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Preventable and Non-Preventable Adverse Drug Events in Hospitalized Patients

A Prospective Chart Review in the Netherlands

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Abstract

Background: Medication safety research and clinical pharmacy practice today is primarily focused on managing preventable adverse drug events (pADEs). Determinants of both pADEs and non-preventable adverse drug reactions (ADRs) have been identified. However, relatively little is known on the overlap between these determinants and the balance of preventable and non-preventable harm inpatients experience in modern computerized hospitals.

Objective: The aim of this study was to analyse the prevalence of pADEs and non-preventable ADRs as well as the determinants, including multimorbidity, of these ADEs, i.e. both pADEs and ADRs.

Methods: Adverse events experienced by patients admitted to two Dutch hospitals with functioning computerized physician order entry (CPOE) systems were prospectively identified through chart review. Adverse events were divided into pADEs (i.e. as a result of a medication error) and non-preventable ADRs. In both cases, a causal relationship between adverse events and patients' drugs was established using the simplified Yale algorithm. Study data were collected anytime between April 2006 and May 2008 over a 5-month period at each hospital ward included in the study, beginning from 8 weeks after CPOE was implemented at the ward.

Results: pADEs and non-preventable ADRs were experienced by 349 (58%) patients, of whom 307 (88%) had non-preventable ADRs. Multimorbidity (adjusted odds ratio [OR_{adj}] 1.90; 95% CI 1.44, 2.50; OR_{adj} 1.28; 95% CI 1.14, 1.45, respectively), length of stay (OR_{adj} 1.13; 95% CI 1.06, 1.21; OR_{adj} 1.11; 95% CI 1.07, 1.16, respectively), admission to the geriatric ward (OR_{adj} 7.78;

95% CI 2.15, 28.13; OR_{adj} 3.82; 95% CI 1.73, 8.45, respectively) and number of medication orders (OR_{adj} 1.25; 95% CI 1.16, 1.35; OR_{adj} 1.13; 95% CI 1.06, 1.21, respectively) were statistically significantly associated with pADEs and ADRs. Admission to the gastroenterology/rheumatology ward (OR_{adj} 0.22; 95% CI 0.06, 0.77; OR_{adj} 0.40; 95% CI 0.24, 0.65, respectively) was inversely related to both pADEs and ADRs. Other determinants for ADRs only were female sex (OR_{adj} 1.77; 95% CI 1.12, 2.80) and use of drugs affecting the nervous system (OR_{adj} 1.83; 95% CI 1.09, 3.07). Age was a significant determinant for pADEs only (OR_{adj} 1.07; 95% CI 1.03, 1.11).

Conclusions: In this study more than half of the patients admitted to the hospitals are harmed by drugs, of which most are non-serious, non-preventable ADRs (after the introduction of CPOE). Determinants of both pADEs and ADRs overlap to a large extent. Our results imply the need for signalling early potential adverse events that occur during the normal use of drugs in multimorbid patients or those in geriatric wards. Subsequent therapeutic interventions may improve the well-being of hospitalized patients to a greater extent than focusing on errors in the medication process only.

Background

Medication safety research and clinical pharmacy practice today is primarily focused on managing preventable adverse drug events (pADEs).[1] These types of adverse drug events (ADEs) are caused, by definition, by errors in the medication process. However, most of these medication errors do not result in ADEs.[2] The introduction of computerized physician order entry (CPOE) and clinical decision support systems (CDSS) has been successful in reducing the number of medication errors;[3-7] however, this has inversely affected the attention given to the management of non-preventable adverse drug reactions (ADRs) that occur during correct use of medication. Although ADRs are non-preventable in nature, their outcome may be modified by early detection.[8,9]

Most studies focus on more serious ADEs that, for example, prolong hospital stay.[10,11] A recent study in *Drug Safety* showed that 0.9% of hospital admissions resulted in serious ADEs, of which approximately 20% were considered preventable.[11] Nevertheless, non-serious ADEs also affect the well-being of hospitalized patients, and timely identification may improve patients' well-being.[12] Determinants for the occurrence of pADEs and ADRs have been studied in the past and even risk scores have been developed.[10,13-16] The potential relationship between age, sex, length of hospital stay, number and type of drugs and the occurrence of ADEs have been commonly studied.[15-18] Although results vary for these determinants, the number and type of drugs (e.g. drugs affecting the cardiovascular system, blood and blood forming organs, nervous system, anti-infectives, etc.) are consistently mentioned as significant determinants for ADEs.[15-18] However, less is known about multimorbidities (i.e. underlying clinical conditions) as a determinant of a patient's vulnerability to experience ADEs. Most studies of determinants have focused, to date, on their relationship with either pADEs or ADRs, or both combined. Rarely have both pADEs and ADRs been studied separately in one study setting.

