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Retrospective analysis of adverse drug reactions leading to short-term emergency hospital readmission

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Summary

AIMS OF THE STUDY: Adverse drug reactions (ADRs) are an important cause of hospital admissions. Insufficient data are available about the frequency and characteristics of ADR-related emergency readmissions in Switzerland. The aim of this retrospective study was to characterise ADRs related to short-term emergency readmissions in a large Swiss University Hospital and to assess their reporting frequency.

METHODS: Electronic records of all patients discharged from the University Hospital Bern within a 12-month period (1 January to 31 December 2012) and emergency readmission within 30 calendar days were reviewed. Case inclusion required a known ADR. Cases with intentional overdosing, lack of compliance or insufficient documentation were excluded. Identified ADR-related readmission cases were searched in the Swiss ADR reporting system to assess reporting rate.

RESULTS: There were 1294 emergency readmissions among the 4792 readmissions (14% of all admissions) within 30 days after discharge. We identified 270 cases of ADR-related readmissions, corresponding to 21% of emergency readmissions and 6% of all readmissions within 30 days. The most frequent ADRs were gastrointestinal disorders (26%), infections and infestations (19%), and nervous system disorders (10%). The most frequent drug classes leading to ADRs were antineoplastic/immunomodulating (35%) and antithrombotic agents (25%). Only 8 (3%) of the 270 cases were reported to the Swiss ADR reporting system.

CONCLUSION: ADR-related readmissions constituted a considerable part of short-term emergency readmissions. Despite being a relevant cause for rehospitalisation, only a minority of the ADRs were reported to the regulatory authorities. Strategies to prevent ADR-related readmissions and to improve reporting rates are needed.

Keywords: *adverse drug reactions, hospital readmission, emergency readmission, pharmacovigilance, drug safety*

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Introduction

Adverse drug reactions (ADRs) are unintended noxious responses to medicinal products and can present a major burden on health care [1, 2]. Approximately 3-5% of hospital admissions are estimated to be related to ADRs [2–4], with even higher rates in geriatric populations [5]. Patients hospitalised owing to an ADR have a significantly prolonged length of hospital stay and an almost 2-fold increased risk of death compared with other hospitalised patients [6]. Therefore, efforts to decrease ADRs are essential to reduce patient harm and healthcare costs.

Hospital readmissions are increasingly used as a measure of healthcare quality [7]. According to a recent systematic review including 19 studies, the median prevalence rate of drug-related hospital readmissions was 21%, with an estimated preventability of 69% [7]. Hospital readmissions shortly after hospital discharge represent a subgroup of great interest in terms of preventive measures and quality improvement. Although short-term hospital readmissions can be associated with non-drug related causes such as premature discharge due to pressure on beds, poor community support services and medical complications [8], in a previous study from the United States nearly one-fourth of the cases with hospital readmission within 30 days had a contributing ADR [9]. In a German study, ADRs led to hospitalisation in 6.2% of first admissions and in 4.2% of readmissions [10]. In some cases, a combination of the above-mentioned reasons may lead to a short-term readmission; for example, an ADR caused by a new drug therapy started during hospitalisation might not be detected in time owing to premature discharge in an effort to reduce

costs, with short-term readmission as a possible consequence [10]. Importantly, approximately half of the ADRs leading to hospital admission have been found to be preventable [8, 10], which highlights the importance of ADR monitoring in clinical practice to optimise patient care and public health.

Spontaneous ADR reports transmitted from health professionals to drug regulatory authorities play an important role in providing postmarketing pharmacovigilance data. In Switzerland, ADR reports are processed by regional pharmacovigilance centres and Swissmedic's national pharmacovigilance centre, which collaborates with the international centre for drug safety run by the World Health Organization (WHO) [11]. In accordance with the new Law on Therapeutic Products [12], all serious adverse reactions must be reported. ADRs are considered serious if they result in death, are life-threatening, lead to or prolong hospitalisation, involve a persistent disability or incapacity, or are otherwise to be considered medically significant (e.g., when a timely medical intervention was needed to prevent one of the above-mentioned outcomes). Spontaneous reports can contribute to drug safety by generating signals of possible ADRs that can then be followed more closely.

Investigation of ADR-related readmissions can contribute to the identification of vulnerable groups and high-risk drugs and to public health by offering guidance regarding preventive measures. Currently, insufficient data are available regarding the frequency and characteristics of ADR-related emergency readmissions in Switzerland. The main aim of this retrospective study was to characterise ADRs leading to short-term emergency readmissions in a large Swiss University Hospital. Further, we aimed to assess the reporting frequency of such ADRs to the Swiss national pharmacovigilance centre.

Materials and methods

This retrospective study included all ADR-related readmissions presenting to the emergency department of the University Hospital Bern within 30 days after hospital discharge between 1 January and 31 December 2012. The emergency department of the University Hospital Bern is both a primary care facility (walk-in patients) and tertiary referral centre for hospitals in the greater Bern area (patients ≥16 years of age), with about 48,000 emergency admissions a year (2018). The division of Clinical Pharmacology and Toxicology of the hospital also hosts the local regional pharmacovigilance centre, which receives and processes ADR reports and forwards them to the national pharmacovigilance centre (Swissmedic). The study was reviewed by the local ethics committee (Cantonal Ethics Committee Bern).

Cases were identified by reviewing the electronic records of all patients discharged from the University Hospital Bern within the 12-month period with emergency readmission within 30 calendar days after hospital discharge. The follow-up period of 30 days has been commonly used in previous studies investigating drug-related hospital readmissions [7], and hospital readmission within 30 days of discharge has also been described as a standard measurement of hospitalisation quality [13]. Case inclusion required a known ADR (listed in the official Swiss [14] or US drug information [15]) and, in line with the definition of ADRs [1], a temporal relationship between the ADR and drug intake. Cases were included if the reason for the readmission was an ADR (causality could be possible, probable or certain). The assessment was based on the reason of admission as stated in the emergency department report and information on patient history (medication history). In some, but not all, cases the drug cause was mentioned in the admission diagnosis section. Cases with intentional overdosing, evident lack of compliance, insufficient documentation, decreasing symptoms despite continuation of the suspected drug(s), or readmitted for non ADR-related signs and symptoms (e.g., in the context of the patient's primary disease, cases of violent assaults) were excluded. Patient records were reviewed independently by two experienced medical professionals and unclear cases (divergent opinions of the two primary assessors) were additionally reviewed together with a senior physician with experience in this field. Identified cases were searched in the Swiss ADR reporting system to assess the reporting rate. A flowchart of the procedures is shown in figure 1.

