REVIEW ARTICLE

Drug Safety 2007; 30 (5): 379-407
0114-5916/07/0005-0379/$44.95/0

Drug-Related Problems in Hospitals
A Review of the Recent Literature

Anita Krähenbühl-Melcher,[1] *Raymond Schlienger*,[2] *Markus Lampert*,[2] *Manuel Haschke*,[2] *Jürgen Drewe*[2] and *Stephan Krähenbühl*[2]

1 Hospital Pharmacy, Regionalspital Emmental, Burgdorf, Switzerland
2 Division of Clinical Pharmacology and Toxicology, University Hospital, Basel, Switzerland

Contents

Abstract

Problems associated with pharmacotherapy (in particular, medication errors and adverse drug events) are frequent and are associated with increased costs for treatment.

Analysis of original publications published between 1990 and 2005 on the topics of medication errors and/or adverse drug events in hospitalised patients, focusing on the frequency of, risk factors for and avoidance of such problems associated with pharmacotherapy, indicated that medication errors occurred in a mean of 5.7% of all episodes of drug administration, but with a high variability among the 35 studies retrieved. This variability was explained by the methods by which medication errors were detected (systematic screening of patients versus chart review or spontaneous reporting) and by the way drugs were administered (intravenously administered drugs are associated with the highest error frequencies). Errors occurred throughout the whole medication process, with administration errors accounting for more than half of all errors. Important risk factors included insufficient pharmacological knowledge of health professionals, errors in the patient charts or documentation by nurses and inadequate pharmacy services.

Adverse events or reactions, on the other hand, affected 6.1 patients per 100 hospitalised and also showed a high variability among the 46 studies retrieved. This variability could also be explained by the different methods of assessment of the frequency of adverse drug events or reactions, as well as by the different wards on which the studies were performed. Important risk factors for adverse drug events or reactions included polypharmacy, female sex, drugs with a narrow therapeutic range, renal elimination of drugs, age >65 years and use of anticoagulants or diuretics.

Since medication errors are strong risk factors for preventable adverse drug events or reactions, strategies have to be put in place for their reduction. Such strategies include ensuring that all persons involved in the medication process

(nurses, pharmacists and physicians) have good pharmacological knowledge, computerisation of the entire medication process, and the engagement of a sufficient number of clinical pharmacists on the wards.

Table I. Definitions of problems associated with pharmacotherapy

Drug-related problems
All circumstances involving a patient's drug treatment that actually, or potentially, interfere with the achievement of an optimal outcome[7]
Medication errors
Any error in the medication process (prescribing, dispensing, administering of drugs), whether there are adverse consequences or not[12]
Adverse drug reactions
Any response to a drug which is noxious and unintended, and which occurs at doses normally used in humans for prophylaxis, diagnosis or therapy of diseases, or for the modification of physiological functions[13]
Adverse drug events
Any injury related to the use of a drug, regardless of whether a therapeutically appropriate dosage is used, although the causality of this relationship may not be proven[12]

Drugs may not only have beneficial effects, but may also be associated with adverse reactions. During the last decade, several studies have been published highlighting the significance of adverse drug reactions in hospitalised patients in terms of frequency,[1-4] consequences for the affected patients[5-7] and costs for the hospitals.[8-10] Adverse drug reactions can be regarded as the top of a pyramid containing all problems associated with drug therapy or 'drug-related problems'. Drug-related problems include all issues that can potentially affect the success of pharmacotherapy in a given patient, in particular medication errors, adverse drug events and adverse drug reactions.[7] These terms are defined more precisely in table I and their relationship is depicted in figure 1.[11]

Medication errors can occur throughout the entire medication process and represent risk factors for adverse drug reactions and events.[5,14,15] As shown in table II, the medication process in hospitals starts with the prescription of a drug; the prescription then has to be transcribed by a medical professional, usually a nurse, and also by the pharmacy for delivery of the prescribed drugs. Nurses usually prepare the drugs on the ward, and distribute and administer them to the patients. The steps that have been reported to be particularly associated with medication errors are drug prescription and drug administration.[7]

Since medication errors can result in adverse drug reactions, knowledge of the origins of medication errors, as well as of possible risk factors for them, is important to limit the frequency of adverse drug reactions. One of the aims of the current investigation, therefore, was to assess these risk factors in order to be able to propose measures for avoiding medication errors in community and university hospitals. Special emphasis was placed on the role of the clinical pharmacists in this setting, since several publications have emphasised the importance of direct supervision of the medication process by pharmacists.[16-18]

We therefore performed a search of the literature between 1990 and 2005 in order to retrieve the relevant original publications reporting the frequen-

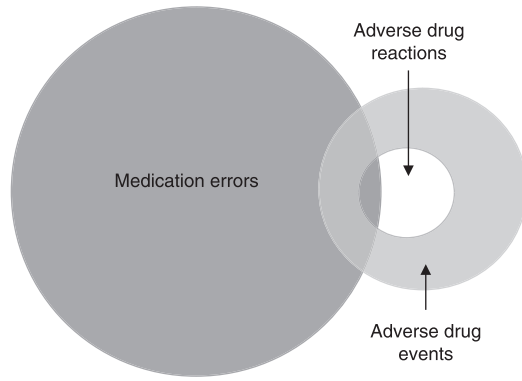

Fig. 1. Problems associated with pharmacotherapy (drug-related problems) can be illustrated by the intersections of three circles representing medication errors, adverse drug events and adverse drug reactions.[11] Medication errors include every mistake in the medication process (prescribing, dispensing, administering of drugs). Only a minority of the medication errors result in an adverse drug reaction or an adverse drug event. Adverse drug events represent any injury related to the use of a drug, even if this relationship has not been proven to be causal. Adverse drug reactions are noxious responses to a drug which are unintended and which occur at normally used doses of this drug. Adverse drug reactions are either predictable (and therefore mostly avoidable; type A reactions), or unpredictable (idiosyncratic or type B reactions).

Table II. Most important medication errors in hospitalised patients

Prescription errors
Wrong drug (e.g. drug not suitable for this indication)
Correct drug, wrong patient (e.g. ignoring contraindications, drug-drug interactions or drug allergies)
Wrong galenic form (e.g. tablets for a patient who is not able to swallow)
Wrong dose
Transcription and/or interpretation errors
Error in transcription of prescriptions (e.g. physicians, nurses)
Misinterpretation of abbreviations, hand-written prescriptions (e.g. illegible writing)
Misinterpretation of spoken prescriptions
Preparation and dispensing errors (correct prescription)
Calculation error, preparation error
Error in dispensing (e.g. wrong patient, wrong drug)
Administration error
Wrong dose
Omission of dose, additional dose
Wrong administration time
Incorrect handling of drugs during administration (e.g. infusions)
Wrong infusion rate

cy of medication errors and/or adverse drug reactions in hospitalised patients. From these data, we extracted the frequency and the risk factors for these drug-related problems, in order to be able to propose suitable measures for their reduction.

1. Literature Search Methodology

We performed an electronic search in MEDLINE and EMBASE using the search terms 'medication error', 'adverse drug reaction' or 'adverse drug event' in combination with 'hospital' and collected the relevant articles published between 1990 and 2005. The articles retrieved were searched manually and those reporting original data concerning the frequency of medication errors, adverse drug events and/or adverse drug reactions in hospitalised patients were included in the review. Furthermore, review articles covering these subjects were also searched and used to ensure comprehensive inclusion of references that reported original data.

Studies reporting only specific medication errors or adverse drug events (e.g. prescription errors or renal adverse events) were not included. Studies reporting the frequency of medication errors or adverse drug events/reactions only at hospital entry were not included. Since the aim of the study was to assess adverse drug events or reactions in hospitalised patients, studies reporting adverse drug events or reactions as a cause of hospital admission only were also excluded. Only reports published in English, French or German were included. In addition, studies were only included if the majority of patients had been studied in internal medicine, surgery and geriatric wards or in intensive care units.

As discussed in the publication by Lazarou et al.,[4] studies reporting adverse drug events or adverse drug reactions can be met with problems in the classification of these events or reactions. In addition to adverse drug reactions, adverse drug events also include the consequences of specific medication errors such as overdosing, and do not require an assessment of their causality (see definitions in table I and in figure 1).[11] Since the differentiation between adverse drug events and adverse drug reactions was not completely clear in all studies and the frequencies did not differ between adverse drug events and reactions, we combined the studies in table III. Since adverse drug reactions are included within adverse drug events (table I, figure 1),[11] we usually use the expression adverse drug events in this article.

The frequencies of errors and events reported were analysed according to the type of hospital (university versus non-university hospitals), the type of ward in which the data were collected, and the detection system used to collect the data. When different hospitals were investigated in the same study, the classification was performed according to the origin of the majority of the patients. When wards with different specialties were investigated, the study was classified as being performed in a 'general medicine' setting.

If not otherwise indicated, data are presented as the median and range, since the frequencies of the medication errors and adverse drug events did not exhibit a normal distribution. When two groups were compared, statistical analysis was performed using the non-parametric Mann-Whitney U test. When more than two groups were compared, the Kruskal-Wallis analysis of ranks was used, followed by the Mann-Whitney U test with Bonferroni correction to localise significant differences. A p-value

Table III. Studies that reported the frequency of adverse drug reactions (ADR) or adverse drug events (ADE) in hospitalised patients

Study	Setting	Duration of study; patients; data collection	Detection method	ADR or ADE frequency (% patients hospitalised)	Most frequent types of ADE/ADR and drugs most frequently associated with ADE/ADRs (% ADE/ADRs); risk factors	Remarks
Classen et al.[19]	University hospital, USA; general medicine	18 months; 36 653 patients; ADEs were recorded and causality was assessed	Combination of spontaneous reporting and computerised monitoring	ADE: 1.67 (731 in 36 653 patients). 9 spontaneous reports and 722 computer-generated signals	Drugs: analgesics 31, antibacterials 23, cardiovascular 19, anticoagulants 9, psychomimetics 2 ADE: pruritus 12, nausea/vomiting 9, rash 9, confusion 8, dysrhythmia 6, hypotension 5 Risk factors: drug exposure (33 drugs per hospitalisation in patients with ADEs vs 13 drugs in patients without), age, female sex	91% type A, 9% type B reactions. Average hospital stay: 13 days in patients with ADE and 6 days in patients without. Causality: 62% definite; 37% probable; 1% possible
Hardmeier et al.[20]	University hospital, Switzerland; internal medicine	5 years; 6383 patients; ADEs were recorded and causality was assessed	Patient monitoring (physicians)	ADE: 7.5 during hospitalisation (481 of 6383 patients). 4.4 at admission	Drugs: anticoagulants 21, cardiovascular 18, antibacterials 18, sedatives 14, NSAIDs 14 Organs: GI tract 21, bleeding 18, allergies 14, respiratory 11, cardiovascular 11	28 of the 481 ADEs during hospitalisation were due to medication errors (5.8%)
Schumock et al.[21]	University hospital, USA; internal medicine	1 month; 160 patients; ADRs and overdoses were recorded	Patient monitoring (clinical pharmacist) vs spontaneous reporting	ADR: 8.8 (14/160) vs 2.5 (4/160). True rate 9.4 (15/160)[a]	Drugs: antibacterials 40 Type of ADR: GI tract 33; kidney 20; liver 13; CNS 13	Intensive screening (clinical pharmacist) is better than spontaneous reporting. Intensive screening detects 93% of ADRs while spontaneous reporting detects 27%
Leape et al.[22]	51 hospitals (type not specified), New York state, USA; general medicine	30 195 patient charts; predefined, serious ADEs were recorded	Retrospective review of charts	ADE: 0.59 (178/30 195)	Drugs: antibacterials 16; cancer chemotherapy 16; anticoagulants 11 Type of ADE: bone marrow 16; bleeding 15; CNS 15; skin 14	18% of ADEs were due to negligence; 14% resulted in permanent disability. Drug-drug interactions accounted for 4.8% of ADE
Lindley et al.[23]	University hospital, UK; geriatrics	10 weeks; 416 patients; ADRs were recorded, causality assessment not specified	Patient monitoring (physicians)	ADR: 27	Drugs: diuretics 55; β-adrenoceptor antagonists (β-blockers) 8; antidepressants 4.5; opioids 4; NSAIDs 4	50% of ADR were due to drugs which were considered to be contraindicated or unnecessary. 240 potential drug-drug interactions in 150 patients, 5% caused ADR

