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

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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 admissions 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

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

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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%), calcium inhibitor (6%) 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 (can-desartan, 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.
| 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)                                                                                                                                                                                              |
|                                                  |                | Haemorrhorax (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 | Exanthera (6) Toxic epidermolysis (1) |
Metabolism and nutrition disorders | 6 | Hyponatraemia (3) Arthritis gouty (1) Hypotonic dehydration (1) Lactic acidosis syndrome (1) |
Musculoskeletal and connective tissue disorders | 5 | Gonarthrosis (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 | Elopode, 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, lecarbidipine | 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 antithrombotic agents and insulin / 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, haematomas) 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 regimes, 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 regimes 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 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., bleaching, 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                               |   | 1 |                     |                        |
| 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)      |                        |
| 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 antagonants                                          | 35 | 7.3 | Phenprocoumon (33), Acenocoumarol (2) | Abdominal wall haematoma, anaemia, bleeding postoperative, cerebral bleeding, epistaxis, gastrointestinal tract bleed NOS, haematnemesis, haematochezia, haematoma post vessel puncture, haematoma postoperative, haemorrhax, intracerebral haemorrhage, joint bleeding, macroscopic haematuria, muscle bleeding, pelvic haematoma, postoperative haematomata, subadult 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, haemorrhax, 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, haemorrhax, heparin-induced thrombocytopenia, intracerebral haemorrhage, lower gastrointestinal bleeding, macroscopic haematuria, muscle bleeding, postoperative haematoma, radiation proctitis, subadult 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) | Haemorrhax |
| C        | CARDIOVASCULAR SYSTEM                                         | 24 | 5.0 |                     |                        |
| C03AA    | Thiiazides, plain                                             | 1 | 0.2 | Hydrochlorothiazide (1) | Hypotraemia |
| C03BA    | Sulfonamides, plain                                            | 9 | 1.9 | Torsemide (5), Metolazine (3), Furosemide (1) | Acute prerenal failure, acute renal failure, arthritis gouty, hypoponic dehydration, prerenal insufficiency |
| C03EA    | Low-ceiling diuretics and potassium-sparing agents             | 1 | 0.2 | Amiloride + Hydrochlorothiazide (1) | Hypotraemia |
| C10AA    | HMG-CoA reductase inhibitors                                   | 1 | 0.2 | Rosuvastatin (1) | Drug-induced liver injury |
| C08CA    | Dipyridydroline derivatives                                   | 1 | 0.2 | Lercanidipine (1) | Acute renal failure |
| C07CB    | Beta blocking agents, selective, and other diuretics           | 1 | 0.2 | Atenolol + Chlorothalidone | 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) | Hypotraemia |
| 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 derivatives                                          | 1 | 0.2 | Metronidazole (1) | Convulsion |
| G04BD    | Drugs for urinary frequency and incontinence                   | 1 | 0.2 | Tolterodine (1) | Obstipation |
| H        | SYSTEMIC HORMONAL PREPARATIONS, EXC. SEX HORMONES AND INSULINS | 50 | 10.5 |                     |                        |
| H02AB    | Glucocorticoids                                               | 50 | 10.5 | Prednisolone (42), Hydrocortisone (3), Desamethasone (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, gonorrhoea, infection, MRSA wound infection, perforation coton, pneumonia, postoperative wound infection, pylonephritis, 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) |
|----------|---------------------------------------------------------------|---|---|---------------------|------------------------|
| J01DA    | 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    | Fluoroquinolones                                              | 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, chonic-tonic convulsions, Clostridium difficile colitis, Clostridium difficile infection recurrence, colitis, convulsion, drug-induced liver injury, gastrointestinal bleeding, urosepsis |
| J01FF    | Lincosamides                                                  | 2 | 0.4| Clindamycin (2)           | Electrocardiogram QT prolonged, macroscopic haematuria |
| J01FA    | Macrolides                                                    | 3 | 0.6| Clarithromycin (3)        | Haemorrhoma postoperative, chonic-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 |
| L01AX    | Other alkylating agents                                       | 3 | 0.6| Temozolomide (3)          | Febrile aplasia, polyneuropathy, maculo-papular exanthema |
| L01XX    | Other antineoplastic agents                                   | 1 | 0.2| Hydroxyurea (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) | Abcess dental, abscess jaw, ascites infection, cholangitis, CMV infection, confusion, convulsion, drug overdose accidental, chills, diaphoresis, Escherichia coli bactearemia, fever, pan-cytopenia, pneumonia, postrenal failure, pyelonephritis, spondylodiscitis, urosepsis |