An ADR was defined as "an appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product" [1]. Drugs were classified using the WHO classification system based on the Anatomical Therapeutic Chemical (ATC) code, a unique code assigned to a medicine according to the organ or system it acts on and how it works [16]. For the evaluation of drug interactions, the drug interaction screening programme Pharmavista was used [17]. For the description of ADRs, the WHO Adverse Reaction Terminology (WHO-ART) Lowest Level Terms (LLTs) were used to provide maximum specificity [18]. The causality assessment was based on the Swiss ADR reporting system criteria (table 1) [19], which are based on the WHO Uppsala Monitoring Centre (UMC) causality assessment system [20].

For the investigation of differences between the ADR-related readmissions (study population) and non ADR-related emergency readmissions during the study period, for which data were collected on age, sex, days between first hospitalisation and readmission, and duration of hospitalisation after readmission, comparisons were tested using the chi-square test for categorical variables, the t-test for normally distributed continuous variables, and the Mann-Whitney test for nonparametric variables. Values of $p < 0.05$ were considered statistically significant. Statistical analyses were conducted using SPSS statistical software (IBM SPSS Statistics 25.0).

Results

During the study period there were 4792 readmissions (14% of all admissions) within 30 days after discharge and 1294 (27% of all readmissions) of these were emergency readmissions. We identified 270 cases of ADR-related emergency readmissions, corresponding to 21% of emergency readmissions and 6% of all readmissions within 30 days. Nine hundred and sixty-one cases were not ADR-related and in 63 cases an adequate evaluation was not pos-

sible because of insufficient or missing documentation (fig. 2).

Among the 270 cases of ADR-related readmissions, 78% were readmitted from home and 22% from a medical institution (hospital or rehabilitation facility). Most patients were elderly (59% ≥65 years old) and were male (63%). The median number of drugs on readmission was 8 (range 0–22; causative drugs already discontinued before presentation at the emergency department in 2 cases and no information on the number of drugs available in 32 cases). The median number of (active) main diagnoses was 6 (range 1–18). In 125 cases (46%), the ADR was associated with a drug that was newly started or changed during the index hospitalisation, in 136 cases (50%) the associated drug was either unchanged or started after the index hospitalisation, and in 9 cases (3%) an evaluation was not possible because of insufficient information. ADR-related cases were

Figure 1: Flowchart of the procedures used for the identification of adverse drug reaction (ADR)-related emergency readmissions. (* = Listed in the official Swiss or US drug information.)

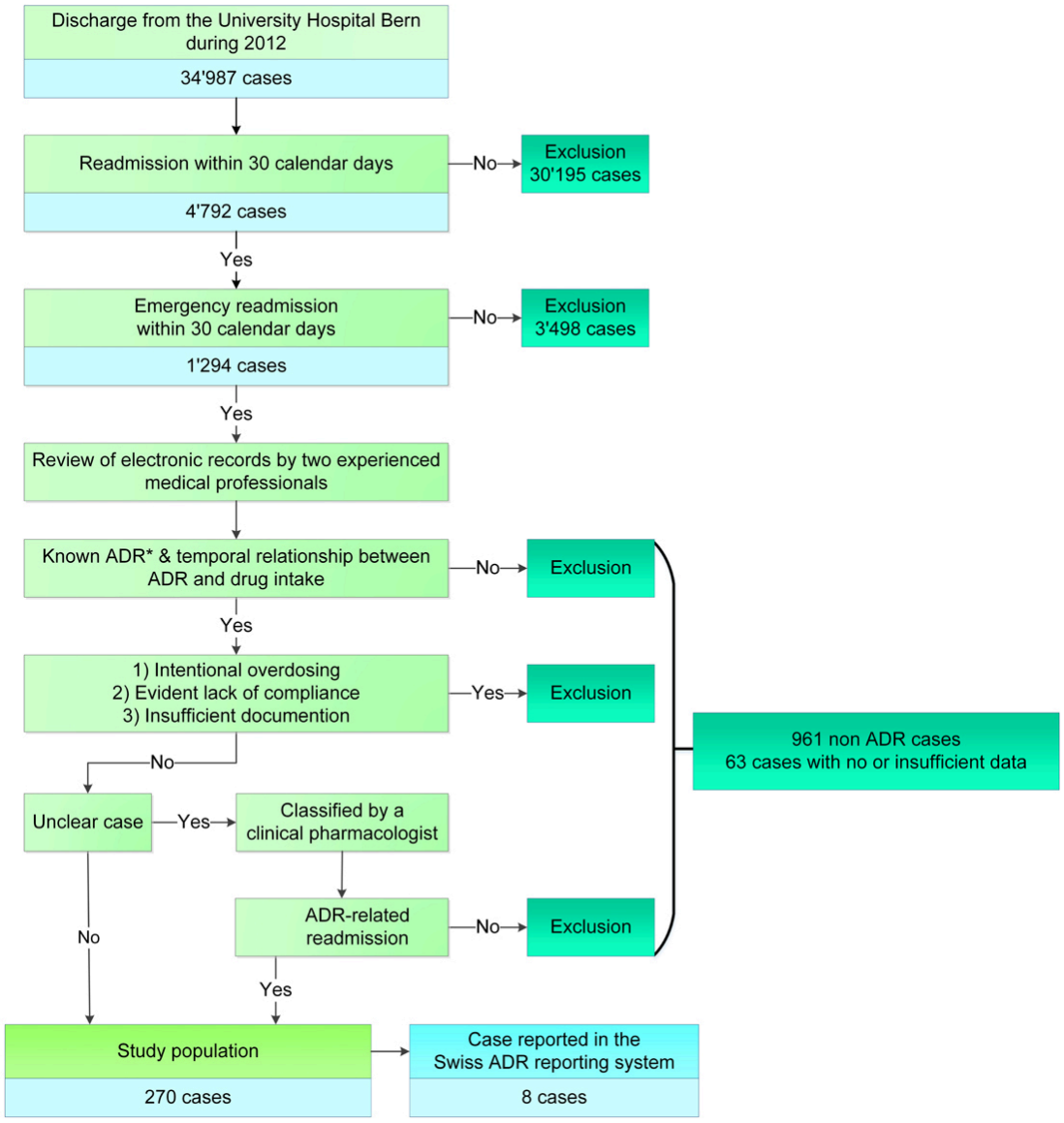

Table 1: Causality assessment criteria [19].

Causality term	Assessment criteria
Certain	– Temporal relationship to drug intake – Response to withdrawal (dechallenge) – Recurrence after reexposure to drug (rechallenge) – Other proof of causality, e.g. response to specific antidote
Probable/likely	– Temporal relationship to drug intake – Response to withdrawal (dechallenge) – Unlikely to be attributed to other (non-drug) cause
Possible	– Time relationship to drug intake – Could also be explained by other (non-drug) cause

significantly older than the non-ADR-related cases, while no significant differences were found regarding sex, number of days between discharge of first hospitalisation and rehospitalisation as well as duration of rehospitalisation (table 2). The most frequent ADRs leading to hospital readmission were gastrointestinal disorders (69 cases, 26%), infections and infestations (52 cases, 19%), and nervous system disorders (27 cases, 10%) (table 3). A total of 477 drugs were classified as possible causes of ADR-related hospital readmissions (more than one drug involved in some cases). The most frequent drug classes were antineoplastic/immunomodulating (35%), antithrombotic agents (25%), and nervous system drugs (16%); the most frequent chemical subgroups were glucocorticoids (11%), platelet aggregation inhibitors (9%), heparins (8%), vitamin K antagonists (7%), calcineurin inhibitors (5%) and other immunosuppressants such as mycophenolate or mTOR (mammalian target of rapamycin) inhibitors (4%) (supplementary table S1 in appendix).