Continued next page

Table III. Contd

Study	Setting	Duration of study; patients; data collection	Detection method	ADR or ADE frequency (% patients hospitalised)	Most frequent types of ADE/ADR and drugs most frequently associated with ADE/ADRs (% ADE/ADRs); risk factors	Remarks
Schneider et al.[24]	University hospital, USA; geriatrics	463 patients; ADRs were recorded, causality was assessed	Retrospective review of charts	ADR: 21	Drugs: ACE inhibitors 17; diuretics 14; antidepressants 10; NSAIDs 10 Risk factors: drug-drug interactions; drugs that required therapeutic drug monitoring	31% of patients received a drug combination with potential for drug-drug interaction
Madsen[25]	University hospital, USA; internal medicine	1 year; 30 057 patients; ADRs were recorded, causality assessment not specified	Spontaneous reporting vs chart review (predefined events)	ADR: spontaneous reporting 1.7; chart review 3.1	Drugs, spontaneous reporting: antibacterials 77; digoxin (digitalis) 7; analgesics 3 Drugs, chart review: antibacterials 32; analgesics 13; psychotropics 9	Chart review of predefined events better than spontaneous reporting
Bowman et al.[17]	Non-university hospital, USA; internal medicine	4 months; 1024 patients; ADRs and overdoses were recorded. Causality was assessed	Chart review	ADR: 23.1 (2.6% of all drug exposures)	Drugs: furosemide (frusemide) 12; diltiazem 3.6; enalapril 3. Type of ADR: metabolic/ haematological 33; GI tract 18; genitourinary 12 Risk factors: age >65 years; female sex; greater number of drug exposures	
Chan & Critchley[26]	University hospital, China; internal medicine	2 months; 440 patients; definite or probable ADRs were recorded	Spontaneous reporting vs chart review	ADR: chart review 9.4 in males, 11.2 in females, 10% total (56 ADRs in 440 patients); spontaneous reporting: 3.4 overall (15 patients with 17 ADR)	ADR: hypokalaemia (diuretics); hyperkalaemia (ACE inhibitors, potassium); hyponatraemia (diuretics)	Spontaneous reporting is less efficient than chart review
Nazario et al. [27]	University hospital, Puerto Rico; internal medicine	2 years; 12 229 patients; ADRs were recorded, causality assessment not specified	Spontaneous reports	ADR: 2.2%	Drugs: antibacterials 29; cardiovascular agents 21; antiepileptic drugs 10; psychotropics 9 Type of ADR: hypersensitivity 29.3; drug intoxication 19.9; cardiovascular 15.9	Preventive interventions: development of a clinical pharmacist-run anticoagulation clinic, evaluation of the use of phenytoin, dosage algorithm for theophylline

Continued next page

Table III. Contd

Study	Setting	Duration of study; patients; data collection	Detection method	ADR or ADE frequency (% patients hospitalised)	Most frequent types of ADE/ADR and drugs most frequently associated with ADE/ADRs (% ADE/ADRs); risk factors	Remarks
Pearson et al.[28]	Non-university hospital, USA; internal medicine	7 months; 10 587 patients; ADRs were recorded, causality was assessed	Spontaneous reports verified by clinical pharmacist	ADRs: 1.9%	Drugs [preventable (non-preventable) ADRs]: antibacterials 42 (58); cardiovascular drugs 16 (6); analgesics 13 (10) Type of ADR [preventable (non-preventable) ADRs]: skin 50 (38); bleeding 13 (0.6); heart 13 (0.6) Risk factors: allergy unrecognised; use of oral anticoagulants; use of drugs that require therapeutic drug monitoring; drugs that are eliminated via the kidneys	19% of the ADRs were considered to be preventable
van Kraaij et al.[29]	University hospital, The Netherlands; geriatrics	3 months; 105 patients; ADRs were recorded, causality was assessed	Systematic review of charts	Certain or probable ADRs during admission and stay: 37	Drugs: diuretics 32; laxatives 21; antibacterials 21 Risk factors: length of stay in hospital, but not number of drugs or number of diagnoses	
Orsini et al.[30]	University hospital, USA; internal medicine	Both phases 1 year; 24 500 vs 25 530 patients; ADRs were recorded, causality was assessed	Spontaneous reports vs patient monitoring (pharmacists)	ADRs: spontaneous reports 0.4; patient monitoring 1.3	Type of ADR: skin 41; respiratory 14; neurological 14; haematological 12	Drug-drug interactions 5%, medication errors 7% of all ADR. Possible improvement from standardisation of the detection system, active participation of hospital pharmacists
Hall et al.[31]	University hospital, Ireland; general medicine	14 months; 25 670 patients; ADRs were recorded, causality assessment not specified	Spontaneous reports (physicians and nurses)	ADR: 0.54 (128 reports)	Type of ADR: skin 44; GI tract 24; CNS 12; cardiovascular 6	100 ADRs were reported by nurses and 28 were reported by physicians. 62% of the affected patients were female. Only one ADR was reported by both a nurse and a physician

Continued next page

Table III. Contd

Study	Setting	Duration of study; patients; data collection	Detection method	ADR or ADE frequency (% patients hospitalised)	Most frequent types of ADE/ADR and drugs most frequently associated with ADE/ADRs (% ADE/ADRs); risk factors	Remarks
Bates et al.[1]	University hospitals, USA; general medicine	6 months; 4031 patients; ADEs were recorded, causality assessment not specified	Systematic review of patient charts (research nurses) and spontaneous reporting	ADE: 6.1 (247 events)	Drugs: analgesics 30; antibacterials 24; anticoagulants 10; sedatives 8	Preventable ADES occurred in 1.7% of patients (28% of all ADEs); ADEs that were not preventable occurred in 4.4%. 12% of ADEs were life-threatening. Computerised ordering could prevent most ADE
Bates et al.[32]	University hospital, USA; internal medicine	51 days; 379 patients; ADE were recorded, causality assessment not specified	Patient monitoring (study nurses)	ADE: 6.6 (25 events)	NR	Severity of ADE: 1 life-threatening, 7 severe, 17 significant. 5 events (20%) judged to be preventable. 0.9% of medication errors resulted in an ADE, all judged as being preventable
Wu et al.[33]	University hospital, Taiwan; internal medicine	9 months; 666 patients; ADR were recorded, causality was assessed	Spontaneous reports	ADR: 2.7	NR	3.5% of patients had an ADR at entry. 51% of ADRs were classified as type A reactions, 49% were classified as type B. 81% of ADRs were of severe or moderate severity
Smith et al.[34]	University hospital, UK; internal medicine	3 years; 20 695 patients; ADRs were recorded, causality was assessed	Spontaneous reporting	ADR: 6.9	Drugs: NSAIDs, anticoagulants, digoxin Type of ADR: GI tract, impaired renal function	80% of ADRs were considered type A reactions, 20% were considered type B. Drug-drug interactions accounted for 20% of ADRs. Most of the ADRs were reported by nurses and pharmacists. Only 6.3% of the ADRs reported were referred to authorities
Bowman et al.[35]	Non-university hospital, USA; internal medicine	4 months; 1024 patients; ADRs and overdoses were recorded, causality was assessed	Chart review (clinical pharmacists, nurses)	ADR: 23.1 (237/1024 patients)	Type of ADR: metabolic 30; GI tract 18; CNS 11; genitourinary 10; cardiovascular 9 Risk factors: female sex; increased serum creatinine level; polypharmacy	55% of ADRs were possibly causally related to drug use, 40% were probably causally related and 5% were definitely causally related. 70% of ADRs were considered type A reactions, 30% were considered type B

Continued next page

Table III. Contd

Study	Setting	Duration of study; patients; data collection	Detection method	ADR or ADE frequency (% patients hospitalised)	Most frequent types of ADE/ADR and drugs most frequently associated with ADE/ADRs (% ADE/ADRs); risk factors	Remarks
Classen et al.[6]	University hospital, USA; internal medicine	4 years; 91 574 patients; ADEs were recorded	Spontaneous reporting. Control group (patients without ADE matched to patients with ADE)	ADE: 2.4	Drugs: morphine, digoxin, pethidine (meperidine), oxycodone	ADEs were associated with prolongation of hospitalisation (increased by 1.74 days), increased mortality (1.05 vs 3.5%) and increased cost ($US2262 per ADE; 1993 values)
Cullen et al.[36]	University hospital, USA; general medicine	6 months; 4031 patients; ADEs were recorded	Patient monitoring (study nurses)	ADE: 1.7 (70 events in 4031 patients); ICU 2.7, non-ICU 1.4	Drugs: antibacterials, electrolytes, analgesics, cardiovascular drugs	Also reports medication errors (4.8% of patients)
Moore et al.[3]	University hospital, France; internal medicine	6 months; 329 patients; ADRs and overdoses were recorded, causality assessment not specified	Patient monitoring (physician). Control group (matched patients without ADR)	6.6 during hospitalisation	Type of ADR: allergy 14; hypotension 12; dehydration 12; sleepiness, falls 12; GI disorders 12	3% of patients with ADR at entry. Excess hospital stay was 8.5 days in patients with ADR. 66% of ADRs were considered to be type A reactions
Gray et al.[37]	Non-university hospital, USA; geriatrics	14 months; 145 patients; ADEs were recorded	Patient monitoring (pharmacist)	ADE: 15.9	Drugs: cardiovascular 21.4; analgesics 17.9; psychotropics 10.7; respiratory 14.3; antibacterials 10.7 Type of ADE: CNS 32; GI tract 32; cardiovascular 14.3; metabolic 7.1	54% of ADEs were considered to be preventable. Length of stay: 8.7 ± 5.0 days in patients who experienced ADEs vs 6.6 ± 3.0 days in those who did not ($p < 0.022$)
Gholami & Shalviri[38]	University hospital, Iran; internal medicine	9 months; 370 patients; ADRs were recorded, causality was assessed	Patient monitoring (pharmacist)	ADR: 16.8 (definite, probable, possible);	Type of ADR: haematological 51; GI tract 22; kidney 7; liver 3	59% of ADRs were considered to be preventable. 7% of patients had ADR at entry. Mortality in patients with ADR was 2.9%