In this study, we determine the prevalence of pADEs versus non-preventable ADRs and identify important determinants for both types of medication harm in a hospital setting with CPOE/CDSS.

Methods

Design

A prospective chart review study was performed as a substudy of a larger study looking at the impact of implementation of a CPOE system and CDSS on medication errors and pADEs.[4] The current study uses data that were collected over a 5-month period that started 8 weeks after CPOE was implemented (post-implementation). CPOE was implemented at different points between 2006 and the end of 2007 in different hospital wards involved in the study; subsequently, data collection took place between April 2006 (start of data collection in the first ward) and May 2008 (end of data collection from the last ward), as described in detail previously by van Doormaal et al.[4]

Setting and Study Population

The study was performed in the University Medical Center Groningen (UMCG) and TweeSteden Hospital, Tilburg and Waalwijk, the Netherlands. Patients admitted for more than 24 hours to the geriatric and general internal medicine wards of TweeSteden Hospital and the general internal medicine and gastroenterology/rheumatology wards in the UMCG were included in the study. Since the objective of this study fell within the boundaries of normal hospital care and quality of care improvement, a waiver from the Medical Ethics Committee was obtained. Patients received information about the study, after which they could object to inclusion.

Computerized Physician Order Entry Systems

The CPOE systems implemented in our hospitals have a 'basic' CDSS that checks drug-drug interactions (DDIs) and basic dosing guidance.[19] In the UMCG, the commercially available system Medicator® (iSOFT, Leiden, the Netherlands) was used. In this system, only the process of ordering medication is computerized; the process of dispensing and administering the medication is still paper-based. In TweeSteden Hospital, Theriak® (Theriak evf, Tilburg, the Netherlands), a partly locally-developed system is used in which the process of patient identification and medication administration is also automated by scanning barcodes on patients' wristbands, and barcodes on the packaging of medication.

Data Collection

Data were prospectively collected during daily ward visits by research pharmacists (AD, JvD and RZ). Weekend data were collected on Mondays. Patient characteristics (age, sex, weight, height and co-morbidities), disease characteristics (medical history, reason for admission and differential diagnoses), drugs used and laboratory results were extracted by reviewing physicians' and nurses' charts, the CPOE system and the hospital information system. Co-morbidities and diagnoses were recorded following the *International Classification of Diseases, 10th revision* (ICD-10).[20] Drugs were classified using the Anatomical Therapeutic Chemical (ATC) classification system.[21]

Outcomes and Assessment of Preventable Adverse Drug Events (pADEs) and Adverse Drug Reactions (ADRs)

The primary outcome parameters were the prevalence of pADEs and ADRs. All adverse events (i.e. untoward medical occurrences not necessarily related to the treatment) were collected. In daily ward visits, all signs and symptoms that could possibly be related to medication use recorded in the physicians' and nurses' charts were included. Adverse events were classified by the research pharmacists according to WHO Adverse Reaction Terminology.[22] In this classification, certain adverse events are classified as 'critical terms'; these adverse events refer to, or are possibly indicative of, 'serious disease states, which have been regarded as particularly important and should be evaluated further'.

Subsequently, a two-step procedure was used to identify any pADEs; remaining ADEs were then assessed to determine relationship to use of a drug, as described in the following section.

pADEs

A pADE was defined as an adverse event related to both a drug and a medication error, as

Table I. National Coordinating Council for Medication Error Reporting and Prevention[24] scheme for medication error (© 2001 National Coordinating Council for Medication Error Reporting and Prevention. All Rights Reserved)