In 231 cases (86%), the ADR concerned a reaction to the drug itself, in four cases (2%) an ADR was caused by a drug-drug interaction (DDI), and in 35 cases (13%) both. The four cases in which a DDI led to an ADR included hyponatraemia under the combination of oxcarbazepine, hydrochlorothiazide and citalopram, hyperammonaemic encephalopathy under the combination of valproic acid and topiramate, drug-induced delirium under ritonavir and midazolam, and a fatal case of acute renal failure under perindopril, indapamide, torasemide and lercanidipine. Further details about cases with fatal outcome can be found in table 4.

The further 31 cases with ADRs caused not only by the drugs themselves but also by a DDI included cases with increased risk of bleeding (drugs involved: acetylsalicylic acid, clopidogrel, nadroparin, enoxaparin, heparin, phenprocoumon, acenocoumarol, escitalopram, ibuprofen, ciprofloxacin, dexamethasone), one case of increased toxicity of fluoropyrimidines (drugs involved: fluorouracil, calcium folinate), one case of increased risk of extended respiratory depression and sedation (drugs involved: morphine, flunitrazepam), one case of a skin reaction in a patient treated with lamotrigine and valproic acid, and one case with two interactions, blood pressure decrease (candesartan, hydrochlorothiazide) and hyponatraemia and ventricular arrhythmias (hydrochlorothiazide, trimipramine).

With respect to causality, according to the Swiss ADR reporting system causality criteria, most cases (244, 90%) were assessed as “possible”, 24 (9%) as “probable/likely” (table S2), and two (<1%) as “certain” (one case of heparin-induced thrombocytopenia under nadroparin and one case of accidental drug overdose under tacrolimus).

In accordance with the new Law on Therapeutic Products [12], all ADRs of the study were classified as “serious” as they led to (re-)hospitalisation; in 228 of the cases (84%), this was the only criterion for “seriousness”, 34 cases (13%) required admission to the intensive care unit and were thus considered to be life-threatening (table S3), and 8 cases (3%) were fatal (table 4). Despite fulfilled criteria for seriousness in all of the included cases, only 8 (3%) of the 270 cases and none of the fatal cases were reported to the Swiss ADR reporting system (table 5).

Discussion

Our data show that ADR-related readmissions constitute a considerable part of short-term emergency readmissions.

Figure 2: Number of cases of non-emergency readmissions and adverse drug reaction (ADR)- and non-ADR-related emergency readmissions.

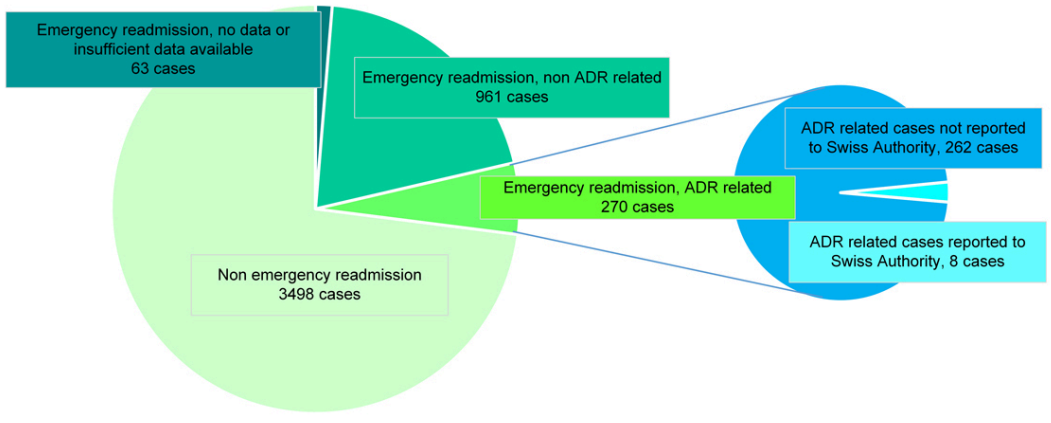

Table 2: Characteristics of emergency readmissions with an adverse drug reaction (ADR)- and non-ADR-related readmissions.

	All cases (n = 1231)	ADR-related cases (n = 270)	Non-ADR-related cases (n = 961)	p-value
Age (years), median (range)	64 (17–95)	67 (17–91)	63 (17–95)	<0.001
Female, n (%)	467 (38)	99 (37)	368 (38)	0.626
Days between first hospitalisation and readmission, median (range)	9 (0–30)	8 (0–30)	9 (0–30)	0.172
Duration of hospitalisation after readmission in days, median (range)	6 (0–100)	7 (1–82)	6 (0–100)	0.089

Table 3: Adverse drug reaction (ADR)-related readmission cases by system organ class (n = 270).

MedDRA system organ class	Number of cases	Details (n)
Gastrointestinal disorders	69	Gastrointestinal bleeding (25) Obstipation (17) Nausea and vomiting (9) Haematochezia (3) Diarrhoea (3) Abdominal pain (1) Acute pancreatitis (1) Colitis (1) Enterocolitis (1) Gastroenteritis noninfectious (1) Gastrointestinal motility disorder (1) Haematemesis (1) Ileus (1) Perforation colon (1) Radiation proctitis (1) Subileus (1)
Infections and infestations	52	Pneumonia (9) Urosepsis (5) *Clostridium difficile* colitis (4) Pyelonephritis (4) Abscess (3) Infection (3) Postoperative wound infection (3) CMV infection (2) Acute osteomyelitis (1) Ascites infection (1) Aspergillosis (1) *C. difficile* infection recurrence (1) Erysipelas (1) *Escherichia coli* bacteraemia (1) MRSA wound infection (1) Pseudomonal sepsis (1) Septic cholangitis (1) Septicaemia (1) Sinusitis (1)
Nervous system disorders	27	Convulsions (7) Subdural haematoma (6) Cerebral bleeding (2) Confusion (2) Somnolence (2) Amnesia (1) Analgesic rebound headache (1) Dyskinesia aggravated (1) Hyperammonaemic encephalopathy (1) Intracerebral haemorrhage (1) Myoclonus (1) Paraesthesia (1) Polyneuropathy (1)
Blood and lymphatic system disorders	22	Febrile aplasia (10) Febrile neutropenia (3) Anaemia (2) Neutropenic colitis (2) Pancytopenia (2) Agranulocytosis (1) Angina agranulocytic (1) Heparin-induced thrombocytopenia (1)
Injury, poisoning and procedural complications	20	Bleeding postoperative (11) Haematoma (5) Fall (2) Drug overdose accidental (1) Wound dehiscence (1)
Renal and urinary disorders	15	Macroscopic haematuria (5) Acute prerenal failure (3) Acute renal failure (2) Bladder tamponade (2) Postrenal failure (1) Prerenal insufficiency (1) Renal infarction (1)
General disorders and administration site conditions	12	Fever (6) Asthenia (2) Chills and fever (1) Fatigue (1) Wound healing delayed (1) Wound healing disturbance of (1)
Respiratory, thoracic and mediastinal disorders	8	Epistaxis (3) Haemothorax (3) Dyspnoea (1) Embolism pulmonary (1)