Continued next page

Table III. Contd

Study	Setting	Duration of study; patients; data collection	Detection method	ADR or ADE frequency (% patients hospitalised)	Most frequent types of ADE/ADR and drugs most frequently associated with ADE/ADRs (% ADE/ADRs); risk factors	Remarks
Schlienger et al.[39]	University hospital, Switzerland; internal medicine	2 years; 1959 patients (941 who received the intervention, 1018 who did not receive the intervention); ADEs were recorded	Spontaneous reporting vs patient monitoring (pharmacist)	ADE: spontaneous reporting 2.1; patient monitoring 14.6	Type of ADE: GI tract 27.2; CNS 16.1; cardiovascular 14.3; metabolic 12.1; blood 7.1; skin 5.4	After stopping comprehensive monitoring, ADE reporting rates rapidly return to pre-intervention levels
Tegeder et al.[40]	University hospital, Germany; internal medicine	17 months; 98 patients; ADRs were recorded, causality was assessed	Retrospective chart review and computerised monitoring	ADR: 17.9 (definite and probable)	Type of ADR: Liver 44; kidney 15; electrolytes 15; blood 11; glucose 11 Risk factors: number of drugs, age	Computerised monitoring yielded 82 events: 27 were considered definite/probably causally related to drug use, 30 were considered possible ADRs (83% of ADRs were type A)
van den Bemt et al.[41]	Non-university hospital, The Netherlands; ICU	2 months; 620 patients; ADEs were recorded	Spontaneous reporting (nurses, physicians) and daily visit (pharmacists)	ADE: 29 (311 events in 179/620 patients)	NR	Patient interviews (daily visits) result the highest frequency of events. Doctors report most severe events
Bates et al.[42]	University hospital, USA; general medicine	6 months; 2019 patients; ADEs were recorded	Patient monitoring (study nurse)	ADE: 6.7 (135 events	Drugs: diuretics, electrolytes, antineoplastic agents, anticoagulants, antiulcer agents Risk factors: electrolyte use, diuretic use, medical ward	24% of ADEs were considered to be preventable
Dormann et al.[43]	University hospital, Germany; internal medicine	7 months; 379 patients; ADRs were recorded, causality was assessed	Chart review vs computer based vs spontaneous reporting	ADR: 12 (46 events); computer-based 8.9 (34/46) and spontaneous reporting 4.4 (17/46)	Drugs: antibacterials 28; cardiovascular drugs 11; antiretrovirals 11; neuroleptics 9	6% of ADRs were severe. Computer-based monitoring detected 73% of ADRs. Mortality due to ADRs was 0.14%. Excess stay of patients with ADRs: 3.5 days. Excess cost of $US1400 per ADR (year of value not specified)

Continued next page

Table III. Contd

Study	Setting	Duration of study; patients; data collection	Detection method	ADR or ADE frequency (% patients hospitalised)	Most frequent types of ADE/ADR and drugs most frequently associated with ADE/ADRs (% ADE/ADRs); risk factors	Remarks
Fattinger et al.[2]	University hospital, Switzerland; internal medicine	3 years; 4331 patients; ADRs were recorded, causality was assessed	Patient monitoring	ADR: clinically relevant 11%	Drugs: chemotherapy 30.7; iloprost 14.3; ciclosporin 4.6; antibacterials 2.8; antivirals 2.6 Type of ADR: GI tract 28; blood 24; skin 20; CNS 13; cardiovascular 6 Risk factors: female sex, polypharmacy	Prolongation of hospitalisation by 1.2 days in patients who experienced ADRs. Mortality 0.14%
Suh et al.[44]	University hospital, USA; general medicine	5 months; 9311 patients; ADRs were recorded, causality was assessed	Actual review of charts (pharmacists, nurses, physicians). Control group (patients without ADRs)	ADR: 2.1	Drugs: antibacterials 17.1; cardiovascular 16.5; NSAIDs 14.6; psychotropics 5.5 Type of ADR: GI tract 24; skin 19; immunological 15; CNS 13	Definite 8%, probable 69%, possible 21%. Severe 17%, lethal 2%. Patients with ADRs spent 3.8 extra days in hospital, incurring an extra cost of approximately $US5000 per ADR (year of value not specified)
Lagnaoui et al.[45]	University hospital, France; internal medicine	4 months; 444 patients; ADRs and overdoses were recorded, causality assessment not specified	Patient monitoring (physicians, pharmacist)	ADR: 4.7	Drugs: antibacterials 38; immunoglobulins 15; topical corticosteroids 15 Type of ADR: neurological 31; skin 23; GI tract 15; liver 15 Risk factors: polypharmacy	42.3% of ADRs were type A reactions, and 50% of all ADRs were considered to be preventable. 7.5% of hospital bed days were due to ADR
Thomas & Brennan[46]	15 hospitals in Colorado, USA and 13 in Utah, USA; general medicine	1 year; 4943 patients in Utah, 9757 in Colorado; predefined, specific ADEs were recorded	Chart review (study nurses)	ADE: patients aged 16–64 years 0.17; patients aged ≥65 years 0.63	NR	Study also reports other events related to medical procedures and falls
Kaushal et al.[47]	2 university hospitals, USA; ICU	Duration not specified; 1120 patients; ADEs were recorded	Patient monitoring (physician)	ADE: 2.3 (4.2% of patients who experienced a medication error)	Drugs: antibacterials 20; analgesics 16; electrolytes 26	Computerised ordering/clinical pharmacist can prevent >90% of medication errors

Continued next page

Table III. Contd

Study	Setting	Duration of study; patients; data collection	Detection method	ADR or ADE frequency (% patients hospitalised)	Most frequent types of ADE/ADR and drugs most frequently associated with ADE/ADRs (% ADE/ADRs); risk factors	Remarks
Bond et al.[5]	1116 hospitals (non-university), USA; general medicine	8 500 000 patients; ADEs were recorded	Spontaneous reports	ADE: 0.25 (5% of the patients with a medication error)	NR	Possible improvement: installation of a decentralised clinical pharmacy service (a clinical pharmacist on the ward)
Bordet et al.[9]	University hospital, France; general medicine	18 months; 16 916 patients; ADRs were recorded, causality was assessed	Spontaneous reporting. Control group (matched patients without ADR)	ADR: 1.69 during hospitalisation	Drugs: contrast media 20; antibacterials 14; anticoagulants 13; diuretics 6 Type of ADR: skin 24; heart 21; metabolic 12; coagulation 10; neurological 10	Frequency is age-dependent. 5% (18) of ADRs were life-threatening, 5% were lethal. Patients who experienced an ADR had a hospital stay that was 4 days longer. In 0.51%, an ADR was the reason for hospitalisation
Cox et al.[48]	University hospital, UK; general medicine	4 months; 21 365 patients; ADRs were recorded, causality assessment not specified	Spontaneous reporting	ADR: 0.2	Drugs: anticoagulants 18; cardiovascular 16; CNS drugs 12; NSAIDs 6 Type of ADR: coagulation 18; neurological 16; cardiovascular 12; GI tract 10%	None of the serious or new ADRs were reported to the authorities
Senst et al.[49]	University hospital, USA; general medicine	53 days; 3187 patients; ADEs were recorded	Spontaneous reporting and patient monitoring (pharmacist)	ADE: 4.2	Drugs: antibacterials 39%, narcotics 30%, antipsychotics 4%, anticonvulsants 4%	15% of ADEs were considered to be preventable, 45% were considered serious; 19% were considered life-threatening; 73% of the ADE were identified by the computer flags. ADE increased the length of stay in the hospital by 1.2 days; cost $US2162 per ADE (year of value not specified)

Continued next page

Table III. Contd

Study	Setting	Duration of study; patients; data collection	Detection method	ADR or ADE frequency (% patients hospitalised)	Most frequent types of ADE/ADR and drugs most frequently associated with ADE/ADRs (% ADE/ADRs); risk factors	Remarks
Thuermann et al.[50]	University hospital, Germany; internal medicine	2 months clinical monitoring; 332 patients. 3 months computerised monitoring; 600 patients; ADRs were recorded, causality was assessed	Patient monitoring vs computerised monitoring	ADRs: clinical monitoring 15.4, computerised monitoring 18.5	Type of ADR: CNS 53; haematology 14; respiratory 12; GI tract 7; cardiovascular 7	45% of all ADRs were detected by monitoring. The sensitivity of clinical monitoring was 72%, and that of computerised monitoring was 45% 2.7% of patients had an ADR at entry
Vargas et al.[51]	University hospital, Spain; ICU	2 years and 7 months; 401 patients; ADRs and overdoses were recorded, causality was assessed	Actual review of charts. Control group (matched patients without ADRs)	ADR: 9.2 (1.1% of drug exposures)	Drugs: morphine 33; pethidine 23; dipyrone (metamizol) 18 Type of ADR: vomiting 18; hypotension 15; nausea 15; itchiness 10	87% of ADRs were considered to be type A reactions. Patients who experienced ADR spent 3.4 days longer in the ICU
Egger et al.[52]	Non-university hospital, Germany; geriatrics	5 months; 163 patients; ADRs were recorded, causality was assessed	Actual review of charts (pharmacist) vs computerised monitoring	ADR: chart review 60.7; computerised monitoring detected 47.5% of the ADRs identified by chart review	Drugs: cardiovascular 26; haematological 22; psychotropics 20 Type of ADR: GI tract 26; liver 18; metabolic 17; cardiovascular 9; skin 7	Drug-drug interactions cause 17% of ADRs. 21% were idiosyncratic, 7% were due to intolerance, 10% were an 'adverse effect', 9% were a 'secondary pharmacological effect', 5% were due to allergy
Somers et al.[53]	University hospital, Belgium; geriatrics	8 months; 168 patients. 5 months; 163 patients; ADRs were recorded, causality was assessed	Spontaneous reporting and patient interviews	ADR: spontaneous reporting 7.1; patient interviews 41	Drugs: cardiovascular drugs 33; CNS 33; antibacterials 8	All ADRs were considered to be type A reactions

