), myopathy (n = 42), digoxin toxicity (n = 26), serotonin syndrome (n = 24), bradycardia (n = 7), and anticholinergic effects (n = 6). Table 1 shows the overview of potentially clinically significant DDIs categorized to potential harms according to Zerah et al. (2021) and Table 2 shows the proportion of patients with the corresponding potential harm of potentially clinically significant DDIs according to Zerah et al., 2021. Potentially clinically significant DDIs involving drugs that affect potassium concentrations accounted for 47% of all potentially clinically significant DDIs according to the international consensus list (Anrys et al., 2021).

184 (23%) patients had at least one potentially clinically significant DDI related to the deterioration of renal function or hyperkalemia. 146 (18%) patients had at least one potentially clinically significant DDI related to serious cardiovascular adverse effects. 116 (14%) patients had at least one potentially clinically significant DDI related to bleeding. 72 (9%) patients had at least one potentially clinically significant DDI related to serious neurologic adverse effects. 42 (5%) patients had at least one potentially clinically significant DDI related to hyponatremia.

Manifest clinically significant DDIs

Table 3 shows the overview of manifest DDIs that were associated with drug-related hospital admissions. Manifest DDIs were involved in 27 drug-related hospital admissions. The most common clinical presentation of manifest DDIs was bleeding (especially gastrointestinal bleeding). Medication classes most frequently involved in manifest DDIs included antithrombotics (antiplatelets, anticoagulants) and CNS depressants.

Table 4 shows the lists of manifest DDIs that were associated with ADEs that were present at hospital admission but did not contribute to drug-related hospital admission (n = 4) and DDIs that were associated with drug-related laboratory deviations (n = 4). Medications with hyperkalemic effects–spironolactone, amiloride, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin II receptor blockers (ARBs) were involved in DDIs that were associated with laboratory deviations (hyperkalemia).

In addition, there were ten additional cases with manifest DDIs that were not included in the international consensus list of potentially clinically significant DDIs in older people (Anrys et al., 2021).

Discussion

Prevalence of drug combinations potentially causing clinically significant DDIs

We have found that almost half of the patients (46%) admitted to the hospital were exposed to potentially clinically significant DDIs according to the international consensus list (Anrys et al., 2021). This prevalence is lower than the prevalence of 54% found in the OPERAM trial (Zerah et al., 2021). However, if we restricted our sample only to similar patients as in the OPERAM trial (≥70 years, with ≥ 3 chronic conditions) and polypharmacy (≥ 5), we would find a slightly higher prevalence of potentially clinically significant DDIs (58%) (303/523).

If we looked at the prevalence of any potential DDIs (not only potentially clinically significant DDIs in older people), the prevalence of potential DDIs would be 85%. Only in 63 cases with at least two medications in the medication history, there was no DDI identified either by Lexicomp, Micromedex, or Stockley drug interaction databases.

Therefore, limiting the identification of DDIs to those listed in the international consensus list of potentially clinically significant in older people has almost halved the prevalence of potential DDIs.

Medications involved in drug combinations potentially causing clinically significant DDIs

In the OPERAM trial, 80% of all potentially clinically significant DDIs involved drugs that reduce potassium (diuretics, inhaled beta2-agonists, systemic corticosteroids),

TABLE 1 The number of drug combinations potentially causing clinically significant DDIs with corresponding potential harm category according to Zerah et al., 2021.

Potential harm category	N of DDIs	% of DDIs
Serious cardiovascular adverse effect	**273**	**34.1**
hypokalemia	240	30.0
digoxin toxicity	26	3.3
bradycardia	7	0.9
Deterioration of renal function or hyperkalemia	**233**	**29.1**
hyperkalemia	139	17.4
additive adverse effects on renal function, antagonist effects on blood pressure	33	4.1
myopathy	42	5.3
deterioration of renal function, hyperkalemia, altered blood pressure control	19	2.4
Bleeding	**156**	**19.5**
bleeding	148	18.5
gastrointestinal ulceration or bleeding	8	1.0
Serious neurologic adverse effects	**93**	**11.6**
excessive sedation and prolonged hypnotic effects	6	0.8
increased risk of falls and fractures, impaired cognition	57	7.1
serotonin syndrome	24	3.0
anticholinergic effects including cognitive decline	6	0.8
Others	**45**	**5.6**
hyponatremia	45	5.6
Total	**800**	**100**

DDI: Drug-drug interaction.
Note: These drug-drug interactions should be interpreted as drug combinations potentially causing clinically significant DDIs, according to the international consensus list (Anrys et al., 2021).

TABLE 2 The proportion of patients with drug combinations potentially causing clinically significant DDIs with the corresponding potential harm category according to Zerah et al., 2021.

Potential harm category	N of patients	% of patients
Deterioration of renal function or hyperkalemia	184	23
Serious cardiovascular adverse effect	146	18
Bleeding	116	14
Serious neurologic adverse effects	72	9
Hyponatremia	42	5
Any harm category	375	46

n = 812 (100%).
Note: These drug-drug interactions should be interpreted as drug combinations potentially causing clinically significant DDIs, according to the international consensus list (Anrys et al., 2021).

centrally acting drugs (psychotropics, antidepressants, opioids, antiepileptics), potassium-sparing drugs (ACE inhibitors, ARBs, spironolactone) and antithrombotics (Zerah et al., 2021).

In our study, DDIs most frequently included a combination of medications that reduce potassium (DDI No. 65), a combination of medications that increase potassium (DDI No. 21 + 22 + 23), a combination of an oral anticoagulant with an antiplatelet drug (DDI No. 12), and concomitant use of ≥ 3 centrally-acting drugs (DDI 36). In 70 cases, both DDIs involving drugs that reduce potassium and DDIs involving drugs that increase potassium were

TABLE 3 List of manifest DDIs that were associated with drug-related hospital admissions (n = 27).

Actual harm category	Manifest drug-drug interaction
Bleeding	apixaban + ASA
	ASA + warfarin + clopidogrel + escitalopram
	ASA + clopidogrel + rivaroxaban
	ASA + warfarin
	ASA + nimesulide
	ASA + warfarin + sertraline
	ASA + rivaroxaban
	NSAID + warfarin
	clopidogrel + warfarin
	ASA + ibuprofen
	ASA + diclofenac
	ASA + dabigatran etexilate + meloxicam
	clopidogrel + warfarin
	ibuprofen + rivaroxaban
	diclofenac + prednisone
	ASA + warfarin
	dabigatran etexilate + meloxicam
	clopidogrel + warfarin + ASA
	ASA + warfarin
CNS depression	pregabalin + tramadol + zolpidem
	baclofen + pregabalin + tramadol
	buprenorphine + gabapentin + trazodone
	dosulepin + tapentadol + tramadol + trazodone + pregabalin
	fentanyl + gabapentin + haloperidol + morphine
Hyperkalemia	perindopril + potassium chloride + spironolactone
	amiloride + telmisartan
	perindopril + spironolactone

ASA: acetylsalicylic acid, CNS: central nervous system, NSAID: non-steroidal anti-inflammatory drug.

present at the same time, which highlights the need for contextualization of DDIs alerts.

The most common potential harm of drug combinations potentially causing clinically significant DDIs

Hypokalemia represented the most common potential harm of potentially clinically significant DDIs according to the international consensus list (Anrys et al., 2021). Manifestations of hypokalemia include muscle weakness, constipation, cardiac arrhythmias, kidney abnormalities, and glucose intolerance. Although hypokalemia represented the most common type of potential harm of potentially clinically significant DDIs in our study, we have not detected any ADEs associated with hypokalemia. Thiazide diuretics were often prescribed in fixed combination with ACE inhibitors, ARBs, or amiloride. The risk was further minimized by using lower doses of thiazide diuretics. Spironolactone and ACE inhibitors were often prescribed in patients with heart failure (heart failure represented the most common admission diagnosis in our study). In addition, medications frequently implicated in potential DDIs associated with hypokalemia included inhaled beta 2 agonists, which do not have a high potential to cause hypokalemia.

Due to the hospital setting of our study, we could only identify cases of hypokalemia with severe types of manifestations (e.g., arrhythmias) as we did not prospectively look for the patient's

TABLE 4 List of other manifest DDIs (*n* = 8).

Manifest drug-drug interaction	Adverse drug event or laboratory deviation
DDIs involved in adverse drug events that were present at hospital admission (n = 4)	
ASA + rivaroxaban	gastroduodenal hemorrhage
gabapentin + trazodone + zolpidem	abnormal dreams
olanzapine + solifenacin	constipation
clonazepam + quetiapine + trazodone	CNS depression
DDIs involved in drug-related laboratory deviations (n = 4)	
spironolactone + telmisartan	hyperkalemia 7.5 mmol/L
perindopril + spironolactone	hyperkalemia 5.4 mmol/L
amiloride + perindopril + spironolactone	hyperkalemia 9.0 mmol/L
furosemide + hydrochlorothiazide	hypokalemia 2.9 mmol/L

ASA: acetylsalicylic acid, CNS: central nervous system, DDI: drug-drug interaction.

reported symptoms (e.g., muscle weakness) outside of the hospital setting. There were very few cases of hypokalemia in our study, and they were mostly related to vomiting, diarrhea, or excessive alcohol use.