MedDRA system organ class	Number of cases	Details (n)
Vascular disorders	8	Haematoma (3) Hypertension exacerbated (2) Bleeding varicose vein (1) Breast bleeding (1) Leucocytoclastic vasculitis (1)
Skin and subcutaneous tissue disorders	7	Exanthema (6) Toxic epitheliolysis (1)
Metabolism and nutrition disorders	6	Hyponatraemia (3) Arthritis gouty (1) Hypotonic dehydration (1) Lactic acidosis syndrome (1)
Musculoskeletal and connective tissue disorders	5	Gonarthritis (1) Jaw fracture (1) Joint bleeding (1) Low back pain (1) Muscle bleeding (1)
Endocrine disorders	4	Hypoglycaemia (2) Adrenocortical insufficiency acute (1) Secondary adrenal insufficiency (1)
Hepatobiliary disorders	4	Acute cholecystitis (1) Cholangitis (1) Decompensated cirrhosis (1) Drug-induced liver injury (1)
Psychiatric disorders	3	Delirium (2) Drug psychoses, other (1)
Immune system disorders	2	Anaphylactic reaction to drug (2)
Investigations	1	Electrocardiogram QT prolonged (1)

CMV = cytomegalovirus; MedDRA = Medical Dictionary for Regulatory Activities; MRSA = methicillin-resistant *Staphylococcus aureus*

The most frequent ADRs associated with emergency readmissions within 30 days after hospital discharge were gastrointestinal disorders (approximately one-fourth of the cases, including cases of gastrointestinal bleeding), as well as infections and infestation, (approximately one-fifth of the cases). In line with this, the most frequent drug classes involved were antineoplastic/immunomodulating and antithrombotic agents, and most (five out of eight) fatal cases were bleeding related. Despite fulfilling the criteria for seriousness, only a minority of the ADRs leading to emergency readmissions was reported to the regulatory authorities.

Table 4: Adverse drug reaction (ADR)-related fatal cases (death in possible relation to ADR and not cases of patients who died during hospitalisation for other reasons; n = 8).

Age group	Drugs involved	ADR	Causality	ADR of the drug itself or ADR caused by DDI	Renal function (eGFR in ml/min)	ADR related to first hospitalisation	Number of drugs on readmission	Number of main diagnoses
61–65	Etoposide, rituximab	Supraventricular tachycardia	Possible	ADR of the drug itself	Unknown	No	13	4
76–80	Phenprocoumon, acetylsalicylic acid, clopidogrel	Gastrointestinal tract bleeding	Possible	Both	>90	Yes	11	6
81–85	Acetylsalicylic acid, heparin	Upper gastrointestinal bleeding	Possible	Both	25	No	Unknown	7
81–85	Azathioprine, prednisolone	Pneumonia	Possible	ADR of the drug itself	<20 (haemodialysis)	Yes	9	11
71–75	Phenprocoumon	Cerebral bleeding	Possible	ADR of the drug itself	57	Yes	Unknown	5
76–80	Phenprocoumon	Cerebral bleeding	Possible	ADR of the drug itself	>90	No	3	6
71–75	Phenprocoumon	Subdural haematoma	Possible	ADR of the drug itself	>90	No	7	4
81–85	Perindopril+indapamide, torsemide, lercanidipine	Acute renal failure	Possible	ADR caused by DDI	9	No	Unknown	8

DDI = drug-drug interaction; eGFR = estimated glomerular filtration rate

Table 5: Cases reported to the Swiss national pharmacovigilance centre (n = 8).

Age group	Drugs involved	Reaction	Dechallenge	Rechallenge	Causality	Outcome	ADR related to first hospitalisation	Days between first hospitalisation and readmission	Days of hospitalisation after readmission
26–30	Tacrolimus	Drug overdose	Yes*	Yes	Certain	Recovered	Yes	13	3
31–35	Ritonavir, midazolam	Drug-induced delirium	Yes	No	Probable/likely	Recovered	Yes	4	4
71–75	Nadroparin	Heparin-induced thrombocytopenia	Yes	No	Certain	Recovered	Yes	3	10
91–95	Venlafaxine	Hypertension exacerbated	Yes	No	Possible	Recovered	No	2	10
61–65	Metamizole	Agranulocytosis, Abscess perianal	Yes	No	Possible	Recovered	No	11	21
46–50	Paracetamol (acetaminophen), amoxicillin + clavulanic acid, rosuvastatin	Drug-induced liver injury	Yes	No	Possible	Recovered	Yes	21	10
46–50	Clindamycin	Maculo-papular exanthema	Yes	No	Possible	Recovered	No	4	1
61–65	Oxcarbazepine	Generalised exanthema	Yes	No	Probable/likely	Recovered	Yes	7	4

ADR: adverse drug reaction * No ADR after normalisation of tacrolimus concentration

In our study, ADR-related emergency readmissions corresponded to 21% of emergency readmissions and 6% of all readmissions within 30 days after discharge. According to a recent systematic review [7], rates of drug-related readmissions in previous studies were 3–64% (median 21%). The follow-up time between first admission and readmission in these studies varied from 28 days to more than 4 years, but readmission within 30 days was the most commonly used measure [7]. Besides data on the rates and causes of readmissions, other aspects such as the patients' emotional costs, loss of quality of life and economic burden should also be considered for the estimation of the global clinical and economic consequences related to hospital readmissions. Although these were not assessed in the current study, previous studies from the United States report approximately 20% rate of rehospitalisations of Medicare patients within 30 days after discharge with an estimated annual cost of unplanned rehospitalisations of US$17 billion [21].