Category	Description
A	Circumstances or events that have the capacity to cause error
B	An error occurred but the error did not reach the patient
C	An error occurred that reached the patient but did not cause patient harm
D	An error occurred that reached the patient and required monitoring to confirm that it resulted in no harm to the patient and/or required intervention to preclude harm
E	An error occurred that may have contributed to or resulted in temporary harm to the patient and required intervention
F	An error occurred that may have contributed to or resulted in temporary harm to the patient and required initial or prolonged hospitalization
G	An error occurred that may have contributed to or resulted in permanent patient harm
H	An error occurred that required intervention necessary to sustain life
I	An error occurred that may have contributed to or resulted in the patient's death

assessed in the framework of our previously-described intervention study.[4] In brief, after data collection of all possible adverse events, the research pharmacists (AD, JvD and RZ) reviewed and classified all medication orders of all included patients using the classification scheme developed by the Netherlands Association of Hospital Pharmacists.[23] The classification distinguishes prescribing, transcribing, dispensing, administering and 'across settings' errors. In this study, only prescribing and transcribing errors were recorded. Prescribing errors were subclassified as administrative errors (errors on readability, patient data, ward and prescriber data, drug name, dosage form and route of administration), dosing errors (errors on strength, dosage, frequency, length of therapy and directions for use) and therapeutic errors (DDIs, contraindications, incorrect monotherapy, duplicate therapy, therapeutic drug monitoring or laboratory monitoring errors). Transcribing errors were defined as errors in interpretation, verification and transcription of medication orders. The severity of all identified medication errors was assessed using the National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) scheme (see table I),[24] while causal relationship between the medication error and an adverse event was assessed using the simplified Yale algorithm.[25] This procedure was followed for all medication errors that reached the patient (i.e. at least NCC MERP class B)[26] The causal relationship could be assessed as unlikely (score <0), possible (score ≥0 and ≤3) and probable (score = 4) [see table II]. In the case of possible or probable, the event was defined as a pADE. When the relationship was unlikely, the medication error was categorized as not associated with a pADE. All assessments were achieved through consensus agreement (JvD, RZ, PvdB,

Table II. Simplified Yale algorithm (adapted from Kramer et al.,[25] with permission from the American Medical Association)

	+1	0	−1	Score
Axis 1	Adverse event is well accepted as ADR to suspected drug	Adverse event is not well known or drug is new	Adverse event is previously unreported as ADR to well known drug	
Axis 2	(a) No good alternative candidate (score +2) (b) Otherwise unexplained exacerbation or recurrence of underlying illness (score +1)	Alternative candidate(s) exist, but no good ones	Good alternative candidate(s) exist	
Axis 3	Timing as expected for ADR for this adverse event-drug pair	Timing equivocal or non-assessable	Timing inconsistent for ADR for this adverse event drug pair (score −2)	
Total score[a]				

a Score <0 means ADR is unlikely; score ≥0 and ≤3 means ADR is possible and score = 4 means ADR is probable.

ADR = adverse drug reaction.

JK and PM). This two-step procedure for identifying pADEs as described here, by combining the NCC MERP and Yale algorithms, has been validated and described in detail elsewhere previously.[26]

ADRs

In a separate procedure, the association between recorded possible adverse events not classified as pADEs and any drug taken by the patient was assessed. The causal relationship between the drug and an adverse event was assessed again using the simplified Yale algorithm (table II)[25] with the same cut-offs for unlikely, possible or probable relationship with medication used. The possibly- and probably-related adverse events were classified as ADRs. All assessments were made by two reviewers in consensus. If more than one drug had a possible/probable relation with an adverse event, the adverse event was ascribed to the drug with the highest Yale score.

In this study, the umbrella term ADE is used when we refer to both pADEs and ADRs.

Determinants of pADEs and ADRs

Determinants for pADEs and ADRs included in the study were organizational characteristics (hospital, ward), patient characteristics (sex, age, length of stay), drug-related characteristics (number of medication orders and drug type) and a patient's clinical condition. Determinants were selected based on those being previously reported.[5,7-11] We used multimorbidity, i.e. the total number of diagnoses, to describe a patient's clinical condition, and hypothesized that a higher number of diagnoses would make patients more vulnerable to experiencing a pADE or ADR.

Data Analysis

Data were processed using Microsoft Access® 2003 (Microsoft Corporation, Redmond, WA, USA). Analysis was performed with SPSS version 16.0 (SPSS Inc., Chicago, IL, USA). Univariate analysis followed by multivariate analysis was performed using a logistic regression (forced entry) model to establish which determinants independently contributed to the probability of pADEs and ADRs. The model included all determinants from the univariate analysis with a p-value < 0.1. Crude and adjusted odds ratios (ORs) with 95% CIs were calculated. In two models, patients with one or more pADEs (model 1) and ADRs (model 2) were compared separately to patients not experiencing ADEs. Length of stay (days), age (years), number of medication orders and number of diagnoses were analysed as continuous variables.