Prevalence of manifest DDIs

In our study, the prevalence of hospital admissions with at least one manifest DDIs according to the international consensus of potentially clinically significant DDIs was 4.3%. This prevalence is higher compared to the median DDI prevalence of 1.1% from the latest systematic review (Dechanont et al., 2014).

However, there are also a few studies with a higher prevalence of DDI-related hospital admissions. In a study from Australia, DDIs were potentially involved in 8.1% of all hospital admissions and 43% of ADR-related admissions (Parameswaran Nair et al., 2017). In a study from Italy, an actual DDI was found in 5.5% of emergency department admissions (Marino et al., 2016). A study from the USA reported that DDIs were the cause of 57% of ADR-related admissions and 4.3% of all hospital admissions. (Rivkin, 2007). The latest systematic review indicated that in ADR patients, the median DDI prevalence rate for hospital admissions is 22.2%. (Dechanont et al., 2014). A recent study (Osanlou et al., 2022) found that 29.4% of ADRs are possibly or probably caused by DDIs.

The prevalence of hospital admissions associated with DDIs ranges from 0% (Hohl et al., 2001) to 18% (De Paepe et al., 2013). The prevalence of hospital admissions related to manifest DDIs is influenced by various factors such as characteristics of the studied population (e.g., age, number of comorbidities, number of medications), the definition of manifest DDI, the method used to identify DDIs, the method of causality assessment, the selected causality threshold, the assessment of contribution to hospital admission, and the emergence of new evidence of ADEs associated with DDIs.

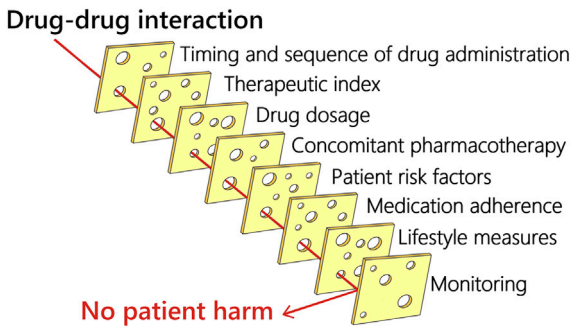

FIGURE 2
Factors that might influence whether potential DDI will lead to patient harm.

Factors that influence the manifestation of potential DDIs

Several factors influence the manifestation of potential DDIs. These factors can be related to the medication (e.g., therapeutic index, drug dosage or duration of treatment, other concomitant pharmacotherapy), patient characteristics (e.g., genetic polymorphism, the status of eliminating organs and comorbidities), drug administration (route, sequence, and correct way of drug administration), and patient behavior (medication adherence, self-monitoring, lifestyle measures). Lifestyle measures such as consumption of certain foods and beverages, hydration, smoking, and alcohol consumption also represent a source of variability. Last but not least, healthcare professionals minimize the risk of DDIs by monitoring (e.g., monitoring drug levels, potassium levels, kidney functions, blood pressure, heart rate, QTc interval, and symptoms of ADEs). Figure 2 shows the various factors that might influence whether potential DDI will lead to patient harm.

DDIs not included in the international consensus list

DDIs that were not listed in the international consensus list of potentially clinically significant DDIs in older patients but were associated with drug-related hospital admissions in our study included the combinations of selective serotonin reuptake inhibitors (SSRIs) with antithrombotic agents (both anticoagulant and antiplatelets), the combination of two antiplatelet agents (acetylsalicylic acid and clopidogrel), the combinations of beta-blockers with amiodarone or digoxin and the combinations of several medications with hypotensive effect.

Considering that bleeding represents the most common clinical manifestation of DDI-related hospital admissions, additional DDIs related to increased risk of bleeding should be considered during the development of an updated list of potentially clinically significant DDI in older adults. Gastrointestinal hemorrhage represented the most common ADE also in our previous study focused on older patients admitted to the geriatric ward (Maříková et al., 2021). A combination of two antiplatelet agents was frequently implicated in serious ADRs associated with DDIs identified *via* a spontaneous reporting database from Italy (Magro et al., 2020). In a pharmacovigilance study from China (Jiang et al., 2022), acetylsalicylic acid represented the most common medication implicated in ADRs caused by actual DDIs. The inclusion of a combination of antidepressants belonging to the SSRI and SNRI class with antithrombotics should also be considered. In the meta-analysis of 32 non-randomized studies (Nochaiwong et al., 2022), serotonin reuptake inhibitor (SRI) antidepressants among patients treated with antithrombotic therapy (either anticoagulant or antiplatelet) were associated with a higher risk of bleeding complications. The combination of vitamin K antagonist with SSRI/SNRI is also included in the Ghent Older People's Prescriptions Community Pharmacy Screening list of DDIs especially relevant in older people (Foubert et al.,2021).

In the current version of the international consensus list of potentially significant DDIs, most DDIs affecting CNS were only included when patients were taking three or more centrally-acting drugs. Nevertheless, the list could also include the combination of opioids with benzodiazepines and the combination of opioids with gabapentinoids as recommended by AGS Beers criteria (AGS, 2019). In addition, the combination of skeletal muscle relaxants with opioids and benzodiazepines is not included in the international consensus list. Concomitant use of specific muscle relaxants (e.g., baclofen), benzodiazepines, and gabapentinoids might increase the risk of opioid overdose (Li et al., 2020; Khan et al., 2021; Khan et al., 2022) and the risk of injuries (Leonard et al., 2020).

Moreover, compared to younger patients, older patients do not require too tight blood pressure and glycemic control. Fortunately, due to the development of new oral antidiabetics, the combinations of antidiabetics with the risk of hypoglycemia are not common in clinical practice. However, the combination of oral antidiabetics with a risk of hypoglycemia (sulphonylureas) or insulin with beta-blockers might result in masking the first symptoms of hypoglycemia (tachycardia, tremor). On the other hand, the combinations of several medications with hypotensive effects are common in clinical practice. Hypotension caused by multiple blood pressure-lowering agents was reported in a study from Australia (Parameswaran Nair et al., 2017). Conversely, medications that antagonize the effect of ACE inhibitors/ARBs or diuretics (e.g., NSAIDs) might contribute to heart failure exacerbations (Page et al., 2016; Swart et al., 2020).

Risk minimization of adverse drug events

Since gastrointestinal bleeding represented the most common ADE associated with manifest DDIs in our study, DDIs that increase the risk of bleeding or gastrointestinal ulceration deserve attention. Risk minimization measures should target inappropriate prescriptions of antiplatelet agents and NSAIDs. Low-dose acetylsalicylic acid use is not recommended for the primary prevention of cardiovascular disease. Since the risk of major bleeding from acetylsalicylic acid increases in older patients, initiation of low-dose acetylsalicylic acid for primary prevention of cardiovascular disease should be avoided and deprescribing should be considered in older patients already taking low-dose acetylsalicylic acid for primary prevention. (2022 AGS Annual Scientific Meeting). For patients with atrial fibrillation on anticoagulation who underwent percutaneous coronary intervention, the use of direct oral anticoagulants is preferred over a vitamin K antagonist when appropriate. Clinical decision-making regarding the duration of antiplatelet therapy should be based on a balanced assessment of three competing risks: cardioembolic stroke, coronary ischemic events, and bleeding. In patients with a low risk of thrombotic events or a high risk of bleeding, early omission of aspirin therapy and treatment with a direct oral anticoagulant plus clopidogrel is entirely warranted (Mehta, 2019). In general, the use of triple therapy (dual antiplatelet therapy plus anticoagulation) is not recommended for most patients due to an increased risk of bleeding. If triple therapy is needed, a short duration (e.g., no more than 30 days) is recommended (Kumbhani et al., 2021). A screening tool for cardiovascular pharmacotherapy in geriatric patients (RASP_CARDIO list) states that triple therapy (dual antiplatelet therapy and one anticoagulant) longer than 1 month after a percutaneous coronary intervention is potentially inappropriate. Treatment duration is preferably limited to 1 week (with mostly stepping down to dual antithrombotic therapy upon discharge from the hospital) (De Schutter et al., 2022). For patients taking two antithrombotic agents, starting or continuing a proton pump inhibitor and avoiding NSAIDs should be employed to reduce gastrointestinal bleeding risk. However, while proton pump inhibitors reduce the risk of upper gastrointestinal bleeding, the risk of lower gastrointestinal bleeding is not reduced. In addition, proton pump inhibitors might be implicated in ADRs that lead to hospital admissions, e.g., due to *C. difficile* enterocolitis (Osanlou et al., 2022).