In a previous study investigating ADR-related emergency department visits leading to hospitalisation among adults ≥65 years of age [22], warfarin / oral antiplatelet agents and insulins / oral hypoglycaemic agents were the implicated drugs / drug classes in two-third of the cases, whereas high-risk drugs, as defined by the Healthcare Effectiveness Data and Information Set (HEDIS) measure for "Use of high-risk medications in the elderly" [23], were involved in only a minority of the cases. In another study from the same group [24], investigating emergency department visits for ADRs involving medications identified as potentially inappropriate based on the Beers criteria (a consensus-based and repeatedly updated list of medications considered potentially inappropriate for use in patients ≥65 years of age, mostly owing to a high risk for adverse events [25]), three drugs (warfarin, insulin, digoxin) were implicated in one-third of the cases, whereas Beers criteria medications caused lower numbers of emergency department visits. Similar findings have been reported in studies in geriatric patients (≥80 years of age) with ADR-related readmission within 30 days, in which anticoagulants / antiplatelet agents and bleeding were the most common drug classes and adverse event [9]; prescription of nervous system drugs (third most frequent drug class in our study) was identified as a risk factor for ADR-related readmissions within 30 days in a previous study with elderly patients [13]. Although our study also included younger patients, antithrombotic agents and bleeding complications (e.g., gastrointestinal, epistaxis, haematuria, haematoma) were among the most commonly reported drugs and disorders, and bleeding was the underlying ADR in five of the eight fatal cases. These findings have important clinical implications, since such reactions (also known as Type A or pharmacological ADRs) are largely dose dependent with known mechanisms and therefore preventable [26]. This is different from idiosyncratic reactions (also known as Type B or hypersensitivity ADRs), such as many cases of drug-induced liver injury or allergic skin reactions which are less influenced by dosage and often are immunologically mediated [26]. Therefore, future strategies to prevent ADRs and ADR-related readmissions should focus not only on available lists of potentially inappropriate medications for specific age groups as listed in the Beers criteria [25] or the German PRISCUS list [27], but also on other considerations such as comorbidities and DDIs that can lead to Type A reactions, and adequate follow-up for a timely check for preventable ADRs, especially in patients treated with anticoagulants and/or antiplatelet agents. Preventive measures to decrease Type A ADRs could include automated red flags and DDI alerts in electronic medical records based on patient profiles and laboratory values to provide reminders for, e.g., a dose reduction based on the renal function or a pharmacodynamic interaction with increased risk of bleeding in the case of a combination of, for example, an anticoagulant agent and a nonsteroidal anti-inflammatory drug (NSAID). Furthermore, pharmacist- or clinical pharmacologist-led medication reconciliation interventions could further contribute to the reduction of medication discrepancies and ADRs [28, 29]. In the case of Type B reactions, some could be prevented with validated pharmacogenetic testing (e.g., human leucocyte antigen (HLA)-B*5701 and associated increased risk for hypersensitivity reactions to abacavir [30]).

Most of the patients in our study belonged to the elderly group and ADR-related cases were significantly older than non-ADR-related cases, most probably as a result of factors such as polypharmacy, impaired renal function or other comorbidities, which are common among older patients. The complexity of medication regimens, which is calculated on the basis of number of prescribed drugs, dosage form and frequency, and additional instructions has also been shown to be predictive for unplanned hospital readmissions within 30 days in previous studies [31]. Not all of those factors were investigated in our study (and a high medication regimen complexity score might also lead to readmission due to lower adherence and not due to an ADR) [31]. However, a median of 8 drugs, extending up to 22 drugs on readmission, can be taken as an indicator of a rather high complexity of medication regimens in the ADR-related cases in our study. The large majority of the cases were readmitted from home, whereas only one-fifth of the patients were readmitted from another medical institution. Returning home after discharge was identified as a risk factor for emergency readmission within 30 days also in another matched case-control study with elderly patients, after adjustment for sex and age [13]. These findings also highlight the importance of regular follow-up as a strategy to prevent ADR-related readmissions, since it can be assumed that patients in medical institutions receive more regular and thorough medical supervision than patients at home. In a previous prospective cohort study investigating preventability of ADRs among outpatients [32], 63% of the ameliorable events were attributed to the physician's failure to respond to drug-related symptoms and 37% to the patient's failure to report the symptoms to the physician. Regular follow-up with enough time available to check the patient's medication list regarding indication, correct dosage and DDIs, and also to ask the patient about any potential drug-related symptoms can thus contribute to the prevention of ADRs. In contrast to previous studies [6, 10], we did not find a significant difference in the duration of hospitalisation of the ADR-related and the non-ADR-related cases, which might be in part attributable to different hospital discharge policies among countries. In our study, there was no significant difference in the days between first hospitalisation for ADR- vs non-ADR-related readmission; in a previous study no signif-

icant difference regarding the delay between hospitalisations was found in patients with only one ADR-related hospitalisation and patients hospitalised twice or more owing to ADRs [33].

Only a minority (8 of the 270 cases) of the ADRs in our study were reported to the regulatory authorities, although all cases identified led to (re-) hospitalisation and thus formally fulfilled the criteria for seriousness. This highlights one of the major limitations of pharmacovigilance data, which are plagued by high underreporting rates [34]. Reasons for underreporting include lack of time or unawareness of reporting requirements; for example, the medical personnel may not be aware that expected or only suspected ADRs also could or must (in the case of serious ADRs) be reported [12, 34]. Based on the reported cases in our study, it seems that the decision to report a case may have been based more on the clinical presentation rather than the formal criteria for seriousness of the adverse reaction. Another possible factor favouring reporting could be knowledge of the possible adverse reactions of the drugs, since many of the reported cases referred to well-described ADRs of the specific agents (e.g., agranulocytosis associated with metamizole, liver injury associated with paracetamol, exanthemas associated with antibiotics, heparin-induced thrombocytopenia). However, none of the fatal cases had been reported, which might be due to lack of time (especially in an emergency setting), unawareness regarding reporting requirements [34] or fear of possible legal consequences. Although currently not the case in Switzerland, policies such as the Hospital Readmission Reduction Program [35] have been introduced in the United States to reduce readmissions, by, for example, imposing payment penalties on hospitals with excessive readmissions for specific diagnoses, and similar developments are seen in some European countries [7, 36]. Since spontaneous reports are a useful drug safety evaluation tool and can generate signals, which can then be followed more closely, it is important to raise awareness regarding the importance of pharmacovigilance among medical personnel and also to clarify relevant aspects such as the anonymity of the reports and that proof of causality is not required. In addition, organisation of ADR monitoring systems by clinical pharmacologists and/or pharmacists within hospitals could also significantly contribute to the timely recognition and reporting of ADRs to the regulatory authorities.