Results

During the study period 609 patients were admitted to the study wards, of whom six (approximately 1%) refused to take part in the study. Overall, 349 (58%) of 603 hospitalized patients experienced one or more ADE. A causal relationship of the event with a medication error (pADE) was established for 42 (12%) patients (7% of the total population studied). The remaining 307 (88%) patients with an ADE (51% of the total population studied) were classified as patients experiencing an ADR (figure 1).

These 349 patients experienced 935 ADRs (14% of these were WHO critical terms) and 54 pADEs (20% of these were WHO critical terms), an average of almost three events per patient. The most common ADRs and pADEs were constipation, diarrhoea, dyspnoea, increased international normalized ratio (INR), nausea, dizziness and fall. Of these common adverse events, INR increase is considered by the WHO as critical and, as such, warrant specific attention. Other 'critical term' pADEs or ADRs experienced by patients were hyperkalaemia, hypoglycaemia, phlebitis and hallucination (table III).

The most common drugs related to both pADEs and ADRs were drugs affecting the nervous system (ATC code N), drugs for the cardiovascular system (ATC code C), anti-infectives for systemic use (ATC code J) and drugs affecting the blood and the blood-forming organs (ATC code B) [table IV]. Patients with pADEs commonly received drugs for the nervous system, drugs affecting the blood and the blood-forming organs, cardiovascular drugs and systemic anti-infectives. Drugs

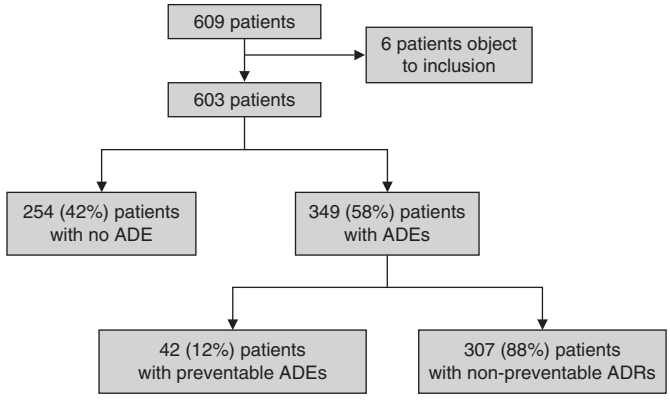

Fig. 1. Description of the study population. **ADE** = adverse drug event; **ADRs** = adverse drug reactions.

for the alimentary tract and metabolism (ATC code A) were the third most frequent cause of ADRs, but were infrequently related to pADEs.

The continuous variables, multimorbidity, length of stay and number of medication orders, were significant determinants for both pADEs (multimorbidity [OR_{adj} 1.90; 95% CI 1.44, 2.50], length of stay [OR_{adj} 1.13; 95% CI 1.06, 1.21], number of medication orders [OR_{adj} 1.25; 95% CI 1.16, 1.35]) and ADRs (multimorbidity [OR_{adj} 1.28; 95% CI 1.14, 1.45], length of stay [OR_{adj} 1.11; 95% CI 1.07, 1.16] and number of medication orders [OR_{adj} 1.13; 95% CI 1.06, 1.21]) [table V]. Admission to the geriatric ward led to an increased risk of both pADEs and ADRs (OR_{adj} 7.78; 95% CI 2.15, 28.13 and OR_{adj} 3.82; 95% CI 1.73, 8.45), and admission to the gastroenterology/rheumatology ward to a lower risk of both pADEs and ADRs (OR_{adj} 0.22; 95% CI 0.06, 0.77 and OR_{adj} 0.40; 95% CI 0.24, 0.65). Other significant determinants for ADRs only were female sex (OR_{adj} 1.77; 95% CI 1.12, 2.80) and use of drugs affecting the nervous system (OR_{adj} 1.83; 95% CI 1.09, 3.07) leading to an increased risk. In the multivariate model, age (OR_{adj} 1.07; 95% CI 1.03, 1.11) was a significant determinant for pADEs only (table V). As only 42 patients experienced a pADE, we restricted our adjustment in model 1 (no ADE vs pADE) to a maximum of three determinants (in addition to the determinant of interest. Therefore, we adjusted each determinant only for the number of medication orders, ATC class B type of drugs, and multimorbidity. This selection was based, in part, on the literature, with ADEs most firmly linked to the number of medication orders[16] and ATC class B drugs (including anticoagulants, especially to pADEs),[18] and in part to the strong univariate relation with a pADE observed in our study. Multimorbidity is our determinant of special interest; again, it was also strongly related to pADEs in the univariate analysis and was thus selected.