Risk minimization of CNS adverse events should focus on off-label prescription of psychotropic drugs–particularly the use of benzodiazepines and antipsychotics should be avoided except in approved evidence-based indications. Non-pharmacologic treatment of insomnia and depression should be promoted. Deprescribing opioids and gabapentinoids might be complicated by the lack of safe and effective alternatives for pain control in older adults. Paracetamol dosages should be checked and possibly increased (up to 1,000 mg) in patients with inadequate pain management. In our study, paracetamol doses of 325–650 mg (paracetamol in fixed combinations with tramadol) or 500 mg were often used. Perhaps, the use of metamizole (dipyrone) for chronic pain could be reevaluated in some countries in light of the high burden of ADRs associated with NSAIDs, opioids, and gabapentinoids. Start low and go slow dosing of many CNS medications is recommended in older patients. Furthermore, CYP2D6 activity affected by genotype and drug exposure (including DDIs) might influence the CNS's vulnerability to ADRs (Just et al., 2021). In the future, the use of pharmacogenetics might increase drug safety by optimizing individual drug treatment (Evans and Relling, 2004).

Risk minimization of hyperkalemia should focus on slow titration of ACE inhibitors/ARBs and spironolactone during the initiation of the treatment of heart failure (start low and go slow approach). In addition,

kidney function and potassium levels should be closely monitored, and medication reconciliation should be in place to avoid situations in which patients are being discharged with potassium chloride once hypokalemia has resolved. A recent study from the United States found a high incidence of loop diuretic-potassium supplementation prescribing cascade, with up to one-third of patients continuing to receive potassium supplementation despite loop diuretic discontinuation (Wang et al., 2022).

Future studies

First of all, future studies on DDIs should assess the evidence of clinical outcomes of DDIs. An absence of evidence about whether a drug-drug interaction affects clinical outcomes not only contributes to DDI alert overload but can also result in suboptimal patient outcomes due to the underutilization of safe and effective medications (Bykov and Gagne, 2017). Bykov and Gagne have highlighted the urgent need for more and better pharmacoepidemiologic studies to understand the clinical impact, or lack thereof, of pharmacologically demonstrated DDIs (Bykov and Gagne, 2017). The evidence of clinical outcomes would benefit from more studies with a self-controlled design (particularly self-controlled case series) which is suited for the evaluation of transient effects of drug-drug interactions and controls for confounders that are stable over the observational period (Bykov et al., 2019).

Furthermore, studies should also focus on higher-order interactions. Drug-drug-drug signal detection using pharmacoepidemiologic screening of health insurance data could have broad applicability across drug classes and databases (Acton et al., 2022).

Most importantly, there is a need to contextualize DDI alerts so that computerized systems alert those DDIs that are relevant to the patient's clinical situation. Clinical decision support systems tools need to be contextualized by taking clinical, user, and institutional factors into consideration (Chou et al., 2021). Warnings for DDIs are frequently overridden because they are often irrelevant for specific patients. Alerting systems for DDIs should incorporate patients' comorbidities (e.g., chronic kidney disease, history of gastrointestinal bleeding), laboratory results (e.g., potassium, blood pressure, QTc values), drug dosages, duration and route of administration, and most importantly concomitant pharmacotherapy (particularly the presence of various DDIs affecting potassium). Concomitant pharmacotherapy can either reduce the clinical relevancy of a DDI by antagonistic effect (simultaneous presence of DDIs that reduce and increase serum potassium level) or further increase the clinical relevancy by synergistic effect (high-order drug interactions involving antithrombotic agents, antiplatelet agents, NSAIDs, and serotonin reuptake inhibitor antidepressants). A problematic issue related to DDI databases is generalizing evidence to members of a drug class and not distinguishing the clinical relevancy between different members of the same drug class. For example, metamizole (dipyrone) generates theoretical DDIs that affect blood pressure and kidney functions due to being listed among other NSAIDs. Recently Wasylewicz et al. have shown that contextualized DDI management can considerably decrease the number of irrelevant DDI alerts and thereby increase the time available to interpret relevant DDI alerts (Wasylewicz et al., 2022). Although it may be difficult to operationalize certain factors to reduce unnecessary alerts, these factors can provide useful information for clinicians to decide whether to override an alert (Reese et al., 2022).

Strengths

The key strength of this study is the assessment of clinical manifestations associated with potentially clinically significant DDIs–laboratory deviations, ADEs that were present at admission, and drug-related hospital admissions. The second strength is the use of electronic health records as a data source. Compared to administrative claims data or spontaneous reporting systems, electronic health records are more likely to capture ADEs associated with DDIs. Electronic health records include presenting complaints, hospital discharge summaries, patient history, results of investigations, and various free text notes which are not available in other data sources. The third strength of this study is the use of the OPERAM drug-related hospital admissions adjudication guide for the identification of drug-related hospital admissions. This standardized guide provides comprehensive information on the definition, screening, and adjudication of drug-related hospital admissions (including ADE causality assessment and assessment of ADE contribution to hospital admission).

In addition, the study was not limited to specific hospital wards or a specific subgroup of older adults, thereby increasing its generalizability. However, since the study was focused on older adults acutely admitted to the hospital *via* the department of emergency medicine, we do not have any information on ADEs that did not result in hospital admissions of older patients. Although the study was single-centered, we have identified almost the same prevalence and characteristics of potentially clinically significant DDIs as the four medical centers from the OPERAM trial (Bern, Brussels, Cork, Utrecht). This study, therefore, contributes to existing knowledge on DDIs in older adults by providing information on the prevalence and characteristics of potentially clinically significant DDIs (medications involved in DDIs, potential harms of DDIs) from a different country.

The study provides additional evidence concerning actual clinical manifestations associated with potentially clinically significant DDIs in older adults. This is the first time that the international consensus list of potentially clinically significant DDIs in older adults has been used to explore drug-related hospital admissions. The information on manifest DDIs has extended our knowledge of the clinical relevance of potentially clinically significant DDIs in older adults. The identified difference between the prevalence of potentially clinically significant DDIs and the prevalence of manifest DDIs adds to a growing body of literature on the need to contextualize DDI alerts.

Limitations

The main limitation of this study is the cross-sectional design. Since we were not able to follow patients in time, we did not have precise information on the time of initiation of each medication. In a prospective cohort study from Ireland, the authors were able to classify identified DDIs as chronic and acute (Hughes et al., 2021). Certain pharmacokinetic DDIs are only relevant when the object drug is initiated, discontinued, or dosage changes are made. Due to a lack of information on the duration of treatment, we were not able to assess the causality of amiodarone + warfarin DDI. Other DDIs were either pharmacodynamic or not associated with any relevant clinical manifestation.

The second limitation concerns the absence of patient interviews. Due to missing patient interviews, we do not have precise information on medication adherence and the use of over-the-counter medications and supplements. The imprecise information on NSAID use represents a major drawback of the study since gastrointestinal bleeding is the most frequent cause of drug-related hospital admissions. Although we have identified some

cases of DDIs that involved the combination of NSAIDs with anticoagulants and antiplatelets, the magnitude of gastrointestinal bleeding associated with NSAIDs is likely greater. According to the systematic review, NSAIDs represent the most common drugs involved in hospital admissions associated DDIs (Dechanont et al., 2014). In addition, the adverse impact of DDIs on the quality of life remains unknown.

Moreover, fixed combinations consisting of two active ingredients were coded as two different active ingredients. The prevalence of hypokalemia is overestimated because the combination of hydrochlorothiazide and amiloride was also implicated in DDIs that potentially lead to hypokalemia.

Conclusion

The results confirm the findings from the European OPERAM trial, which found that drug combinations potentially causing clinically significant DDIs are very common in older patients. Manifest DDIs were present in 4% of older patients admitted to the hospital. In 3%, manifest DDIs contributed to drug-related hospital admissions. The difference in the prevalence of potential and manifest DDIs suggests that if a computerized decision support system is used for alerting potentially clinically significant DDIs in older patients, it needs to be contextualized (e.g., take concomitant medications, doses of medications, laboratory values, and patients' comorbidities into account).

Manuscript contribution to the field

This is the first study that applied the International Consensus List of Potentially Clinically Significant Drug-Drug Interactions in Older People outside of the OPERAM trial. The results confirm the findings from the European OPERAM trial, which found that potentially clinically significant DDIs are very common in older patients. This study has identified potentially clinically significant drug-drug interactions that were missed in the consensus list (the combination of anticoagulants with SSRI antidepressants, the combination of two antiplatelet agents, and the combination of opioids with gabapentinoids). Therefore, this study could serve as an important guide for the development of the updated version of the international consensus list of potentially clinically significant drug-drug interactions in older people.

The strengths of this study include the assessment of clinical manifestations associated with drug-drug interaction in older patients (particularly drug-related hospital admissions) as well as laboratory deviations and adverse drug events that were present at hospital admission. The assessment of drug-related hospital admissions was performed using a standardized drug-related hospital admission adjudication guide developed during the European OPERAM trial.

The paper also proposed possible risk minimization measures for the most common ADEs associated with drug-drug interactions (bleeding, CNS depression, hyperkalemia), highlighted the factors that influence the manifestation of drug-drug interactions, and the importance of contextualization (e.g., taking concomitant medications, doses of medications, laboratory values, and patients' comorbidities into account).