Limitations of our study include the retrospective design, with some missing information in some cases, and data from only one emergency department, which may not be representative for the whole country or other health systems. Furthermore, most cases were assessed as “possible” and only few cases as “probable/likely” or “certain” based on the formal causality criteria, and our data represent prescription patterns that reflect clinical practice during the observation period of the study, and new drug categories (e.g., direct oral anticoagulants) have been introduced into the Swiss market since then. It is also possible that newly introduced ADR screenings by clinical pharmacologists and pharmacists on hospital wards have contributed to increased ADR reporting in the recent years. We investigated emergency department readmissions, and thus the total number of ADR-related readmissions is most likely higher, since cases admitted directly to a hospital ward (>70% of the total readmissions) were not included in the analysis. The strengths of the study include the sensitive search, the individual review of the cases and the investigation of the reporting frequency to drug regulatory authorities. To our knowledge, this is the first study to investigate the frequency and characteristics of ADR-related emergency readmissions in a large Swiss University Hospital. It could thus contribute to public health by offering guidance regarding ADR preventive measures and also raise awareness regarding the importance of ADR reporting as a drug safety tool.

In conclusion, ADR-related readmissions constituted a considerable part of short-term emergency readmissions, with potentially preventable ADRs (e.g., bleeding, which might have been prevented by more regular measurement of the international normalised ratio (INR), prescription of a proton pump inhibitor together with NSAID to prevent gastroduodenal toxicity, dental hygiene and regular dental visits in case of bisphosphonates) involved in many of the cases. Despite being a relevant cause for rehospitalisation, only a minority of the ARDs were reported to the regulatory authorities. Strategies to prevent ADR-related readmissions and to improve reporting rates are needed.

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Appendix: Supplementary tables

Table S1: Adverse reactions and drugs involved by Anatomical Therapeutic Chemical (ATC) code (>1 drug involved in some cases, n = 477 drugs).

ATC code	Drug group (ATC classification, 4th level, chemical subgroup)	n	%	Active ingredients	Adverse reactions (LLT)
A	**ALIMENTARY TRACT AND METABOLISM**	**6**	**1.3**		
A02BC	Proton pump inhibitors	1	0.2	Esomeprazole (1)	Obstipation
A10AB	Insulins and analogues for injection, fast-acting	2	0.4	Insulin aspart (2)	Hypoglycaemia
A10AE	Insulins and analogues for injection, long-acting	1	0.2	Insulin glargine (1)	Hypoglycaemia
A10BA	Biguanides	1	0.2	Metformin (1)	Lactic acidosis syndrome
A12AX	Calcium, combinations with vitamin D and/or other drugs	1	0.2	Cholecalciferol (1)	Obstipation
B	**BLOOD AND BLOOD FORMING ORGANS**	**118**	**24.7**		
B01AA	Vitamin K antagonists	35	7.3	Phenprocoumon (33), Acenocoumarol (2)	Abdominal wall haematoma, anaemia, bleeding postoperative, cerebral bleeding, epistaxis, gastrointestinal tract bleed NOS, haematemesis, haematochezia, haematoma post vessel puncture, haematoma postoperative, haemothorax, intracerebral haemorrhage, joint bleeding, macroscopic haematuria, muscle bleeding, pelvic haematoma, postoperative haematoma, subdural haematoma, upper gastrointestinal bleeding
B01AC	Platelet aggregation inhibitors excl. heparin	45	9.4	Acetylsalicylic acid (32), Clopidogrel (13)	Bladder tamponade, bleeding postoperative, bleeding varicose vein, epistaxis, exanthema, gastrointestinal tract bleed NOS, haematochezia, haematoma post vessel puncture, haemorrhage oral, haemothorax, lower gastrointestinal bleeding, macroscopic haematuria, muscle bleeding, upper gastrointestinal bleeding, wound haematoma
B01AB	Heparin group	36	7.5	Nadroparin (17), Enoxaparin (13), Dalteparin (3), Heparin (3)	Anaemia, bladder tamponade, bleeding postoperative, breast bleeding, chronic subdural haematoma, haematochezia, haematoma post vessel puncture, haematoma postoperative, haemothorax, heparin-induced thrombocytopenia, intracerebral haemorrhage, lower gastrointestinal bleeding, macroscopic haematuria, muscle bleeding, postoperative haematoma, radiation proctitis, subdural haematoma, upper gastrointestinal bleeding
B03AA	Iron bivalent, oral preparations	1	0.2	Ferrous 2+ (1)	Obstipation
B01AX	Other antithrombotic agents	1	0.2	Fondaparinux (1)	Haemothorax
C	**CARDIOVASCULAR SYSTEM**	**24**	**5.0**		
C03AA	Thiazides, plain	1	0.2	Hydrochlorothiazide (1)	Hyponatraemia
C03BA	Sulfonamides, plain	9	1.9	Torsemide (5), Metolazone (3), Furosemide (1)	Acute prerenal failure, aute renal failure, arthritis gouty, hypotonic dehydration, prerenal insufficiency
C03EA	Low-ceiling diuretics and potassium-sparing agents	1	0.2	Amiloride + Hydrochlorothiazide (1)	Hyponatraemia
C10AA	HMG-CoA reductase inhibitors	1	0.2	Rosuvastatin (1)	Drug-induced liver injury
C08CA	Dihydropyridine derivates	1	0.2	Lercanidipine (1)	Acute renal failure
C07CB	Beta blocking agents, selective, and other diuretics	1	0.2	Atenolol + Chlorthalidone	Orthostatic presyncope
C07AB	Beta blocking agents, selective	2	0.4	Metoprolol (1), Nebivolol (1)	Fatigue, obstipation
C09DA	Angiotensin-II receptor blockers (ARBs) and diuretics	1	0.2	Candesartan + Hydrochlorothiazide (1)	Hyponatraemia
C09CA	Angiotensin-II receptor blockers (ARBs), plain	2	0.4	Telmisartan (1), Olmesartan (1)	Orthostatic presyncope, acute renal failure
C03DA	Aldosterone antagonists	3	0.6	Spironolactone (3)	Decompensated cirrhosis, acute prerenal failure, prerenal insufficiency
C09BA	ACE inhibitors and diuretics	1	0.2	Perindopril + Indapamide (1)	Acute renal failure
C09AA	ACE inhibitors, plain	1	0.2	Lisinopril (1)	Acute pancreatitis
G	**GENITO URINARY SYSTEM AND SEX HORMONES**	**2**	**0.4**		
G01AF	Imidazole derivates	1	0.2	Metronidazole (1)	Convulsion
G04BD	Drugs for urinary frequency and incontinence	1	0.2	Tolterodine (1)	Obstipation
H	**SYSTEMIC HORMONAL PREPARATIONS, EXCL. SEX HORMONES AND INSULINS**	**50**	**10.5**		
H02AB	Glucocorticoids	50	10.5	Prednisolone (42), Hydrocortisone (3), Dexamethasone (3), Deflazacort (1), Prednisone (1)	Abdominal abscess, abscess dental, acute osteomyelitis, adrenocortical insufficiency acute, ascites infection, aspergillosis, chills and fever, cholangitis, CMV infection, confusion, drug psychoses, erysipelas, *Escherichia coli* bacteraemia, fever, gonarthritis, infection, MRSA wound infection, perforation colon, pneumonia, postoperative wound infection, pyelonephritis, secondary adrenal insufficiency, septicaemia, spondylodiscitis, surgical wound infection, upper