Of note, in model 2 (no ADE vs ADRs) we included all determinants that were significant in the univariate analysis. In our sensitivity analyses, we performed the same analysis for model 1 (no ADE vs pADE) with age instead of ATC class B drugs, and for model 2 (no ADE vs ADR) we performed the same analysis but adjusted for these three determinants: number of medication orders, ATC class B type of drugs and multimorbidity. These sensitivity analyses resulted in only minimal changes in point estimates and their CIs (data not shown), except in two cases: one determinant became just not significant, gastroenterology ward (OR_{adj} 0.29; 95% CI 0.08, 1.06) for pADE, and one became just significant, age (OR_{adj} 1.01; 95% CI 1.00, 1.02) for ADR.

Discussion

In our study, 58% of patients experienced one or more ADEs, an average of three per patient. Most of these ADEs were non-preventable ADRs

(51% of all patients). Only 7% of all patients experienced an ADE that was caused by a medication error (pADE). This situation occurred after CPOE was installed, which had reduced medication errors significantly, as shown in our previous study that focused on preventable harm.[4] Determinants of both ADRs and pADEs overlap to a considerable extent (i.e. multimorbidity, length of stay, number of medication orders, and admission to geriatric and gastroenterology/rheumatology wards). In addition, female sex and drugs for the nervous system were determinants for ADRs, and age was a determinant for pADEs.

Table III. Most common adverse drug events[a]

Common adverse event	pADE [no. of events (%)]	ADR [no. of events (%)]
Constipation	8 (14.8)	68 (7.3)
Diarrhoea	4 (7.4)	67 (7.2)
Headache	0 (0.0)	52 (5.6)
Nausea	3 (5.6)	45 (4.8)
Oedema	0 (0.0)	45 (4.8)
Sedation	0 (0.0)	38 (4.1)
Agitation	0 (0.0)	35 (3.7)
Dyspnoea	5 (9.3)	31 (3.3)
Dizziness	2 (3.7)	25 (2.7)
Fatigue	0 (0.0)	21 (2.2)
Confusion	0 (0.0)	19 (2.0)
Hyperglycaemia	0 (0.0)	19 (2.0)
Hypotension	0 (0.0)	19 (2.0)
Fall	2 (3.7)	17 (1.8)
Hypoglycaemia[b]	0 (0.0)	17 (1.8)
Pain	0 (0.0)	17 (1.8)
Sleep difficult	0 (0.0)	17 (1.8)
Abdominal pain	0 (0.0)	13 (1.4)
Disorientation	0 (0.0)	13 (1.4)
Phlebitis[b]	0 (0.0)	12 (1.3)
Emesis	0 (0.0)	11 (1.2)
INR increased[b]	4 (7.4)	10 (1.0)
Hallucination[b]	0 (0.0)	10 (1.0)
Haematoma	2 (3.7)	3 (0.3)
Hyperkalaemia[b]	2 (3.7)	2 (0.2)
Other	22 (40.7)	309 (33.0)
Total[c,d]	**54 (100)**	**935 (100)**

a Adverse drug events were classified according to the WHO Adverse Reactions Terminology.[22]

b These ADEs are WHO critical terms.

c Percentages do not sum exactly to 100% because of rounding.

d The number of pADEs and ADRs are higher than the total number of patients as some patients experienced more than one event.

ADR = adverse drug reaction; **INR** = international normalized ratio; **pADE** = preventable adverse drug event.

The most common pADEs or ADRs experienced by patients were constipation, diarrhoea, dyspnoea, increased INR, nausea and dizziness, as well as falls. Although most of these observed events were non-serious, they affected patients' quality of life and stand as signals to problems that need intervention. Increased INR is considered a 'critical term' by WHO standards, i.e. an adverse event warranting follow-up. In a hospital setting, these events and others such as abnormal laboratory values, could be addressed promptly, and are typical examples of where more advanced information technology-centred solutions (CPOE with CDSS) could be of value.