Continued next page

Table III. Contd

Study	Setting	Duration of study; patients; data collection	Detection method	ADR or ADE frequency (% patients hospitalised)	Most frequent types of ADE/ADR and drugs most frequently associated with ADE/ADRs (% ADE/ADRs); risk factors	Remarks
Briant et al.[54]	Public hospitals, New Zealand; general medicine	1 year; 6579 medical records (cases); ADEs were recorded	Chart review	ADE: 2.92 (192 events)	Drugs: cardiovascular 45; CNS 17.5; NSAIDs 7	74.5% of ADEs were considered to be preventable
Rothschild et al.[55]	University hospital, USA; ICUs	27 weeks; 391 patients or 420 admissions; ADEs were recorded	Patient monitoring (physicians and pharmacists)	ADE: 14.3 (56 events)	NR	61% of the events were associated with medication errors. 19 were considered to be preventable. The wrong dosage was administered in 36% of the ADEs
Nebeker et al.[56]	University hospital, USA; general medicine	20 weeks; 937 patients; ADEs and ADRs were recorded	Patient monitoring (clinical pharmacists)	ADE: 52 (483 events, 448 ADRs)	Drugs: narcotics 26; diuretics 18; cardiovascular 17; antibacterials 8 Type of ADE: obstipation 14; hypokalaemia 10; hypotension 10; hyperglycaemia 4	35 ADEs were caused by under- or overdosing, 90% of the ADRs were considered to be type A reactions and to be preventable. Medication errors were the reason for 27% of ADEs and included prescription errors (61%), monitoring errors (25%) and administration errors (13%) Possible improvement: Good database for drug prescription, with decision support for drug selection, administration and monitoring
Gurwitz et al.[57]	2 university hospitals; geriatrics	9 months; 1247 patients; ADEs were recorded	Chart review, interviews with residents, computer-assisted screening	ADEs: 65; (815 events); 9.8 events per 100 resident-months	Drugs: warfarin 15; atypical neuroleptics 11; diuretics 8; opioids 6 Type of ADE: CNS 24; haemorrhage 20; GI tract 17; kidney 10 Risk factors (relative risk; 95% CI): antipsychotics (3.4; 2.0, 5.9); anticoagulants (2.8; 1.6, 4.7); diuretics (2.2; 1.2, 4.0); antiepileptic drugs (2.0; 1.1, 3.7)	28% of the events were severe. 41% of the events were preventable (including 61% of the severe events)

a Differs from the sum of both methods, as some ADRs were detected by both methods.

GI = gastrointestinal; **ICU** = intensive care unit; **NR** = not reported.

of < 0.05 was considered to be statistically significant.

A total of 77 articles matching the predefined criteria were detected. We identified 35 articles that reported the frequencies of medication errors[1,5,15,32,47,58-87] and 46 articles reporting frequencies of adverse drug reactions or adverse drug events[1-3,5,6,9,17,19-57] in hospitalised patients. Four studies reported both medication errors and adverse drug events;[1,5,32,47] these studies are documented in both the table on medication errors (table IV) and the table on adverse drug events (table III). Several studies were conducted in more than one hospital and/or ward and many reported more than one frequency of medication errors or adverse drug events. The number of reported values can therefore exceed the number of the studies included.

2. Medication Errors

With regard to medication errors, we took into account that the methods used to measure errors and the ways used to express error rates differed among the studies, rendering the results difficult to compare. As shown in figure 2, the rates of medication errors were most often determined as the percentage of administrations. Alternatively, errors were also expressed as the number per 100 patient-days or as the percentage of patients hospitalised. The reported error rates were 5.7% of administrations (range 0.038–56.1%, n = 31 studies), 1.07 errors per 100 patient-days (range 0.35–12, n = 9) or 6% of patients hospitalised (range 0.93–24%, n = 7). A close inspection of the data in figure 2 reveals that the variability in the error frequencies is large, even within the groups using the same units for error frequencies. The reasons for this high variability were primarily the different drugs the patients were treated with and the different methods used to determine the error rate. Looking only at the error rates given as a percentage of administrations (figure 2), the three error rates exceeding the 95th percentile originate from studies where intensive monitoring of administration (mainly of intravenous fluids) was performed.[81,86,87] On the other hand, the error rate below the 5th percentile in the same figure originate from large multicentre trials employing either collection of spontaneous reports[58] or systematic review of prescriptions.[15,66]

The influence of the method used for error detection was investigated further for all studies reporting the error rate as a percentage of administrations (figure 3). Although the variability remained large, comprehensive patient monitoring (median 10.4% of administrations, range 2.4–56.1%, n = 21) detected significantly more errors than spontaneous reporting (median 2.3%, range 0.038–3.3%, n = 3) or chart review (median 4.7%, range 0.287–5.3%, n = 7).

In studies reporting the error rate as a percentage of administrations, the type of hospital (university versus non-university) was associated with a significant difference in the error rate. The median error rate was 5.1% (range 0.038–26.0%, n = 19) in university hospitals[15,32,47,58,63,66,69,72,75-77,82-84] and 13.65% (range 3.5–49%, n = 12) in non-university hospitals[64,65,67,68,78,79,81,86,87] ($p < 0.05$). Regarding the types of wards in which the investigation was performed, the numbers in each subgroup were too small for statistically meaningful comparisons. However, comparison of the medians (between 3.5% and 10.35% of administrations, with large ranges), did not reveal substantial differences. As stated above, the ward of administration *per se* appears to be less important than the type of drugs administered on the ward (that is, parenteral administration of drugs is associated with a higher error rate).[81,85,86]

Drugs and classes that were associated with high rates of medication errors include antibacterials, cardiovascular drugs, oral anticoagulants, theophylline and antineoplastic drugs (table IV).[1,15,47,59,66,77,80] Errors occurred at all stages of the medication process, but most often occurred at the administration stage (median 53% of all errors, range 9–90.7%, 25 studies),[1,15,32,47,58,60,62-69,71,75,77-79,81-85,87] involved unauthorised administration of drugs (25%, range 4–28%, three studies)[58,63,78] or errors in drug prescription (16.5%, range 13–74%, six studies),[1,15,47,66,68,71] transcription (11%, range 2–14%, three studies)[1,47,72] and preparation (13.5%, range 7–23%, four studies).[63,75,81,82] Considering drug administration, frequently occurring errors were the omission of a dose (22.1%, range 5.1–58%, 14 studies),[32,58,63-65,67,69,72,78,82-85,87] administration at an incorrect time (34.5%, range 14.8–80.4; eight observations in seven studies[58,64,68,69,78,79,83]), administra-

Table IV. Studies reporting the frequency of medication errors in hospitalised patients

Study	Setting	Duration of study; number of doses administered	Detection methods	Error frequency	Most frequent medication errors; drugs; risk factors (% errors, unless otherwise stated)	Remarks
Hartwig et al.[58]	University hospital, USA; general medicine	12 months; 279 818 doses administered per month	Spontaneous reporting	0.038% of all doses administered (107 errors per month)	Type of error: dose omission 37; unauthorised drugs 28; wrong time 14.8; wrong dose 11.6; wrong infusion rate 5.5	Frequency increased with duration of study (suggesting that the reporters became accustomed to reporting)
Bates et al.[59]	University hospital, USA; general medicine	37 days; 2967 patient-days	Systematic review of patient charts and spontaneous reporting	10 per 1000 patient-days (33 per 1000 patient-days in coronary care units, 13 on medical wards, 7 on surgical units and 0 in obstetric units)	Drugs: antibacterials 25; cardiac drugs 15; anticoagulants 10	72% of the errors by physicians, 10% by pharmacists, 8% by nurses
Schumock et al.[60]	University hospital, USA; internal medicine	294 discharge medications	Actual verification of prescriptions (clinical pharmacists)	5.8% of prescriptions (17 errors in 294 prescriptions)	Type of error: wrong dose 41 Risk factors: lacking information about therapy and/or patient	11 errors were potentially harmful. Most errors were by first-year residents. Clinical pharmacists detected two-thirds of errors
Shaughnessy & D'Amico[61]	Non-university hospital, USA; general medicine	Year 1: 691 prescriptions (baseline) Year 2: 921 prescriptions (post-intervention)	Actual verification of prescriptions (clinical pharmacists); comparison pre-/post-intervention	Baseline: 14.4% of prescriptions. Post-intervention: 6% of prescriptions	NR	The intervention was the provision of feedback on baseline errors. Results show that prescribing errors can be reduced by teaching
Nettleman & Nelson[62]	University hospital, USA; internal medicine	8 months; 1484 patient-days	Systematic review of patient charts (research nurses)	120 per 1000 patient-days (178 medication errors)	Type of error: missed dose 74	Administration records by nurses are the best source for detection of medication errors
Bates et al.[1]	University hospitals, USA; general medicine	6 months; 21 412 patient-days	Systematic review of patient charts (research nurses) and spontaneous reporting	20.6 errors per 1000 patient-days	Drugs: analgesics 30; antibacterials 24; sedatives 8 Type of error: prescription 49; transcription 11; dispensing 14; administration stage 26	Study also reports adverse drug events (11.5 per 1000 patient-days or 6.1% of hospitalised patients)
Dean et al.[63]	University hospital, USA; general medicine	1 month; 919 doses administered	Patient monitoring (study nurse)	6.9% of doses administered	Type of error: wrong selection or preparation by nurse 52; unclear prescription 37; wrong dose 30; unordered drug 25; wrong drug supplied by pharmacy 6	English system (clinical pharmacists on ward) better than US system (single dose unit)

Continued next page

Table IV. Contd

Study	Setting	Duration of study; number of doses administered	Detection methods	Error frequency	Most frequent medication errors; drugs; risk factors (% errors, unless otherwise stated)	Remarks
	University hospital, UK; general medicine	2 months; 2756 doses administered	Retrospective review of prescription (study nurse)	3.0% of doses administered	Type of error: dose omission 58; wrong selection or preparation 40; drug unavailable in unit 39; incorrect dose 14; unclear prescription 13	
Bates et al.[32]	University hospital, USA; internal medicine	51 days; 10 070 medication orders in 1704 patient-days	Self-reporting by pharmacists, nurse review of patient charts, review of prescriptions by hospital pharmacy	5.3% of orders (530 errors)	Type of error: dose omission 53; wrong dose 15	0.9% of medication errors resulted in an adverse event, all judged to be preventable
Borel & Rascati[64]	Type of hospital not specified, USA; orthopaedic and general surgical units	873 observations before intervention, 929 after	Patient monitoring	16.9% (148 errors) before intervention, 10.4% (97 errors) after	Type of error (before/after intervention: dose omission 24.3/ 10.3; wrong time 61.5/ 80.4)	None of the medication errors was detected by the usual reporting system of the hospital
Ridge et al.[65]	Non-university hospital, UK; general medicine	4 months; 3312 drug doses administered	Direct observation by nurses during drug rounds	3.5% of doses administered (115 errors)	Type of error: non-available drug 69; dose omission 36; wrong dose 23; timing errors: 81% of doses were given ±1 hour of time indicated by prescriber, 98% were given within ±2 hours	
Lesar et al.[15]	University hospital, USA; general medicine	9 years; 3 903 433 prescriptions	Systematic review of all prescriptions (clinical pharmacists)	11 186 errors; 6.52 errors per 1000 patient-days (2.87 per 1000 orders). 1.22 serious errors per 1000 patient-days	Drugs: xanthines 20; antibacterials 12; cough medicines 7 Type of error: overdose 37; underdose 19; administration of drug to an allergic patient 14; dose duplication 6; wrong drug 4 Risk factors: complex therapies; new drugs	