ATC code	Drug group (ATC classification, 4th level, chemical subgroup)	n	%	Active ingredients	Adverse reactions (LLT)
					gastrointestinal bleeding, urosepsis, wound dehiscence, wound healing delayed, wound healing disturbance of, wound infection, wound infection bacterial, wound sepsis
J	**ANTIINFECTIVES FOR SYSTEMIC USE**	**26**	**5.5**		
J01DH	Carbapenems	3	0.6	Ertapenem (2), Meropenem (1)	*Clostridium difficile* infection recurrence, *Clostridium difficile* colitis
J01DD	3rd Generation cephalosporins	2	0.4	Ceftriaxone (2)	*Clostridium difficile* infection recurrence, anaphylactic reaction to drug
J01DE	4th Generation cephalosporins	1	0.2	Cefepime (1)	*Clostridium difficile* colitis
J01MA	Fluorquinolones	3	0.6	Ciprofloxacin (3)	Fever, electrocardiogram QT prolonged, macroscopic haematuria
J01CR	Combinations of penicillins, incl. beta-lactamase inhibitors	10	2.1	Amoxicillin + Clavulanic acid (10)	Antibiotic-associated diarrhoea, clonic-tonic convulsions, *Clostridium difficile* colitis, *Clostridium difficile* infection recurrence, colitis, convulsion, drug-induced liver injury, gastroenteritis noninfectious, maculo-papular exanthema
J01FF	Lincosamides	2	0.4	Clindamycin (2)	Electrocardiogram QT prolonged, maculo-papular exanthema
J01FA	Macrolides	3	0.6	Clarithromycin (3)	Haematoma postoperative, clonic-tonic convulsions, leucocytoclastic vasculitis
J01CA	Penicillins with extended spectrum	1	0.2	Amoxicillin (1)	Maculo-papular exanthema
J05AE	Protease inhibitors	1	0.2	Ritonavir (1)	Drug-induced delirium
L	**ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS**	**169**	**35.4**		
L01AX	Other alkylating agents	3	0.6	Temozolomide (3)	Febrile aplasia, polyneuropathy, maculo-papular exanthema
L01XX	Other antineoplastic agents	1	0.2	Hydroxycarbamide (1)	Febrile aplasia
L04AX	Other immunosuppressants	5	1.0	Azathioprine (5)	Acute osteomyelitis, erysipelas, pneumonia, pyelonephritis, urosepsis
L01DC	Other cytotoxic antibiotics	1	0.2	Bleomycin (1)	Embolism pulmonary
L01DB	Anthracyclines and related substances	14	2.9	Doxorubicin (12), Epirubicin (1), Mitoxantrone (1)	Escherichia sepsis, febrile aplasia, febrile neutropenia, fever, pneumonia, urosepsis, viral upper respiratory tract infection, vomiting post chemotherapy
L04AD	Calcineurin inhibitors	22	4.6	Ciclosporin (15), Tacrolimus (7)	Abscess dental, abscess jaw, ascites infection, cholangitis, CMV infection, confusion, convulsion, drug overdose accidental, erysipelas, *Escherichia coli* bactearemia, fever, pancytopenia, pneumonia, postrenal failure, pyelonephritis, spondylodiscitis, urosepsis
L01BA	Folic acid analogues	1	0.2	Pemetrexed (1)	Nausea post chemotherapy
L03AB	Interferons	1	0.2	Interferon alpha-2a (1)	Pseudomonal sepsis
L03AA	Colony stimulating factors	1	0.2	Filgrastim (1)	Low back pain
L01XB	Methylhydrazines	1	0.2	Procarbazine (1)	Fever
L01XC	Monoclonal antibodies	16	3.4	Rituximab (13), Cetuximab (1), Pertuzumab (1), Trastuzumab (1)	Angina agranulocytic, diarrhoea, *Escherichia* sepsis, febrile aplasia, febrile neutropenia, fever, neutropenic colitis, pancytopenia, pneumonia, supraventricular tachycardia, toxic epitheliolysis, urosepsis, viral upper respiratory tract infection
L01XA	Platinum compounds	16	3.4	Cisplatin (10), Carboplatin (4), Oxaliplatin (2)	Asthenia, embolism pulmonary, enterocolitis, febrile aplasia, hypertension exacerbated, hyponatraemia, nausea post chemotherapy, obstipation, pyelonephritis fungal, rRenal infarction, septic cholangitis, vomiting post chemotherapy
L01CB	Podophyllotoxin derivates	11	2.3	Etoposide (11)	Febrile aplasia, febrile neutropenia, fever, neutropenic colitis, supraventricular tachycardia
L01XE	Protein kinase inhibitors	3	0.6	Sorafenib (2), Imatinib (1)	Tachycardia, diarrhoea, acute cholecystitis
L01BB	Purine analogues	1	0.2	Fludarabine (1)	Angina agranulocytic
L01BC	Pyrimidine analogues	14	2.9	Cytarabine (6), 5-Fluorouracil (4), Gemcitabine (2), Capecitabine (1), Azacitidine (1)	Enterocolitis, *Escherichia* sepsis, febrile aplasia, heart failure NYHA class III, infection, neutropenic colitis, obstipation, pyelonephritis fungal, septic cholangitis, sinusitis, vomiting post chemotherapy
L04AA	Selective immunosuppressants	20	4.2	Mycophenolic acid (15), Everolimus (3), Sirolimus (1), Antithymocyte immunoglobulin (1)	Abdominal pain, abscess dental, ascites infection, CMV infection, Escherichia coli bacteraemia, nausea and vomiting, pancytopenia, pneumonia, postoperative wound infection, postrenal failure, pyelonephritis, urosepsis, wound sepsis
L01AA	Nitrogen mustard analogues	18	3.8	Cyclophosphamide (9), Ifosfamide (6), Bendamustine (2), Melphalan (1)	Angina agranulocytic, chills and fever, diarrhoea, *Escherichia* sepsis, febrile aplasia, febrile neutropenia, fever, neutropenic colitis, pancytopenia, urosepsis, viral upper respiratory tract infection
L01CD	Taxanes	4	0.8	Docetaxel (3), Paclitaxel (1)	Tracheobronchitis, enterocolitis, infection, pneumonia
L01CA	Vinca alkaloids and analogues	16	3.4	Vincristine (12), Vinorelbine (2), Vindesine (1), Vinflunine (1)	Asthenia, *Escherichia* sepsis, febrile aplasia, febrile neutropenia, fever, nausea post chemotherapy, urosepsis, viral upper respiratory tract infection
M	**MUSCULO-SKELETAL SYSTEM**	**6**	**1.3**		
M01AE	Propionic acid derivatives	1	0.2	Ibuprofen (1)	Gastrointestinal tract bleed NOS