In our study, and after implementation of a CPOE system, hospitalized patients primarily experienced ADEs that were not caused by medication errors (i.e. ADRs). This implies that basic CPOE systems are not enough to prevent ADRs since they focus primarily on detecting medication errors, e.g. DDI or overdosage. A similar high rate in ADRs versus pADEs was observed in a hospital setting where a medication review by pharmacists had led to a reduction in pADEs but where no effect was observed on ADRs.[5,27]

In contrast to recent reviews on ADEs in hospitalized patients, the proportion of patients with ADEs is high in our study. This difference could be explained by the fact that these reviews focused on serious, life-threatening or fatal ADEs,[10,17] whereas in this study we also included non-serious ADEs. Our data collection included review of often overlooked nurses' charts, which are considered a good source for less serious ADEs such as nausea, rash or changes in mental status. Nurses are in closest contact with patients and their relatives and are informed first of any complaints and observations they may have.[28] We think that such events, from the perspective of the hospitalized patient, are very important and can negatively affect their well-being, and should thus receive appropriate attention. Although the majority of these ADEs may not be preventable,

Table IV. Most commonly prescribed drugs for patients with adverse drug events[a]

ATC code	Drug class	pADE [no. of events (%)]	ADR [no. of events(%)]
A	Alimentary tract and metabolism	1 (1.9)	141 (15.1)
B	Blood and blood-forming organs	11 (20.4)	61 (6.5)
C	Cardiovascular system	8 (14.8)	214 (22.9)
D	Dermatological	0 (0.0)	1 (0.1)
G	Genito-urinary system and sex hormones	0 (0.0)	9 (1.0)
H	Systemic hormonal preparations, excluding sex hormones and insulins	0 (0.0)	33 (3.5)
J	Anti-infectives for systemic use	7 (13.0)	97 (10.4)
L	Antineoplastic and immunomodulating agents	0 (0.0)	10 (2.6)
M	Musculo-skeletal system	5 (9.3)	33 (3.5)
N	Nervous system	17 (31.5)	298 (31.9)
P	Antiparasitic products, insecticides and repellents	0 (0.0)	5 (0.5)
R	Respiratory system	5 (9.3)	31 (3.3)
S	Sensory organs	0 (0.0)	2 (0.2)
Total[b,c]		**54 (100)**	**935 (100)**

a Relationships in terms of frequencies and percentages of ADRs or pADEs with the most commonly used drugs (classified by the first character of their ATC code) are given in this table.

b Percentages do not sum exactly to 100% because of rounding.

c The number of pADEs and ADRs are higher than the total number of patients as some patients experienced more than one event.

ADR = adverse drug reaction; **ATC** = Anatomical Therapeutic Chemical; **pADE** = preventable adverse drug event.

a number of them could be managed at an early stage by, for example, stopping or switching to a different drug, adapting a dose, or sometimes adding a drug to alleviate symptoms.

Detection of ADEs and medication errors is also known to be influenced by the way the data are collected and reviewed.[29] Prospective/retrospective chart review, spontaneous reporting and use of trigger tools are shown to generally identify different ADEs. Among these methods, prospective methods have been shown to be the more sensitive strategy for detecting ADEs compared with retrospective review.[30] Moreover, an intensive, prospective, frequent chart review, such as the one we performed, consistently identifies the highest number of ADEs and medication errors.[29] Lastly, we used a low threshold for causal relationship between the adverse events and medication, i.e. we considered an adverse event as being drug-related when it had a possible or probable relationship with the drug taken. A study by Nebeker et al.[5] found a similar rate of ADEs per admission as to that found in our study; however, their CPOE was even more basic than ours, lacking dosing or interaction control, thus translating into a higher proportion of pADEs than we observed. The daily ward visits by the research pharmacists may have had a slight impact on the reporting of adverse events, which may have been higher due to their awareness of drug-related issues. Other staff on the wards may also have been made more aware of drug issues and the potential for ADEs because of the daily ward visits by the research pharmacists. However, we expect this to be minimal as in our hospitals many different staff members, including researchers, frequently visit the wards.