Continued next page

Table IV. Contd

Study	Setting	Duration of study; number of doses administered	Detection methods	Error frequency	Most frequent medication errors; drugs; risk factors (% errors, unless otherwise stated)	Remarks
Lesar et al.[66]	University hospital, USA; general medicine	1 year; 525 750 prescriptions	Systematic review of all prescriptions (clinical pharmacists). Only clinically relevant errors were included	2103 errors; 3.99 errors per 1000 orders. 696 could potentially cause adverse drug reactions	Drugs (per 1000 orders): xanthines 20.6; antibacterials 13.6; cardiovascular drugs 5.01; hormones 3.84 Type of error: overdose 42; underdose 16; administration of drug to an allergic patient 13; wrong dosage form 12; wrong drug 5 Risk factors: limited knowledge of drug therapy 30; limited knowledge of patient factors 29	Education in pharmacotherapy must be improved
Mehrtens & Carstens[67]	Non-university hospital, Germany; geriatric unit	14 days; 2335 prescriptions	Systematic review of all patient charts (clinical pharmacists)	5.1% of orders (1.5% if documentation errors not counted)	Type of error: documentation errors (failures in nurses' notes) 67; wrong dose 19; dose omission 9	Adverse events could have possibly resulted from a third of all medication errors
Lacasa et al.[68]	Non-university hospital, Spain; general medicine	Baseline, 1 month: 839 doses administered. After intervention, 1 month: 855 doses administered	Systematic investigation of drug orders and doses administered (study nurses)	6.8% of all doses administered before and 3.5% after intervention	Type of error before intervention: wrong time 28; wrong route of administration 25; wrong prescription 19 Type of error after intervention: NR	Intervention included teaching of personnel about medication errors. Particularly effective in nurses
McNally & Sunderland[69]	University hospital, Australia; surgery	Before intervention: 23 days, 5515 doses administered. After intervention: 31 days, 7391 doses administered	No-blame spontaneous reporting	3.3% of doses administered before intervention, 2.3% after intervention	Type of error (before/after intervention): dose omission 36/28; wrong documentation 21/39; wrong time 25/19; wrong dose 1.7/2.4	No-blame self-reporting system better than other self-reporting systems
Raschke et al.[70]	University hospital, USA; general medicine	6 months; 9306 patients	Computerised registration of 37 predefined risk situations	Risk situation (adverse event or error) in 6.4% of patients	NR	Most frequent adverse events: risk situation for digoxin toxicity (e.g. hypokalaemia), renal failure due to radiocontrast media, phenytoin toxicity. 28% of all events and 42% of life-threatening events may be prevented. Computerised alert system recommended

Continued next page

Table IV. Contd

Study	Setting	Duration of study; number of doses administered	Detection methods	Error frequency	Most frequent medication errors; drugs; risk factors (% errors, unless otherwise stated)	Remarks
Bates et al.[71]	University hospital, USA; general medicine	Baseline: 6 months, 11 869 patient-days After introduction of CPOE: 9 months, 27 572 patient-days	Reporting of errors by pharmacists and nurses; chart review	Baseline: 10.7 errors per 1000 patient-days (127 errors). After CPOE: 4.86 per errors 1000 patient-days (134 errors)	Types of errors at baseline: wrong dose 18; wrong drug 13; wrong technique 9 Types of errors after CPOE: wrong dose 31; wrong drug 16; wrong technique 5	Study demonstrated a positive effect of CPOE
Flaatten & Hevroy[73]	University hospital, Norway; ICU (general, cardiology, recovery room)	13 months; 385 patients in general ICU, 552 in cardiology ICU, 8429 in recovery room	Spontaneous reports	Total 0.93% of patients (87/9366). General ICU 13.2% patients (51/385)	Type of error: wrong dose or preparation; wrong medication/infusion; errors in administration	37% of errors had consequences for the patient. Most of the errors were reported in the ICU rather than the recovery room
Leape et al.[74]	University hospital, USA; ICU (cardiology)	75 patients before and after intervention, 75 from control unit (coronary care unit not participating in intervention)	Systematic review of all prescriptions (clinical pharmacists)	Errors decreased from 10.4 per 1000 patient-days before the intervention to 3.5 per 1000 patient-days after the intervention. Rates in the control group were 10.9 and 12.4 per 1000 patient-days, respectively	Type of error: incomplete order; wrong dose; wrong frequency; duplicate therapy	Clinical pharmacists can prevent two-thirds of the medication errors during prescription
Taxis et al.[72]	University hospital, UK; general medicine (clinical pharmacist)	842 solid oral doses	Patient monitoring	8% of doses administered	Type of error: dose omission 5.2; administration 5.3; ordering 2.4; wrong dose 1.2	Lower medication error rate associated with the unit dose system
	University hospital, Germany; surgery (traditional distribution system)	973 solid oral doses		5.1%	Type of error: transcription 2.8; wrong dose 2.8; dose omission 2.7; administration 1.4	
	University hospital, Germany; internal medicine (unit dose system)	1318 solid oral doses		2.4%	Type of error: transcription 2.0; dose omission 1.6; wrong drug 0.7; administration 0.4	

Continued next page

Table IV. Contd

Study	Setting	Duration of study; number of doses administered	Detection methods	Error frequency	Most frequent medication errors; drugs; risk factors (% errors, unless otherwise stated)	Remarks
Tissot et al.[75]	University hospital, France; medical ICU	2009 doses administered	Patient monitoring	6.6% of doses administered (132 errors)	Type of error: wrong dose 31; wrong rate 22; wrong preparation technique 18; incompatibility with coadministered drugs 14 Risk factors: lack of standardisation of the medication process; insufficient staff training	26 errors were potentially life-threatening
Bates et al.[76]	University hospital, USA; internal medicine	31 weeks (4 periods: baseline and 3 intervention periods); 10 070 doses administered (baseline)	Review of prescriptions, medication sheets and charts (pharmacist)	Baseline: 5.3% of doses administered. After intervention: 4.7% of doses administered	Type of error (baseline/after intervention): errors excluding dose omission 2.4/0.4; dose omission 2.9/4.3	Intervention reduces medication errors, excluding dose omissions, by 80%. Adverse drug events were reduced from 14.7 per 1000 patient-days to 9.6 per 1000 patient-days
Bond et al.[5]	1116 hospitals (university and non-university), USA; general medicine	8 500 000 patients	Spontaneous reports	5.07% of patients with errors; more errors in non-university than university hospitals	Risk factors: lack of clinical pharmacists; high pharmacist workload	Error rate may be reduced by installing a decentralised clinical pharmacy service. Study also reports adverse drug events (table III)
Calabrese et al.[77]	5 university hospitals, USA; ICUs	5744 doses administered in 851 patients	Monitoring of certain medications	3.3% of all doses administered (187 errors)	Drugs: cardiovascular drugs 32.6; sedatives/analgesics 25.7 Type of error: wrong infusion rate 40.1	20 errors did not reach patient, 159 reached patient but did not result in harm, 5 errors reached the patient and resulted in effects that required monitoring, 2 reached the patient and resulted in effects that required intervention. None of the errors resulted in death
Kaushal et al.[47]	2 university hospitals, USA; ICUs	10 778 doses administered in 1120 patients	Patient monitoring (physician)	5.7% of doses administered (616 errors)	Drugs: antibacterials 20; analgesics 16; electrolytes 26 Type of error: physician ordering 74; wrong dose 28; wrong route of administration 18; transcription 14 Type of administration associated with error: intravenous 55; oral 21	26 of the errors (4.2% of the errors) resulted in adverse drug events (in 2.3% of patients). Computerised ordering/ clinical pharmacist can prevent >90% of errors

Continued next page

Table IV. Contd

Study	Setting	Duration of study; number of doses administered	Detection methods	Error frequency	Most frequent medication errors; drugs; risk factors (% errors, unless otherwise stated)	Remarks
Barker et al.[78]	36 hospitals and nursing facilities, USA; general medicine	3216 doses administered	Patient monitoring (research pharmacist)	19% of doses administered (605 errors)	Type of error: wrong time 43; dose omission 30; wrong dose 17; unauthorised drug 4%	7% of errors potentially harmful; no difference between university and community hospitals
van den Bemt et al.[79]	2 non-university hospitals, The Netherlands; mixed surgical-medical ICUs	No duration reported; 233 doses administered for 24 patients	Patient monitoring	45% of doses administered (including time errors); 33.0% (excluding time errors)	Type of error: wrong time 50; wrong administration technique 34; wrong dose 23 Risk factors: Mondays; gastric feeding tube and drugs for the gastrointestinal tract	The two hospitals differed substantially in ICU characteristics
LaPointe & Jollis[80]	University hospital, USA; internal medicine	4.5 years; 24 538 patients	Patient monitoring (clinical pharmacist)	24 per 100 admissions (4768 errors): 63% of the errors involved physicians, 26% involved pharmacists, 5% involved nurses and 6% involved other health professionals	Drugs: cardiovascular drugs 41; antibacterials 14.9; drugs for the gastrointestinal tract 9.5 Type of error: wrong drug 36; wrong dose 35; dose omission 10	Recommendations: up-to date information for physicians and nurses, better education for interns
Taxis & Barber[81]	1. University hospital, UK; general medicine 2. Non-university hospital, UK; general medicine	430 intravenous doses administered (106 patients)	Comprehensive monitoring (clinical pharmacists, physician, nurses)	49% of all doses administered (212 doses administered); 3 rated as serious	Type of error: wrong preparation 7; wrong administration 36; wrong preparation and wrong administration 6 Risk factors: multiple preparation steps; bolus injection	Recommendations: central preparation of complex products; short infusion instead of bolus dose
Greengold et al.[82]	2 university hospitals, USA; general medicine	12 weeks in every hospital; 5792 doses administered by medication nurses (training of 2 days) and 3661 doses administered by general nurses	Patient monitoring (trained nurses or pharmacy technicians)	15.4% of all doses administered; 14.9% by general nurses; 15.7% by medication nurses. Medical units 13.2%; surgical units 11.7%	Type of errors: administration technique 42; preparation 9; omitted drug 6; wrong dose 5; wrong route 4	No adverse drug events were observed. Simple education of nurses to become medication nurses has no benefit. Education must be more detailed and deserves more study
Tissot et al.[83]	University hospital, France; general medicine	20 days; 523 doses administered	Direct observation of nurses during preparation and administration of drugs	14.9% of doses administered (78 errors); error frequency excluding timing errors: 11.1%	Type of error: wrong time 26; dose omission 16; wrong dose 13 Risk factors: nurses' workload (OR 2.44; 95% CI 1.3, 4.6); incomplete or illegible prescription (OR 4.75; 95% CI 2.41, 9.36)	Significance of errors: life-threatening 10%; significant 26%; minor 64%