ATC code	Drug group (ATC classification, 4th level, chemical subgroup)	n	%	Active ingredients	Adverse reactions (LLT)
M03BX	Other centrally acting agents	2	0.4	Baclofen (2)	Myoclonus, somnolence
M04AA	Preparations inhibiting uric acid production	1	0.2	Allopurinol (1)	Maculo-papular exanthema
M05BA	Bisphosphonates	2	0.4	Ibandronic acid (1), Zoledronic acid (1)	Jaw fracture, fever
N	**NERVOUS SYSTEM**	**74**	**15.5**		
N01AX	Other general anesthetics	1	0.2	Propofol (1)	Convulsions generalised
N06AX	Other antidepressants	8	1.7	Venlafaxine (5), Mirtazapine (3)	Clonic-tonic convulsions, sall, hypertension exacerbated, obstipation, upper gastrointestinal bleeding
N03AX	Other antiepileptics	3	0.6	Lamotrigine (1), Topiramate (1), Levetiracetam (1)	Somnolence, hyperammonaemic encephalopathy, amnesia
N02AX	Other opioids	2	0.4	Tramadol (2)	Obstipation
N02BE	Anilides	1	0.2	Paracetamol (acetaminophen) (1)	Drug-induced liver injury
N05BA	Benzodiazepine derivatives	6	1.3	Lorazepam (2), Oxazepam (1), Clobazam (1), Flunitrazepam (1), Midazolam (1)	Amnesia, delirium, drug-induced delirium, dyspnoea, fall
N05CF	Benzodiazepine related drugs	2	0.4	Zolpidem (2)	Fall, dyspnoea
N03AF	Carboxamide derivatives	4	0.8	Oxcarbazepine (4)	Obstipation, hyponatraemia, amnesia, exanthema generalised
N05AH	Diazepines, oxazepines, thiazepines and oxepines	2	0.4	Clozapine (1), Quetiapine (1)	Cardiomyopathy, convulsions generalised
N04BC	Dopamine agonists	3	0.6	Pramipexole (2), Ropinirole (1)	Dyskinesia aggravated, obstipation, confusion
N04BA	Dopa and dopa derivatives	1	0.2	Entacapone+ Levodopa+ Carbidopa (1)	Dyskinesia aggravated
N03AG	Fatty acid derivatives	2	0.4	Valproic acid (2)	Hyperammonaemic encephalopathy, somnolence
N03AB	Hydantoin derivatives	1	0.2	Phenytoin (1)	Maculo-papular exanthema
N07BA	Drugs used in nicotine dependence	1	0.2	Nicotine (1)	Leucocytoclastic vasculitis
N07BC	Drugs used in opioid dependence	4	0.8	Methadone (4)	Obstipation
N02AA	Natural opium alkaloids	6	1.3	Oxycodone + Naloxone (4), Oxycodone (1), Morphine (1)	Delirium, analgesic rebound headache, obstipation
N06AA	Non-selective monoamine reuptake inhibitors	1	0.2	Trimipramine (1)	Hyponatraemia
N02AB	Phenylpiperidine derivatives	11	2.3	Fentanyl (10), Pethidine (1)	Delirium, gastrointestinal motility disorder, ileus, nausea and vomiting, obstipation, subileus
N02BB	Pyrazolones	4	0.8	Metamizole (4)	Agranulocytosis, nausea and vomiting, anaphylactic reaction to drug
N02BA	Salicylic acid and derivatives	1	0.2	Acetylsalicylic acid (1)	Subdural haematoma
N06AB	Selective serotonin reuptake inhibitors	10	2.1	Escitalopram (8), Citalopram (1), Sertraline (1)	Bleeding postoperative, hyponatraemia, macroscopic haematuria, obstipation, paraesthesia, pelvic hematoma, radiation proctitis, somnolence
R	**RESPIRATORY SYSTEM**	**1**	**0.2**		
R03BB	Anticholinergics	1	0.2	Ipratropium bromide (1)	Obstipation
V	**VARIOUS**	**1**	**0.2**		
V03AF	Detoxifying agents for antineoplastic treatment	1	0.2	Calcium folinate (1)	Septic cholangitis

ATC = Anatomical Therapeutic Chemical; CMV = cytomegalovirus; LLT = lowest level term; MRSA = methicillin-resistant *Staphylococcus aureus;* NOS = not otherwise specified; NYHA = New York Heart Association

Table S2: Cases classified as "probable/likely" according to the Swiss adverse drug reaction (ADR) reporting system causality criteria.

Adverse drug reaction (LLT)	Cases (n)	Drugs (n)
Clostridium difficile colitis	3	Amoxicillin + Clavulanic acid (2), Ertapenem (1)
Nausea post chemotherapy	2	Cisplatin (1), Vinorelbine, Carboplatin (1)
Adrenocortical insufficiency acute	1	Prednisolone (1)
Anaphylactic reaction to drug	1	Ceftriaxone (1)
Bleeding postoperative	1	Phenprocoumon (1)
Cardiomyopathy	1	Clozapine (1)
Clonic-tonic convulsions	1	Venlafaxine (1)
Drug psychoses, other	1	Dexamethasone (1)
Drug-induced delirium	1	Ritonavir, Midazolam (1)
Enterocolitis	1	Cisplatin, Docetaxel, Fluorouracil (1)
Epistaxis	1	Phenprocoumon (1)
Exanthema generalised	1	Oxcarbazepine (1)
Gastroenteritis noninfectious	1	Amoxicillin + Clavulanic acid (1)
Hypoglycaemia	1	Insulin aspart (1)
Hyponatraemia	1	Hydrochlorothiazide, Oxcarbazepine, Citalopram (1)
Hypotonic dehydration	1	Metolazone, Torasemide (1)
Jaw fracture	1	Ibandronic acid (1)
Joint bleeding	1	Phenprocoumon (1)
Low back pain	1	Filgrastim (1)
Paraesthesia	1	Escitalopram (1)
Secondary adrenal insufficiency	1	Hydrocortisone (1)

LLT = lowest level term

Table S3: Cases requiring admission to the intensive care unit (assessed as "life-threatening"; n = 34).

Adverse drug reaction	n
Upper gastrointestinal bleeding	5
Chronic subdural haematoma	3
Clonic-tonic convulsions	3
Haemothorax	3
Obstipation (ileus)	2
Subdural haematoma	2
Abscess dental	1
Anaphylactic reaction	1
Clostridium difficile colitis	1
Convulsion	1
Epistaxis	1
Escherichia coli bacteraemia	1
Fatigue*	1
Gastrointestinal tract bleed not otherwise specified	1
Hematemesis	1
Hematochezia	1
Intracerebral haemorrhage	1
Lactic acidosis syndrome	1
Postoperative wound infection	1
Somnolence†	1
Vomiting post chemotherapy	1
Wound haematoma	1

* Road traffic accident; † somnolence, dysarthria, anomia, walking disability