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Ethics Committee of the University Hospital Hradec Králové and Ethics Committee of the Faculty of Pharmacy in Hradec Králové. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

ZO conceived and designed the study. ZO created a Microsoft Access database for data analysis and performed data analysis. ZO, MM, and JV were involved in clinical adjudication of adverse drug events. ZO, MM, and JV were involved in the interpretation of data. JV supervised the study and critically revised the manuscript for important intellectual content. ZO drafted the manuscript, and all co-authors contributed to and approved the final manuscript.

Funding

This work was supported by the EFSA-CDN project (Reg. No. CZ.02.1.01/0.0/0.0/16_019/0000841) co-funded by the European Union, by Charles University (project SVV 260 551), by Charles University Grant Agency (project GA UK 14120).

Acknowledgments

We are grateful to pharmacy students (Kateřina Holmanová, Daniela Mašková) for the screening for potential drug-drug interactions via drug interaction databases during their master's thesis research.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2023.1088900/full#supplementary-material

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Supplementary Material

Supplement to: Očovská Z, Maříková M, Vlček J. Potentially clinically significant drug-drug interactions in older patients admitted to the hospital: A cross-sectional study. *Front. Pharmacol.* 2023;14:1088900. doi: 10.3389/fphar.2023.1088900

This supplementary material has been provided by the authors to give readers additional information about their work.

Contents

1 Sample characteristics

Supplementary Table S1: Demographic characteristics of the sample of older patients with at least two medications in the medication history

Demographic characteristic	Value
Age	
median	79
IQR	72–86
Sex	
female – N (%)	386 (51)
male – N (%)	369 (49)
Number of medications in the medication history	
median	7
IQR	5–10
Polypharmacy	
≥ 5 medications – N (%)	597 (79)
≥ 10 medications – N (%)	228 (30)
Charlson comorbidity index	
median	5
IQR	4–7

n = 755 (100%) – the number of patients with at least two medications in the medication history
IQR: Interquartile range

Supplementary Table S2: The most common baseline medications in a sample of older patients with at least two medications in the medication history

Medication	N of patients	% of patients
acetylsalicylic acid (low-dose)	301	39.9
furosemide	240	31.8
atorvastatin	214	28.3
amlodipine	154	20.4
allopurinol	151	20.0
bisoprolol	151	20.0
hydrochlorothiazide	136	18.0
omeprazole	135	17.9
warfarin	122	16.2
perindopril	120	15.9
pantoprazole	119	15.8
levothyroxine sodium	119	15.8
metoprolol	117	15.5
ramipril	107	14.2
metformin	105	13.9
colecalciferol	101	13.4
amiloride	87	11.5
metamizole sodium	87	11.5
tamsulosin	83	11.0
spironolactone	76	10.1
ipratropium bromide	71	9.4
calcium carbonate	69	9.1
potassium chloride	62	8.2
tramadol	61	8.1
amiodarone	58	7.7
diosmin, combinations	55	7.3
fenoterol	54	7.2
telmisartan	51	6.8
indapamide	50	6.6
paracetamol	49	6.5
betaxolol	49	6.5
glimepiride	44	5.8
losartan	42	5.6
formoterol	41	5.4
zolpidem	41	5.4
clopidogrel	40	5.3
rosuvastatin	38	5.0
simvastatin	36	4.8
escitalopram	36	4.8
nadroparin	35	4.6
insulin glargine	34	4.5

n = 755 (100%) – the number of patients with at least two medications in the medication history

Supplementary Table S3: Comorbidities of the sample of older patients with at least two medications in the medication history

Comorbidity	N of patients	% of patients
Arterial hypertension	588	77.9
Dyslipidemia	331	43.8
Diabetes	286	37.9
Coronary artery disease	235	31.1
Valvular heart disease	198	26.2
Atrial fibrillation	195	25.8
Tumors	171	22.6
Vertebrogenic algic syndrome (chronic pain)	169	22.4
Heart failure	154	20.4
Post fracture	145	19.2
Chronic kidney disease	134	17.7
Benign prostatic hyperplasia	120	15.9
Osteoarthrosis	117	15.5
Hyperuricemia/gout	106	14.0
Post stroke	105	13.9
Post fall	103	13.6
Hypothyroidism	103	13.6
Chronic venous insufficiency	94	12.5
Anemia	91	12.1
Dementia	91	12.1
Peripheral artery disease	76	10.1
Venous thromboembolism	75	9.9
Chronic obstructive pulmonary disease	74	9.8
Osteoporosis	73	9.7
Peptic ulcer	63	8.3
Heart arrhythmia	62	8.2
Liver disease	62	8.2
Depression and/or anxiety	60	7.9
Gastroesophageal reflux disease	46	6.1
Asthma	44	5.8

n = 755 (100%) – the number of patients with at least two medications in the medication history

2 Potentially clinically significant drug-drug interaction in older adults

Supplementary Table S4: The most common potentially clinically significant DDIs according to Anrys et al. 2021 listed in the medication history of older patients

Potentially clinically significant DDIs in older people	N of patients	% of patients
furosemide + hydrochlorothiazide	35	4.6
fenoterol + furosemide	29	3.8
ASA + warfarin	28	3.7
amiodarone + atorvastatin	25	3.3
fenoterol + formoterol	22	2.9
amiodarone + warfarin	22	2.9
formoterol + furosemide	17	2.3
digoxin + furosemide	16	2.1
amiloride + ramipril	13	1.7
amiloride + perindopril	12	1.6
furosemide + sertraline	12	1.6
perindopril + potassium chloride	11	1.5
perindopril + spironolactone	11	1.5
potassium chloride + spironolactone	11	1.5
ramipril + spironolactone	11	1.5
fenoterol + theophylline	11	1.5
escitalopram + furosemide	10	1.3
fenoterol + hydrochlorothiazide	10	1.3
furosemide + theophylline	10	1.3
potassium chloride + ramipril	10	1.3
ASA + ibuprofen	9	1.2
apixaban + ASA	9	1.2
formoterol + hydrochlorothiazide	8	1.1
digoxin + hydrochlorothiazide	8	1.1
clopidogrel + warfarin	8	1.1
citalopram + furosemide	8	1.1
atorvastatin + verapamil	7	0.9
ASA + dabigatran etexilate	7	0.9
amlodipine + simvastatin	7	0.9
amiodarone + dabigatran etexilate	7	0.9
furosemide + chlortalidone	7	0.9
fenoterol + olodaterol	7	0.9
furosemide + prednisone	7	0.9
amiloride + telmisartan	7	0.9

n = 755 (100%) – the number of patients with at least two medications in the medication history
ASA: acetylsalicylic acid, DDI: Drug–drug interaction
Note: Central nervous system medications are not included in the table as there had to be a combination of three medications to be considered potentially clinically significant DDI (There were 57 additional potentially clinically significant DDIs that involved central nervous system medications)

Supplementary Table S5: The most common combinations of medication classes that represented potentially clinically significant DDIs according to Anrys et al. 2021 and were listed in the medication history of older patients

ATC code	ATC name	ATC code	ATC name	N
C03	Diuretics	**R03**	Drugs for obstructive airway diseases	109
C03	Diuretics	**C09**	Agents acting on the renin-angiotensin system	82
R03	Drugs for obstructive airway diseases	**R03**	Drugs for obstructive airway diseases	60
B01	Antithrombotic agents	**B01**	Antithrombotic agents	59
C03	Diuretics	**C03**	Diuretics	45
C03	Diuretics	**N06**	Psychoanaleptics	45
B01	Antithrombotic agents	**C01**	Cardiac therapy	38
B01	Antithrombotic agents	**M01**	Antiinflammatory and antirheumatic products	34
C09	Agents acting on the renin-angiotensin system	**M01**	Antiinflammatory and antirheumatic products	33
C03	Diuretics	**M01**	Antiinflammatory and antirheumatic products	30
A12	Mineral supplements	**C09**	Agents acting on the renin-angiotensin system	27
C01	Cardiac therapy	**C10**	Lipid modifying agents	27
C01	Cardiac therapy	**C03**	Diuretics	24
N06	Psychoanaleptics	**N02**	Analgesics	20
C03	Diuretics	**H02**	Corticosteroids for systemic use	17
C08	Calcium channel blockers	**C10**	Lipid modifying agents	15
A12	Mineral supplements	**C03**	Diuretics	13
M01	Antiinflammatory and antirheumatic products	**N06**	Psychoanaleptics	9
H02	Corticosteroids for systemic use	**M01**	Antiinflammatory and antirheumatic products	8