Continued next page

Table IV. Contd

Study	Setting	Duration of study; number of doses administered	Detection methods	Error frequency	Most frequent medication errors; drugs; risk factors (% errors, unless otherwise stated)	Remarks
Wirtz et al.[84]	University hospital, UK (traditional British ward pharmacy service)	6 days/ward; 337 preparations	Patient monitoring	Overall error frequency 26% of doses administered (88 errors). Preparation errors 22%; administration errors 27%	Type of error: wrong administration rate 20–32; wrong dose 21; dose omission 20; incompatibility with coadministered drugs 17	More direct involvement of pharmacy service correlates with less severe medication errors
	University hospital, Germany, with ward stock supply; general medicine			Preparation errors 23%; administration errors 49%		
	University hospital, Germany, with satellite pharmacy on ward; general medicine			Preparation errors 31%; administration errors 22%		
Herout & Erstad[85]	University hospital, USA; surgical ICU	1 month; 42 patients who received 206 continuous intravenous infusions	Comparison of chart documentation and actual observed infusion regimen	106 errors per 1000 patient-days	Type of error: charting inconsistencies (drug omitted from flow sheet, wrong concentration reported, wrong infusion rate) 13; dose errors 7.8 Risk factors: weight-based dose calculation	The study focused on different methods of dose calculation
Taxis & Barber[86]	Non-university hospital, Germany; surgical ward and surgical ICU	122 intravenous drug doses	Patient monitoring (nurses)	48% of doses administered (58 errors): preparation errors 19%; administration errors 23%; both preparation and administration errors 6%	Type of error: incompatibility with coadministered drugs 25; wrong solvent/diluent 20 Risk factors: multiple step preparation; bolus injection	Importance of errors with regards to potential consequences: severe 3%, moderate 31%, minor 13%
van Gijssel-Wiersma et al.[87]	Non-university hospital, The Netherlands; internal medicine	2×3 weeks; 611 prescriptions before and 598 prescriptions after introduction of a computerised medication chart	Prescribing errors by evaluation of all medication orders, administration errors by patient monitoring	Total errors: baseline: 30.8% of doses administered, after intervention: 56.1% Prescribing errors: baseline: 20.3%, after 50.0% Administration errors: baseline: 10.5%, after 6.1%	Type of error (before/after intervention: dose omission 5.1/3.9	Prescribing errors due to administrative errors (missing data or prescriber name) increased, but in therapeutic errors (OR 0.16; 95% CI 0.06, 0.42) significantly decreased wrong dose (OR 0.33; 95% CI 0.12, 0.95) and time errors significantly decreased (OR 0.35; 95% CI 0.15, 0.84)

CPOE = computerised physician order entry; **ICU** = intensive care unit; **NR** = not reported; **OR** = odds ratio.

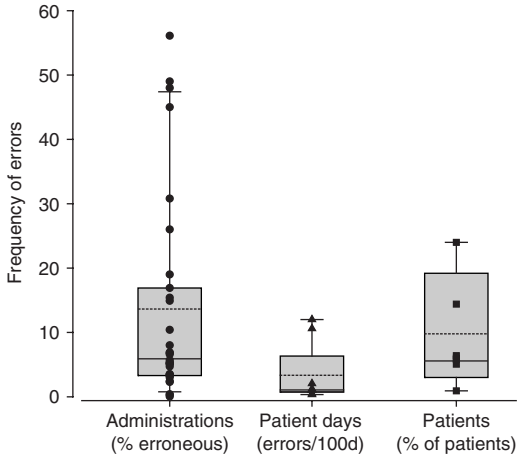

Fig. 2. The frequency of medication errors is 5.7% of all episodes of drug administration, 1.07 errors per 100 patient-days, or 6 patients affected per 100 hospitalised. The variability in the error frequencies is large, irrespective of how the error rate was determined. The most important reasons for this high variability were the different drugs that the patients were treated with and the different methods used to determine the error rate. In the error rates expressed as a percentage of administrations, the error rates exceeding the 95th percentile originate from studies where intensive monitoring of administration (mainly of intravenous fluids) was performed.[81,86,87] The error rates below the 5th percentile originate from large trials that employed either collection of spontaneous reports[58] or with systematic review of prescriptions.[15,66] Data are represented as box plots (25–75th percentile) containing both the median (solid line) and the mean (dotted line). T-bars indicate the 5th and 95th percentile.

tion of the wrong dose (20%, range 1.7–74, 18 studies)[15,32,47,58,60,63,65-67,69,71,75,78,79,81-84] and wrong administration velocity (21%, range 5.5–40.1, four studies).[58,75,77,84]

The most important risk factors for medication errors included a lack of information about drugs or about the patients to be treated, errors in patient charts and/or in the documentation by nurses, and inadequate or decentralised pharmacy services.[5,15,60,63,66,75,79,81,83,85,86]

Recommendations for reducing the frequency of medication errors included the engagement of clinical pharmacists who must be present on the wards,[5,47,60,74,84] improved education in pharmacotherapy for all the persons involved in drug treatment,[61,66,80] an electronic ordering and patient survey system,[47,70,71,76] and the installation of a 'no-blame' error reporting system.[69] Regarding the intravenous administration of drugs, central preparation of complex solutions and replacement of bolus administration with short duration infusions were recommended.[81]

3. Adverse Drug Events or Reactions

As mentioned in section 1, some studies did not differentiate well between adverse drug events and adverse drug reactions. The WHO definition of adverse drug reactions implies that events originating from over- or under-dosing are not adverse drug reactions.[13] In addition, in contrast to adverse drug events, the causality between the drug and the event has to be clear in the case of adverse drug reactions. As shown in table III, these two points were not fulfilled for all studies reporting adverse drug reactions. Since the frequency of the events was not different between studies reporting adverse drug events and those reporting adverse drug reactions (median 6.75% of patients hospitalised, range 0.2–60.7% for adverse drug reactions; median 4.2% of the patients, range 0.17–65% for adverse drug events), we decided to pool the data in one table (table III) and to use the term 'adverse drug event'.

Similar to the studies reporting medication errors, most of the studies about adverse drug events were carried out in university hospitals, mainly on internal medicine wards.[1-3,6,9,19-21,23-27,29-34,36,38-40,42-45,47-51,53,55-57] Nine of the 46 reports originate predominantly from non-university hospitals, three each from internal[17,28,35] and general medicine wards,[5,46,54] two from geriatric wards,[37,52] and one predominantly from intensive care units[41] (table III). The frequencies of adverse drug events reported were not different between university and non-university hospitals, with a median of 6.05% (range 0.2–65%, n = 46 observations) for university hospitals and 15.9% (range 0.17–60.7%, n = 11 observations) for non-university hospitals.

In contrast to the medication errors, the frequency of adverse drug events was reported using the same units in most studies, namely as the percentage of patients who experienced at least one adverse drug reaction while hospitalised. In order to be able to compare the studies, studies reporting the frequency using other units (e.g. adverse events or reactions per 1000 patient-days) were not included. While the units used (percentage of patients hos-

pitalised affected) are helpful for a comparison of the frequencies between studies, they disregard the fact that an individual patient can experience more than one adverse drug event per hospitalisation. The true frequency of adverse drug events may therefore be higher than reported in table III and figure 4 and figure 5. The median overall frequency of adverse drug events was 6.1% of hospitalised patients (range 0.17–65%, 57 observations from 46 studies). The large range in the overall frequency of adverse drug events suggests differences among the studies, possibly due to the methods used to detect adverse drug events and also due to the different wards where the patients were studied. The frequency of adverse drug events was determined by spontaneous reporting (physicians, pharmacists, nurses), by monitoring of the patients (regular review of patient charts and visit of the patients by physicians, pharmacists and/or study nurses), by chart review (either during or after hospitalisation) or by computerised monitoring of predefined adverse drug events. As shown in figure 4, the frequency of adverse drug events detected by spontaneous reporting (median 2.1% of patients, range 0.2–7.1%, 16 studies)[5,6,9,21,25-28,30,31,33,34,39,43,48,53] was significantly lower than that obtained by patient monitoring (11% of patients, 1.3–52%, 19 studies)[2,3,20,21,23,30,32,36-39,41,42,45,47,49,50,53,55,56] or by chart review (9.2% of patients, 0.17–65%, 16 studies).[1,17,22,24-26,29,35,40,43,44,46,51,52,54,57] Since only four studies reported data obtained using computerised monitoring (11.5% of patients, range 1.7–28.8%, not significantly different from spontaneous reporting),[19,43,50,52] this technique was not included in figure 4.

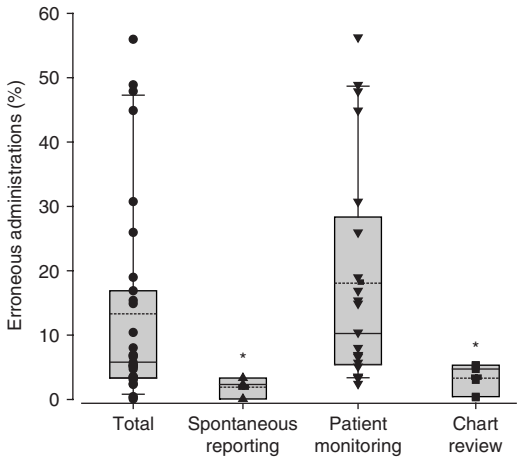

Fig. 3. Dependency of the medication error frequency on the mode of error detection. The influence of the method used for error detection was investigated further for all studies reporting the error rate per administration (first plot in figure 2). Patient monitoring (daily monitoring of patients for a series of predefined events) detected significantly more errors than spontaneous reporting or chart review. Data are represented as box plots (25–75th percentile) containing both the median (solid line) and the mean (dotted line). T-bars indicate the 5th and 95th percentile. * $p < 0.001$ vs patient monitoring.

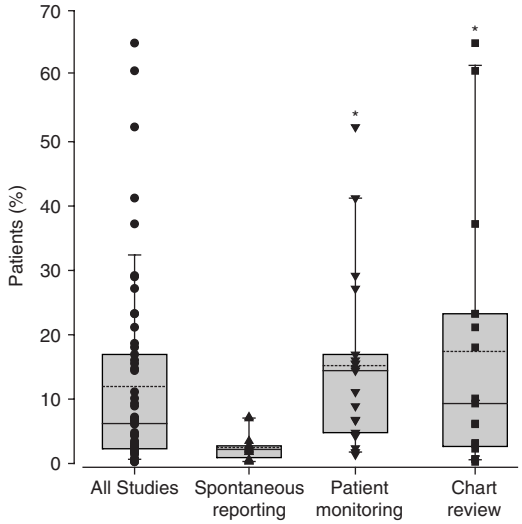

Fig. 4. The frequency of adverse drug events by the mode of detection. The overall frequency of the adverse drug events is 6.1 (median) affected patients per 100 hospitalised. Similar to the medication errors (figure 2), the variability between studies is large, possibly originating from the different methods used to determine adverse drug events and from different wards studied. The frequency of adverse drug events detected by spontaneous reporting (median 2.1% of patients hospitalised) was significantly lower than that obtained by patient monitoring (9.9%) or by chart review (9.2%). Data are represented as box plots (25–75th percentile) containing both the median (solid line) and the mean (dotted line). T-bars indicate the 5th and 95th percentiles. * $p < 0.01$ vs spontaneous reporting.