We identified approximately the same determinants for pADEs and ADRs as reported elsewhere: number of medication orders, length of hospital stay, organizational characteristics (geriatric ward increases and gastroenterology/rheumatology ward decreases risk)[14,15,31] and also multimorbidity.[32,33] The role of drug classes was less pronounced, with some exceptions. Drugs for the nervous system (ATC group N) increased and those grouped under 'Others' decreased the risk for ADRs only, but no drug class was a determinant for pADEs in the multivariate analyses. This underlines the relevance of closely

Table V. Risk factors for patients with preventable adverse drug event (pADE) and adverse drug reaction (ADR) vs no adverse drug event (ADE)

Determinants[a]	No ADE [n (%)] (n = 254)	Model 1[b]			Model 2[b]		
		pADE [n (%)] (n = 42)	OR (95% CI)	OR_{adj}[c] (95% CI)	ADR [n (%)] (n = 307)	OR (95% CI)	OR_{adj}[d] (95% CI)
Sex							
male	127 (50.0)	17 (40.5)	Ref (ref)	Ref (ref)	118 (38.4)	Ref (ref)	Ref (ref)
female	127 (50.0)	25 (59.5)	1.47 (0.76, 2.86)	1.20 (0.48, 2.99)	189 (61.6)	**1.60** (**1.14**, **2.24**)	**1.77** (**1.12**, **2.80**)
Age (mean ± SD)[e]	58.7 (19.03)	77.6 (10.7)	**1.09** (**1.06**, **1.13**)	**1.07** (**1.03**, **1.11**)	68.7 (18.4)	**1.03** (**1.02**, **1.04**)	0.99 (0.98, 1.01)
Hospital department							
internal medicine	99 (39.0)	17 (40.5)	Ref (ref)	Ref (ref)	119 (38.8)	Ref (ref)	Ref (ref)
gastroenterology/rheumatology	144 (56.7)	5 (11.9)	**0.20** (**0.70**, **0.57**)	**0.22** (**0.06**, **0.77**)	84 (27.4)	**0.48** (**0.33**, **0.71**)	**0.40** (**0.24**, **0.65**)
geriatric	11 (4. 3)	20 (47.6)	**10.60** (**4.31**, **25.98**)	**7.78** (**2.15**, **28.13**)	104 (33.9)	**7.87** (**4.00**, **15.47**)	**3.82** (**1.73**, **8.45**)
Length of stay (mean ± SD)[e]	6.13 (5.3)	20.8 (17.2)	**1.21** (**1.15**, **1.28**)	**1.13** (**1.06**, **1.21**)	15.84 (12.2)	**1.20** (**1.15**, **1.24**)	**1.11** (**1.07**, **1.16**)
Multimorbidity (mean ± SD)[e]	3.13 (1.63)	4.8 (1.6)	**1.72** (**1.41**, **2.11**)	**1.90** (**1.44**, **2.50**)	4.03 (1.95)	**1.32** (**1.20**, **1.46**)	**1.28** (**1.14**, **1.45**)
Number of medication orders (mean ± SD)[e]	7.1 (4.9)	18.2 (9.2)	**1.29** (**1.20**, **1.39**)	**1.25** (**1.16**, **1.35**)	14.7 (9.3)	**1.21** (**1.16**, **1.25**)	**1.13** (**1.06**, **1.21**)
Type of drug (ATC code)							
Alimentary tract and metabolism (A)	185 (72.8)	38 (90.5)	**3.54** (**1.22**, **10.30**)	0.37 (0.09, 1.48)	268 (87.3)	**2.56** (**1.66**, **3.96**)	1.06 (0.56, 2.03)
Blood and blood-forming organs (B)	130 (51.2)	37 (88.0)	**7.06** (**2.69**, **18.54**)	2.33 (0.71, 7.59)	231 (75.2)	**2.90** (**2.03**, **4.14**)	1.20 (0.73, 1.98)
Cardiovascular system (C)	130 (51.2)	31 (73.8)	**2.69** (**1.30**, **5.58**)	0.67 (0.23, 1.91)	224 (72.3)	**2.57** (**1.18**, **3.66**)	1.00 (0.60, 1.71)
Anti-infectives for systemic use (J)	84 (33.1)	23 (54.8)	**2.45** (**1.26**, **4.75**)	0.90 (0.36, 2.30)	156 (50.8)	**2.09** (**1.48**, **2.95**)	1.12 (0.69, 1.82)
Nervous system (N)	133 (52.4)	35 (83.3)	**4.55** (**1.95**, **10.62**)	2.58 (0.86, 7.79)	257 (83.7)	**4.68** (**3.16**, **6.91**)	**1.83** (**1.09**, **3.07**)
Others	145 (57.1)	36 (85.7)	**4.51** (**1.84**, **11.09**)	0.88 (0.27, 2.89)	208 (67.8)	**1.58** (**1.12**, **2.23**)	**0.55** (**0.33**, **0.92**)

a Determinants influencing the prevalence of ADR vs no ADE and determinants influencing the prevalence of pADE vs no ADE were determined for their significance based on the values of the crude and adjusted ORs with their 95% CI. Values in bold are statistically significant.