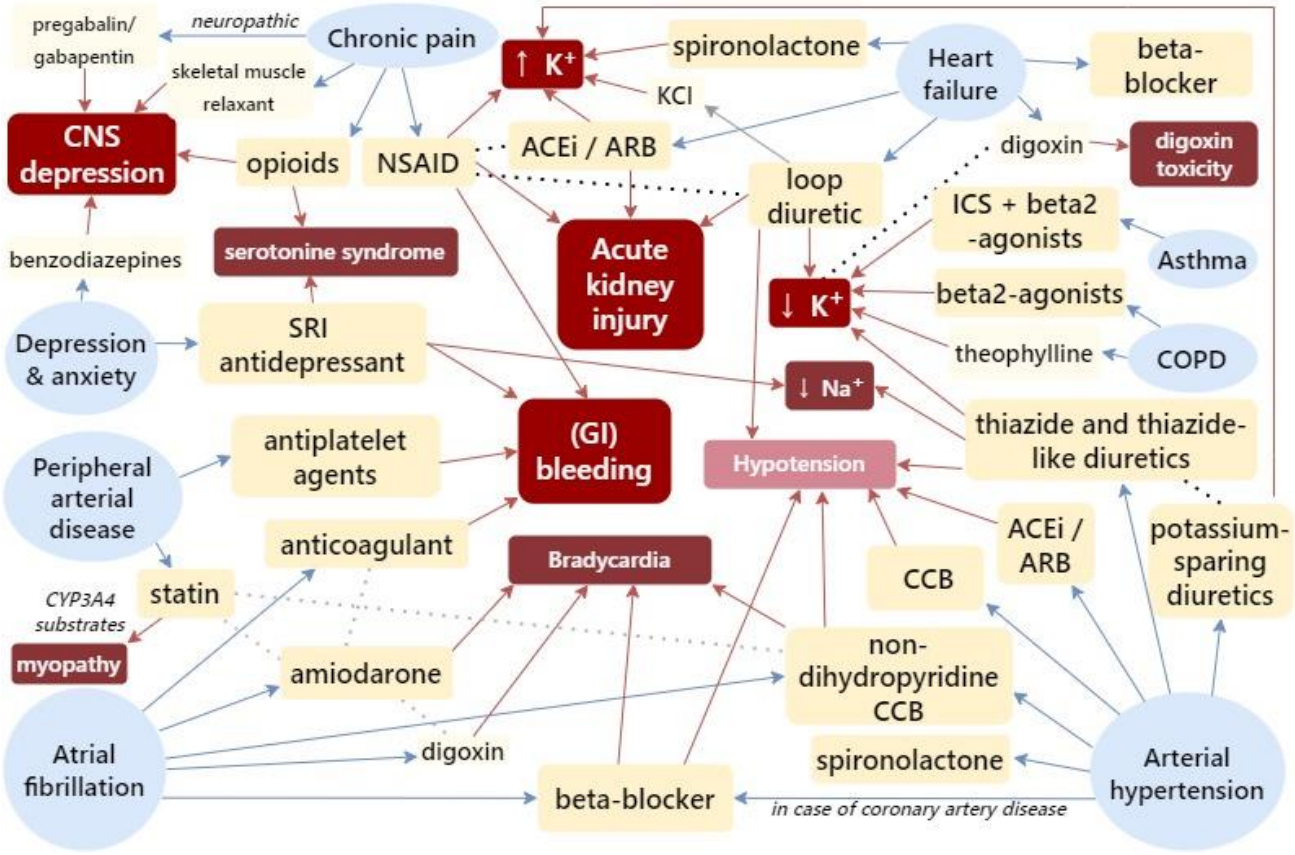
ATC: Anatomical Therapeutic Chemical

Note: While diuretics involved in potential hypokalemia included furosemide, hydrochlorothiazide, and indapamide, diuretics involved in potential hyperkalemia included spironolactone and amiloride

3 Comorbidities associated with the presence of potentially clinically significant DDIs

The following comorbidities were associated with the presence of potentially clinically significant DDI: chronic obstructive pulmonary disease (Odds ratio, OR = 5.1), asthma (OR = 2.2), atrial fibrillation (OR = 2.3), depression and/or anxiety (OR = 2.2), peripheral artery disease (OR = 2.0), heart failure (OR = 2.0), arterial hypertension (OR = 1.9), and chronic pain (OR = 1.5).

Supplementary Figure S1 shows the possible relationship between these comorbidities, indicated medication classes, and potential harms resulting from potentially clinically significant DDIs between these medication classes.



Supplementary Figure S1: Comorbidities associated with the presence of potentially clinically significant DDIs and their possible relationships with indicated medication classes and potential harms resulting from potentially clinically significant DDI between these medication classes.

ACEi: Angiotensin-converting enzyme inhibitors, ARB: Angiotensin receptor blockers, CCB: Calcium channel blocker, CNS: central nervous system, COPD: Chronic obstructive pulmonary disease, CYP: Cytochrome P450, GI: Gastrointestinal, ICS: Inhaled corticosteroids, NSAID: Non-steroidal anti-inflammatory drug, SRI: Serotonin reuptake inhibitor

Notes:

- *DDIs associated with hypotension were not listed in the consensus list.*
- *Only certain opioids might lead to serotonin syndrome (e.g., tramadol, tapentadol, fentanyl)*

Příloha č. 3

Maříková M, Očovská Z, Nerad V, Kuběna AA, Blaha V, Vlček J.

Hospital admissions to geriatric ward related to adverse drug events: a cross-sectional study from the Czech Republic.

International Journal of Clinical Pharmacy. 2021;43(5):1218-1226.

doi: 10.1007/s11096-021-01237-y

International Journal of Clinical Pharmacy (2021) 43:1218–1226
https://doi.org/10.1007/s11096-021-01237-y

RESEARCH ARTICLE

Hospital admissions to geriatric ward related to adverse drug events: a cross-sectional study from the Czech Republic

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Received: 25 September 2020 / Accepted: 13 January 2021 / Published online: 24 March 2021

Abstract

Background Geriatric patients represent a vulnerable population in terms of adverse drug events (ADEs). *Objective* The aims of this study were to determine the prevalence and preventability of hospital admissions to a geriatric ward related to ADEs, to identify medications involved in these ADEs and to describe potential preventability aspects of ADE-related admissions. *Setting* University Hospital Hradec Králové, Czech Republic. *Methods* This cross-sectional study evaluated acute hospital admissions to the geriatric ward of University Hospital Hradec Králové over a period of nine months (April–December 2017). Medication reviews were performed in order to identify ADE-related hospital admissions. Causality was assessed using the World Health Organization-Uppsala Monitoring Centre criteria. Modified Schumock-Thornton algorithm was used to assess the preventability of ADEs. *Main outcome measure* 9-month-prevalence of ADE-related hospital admissions. *Results* A total of 366 hospital admissions were included. The 9-month-prevalence of ADE-related hospital admissions was 11.75% [95% confidence interval 8.45–15.05]. Antithrombotic agents and diuretics represented the most common medication classes associated with ADEs (30.2% each). Electrolyte disturbances and gastrointestinal haemorrhages and ulcerations were the most frequently observed ADEs associated with hospital admission. Out of 43 ADE-related hospitalisations, 23 (53.5%) were considered potentially preventable. *Conclusion* The contribution of ADEs to hospital admission to the geriatric ward was not negligible. Our results also suggest that 53.5% of identified ADE-related admissions could be potentially prevented. This finding demonstrates just how important the research on the preventability of medication-related hospitalisations is. Further studies and implementations are still needed aiming to minimize the risk of medication-related harm.

Keywords Aged · Czech republic · Drug-related side effects and adverse reactions · Hospitalization · Pharmacoepidemiology

Impacts on practice

- Since a large proportion of hospital admissions related to adverse drug events were found to be potentially preventable, clinical pharmacists could play an important role in healthcare-system by preventing medication-related hospital admissions.
- In order to reduce the burden of medication-related hospital admissions, more attention should be paid to medications requiring renal dosage adjustments, combining medications with additive pharmacodynamic effects and medications with a narrow therapeutic range.

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Introduction

Medication-related harm is generating an unnecessary economic burden. The first objective of the third World Health Organization Global Patient Safety Challenge [1, 2] is to assess the scope and nature of avoidable harm. Medication-related admissions have been the topic of many studies worldwide with prevalence ranging up to 23% [3]. According to the latest review conducted by Linkens et al. [4], there is much heterogeneity in definitions for medication-related hospital admissions and their incidence. The most commonly used definitions of medication-related hospital admissions include ADR (adverse drug reaction), ADE (adverse drug event) or DRP (drug-related problem). In clinical pharmacy, we are not only interested in ADR (defined as a 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), but also in broader concepts—ADE or DRP. ADE is defined as an injury resulting from the use of a drug [5], and DRP is defined as an event or circumstance that involves a patient's drug treatment that actually, or potentially, interferes with the achievement of an optimal outcome [6]. Even though medication-related admissions represent a commonly discussed topic, the issue has rarely been researched in the Czech Republic, nevertheless. To our knowledge, there is only one published study on this topic in the Czech Republic Langerová et al. [7]. This study was limited to patients aged 19 years or under and found that the prevalence of admissions caused by ADR was 2.2% [7]. Generally, a relatively low prevalence of medication-related admissions has been found in paediatric wards [8]. While elderly patients are particularly known for being prone to ADEs, data specific to the geriatric population are still lacking in the Czech Republic. The meta-analysis of observational studies by Beijer et al. [9] found that the odds of being hospitalized by ADR related problems are four times higher for the elderly compared to non-elderly patients. Apart from the high prevalence of medication-related admissions among elderly patients, their preventability has also been observed to be considerably higher. Therefore, we aimed to investigate the scope of this problem in patients admitted to a geriatric ward.