| L04AD    | Calcineurin inhibitors                                        | 22| 4.6| Ciclosporin (15), Tacrolimus (7) | Abscess dental, abscess jaw, chills and fever, diarrhoea, postrenal failure, pyelonephritis fungal, septic cholangitis, sinusitis, vomiting post chemotherapy |
| 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    | Methylmethasazinines                                          | 1 | 0.2| Procarbazine (1)          | Fever |
| L01XC    | Monoclonal antibodies                                         | 16| 3.4| Rituximab (13), Celoximab (1), Pertuzumab (1), Trastuzumab (1) | Angina agranulocytic, diaphorea, Escherichia sepsis, febrile aplasia, febrile neutropenia, fever, neutropenic colitis, pan-cytopenia, pneumonia, supraventricular tachycardia, toxic epitellosis, 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, hyponaetraemia, nausea post chemotherapy, obesitation, pyelonephritis fungal, rRenal infarction, septic cholangitis, vomiting post chemotherapy |
| L01CA    | Podophyllotoxin derivates                                     | 11| 2.3| Etoposide (11)            | Febrile aplasia, febrile neutropenia, febrile neutropenic colitis, supraventricular tachycardia |
| L01XE    | Protein kinase inhibitors                                     | 3 | 0.6| Sorafenib (2), Imatinib (1) | Tachycardia, diaphorea, acute cholecytolysis |
| L01BB    | Purine analogues                                              | 1 | 0.2| Fludarabine (1)           | Angina agranulocytic |
| L01BC    | Pyrimidine analogues                                          | 14| 2.9| Cytarabine (6), 5-Flourouracil (4), Gemcitabine (2), Capetitabine (1), Azacitidine (1) | Enterocolitis, Escherichia sepsis, febrile aplasia, heart failure NYHA class III, infection, neutropenic colitis, obstitution, pyelonephritis fungal, septic cholangitis, sinusitis, vomiting post chemotherapy |
| L04AA    | Selective immunosuppressants                                  | 20| 4.2| Mycophenolic acid (15), Etoprolimus (3), Sirolimus (1), Antithymocyte immunoglobulin (1) | Abdominal pain, abscess dental, ascites infection, CMV infection, Escherichia coli bactearemia, nausea and vomiting, pan-cytopenia, 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, diaphorea, Escherichia sepsis, febrile aplasia, febrile neutropenia, fever, neutropenic colitis, pan-cytopenia, 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| Vinoreistine (12), Vinoreistine (2), Vindesine (1), Vinflunine (1) | Asthenia, Escherichia sepsis, febrile aplasia, febrile neutropenia, fever, nausea post chemotherapy, urosepsis, viral upper respiratory tract infection |
| 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)           | Clonitonic convulsions, tachycardia, hypotension exacerbated, obtipation, 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)                                | Obstruction                               |
| N02BE    | Anilides                                                   | 1  | 0.2| Paracetamol (acetaminophen) (1)            | Drug-induced liver injury                 |
| N05BA    | Benzodiazepine derivatives                                 | 6  | 1.3| Lorazepam (2), Oxazepam (1), Clonazepam (1), Flunitrazepam (1), Midazolam (1) | Amnesia, delirium, drug-induced delirium, dyspnoea, fall |
| N05CF    | Benzodiazepine related drugs                               | 2  | 0.4| Zolpidem (2)                                | Fall, dyspnoea                            |
| N03AF    | Carboxamid derivates                                       | 4  | 0.8| Oxcarbazepine (4)                          | Obstruction, hyponatraemia, amnesia, exanthema generalised |
| N05AH    | Diazipines, 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, obtipation, 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)                              | Obstruction                               |
| N02AA    | Natural opioid alkaloids                                   | 6  | 1.3| Oxycodeine + Naloxone (4), Oxycodeine (1), Morphine (1) | Delirium, analgesic rebound headache, obtipation |
| 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, obtipation, subleus |
| 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 haematomata                      |
| N06AB    | Selective serotonin reuptake inhibitors                    | 10 | 2.1| Escitalopram (8), Citalopram (1), Sertraline (1) | Bleeding postoperative, hyponatraemia, macroscopic haematuria, obtipation, paraesthesia, pelvic hematoma, radiation proctitis, somnolence |
| R RESPIRATORY SYSTEM                                 | 1  | 0.2|                                             |                                           |
| R03BB    | Anticholinergics                                           | 1  | 0.2| Ipratropium bromide (1)                    | Obstruction                               |
| V VARIOUS                                      | 1  | 0.2|                                             |                                           |
| V03AF    | Detoxifying agents for antineoplastic treatment            | 1  | 0.2| Calcium fumarate (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), Vincristine, 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)                              |
| Hypotonic dehydration                             | 1         | Hydrochlorothiazide, Oxcarbazepine, Citalopram (1) |
| Jaw fracture                                       | 1         | Ibendronic 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 (ileus)                              | 3         |
| Obstipation (ileus)                              | 2         |
| Subdural haematoma                               | 2         |
| Abscess dental                                   | 1         |
| Anaphylactic reaction                            | 1         |
| Clostridium difficile colitis                    | 1         |
| Convulsion                                       | 1         |
| Epistaxis                                        | 1         |
| Escherichia coli bacteremias                     | 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, anoma, walking disability