For computerised monitoring, an array of pathological laboratory values and clinical events are predefined and 'hits' are registered when the corresponding signs or values of a patient fall into this predefined pathological range.[19,40,43,50,52,88,89] Since not every hit corresponds to a true adverse drug event, such studies were only included if the presence of an adverse drug event was confirmed by

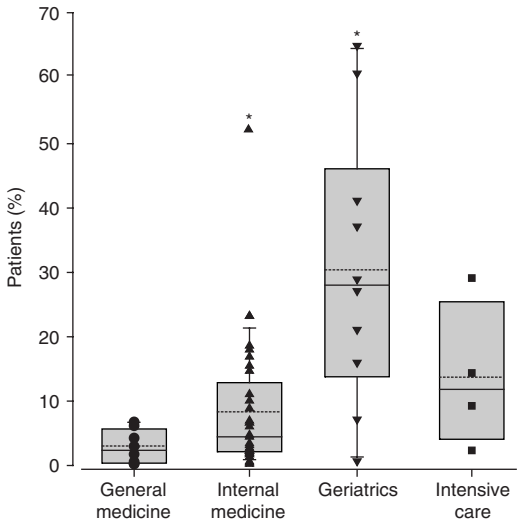

Fig. 5. The frequency of adverse drug events by the wards in which the patients were studied. The frequency of adverse drug events was higher on geriatric wards (median 27.9%) or internal medicine wards (median 4.55%) compared with general medicine wards (median 1.7%). Data are represented as box plots (25–75th percentile) containing both the median (solid line) and the mean (dotted line). T-bars indicate the 5th and 95th percentiles. * $p < 0.01$ vs general medicine.

monitoring of the patients or by chart review. The comparison with the conventional techniques shows that computerised monitoring detects approximately 50% (median 47.5%, range 45–73%, 3 studies) of the adverse drug events.[43,50,52] Since computerised monitoring is less time consuming than patient monitoring or systematic review of patient charts and can be developed further, this technique clearly deserves more attention in the future.

In addition to the technique used for data collection, the frequency of adverse drug events detected may also depend on the ward where the data were collected. As shown in figure 5, higher frequencies of adverse drug events were seen in studies performed on internal medicine wards (median 4.55% of hospitalised patients, range 0.2–52%, 34 observations in 26 studies)[2,3,6,9,17,20-22,25-28,30,32-35,38-40,43-45,48,50,56] or geriatric wards (median 27.9%, range 0.63–65%, ten observations in eight studies)[23,24,29,37,46,52,53,57] than in studies performed on general medicine wards (median 1.7%, range 0.17–6.7%, nine studies).[1,5,19,31,36,42,46,49,54] The frequencies of adverse events obtained in intensive care units (median 11.75%, range 2.3–29%, four studies)[41,47,51,55] also showed a tendency to be higher than those obtained on general medical wards, but the difference did not reach statistical significance due to the paucity of observations.

In 2.9% of the patients (range 0.14–5%, five studies) affected by an adverse event, the event was fatal.[2,6,9,38,43] Forty-six percent (range 15–90%, 12 studies)[1,28,32,37,38,42,45,49,54-57] of the adverse events were judged to be preventable using different algorithms. Eighty percent (range 51–100%, nine studies) of the adverse events were judged to be type A reactions and thus potentially, although not necessarily, preventable.[3,19,33-35,40,45,51,53] In 17.1% (range 4.8–31%, five studies)[22,24,30,34,52] of the adverse drug events, the reason was a drug-drug interaction.

Risk factors for the occurrence of adverse drug reactions were reported in 11 studies.[2,17,19,24,28,29,35,40,42,45,57] The most important risk factors were polypharmacy (observed in six of the

Table V. Prevention of problems associated with pharmacotherapy

Medication errors
Improved pharmacological education of health professionals (nurses, pharmacists, physicians)
'Computerisation' of the medication process
prescribing aids
improved transcription
improved monitoring of patients
Clinical pharmacists on the ward
identification of reporting of medication errors/adverse events
control for drug-drug interactions
dose adaptation in patients with impaired renal and/or liver function
monitoring of complex therapies
Critical incident reporting systems
Adverse drug reactions
Type A (dose-dependent, predictable)
limit polypharmacy as much as possible
dose adjustment according to the function of the elimination organs
avoid drug-drug interactions and other medication errors
Type B (not predictable, idiosyncratic)
difficult to avoid, since not predictable
avoid risk factors; e.g. prior reactions to drugs, and family history of drug reactions
limit damage in case of an adverse drug event (stop all drugs that are not life-saving)

11 studies),[2,17,19,35,40,45] female sex (four studies),[2,17,19,35] use of drugs with a narrow therapeutic range (three studies),[24,28,57] age >65 years (three studies),[17,19,40] renal elimination of drugs (two studies)[28,35] and use of oral anticoagulants (two studies)[28,57] or of diuretics (two studies).[42,57] In patients who had an adverse drug reaction, the duration of hospitalisation was prolonged by 3.4 days (range 1.2–8.5 days, n = 9),[2,3,6,9,19,37,44,49,51] compared with patients who did not experience an adverse drug reaction leading to an increase in costs for each episode of hospitalisation.

4. Discussion

Our analysis of data from the literature demonstrates that medication errors occur in about 5% of all episodes of drug administration and that adverse drug events occur in about 6% of patients hospitalised. Since, at least on medical wards, patients are usually treated with 5–10 drugs per day and stay in the hospital for approximately 8 days,[2] they may undergo 50 episodes of drug administration per hospitalisation, suggesting that most patients will be affected by one or more medication errors. On the other hand, as only approximately 6% of the patients have an adverse drug event it indicates that a minority of medication errors will lead to a clinical manifestation. In agreement with these considerations, it has been estimated in several studies that not more than 10% of all medication errors result in adverse drug events.[5,32,47,77,78] The importance of medication errors is therefore primarily due to their nature as risk factors for adverse drug events and the fact that they are avoidable.

A median of 46.5% of the adverse drug reactions reported were judged to be preventable[1,28,32,37,38,42,45,49,54-57] and can therefore be considered to result from medication errors. Looking at the risk factors for adverse drug events (e.g. polypharmacy, female sex, administration of drugs with a narrow therapeutic range, renal elimination of drugs, age >65 years, and use of anticoagulants or diuretics; see section 2.2), it becomes evident that failure of dose adjustment in patients with impaired renal function represent medication errors.

Drug-drug interactions were the underlying cause of approximately 17% of all adverse drug events. Since approximately 6% of patients hospitalised are affected by at least one adverse drug event, approximately 1% of the hospitalised patients will experience an adverse drug event due to a drug-drug interaction. Since the prevalence of potentially severe drug-drug interactions in hospitalised patients is approximately 60%,[88] only a small fraction (<5%) of the potential drug-drug interactions appear to cause adverse drug events. Looking at individual drug-drug interactions, the proportion of patients who are affected by an adverse drug reaction depends on the drugs involved. For instance, the incidence of severe hyperkalaemia (>6 mmol/L) in ambulatory patients treated with an ACE inhibitor or an angiotensin receptor antagonist and low-dose (25 mg/day) spironolactone is in the range of 6% per year.[90] In contrast, rhabdomyolysis in patients treated with atorvastatin or simvastatin and a cytochrome P450-3A4 inhibitor occurs with an incidence that is at least 50 times lower.[91]

Medication errors occur throughout the entire medication process, from drug prescription to drug administration.[7] Drug administration was found to be associated with medication errors most often, followed by unauthorised drug administration, prescription, transcription and drug preparation. Regarding drug administration, intravenously administered drugs are particularly likely to be associated with errors.[81,86,92] To increase drug safety, intravenous administration of bolus doses should be replaced by short infusions, and complex drug combinations for infusion should be prepared in the local pharmacy.[81] While unauthorised drug administration and transcription errors can be reduced by organisational measures and/or computerised prescription,[93] reduction of prescription errors is more complex. Important risk factors for prescription errors include high workload, prescribing for a foreign patient, communication deficits within the medical team, and a lack of knowledge about pharmacotherapy.[94] Real-time electronic prescription aids (computerised physician order entry systems) may be helpful to reduce such errors.[1,18,47,70]

A list of possible strategies to reduce medication errors is given in table V. Several studies have shown that improved pharmacological knowledge in physicians and nurses is an efficient measure for error reduction.[61,66,68,80] With regards to nurses, a single short instruction session is not sufficient:[82]

repeated instructions are necessary. Furthermore, as discussed above, prescription and transcription errors (but not administration errors) can be reduced by computerising the medication process, e.g. by introducing electronic patient charts and electronic alert systems.[1,18,47,70] Regarding prescription, real-time information containing important drug data such as recommended dosages (with suggestions for dose adaptation in the case of impaired renal or hepatic function), adverse drug reactions, contraindications and drug-drug interactions that is customised for individual patients, would be most helpful. Several studies have shown that clinical pharmacists on the ward can help to reduce the occurrence of medication errors.[5,18,47,60,63,74] Taking into account the costs caused by adverse drug reactions,[6,8,10,43,44,49,95] employment of clinical pharmacists on medical and surgical wards may not only reduce the occurrence of medication errors and adverse drug reactions[5,18,47,60,63,74] but may also be cost effective. Furthermore, medication errors should be discussed in an open, no-blame, non-punishing atmosphere.[69] Voluntary critical incident reporting systems that include regular discussions among all involved professional groups appear to be most suitable for this purpose.[96]

Our analysis shows that a median of 6.1% of patients will experience an adverse drug event during their hospitalisation. This figure is close to the frequency of 6.7% reported in a meta-analysis of publications from between 1966 and 1996,[4] suggesting that the frequency of adverse drug reactions in hospitalised patients has remained constant over the last 4 decades. In our study, approximately 46% of the adverse drug events were considered to be preventable, and thus to originate from a medication error. In comparison, in a recent report from a Swiss university hospital, where patients on a medical ward were monitored comprehensively for adverse drug events, the proportion of adverse events that were due to medication errors was much lower, i.e. in the range of 6%.[20] Possible explanations for this discrepancy include differences in the definition of the preventability of adverse drug events and differences in the wards involved in the studies.