Aim of the study

The aims of the present study were to determine the 9-month prevalence of hospital admissions related to ADEs, to identify medications involved in these cases of ADEs, and further to determine the preventability of ADE-related hospital admission, as well as to describe the potential preventability aspects of ADE-related admissions.

Method

Study design

The design of this observational study was cross-sectional. Data were obtained from electronic medical records using the hospital information system.

Inclusion and exclusion criteria

Hospital admissions to geriatric ward between April and December 2017 were included. Planned hospital admissions were excluded from the study.

Setting

Investigated geriatric ward is part of the 3rd Department of Internal Medicine – Metabolic Care and Gerontology of University Hospital Hradec Králové in the Czech Republic. The geriatric ward admits patients who are mostly at least 78 years old. The cut-off age is an internal recommendation of the geriatric ward due to a limited number of beds (21 beds).

Data collection

Data were collected using electronic medical records from the hospital information system once weekly at the Department of Clinical Pharmacy, Hospital Pharmacy of University Hospital, Hradec Králové. The identification of hospitalisations was based on a summary of currently admitted patients generated by the hospital information system. The following data were entered into a Microsoft Excel spreadsheet: admission diagnosis, age and sex of patients, medication history, the total number of medications used prior to admission and laboratory results (sodium, potassium, chloride, glucose, urea, creatinine, estimated glomerular filtration rate, C-reactive protein, erythrocyte, leucocyte and platelet count, blood pressure, heart rate and other relevant results).

Primary and secondary outcomes

The primary outcome of this study was to determine the 9-month-prevalence of hospital admissions to the geriatric ward of University Hospital Hradec Králové related to ADEs. The secondary outcomes were to identify medications implicated in ADE-related hospitalisations, to determine the

preventability of these hospitalisations and to identify preventability aspects of ADE-related hospitalisations.

Data evaluation

Medication review was performed in order to estimate whether the hospitalisation was a result of ADE. Medication review involved evaluation of medication history, and detecting DRPs. DRPs related to treatment safety resulting in patient harm were further taken into account and referred to as ADEs. An ADE was defined as an injury resulting from the use of a drug [5]. The term ADE includes ADR as well as medication errors. Hospital admission was considered ADE-related whenever the presenting symptoms were associated with ADE. The harm resulting from the omission of treatment or suboptimal treatment was not included.

For every ADE identified, causality was assessed applying the World Health Organization-Uppsala Monitoring Centre (WHO-UMC) criteria [10]. These criteria classify ADEs as certain, probable, possible, unlikely, conditional and unassessable. Only ADEs classified as certain, probable, or possible were recorded. During the causality assessment medication history, admission notes, laboratory and clinical findings, current treatment and changes in medication at admission were taken into account. The following aspects were considered for causality assessment: plausible time relationship to intake of medication, response to medication withdrawal or dose reduction (dechallenge), response to medication readministration (rechallenge) and the presence of alternative causes. Cases with a certain causal relationship were events recognised as a pharmacological phenomenon. Cases with probable causal relationships were events unlikely to be attributed to disease or other drugs, and response to withdrawal was clinically reasonable. Cases with possible causal relationships included events which could also be explained by disease or other drugs, or no information on drug withdrawal was available. Medications implicated in ADEs were classified according to the Anatomical Therapeutic Chemical (ATC) classification system.

Assessment of preventability was performed using the Schumock-Thornton algorithm modified by Schmiedl et al. [11], which includes the following aspects of preventability: inappropriate drug use (drug not indicated; exceeding treatment duration; previous ADR or drug allergy; inappropriate drug due to age, body weight, comorbidities; contraindication), inappropriate dose (inappropriate dose due to age, body weight, comorbidities; insufficient dose adjustment of renally excreted drugs), relevant drug-drug interaction, missing ADR prevention (drug-related, non-drug-related), and others (nonadherence, self-medication). At least one aspect had to be present in order to consider ADE potentially preventable. Assessments of causality and preventability were performed by two researchers (M.M., a senior clinical pharmacist and Z.O., a pharmacist), in cases of discrepancies a third researcher (J.V., a senior clinical pharmacist) was consulted until a consensus was found.

Statistical methods

Categorical variables (sex, presence of polypharmacy – defined as five or more medications in medication history) were expressed by frequencies and percentages. Numeric variables (age, number of medications) were reported as mean ± standard deviation for normally distributed data or as median and interquartile range for not normally distributed data. The Mann–Whitney test was used to compare two groups with respect to numeric variables. For comparison of categorical variables, a generalized linear model with logit link function was used. *P*-values less than 0.05 were considered statistically significant. Statistical analysis was performed using Wolfram Mathematica software (version 11.3).

Results

Descriptive data

A total of 366 acute admissions were included. Polypharmacy (the presence of five or more medications in medication history) was present in 78.4% of hospital admissions. The number of medications taken prior to admission ranged from 0 to 16. Table 1 shows demographics and the number of medications taken prior to admission in relation to the type of hospital admissions (ADE-related or non-ADE-related).

Outcome data

The 9-month-prevalence of admissions related to ADEs was 11.75% (95% CI 8.45–15.05). The overview of these ADEs (n = 43) is provided in Table 2. Gastrointestinal haemorrhages and ulcerations represented the most common type of ADE (30.2%), followed by hyponatraemia (23.3%) and digoxin intoxication (11.6%). Overall electrolyte disturbances accounted for 32.6% of all observed ADEs.

Based on the WHO-UMC scale [10], causality assessment yielded 33 (76.7%) probable and 10 (23.3%) possible ADEs. Hyponatraemia, due to multifactorial aetiology, was assessed as possible. There was no certain ADE since rechallenge was not performed.

According to the ATC classification, antithrombotic agents (B01) and diuretics (C03) were the most commonly implicated medication classes, each accounting for 13 cases (30.2%). Associated outcomes of antithrombotic agents included gastrointestinal haemorrhage, ulceration and haematoma. Diuretic-related ADEs comprised electrolyte disturbances (hyponatraemia and hypokalaemia) and

Table 1 Comparison of demographic variables in relation to the type of hospital admissions

Variable	All admissions (n = 366)	non-ADE related (n = 323)	ADE-related (n = 43)	*p*-value
Sex				
Female	240 (65.6%)	205 (63.5%)	35 (81.4%)	0.0238*
Age (years)				
Median (IQR)	86 (82–89)	86 (82–89)	86 (82–89)	0.7985
Number of medications				
Median (IQR)	7 (5–9)	7 (5–9)	7 (6–10)	0.4190
Presence of polypharmacy				
Present	287 (78.4%)	247 (76.5%)	40 (93.0%)	0.0213*

ADE adverse drug event *IQR* interquartile range

*Statistically significant

dehydration. The summary of implicated medications sorted by ATC code is displayed in Table 3.

Out of 43 ADE-related admissions, 23 (53.5%) were considered potentially preventable. Table 4 classifies preventable cases according to preventability aspects proposed by Schmiedl et al. [11] In cases when several preventability aspects were present, further identified preventability aspects are mentioned in the description.

Discussion

This study focused on patients admitted to the geriatric ward. Geriatric patients are particularly prone to developing ADEs. Patients in this study often had age-related comorbidities that increase the risk of ADE-related hospital admission. A decline in kidney function predisposed these patients to hyperkalaemia and toxicity of renally excreted medications (e.g. digoxin). Heart failure and its treatment contributed to the high prevalence of electrolyte and fluid disturbances. The presence of coronary artery disease and arterial fibrillation was associated with frequent use of antiplatelet and anticoagulant agents in these patients. The identification of ADE-related admissions based on the International Classification of Diseases would underestimate the total prevalence, as observed earlier [8, 12]. Moreover, the presentation of an ADR in elderly adults is often both atypical [13] and non-specific, besides, ADEs are often left unrecognized. Common reasons for admission in this sample included faintness, malaise, nausea, functional decline and dependence.

Key results

The study found that ADEs still contribute to hospital admissions at a geriatric ward and that a large proportion of ADE-related hospital admissions are potentially preventable.

Prevalence of ADE-related hospital admissions

The estimated 9-month prevalence of 11.75% (95% CI 8.45–15.05) in our study is similar to that of Conforti et al. [14] findings (6-month prevalence of 11.1%). Although the methodology differs slightly, both studies were performed on the geriatric ward, and the mean age of patients was also above 80 years. Therefore, these studies were focused on a particularly vulnerable population. The meta-analysis by Oscanoa et al. [15] found that 8.7% of hospital admissions in older patients are due to ADRs. The relatively high prevalence in this study could also be explained by the definition of medication-related hospital admission. Medication-related hospital admission is defined in several ways: 1. as an admission due to ADR, 2. as an admission due to ADE or 3. as an admission due to DRP [4]. This study was focused on ADEs. Considering that ADEs include not only ADRs but also the harm caused by medication errors, ADEs will naturally indicate higher prevalence compared to ADRs [4, 8]. Latest studies investigating ADE-related hospital admissions (Jolivot et al. [3], Laatikainen et al. [16]), have reported prevalence up to 23%. Two new guides [17, 18] developed recently for the identification of medication-related hospital admissions in older patients include a broader definition of medication-related hospital admissions. The inclusion of suboptimal treatment or omission of treatment would have yielded even higher estimates of prevalence in this study.