b Analysed vs no ADE.

c Adjusted for multimorbidity, ATC code B type of drugs (Blood and blood-forming organs) and number of medication orders.

d Adjusted for all other variables.

e Analysed as a continuous variable.

ATC = Anatomical Therapeutic Chemical; **OR** = odds ratio; **OR_{adj}** = adjusted OR; **Ref** = reference.

monitoring patients with multiple morbidities to identify ADRs and pADEs that may be manageable (e.g. symptomatic treatment or drug discontinuation). Age was a risk factor for pADE but was significant in a sensitivity analysis for ADRs also, stressing the fact that the elderly should receive appropriate attention because they are a vulnerable population who often have multiple co-morbidities for which they receive multiple drugs.[34]

This study confirms findings from other studies that women have a greater risk of developing ADRs compared with men, and this may be explained by intrinsic differences in pharmacokinetic, immunological, hormonal and behavioural sex-related factors.[35,36] However, it is unclear to us, in this study, why women were not more prone to be harmed when an error in the medication process was made. The observation that more non-preventable ADRs were identified in patients admitted to a geriatric ward could be explained by an increased awareness of medical, nursing and pharmacy staff that frail elderly patients in particular may be more vulnerable to medication harm.[37,38]

At present, interventions in hospital processes focus primarily on reducing medication errors and pADEs, but our study shows that this may need to change to ensure ADRs are also managed. The current focus on Information and Communications Technology (ICT) solutions through CPOE and CDSS, even when addressing risk factors common to pADEs and ADRs, will not suffice in ameliorating the large proportion of medication-related patient harm that is not captured in a structured manner (e.g. laboratory results) in the hospital information system. Increased attention on the early detection of patient harm is of paramount importance in view of the frequent occurrence of non-preventable ADRs. ICT systems are not yet able to detect these non-preventable ADRs comprehensively. Hospital staff directly attending the patient, with a possible role for the clinical pharmacist, should pay more attention to medication safety. Early identification and management of these non-preventable ADRs, even when considered minor compared with the reason for admission, may contribute considerably to the well-being of an inpatient. This may need further research, for example, into protocols for nursing staff to raise awareness of minor ADRs and to systematically check for potentially manageable medication harm.

This study has some limitations. Only patients from gastroenterology, rheumatology, geriatrics and general internal medicine wards of two hospitals were included in this study; therefore, our results may not apply to other departments or other hospitals. For example, time constraints in the emergency department and hierarchical structures in surgical teams have been shown to negatively affect handling of patient safety issues compared with an internal medicines setting.[39] Furthermore, our study only considered prescribing and transcribing errors and did not include errors made when administering medication to patients. We used a sensitive and low threshold approach for detecting ADEs that may explain our observed high incidence of ADEs. In clinical practice it is not feasible to perform a full causality assessment using, for example, the complete Yale algorithm. The recognition that patients experience many discomforting ADEs while in hospital, albeit not caused by medication errors, could, nevertheless, be of considerable importance from the patient's perspective as they may be manageable. A strong point of our study is the method of detection of ADEs. This study prospectively reviewed charts daily, which has been previously described as an effective strategy for detecting ADEs compared with a retrospective approach.[23]

Conclusions

Our study shows that ADEs are a frequent problem in hospitalized patients. Most interventions in hospital processes (CPOE/CDSS and/or medication review) target pADEs, but the majority of ADEs are not preventable, even when a CPOE is in place. Our study also shows that determinants are to a large extent similar for both preventable ADEs and non-preventable ADRs. Signalling early potential adverse events that occur during the normal use of drugs in multimorbid patients and subsequent therapeutic interventions

may improve the well-being of hospitalized patients to a greater extent than focusing on errors in the medication process only. Aside from the more commonly known determinants, our study confirmed that multimorbidity is associated with an increased risk of pADEs and ADRs, suggesting that it is important to identify high-risk patients who need close monitoring for early detection of these events.

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