Preventability

The current study suggests that a considerable proportion of ADE-related hospital admissions are potentially preventable (53.5%). We have applied the Schumock-Thornton algorithm modified by Schmiedl et al. [11] for assessing preventability. This algorithm is principally consistent with the generally accepted criteria that classify medication errors as preventable and ADRs as non-preventable. Supposing that ADRs type A, in accordance

Table 2 Adverse drug events related to hospital admissions and implicated medications

Adverse drug event	Implicated medications	N
Gastrointestinal haemorrhage, ulceration or dyspepsia		13
	Acetylsalicylic acid[a]	4
	Warfarin	2
	Warfarin, acetylsalicylic acid[a], ibuprofen	1
	Warfarin, acetylsalicylic acid[a],	1
	Clopidogrel, acetylsalicylic acid[a]	1
	Diclofenac	1
	Acetylsalicylic acid[a], citalopram	1
	Dabigatran, sertraline	1
	Ketoprofen, nimesulide	1
Hyponatraemia		10
	Hydrochlorothiazide and amiloride	4
	Indapamide	3
	Hydrochlorothiazide	2
	Losartan	1
Digoxin intoxication		5
	Digoxin	5
Hyperkalaemia		2
	Perindopril	2
Hypokalaemia		2
	Furosemide	2
Haematoma		2
	Warfarin	1
	Nadroparin	1
Hyperglycaemia		2
	Prednisone	2
Bradycardia		2
	Betaxolol	1
	Betaxolol, amiodarone	1
Dehydration		2
	Furosemide	2
Syncope		1
	Metoprolol, isosorbide mononitrate	1
Hypoglycaemia		1
	Insulin lispro	1
Orthostatic hypotension		1
	Doxazosin	1
Total		43

[a] Low-dose

with the World Health Organization, are predictable and therefore preventable, as was employed by Wawruch et al. [19], it would falsely imply, that every medication-related admission was preventable.

Medications associated with the highest number of preventable ADE-related admissions included digoxin, warfarin and acetylsalicylic acid. These results share a number of similarities with Schmiedl et al. [11] and Franceschi al. [20] findings.

Strategies for minimizing the risk of medication-related hospital admissions should include adjusting doses for renally excreted medications in case of kidney impairment, careful risk–benefit assessment when combining medications with an elevated risk of bleeding, and increased monitoring of medications with narrow therapeutic range (e.g. digoxin, warfarin).

Table 3 Summary of main implicated medications sorted by ATC code

ATC code of therapeutic subgroup	ATC name of a therapeutic subgroup	N (%)	Implicated medications
B01	Antithrombotic agents	13 (30.2)	Warfarin (5), acetylsalicylic acid (5), nadroparin (1), clopidogrel (1), dabigatran etexilate (1),
C03	Diuretics	13 (30.2)	Hydrochlorothiazide and amiloride (4), furosemide (4), indapamide (3), hydrochlorothiazide (2)
C01	Cardiac therapy	5 (11.6)	Digoxin (5)
C09	Agents acting on the renin-angiotensin system	3 (7.0)	Perindopril (2), losartan (1)
C07	Beta blocking agents	3 (7.0)	Betaxolol (2), metoprolol (1)
M01	Anti-inflammatory and antirheumatic products	2 (4.7)	Diclofenac (1), ketoprofen (1)
H02	Corticosteroids for systemic use	2 (4.7)	Prednisone (2)
A10	Drugs used in diabetes	1 (2.3)	Insulin lispro (1)
C02	Antihypertensives	1 (2.3)	Doxazosin

ATC anatomical therapeutic chemical

Adverse drug events and implicated medication classes

Medication classes repeatedly linked to ADE-related admissions included diuretics (n = 13), anticoagulants (n = 7), antiplatelets (n = 6), cardiac glycosides (n = 5), beta-blockers (n = 3), nonsteroidal anti-inflammatory drugs (NSAIDs, n = 2), corticosteroids (n = 2) and angiotensin-converting enzyme inhibitors (n = 2).

The ADEs associated with diuretics included hyponatraemia, hypokalaemia and dehydration. The presenting symptoms associated with hyponatraemia were confusion, weakness, fatigue, nausea and fall. The mean serum sodium concentration was 123 mmol/l. The most common cause was a combination of hydrochlorothiazide and amiloride, followed by indapamide and plain hydrochlorothiazide. The results correlate with previous findings by Conforti et al. [14], Nair et al. [21], Ognibene et al. [22], Rogers et al. [23] and Onder et al. [24], which have identified diuretics as a leading cause of medication-related admission. The associated ADEs observed in these studies (electrolyte disturbances, volume depletion and acute kidney injury) are consistent with our findings.

The ADEs associated with anticoagulants included gastrointestinal haemorrhage and haematoma, while the ADEs associated with antiplatelets included gastrointestinal haemorrhage and gastrointestinal ulcerations. This supports the findings of previous studies [11, 25–29], which found antithrombotic agents among the most frequently implicated medication classes.

The reasons for admission related to digoxin were vomiting and other gastrointestinal disturbances. In a study of Cabré et al. [30] and Passarelli et al. [31], digoxin was the most frequently implicated medication. Schmiedl et al. [11] and Franceschi et al. [20] have also indicated a high contribution of cardiac glycosides to medication-related admissions. In contrast with previous studies [19, 20, 32], we have not observed any cardiac arrhythmias associated with cardiac glycosides.

The ADEs related to beta-blockers included bradycardia and syncope. In the studies of Marcum et al. [32], Wawruch et al. [19], Parameswaran Nair et al. [21] and Schmiedl et al. [11], beta-blockers were among the most common medication classes leading to hospital admissions.

NSAIDs were involved in gastrointestinal ulceration and dyspepsia. Franceschi et al. [20] and Cabré et al. [30] have also found NSAIDs to be a frequent reason for admissions related to gastrointestinal system disorders.

Previous studies have reported a higher prevalence of hypoglycaemia related to antidiabetics [11, 25, 32]. In the study of Wojszel et. [33], the authors have emphasized that there is a higher probability of too tight diabetes control among geriatric patients. The likely reason for the lower prevalence of hypoglycaemia in our study is the fact that there is widespread knowledge of different treatment goals and strategies for controlling diabetes applied to adult and geriatric patients in the Czech Republic.

In agreement with Conforti et al. [14] and Ognibene et al. [22] findings, we have identified electrolyte disturbances to be the main cause of medication-related hospitalisations. Our results are also consistent with those of previous studies that found haemorrhage [11, 14, 20, 22, 25, 28] frequently implicated in medication-related admissions.

Table 4 Classification of preventable ADEs in relation to aspects of preventability

Aspects of preventability[a]	Associated medications	N	Description
Inappropriate drug use			
Prior ADR in history (n = 3)	Clopidogrel	1	Gastrointestinal ulceration recorded in medical history
	Furosemide	1	Dehydration and falls recorded in medical history
	Prednisone	1	Hyperglycaemia recorded in medical history. Insufficient measures were taken to prevent recurrence of corticoid-induced hyperglycaemia
Drug inappropriate due to age and comorbidities (n = 1)	Doxazosin	1	Medication with a high risk of orthostatic hypotension was administered to a patient with a history of falls, even when safer alternatives were available
Inappropriate dose			
Insufficient dose adjustment of renally excreted drugs (n = 8)	Digoxin	5	No dosage adjustments were performed in patients with CKD. Additionally, serum digoxin level was above therapeutic range (1.54 nmol/l = 1.2 ng/ml[b]) in every case. Furosemide-induced hypokalaemia was present in two cases, and nonadherence was present in one case
	Perindopril	2	No dosage adjustments were performed in patients with CKD
	Nadroparin	1	No dosage adjustment was performed in a patient with CKD
Drug-drug interaction			
Relevant drug-drug interaction (n = 3)	Ketoprofen, nimesulide	1	Increased gastrotoxic potential. Additionally, ketoprofen is inappropriate in the elderly due to its high ulcerogenic effect
	Betaxolol, amiodarone, methyldopa	1	Increased risk of bradycardia. Additionally, methyldopa is not recommended as routine treatment for hypertension in the elderly
	Warfarin, ibuprofen acetylsalicylic acid[c],	1	Increased risk of gastrointestinal bleeding
Missing ADR prevention			
Drug-related (n = 3)	Acetylsalicylic acid[c], citalopram	1	Gastroprotection was not provided for a patient with an increased risk of gastrointestinal bleeding
	Acetylsalicylic acid[c]	1	Gastroprotection was not provided for the patient with an increased risk of gastrointestinal bleeding
	Diclofenac	1	Gastroprotection was not provided for a patient with a history of ulcers
Non-drug-related (n = 4)	Warfarin	4	Insufficient monitoring of INR
Others			
Nonadherence (n = 1)	Insulin	1	The dose of insulin was not adjusted to food intake

ADE adverse drug event, *ADR* adverse drug reaction, *CKD* chronic kidney disease, *INR* international normalized ratio

[a]Proposed by Schmiedl et al.[11]

[b]Upper serum digoxin concentration limit for elderly in the Czech Republic is 1.54 nmol/l (1.2 ng/ml) according to the CZ expert consensus for potentially inappropriate medication use in old age

[c] Low-dose

Concerning the Anatomical Therapeutic Chemical Classification System, medications listed under code C (Cardiovascular system) and code B (Blood and blood forming organs) were most commonly implicated in ADE-related hospital admissions.

Potentially inappropriate medications implicated in ADE-related admissions in this study included digoxin, NSAIDs and doxazosin. The meta-analysis by Oscanoa et al. [15] has identified NSAIDs and digoxin as being among the medication classes most frequently related to hospital admissions. Apart from the mentioned groups of potentially inappropriate medications, Cabré et al. [30] have revealed a considerable contribution of benzodiazepines to medication-related admissions.

Strengths and limitations

To our knowledge, this is the first study examining ADE-related hospital admissions to a geriatric ward in the Czech Republic. The principal investigator (M.M.) as a clinical pharmacist was a member of a collaborative team involved in the care of geriatric patients. The direct use of electronic medical records from the hospital information system enabled performing a comprehensive medication review.

The results of this study suggest that medication-related hospitalisations still occur, and a great proportion of these admissions could potentially be prevented. The identified preventability aspects may draw attention to possible safety problems in the pharmacotherapy of geriatric patients.

This study has several limitations worth mentioning. The major limitation of this study is the small sample, which was partly due to the time-consuming nature of data collection. Secondly, the assessment of causality and preventability of ADE-related hospital admissions should have been conducted by a multidisciplinary team. Another limitation which must be acknowledged is the fact that the verification of medication history was not performed. Medication reconciliation should be implemented in the hospital setting in order to minimize potential discrepancies.

Interpretation of results

Our findings add to a growing body of literature on medication-related harm among geriatric patients. Meaningful insight has been gained with regard to ADEs occurring on the geriatric ward. Our research has underlined the contribution of antithrombotic agents and diuretics to ADE-related admission. Despite existing awareness, these medication classes continue to cause a substantial proportion of medication-related hospital admissions. Further work needs to be carried out to propose tools for minimizing the risk of medication-related harm. The detection of a high proportion of potentially preventable ADEs in this study should encourage researchers to address preventability issues.

Generalisability

The study was limited to the description of ADE-related hospital admissions on a single geriatric ward, to which patients aged 78 years and older are admitted. In order to generalize the results to the overall population, patients of all ages would have to be included since the prevalence of medication-related hospital admission among geriatric patients is considerably higher compared to the non-elderly.

In addition, ADEs that resulted in admissions of geriatric patients to other hospital wards were not investigated. Previous studies have frequently identified falls [19, 22, 30, 32], psychiatric conditions [14, 21, 22, 30, 32] or acute kidney injuries [14, 21, 22, 30] as a reason for hospital admission in elderly patients. These ADEs contribute to hospital admission mostly to other wards (e.g. surgery, psychiatry and nephrology) of the hospital than in which this study took place. Moreover, certain ADEs, e.g. hypoglycaemia, are corrected at the emergency department without requiring hospital admission. Therefore, the findings are not representative of the entire geriatric population.

Suggestions for future research

Further studies should use a standardized definition od medication-related hospital admission. The latest definitions [17, 18] also include hospital admissions due to underuse of medications (e.g. untreated indication, subtherapeutic dosage, too short duration, medication nonadherence). Studies accessing interventions for the prevention of medication-related hospital admissions are also needed.

Conclusion

The contribution of ADEs to hospital admission to the geriatric ward was not negligible. Our results suggest that 53.5% of identified ADE-related admissions could be potentially prevented. This finding demonstrates just how important the research on the preventability of medication-related hospitalisations is. Further studies and implementations are still needed aiming to minimize the risk of medication-related harm.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11096-021-01237-y.

Acknowledgments This study was supported by Charles University (Project SVV 260 551).

Funding This study was supported by Charles University (Project SVV 260 551).

Conflicts of Interest The authors have no conflicts of interest to declare that are relevant to the content of this article.

Ethics Aprroval This study was approved by University Hospital Hradec Králové (number of the ethics approval letter 201701S13R). Patient informed consent was not required due to the observational design of the study.

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Supplement to: Maříková M, Očovská Z, Nerad V, Kuběna AA, Blaha V, Vlček J. Hospital admissions to geriatric ward related to adverse drug events: a cross-sectional study from the Czech Republic. *Int J Clin Pharm*. 2021;43(5):1218-1226. doi: 10.1007/s11096-021-01237-y

Age	Sex	Implicated medications, (+potentially contributing medications)	Adverse drug event (+details)	Preventability aspects
80	woman	warfarin	gastrointestinal haemorrhage (INR 5.21)	INR monitoring
80	woman	insulin lispro	hypoglycaemia (glucose 0.8 mmol/l)	adherence in food intake, glucose monitoring
88	woman	warfarin	haematoma (INR 3.9)	INR monitoring
93	woman	betaxolol	bradycardia (heart rate 49)	-
85	man	diclofenac	gastrointestinal haemorrhage and ulceration	gastroprotection
85	woman	furosemide	hypokalaemia (potassium 3.2 mmol/l)	-
80	woman	hydrochlorothiazide, amiloride	hyponatraemia (sodium 123 mmol/l)	-
85	man	acetylsalicylic acid, citalopram	gastrointestinal ulceration	gastroprotection
86	man	perindopril	hyperkalaemia (potassium 6.3 mmol/l)	dosage adjustments in CKD
79	woman	doxazosin	orthostatic hypotension	potentially inappropriate medication
96	woman	warfarin, acetylsalicylic acid, ibuprofen	gastrointestinal haemorrhage	drug-drug interaction
86	woman	prednisone	hyperglycaemia (glucose 21.2 mmol/l)	-
89	woman	indapamide, (perindopril)	hyponatraemia (sodium 128 mmol/l)	-
79	man	betaxolol, amiodarone, (methyldopa)	bradycardia (heart rate 48)	drug-drug interaction
79	woman	indapamide, (trandolapril)	hyponatraemia (sodium 109 mmol/l)	-
86	woman	prednisone	hyperglycaemia (glucose 28 mmol/l)	ADR in history, insufficient ADR prevention
96	woman	furosemide	dehydratation	ADR in history; insufficient ADR prevention
91	woman	metoprolol, isosorbide mononitrate	syncope	-
86	woman	digoxin, (furosemide)	digoxin intoxication (digoxin 2.2 nmol/l)	dosage adjustments in CKD
79	man	warfarin, acetylsalicylic acid	gastrointestinal haemorrhage (INR 10.59)	INR monitoring

93	woman	digoxin, (furosemide)	digoxin intoxication (digoxin 4.19 nmol/l)	dosage adjustments in CKD
82	woman	perindopril	hyperkalaemia (potassium 7 mmol/l)	dosage adjustments in CKD
88	woman	hydrochlorothiazide, amiloride	Hyponatraemia (sodium 120 mmol/l)	-
89	woman	ketoprofen, nimesulid	dyspepsia	drug-drug interaction; potentially inappropriate medications
87	woman	digoxin	digoxin intoxication (digoxin 4.09 nmol/l)	dosage adjustments in CKD, nonadherence
87	woman	hydrochlorothiazide, (candesartan)	hyponatraemia (sodium 130 mmol/l)	-
88	woman	acetylsalicylic acid, (pentoxifylline)	gastrointestinal haemorrhage and ulceration	gastroprotection
86	woman	losartan	hyponatraemia (sodium 127 mmol/l)	-
81	woman	nadroparin	haematoma	dosage adjustments in CKD
87	man	indapamide, (telmisartan)	hyponatraemia (sodium 130 mmol/l)	-
85	woman	hydrochlorothiazide, (telmisartan)	hyponatraemia (sodium 121 mmol/l)	-
81	man	warfarin	gastrointestinal haemorrhage (INR 11,7)	INR monitoring
93	woman	acetylsalicylic acid	gastrointestinal haemorrhage and ulceration	-
84	man	clopidogrel, acetylsalicylic acid	gastrointestinal ulceration	ADR in history
91	woman	acetylsalicylic acid (naftidrofuryl)	gastrointestinal haemorrhage	-
82	woman	furosemide	hypokalaemia (potassium 3.1 mmol/l)	-
87	woman	digoxin	digoxin intoxication (digoxin 1.99 nmol/l)	dosage adjustments in CKD
93	woman	acetylsalicylic acid	gastrointestinal haemorrhage and ulceration	-
90	woman	furosemide (spironolacton, telmisartan)	dehydration, reduction in glomerular filtration rate	-
96	woman	hydrochlorothiazide, amiloride	hyponatraemia (sodium 126 mmol/l)	-
84	woman	digoxin	digoxin intoxication (digoxin 1.87 nmol/l)	dosage adjustments in CKD
79	woman	hydrochlorothiazide, amiloride, (ramipril)	hyponatraemia (sodium 122 mmol/l)	-
83	woman	dabigatran, sertraline	gastrointestinal haemorrhage	-

ADR adverse drug reaction, *CKD* chronic kidney disease, *INR* international normalized ratio