Important risk factors for adverse drug events reported included polypharmacy, female sex, administration of drugs with a narrow therapeutic range, renal elimination of drugs, age >65 years and the administration of anticoagulants or diuretics. Polypharmacy is a frequent finding particularly in aged, polymorbid patients, but is often difficult to avoid.[97,98] Polypharmacy is associated with an increased risk for adverse drug reactions, not only because of the additive risks of the individual drugs, but also because of possible drug-drug interactions.[91] Polypharmacy may therefore explain, at least partially, the higher frequency of adverse events observed in patients on geriatric or internal medical wards compared with those on general medicine wards (see figure 5).

As shown in table V, the preventive strategies differ between type A (predictable and preventable) and type B (not predictable and, in most cases, not preventable) adverse drug reactions. Prevention of type A reactions is principally targeted at avoiding polypharmacy and medication errors. For type B reactions, prevention is much more difficult, since these reactions are, by definition, not predictable. Preventive strategies for the reaction and its consequences include avoiding drug administration in patients with risk factors (e.g. drug allergies) and limiting damage to the individual once an adverse reaction has occurred. In addition, we are convinced that installing a system for the collection and assessment of reports of adverse drug events is, in itself, a way to avoid such events. If quality control of pharmacotherapy is an aim of such a system, the collection of spontaneous reports is not sufficient, and computerised monitoring – possibly in combination with chart review or monitoring of patients – would be necessary.

5. Conclusions

In conclusion, medication errors and adverse drug events are frequent findings in hospitalised patients, potentially leading to an increased duration of the stay in the hospital, fatalities and increased costs for hospitals and society. Risk factors are known and should guide the preventive measures used to decrease their occurrence. In particular, computerised systems for recording adverse drug events and/or reactions and for guiding drug prescription appear to be able to reduce adverse drug events and/or reactions. Such systems could support drug prescription in many ways, e.g. by detecting

the need for dose adjustment in patients with renal and/or liver failure and proposing an appropriate dosage regimen; by detecting drug-drug interactions and contraindications; and by alerting the prescriber in the case of a wrong drug or dosage. In addition, clinical pharmacists should be engaged to supervise drug preparation and administration. The high costs that are associated with adverse drug events and/or reactions should render most efforts in this area cost effective. Furthermore, such efforts increase the safety of pharmacotherapy, which is beneficial for both patients and health care providers.

Acknowledgements

This work was supported by a grant from the Swiss National Science Foundation to S.K. (310000-112483/1). The authors have no conflicts of interest that are directly relevant to the content of this manuscript.

References

1. Bates DW, Cullen DJ, Laird N, et al. Incidence of adverse drug events and potential adverse drug events: implications for prevention. ADE Prevention Study Group. JAMA 1995; 274 (1): 29-34
2. Fattinger K, Roos M, Vergeres P, et al. Epidemiology of drug exposure and adverse drug reactions in two Swiss departments of internal medicine. Br J Clin Pharmacol 2000 Feb; 49 (2): 158-67
3. Moore N, Lecointre D, Noblet C, et al. Frequency and cost of serious adverse drug reactions in a department of general medicine. Br J Clin Pharmacol 1998 Mar; 45 (3): 301-8
4. Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. JAMA 1998 Apr 15; 279 (15): 1200-5
5. Bond CA, Raehl CL, Franke T. Medication errors in United States hospitals. Pharmacotherapy 2001 Sep; 21 (9): 1023-36
6. Classen DC, Pestotnik SL, Evans RS, et al. Adverse drug events in hospitalized patients: excess length of stay, extra costs, and attributable mortality. JAMA 1997 Jan 22-29; 277 (4): 301-6
7. van den Bemt PM, Egberts TC, de Jong-van den Berg LT, et al. Drug-related problems in hospitalised patients. Drug Saf 2000 Apr; 22 (4): 321-33
8. Bates DW, Spell N, Cullen DJ, et al. The costs of adverse drug events in hospitalized patients. Adverse Drug Events Prevention Study Group. JAMA 1997 Jan 22-29; 277 (4): 307-11
9. Bordet R, Gautier S, Le Louet H, et al. Analysis of the direct cost of adverse drug reactions in hospitalised patients. Eur J Clin Pharmacol 2001 Mar; 56 (12): 935-41
10. Gautier S, Bachelet H, Bordet R, et al. The cost of adverse drug reactions. Expert Opin Pharmacother 2003 Mar; 4 (3): 319-26
11. Nebeker JR, Barach P, Samore MH. Clarifying adverse drug events: a clinician's guide to terminology, documentation, and reporting. Ann Intern Med 2004; 140 (10): 795-801
12. Leape LL. Preventing adverse drug events. Am J Health Syst Pharm 1995; 52 (4): 379-82
13. American Society of Hospital Pharmacy. ASHP guidelines on adverse drug reaction monitoring and reporting. Am J Health Syst Pharm 1995; 52 (4): 417-9
14. Cox Jr PM, D'Amato S, Tillotson DJ. Reducing medication errors. Am J Med Qual 2001 May-Jun; 16 (3): 81-6
15. Lesar TS, Lomaestro BM, Pohl H. Medication-prescribing errors in a teaching hospital: a 9-year experience. Arch Intern Med 1997 Jul 28; 157 (14): 1569-76
16. Bond CA, Raehl CL, Franke T. Clinical pharmacy services, hospital pharmacy staffing, and medication errors in United States hospitals. Pharmacotherapy 2002 Feb; 22 (2): 134-47
17. Bowman L, Carlstedt BC, Black CD. Incidence of adverse drug reactions in adult medical inpatients. Can J Hosp Pharm 1994 Oct; 47 (5): 209-16
18. Fortescue EB, Kaushal R, Landrigan CP, et al. Prioritizing strategies for preventing medication errors and adverse drug events in pediatric inpatients. Pediatrics 2003 Apr; 111 (4 Pt 1): 722-9
19. Classen DC, Pestotnik SL, Evans RS, et al. Computerized surveillance of adverse drug events in hospital patients. JAMA 1991 Nov 27; 266 (20): 2847-51
20. Hardmeier B, Braunschweig S, Cavallaro M, et al. Adverse drug events caused by medication errors in medical inpatients. Swiss Med Wkly 2004; 134 (45-46): 664-70
21. Schumock GT, Thornton JP, Witte KW. Comparison of pharmacy-based concurrent surveillance and medical record retrospective reporting of adverse drug reactions. Am J Hosp Pharm 1991 Sep; 48 (9): 1974-6
22. Leape LL, Brennan TA, Laird N, et al. The nature of adverse events in hospitalized patients: results of the Harvard Medical Practice Study II. N Engl J Med 1991 Feb 7; 324 (6): 377-84
23. Lindley CM, Tully MP, Paramsothy V, et al. Inappropriate medication is a major cause of adverse drug reactions in elderly patients. Age Ageing 1992 Jul; 21 (4): 294-300
24. Schneider JK, Mion LC, Frengley JD. Adverse drug reactions in an elderly outpatient population. Am J Hosp Pharm 1992 Jan; 49 (1): 90-6
25. Madsen JJ. Comparison of concurrent and retrospective methods of detecting adverse drug reactions. Am J Hosp Pharm 1993 Dec; 50 (12): 2556-7
26. Chan TY, Critchley JAJH. Reporting of adverse drug reactions in relation to general medical admissions to a teaching hospital in Hong Kong. Pharmacoepidemiol Drug Saf 1994; 3: 85-9
27. Nazario M, Feliu JF, Rivera GC. Adverse drug reactions: the San Juan Department of Veterans Affairs Medical Center experience. Hosp Pharm 1994 Mar; 29 (3): 244-6, 9-50
28. Pearson TF, Pittman DG, Longley JM, et al. Factors associated with preventable adverse drug reactions. Am J Hosp Pharm 1994 Sep 15; 51 (18): 2268-72
29. van Kraaij DJ, Haagsma CJ, Go IH, et al. Drug use and adverse drug reactions in 105 elderly patients admitted to a general medical ward. Neth J Med. 1994 May; 44 (5): 166-73
30. Orsini MJ, Orsini PA, Thorn DB, et al. An ADR surveillance program: increasing quality, number of incidence reports. Formulary 1995 Aug; 30 (8): 454-61
31. Hall M, McCormack P, Arthurs N, et al. The spontaneous reporting of adverse drug reactions by nurses. Br J Clin Pharmacol 1995; 40 (2): 173-5
32. Bates DW, Boyle DL, Vander Vliet MB, et al. Relationship between medication errors and adverse drug events. J Gen Intern Med 1995; 10 (4): 199-205
33. Wu FL, Yang CC, Shen LJ, et al. Adverse drug reactions in a medical ward. J Formos Med Assoc 1996 Mar; 95 (3): 241-6
34. Smith CC, Bennett PM, Pearce HM, et al. Adverse drug reactions in a hospital general medical unit meriting notification to the Committee on Safety of Medicines. Br J Clin Pharmacol 1996 Oct; 42 (4): 423-9
35. Bowman L, Carlstedt BC, Hancock EF, et al. Adverse drug reaction (ADR) occurrence and evaluation in elderly inpatients. Pharmacoepidemiol Drug Saf 1996; 5 (1): 9-18
36. Cullen DJ, Sweitzer BJ, Bates DW, et al. Preventable adverse drug events in hospitalized patients: a comparative study of

intensive care and general care units. Crit Care Med 1997; 25 (8): 1289-97
37. Gray SL, Sager M, Lestico MR, et al. Adverse drug events in hospitalized elderly. J Gerontol Biol Sci Med Sci 1998; 53 (1): M59-63
38. Gholami K, Shalviri G. Factors associated with preventability, predictability, and severity of adverse drug reactions. Ann Pharmacother 1999 Feb; 33 (2): 236-40
39. Schlienger RG, Luscher TF, Schoenenberger RA, et al. Academic detailing improves identification and reporting of adverse drug events: retrospective analysis of the frequency and recognition of adverse drug reactions by means of automatically recorded laboratory signals. Pharm World Sci 1999; 21 (3): 110-5
40. Tegeder I, Levy M, Muth-Selbach U, et al. Retrospective analysis of the frequency and recognition of adverse drug reactions by means of automatically recorded laboratory signals. Br J Clin Pharmacol 1999 May; 47 (5): 557-64
41. van den Bemt PM, Egberts AC, Lenderink AW, et al. Adverse drug events in hospitalized patients: a comparison of doctors, nurses and patients as sources of reports. Eur J Clin Pharmacol 1999 Apr; 55 (2): 155-8
42. Bates DW, Miller EB, Cullen DJ, et al. Patient risk factors for adverse drug events in hospitalized patients. ADE Prevention Study Group. Arch Intern Med 1999; 159 (21): 2553-60
43. Dormann H, Muth-Selbach U, Krebs S, et al. Incidence and costs of adverse drug reactions during hospitalisation: computerised monitoring versus stimulated spontaneous reporting. Drug Saf 2000 Feb; 22 (2): 161-8
44. Suh DC, Woodall BS, Shin SK, et al. Clinical and economic impact of adverse drug reactions in hospitalized patients. Ann Pharmacother 2000 Dec; 34 (12): 1373-9
45. Lagnaoui R, Moore N, Fach J, et al. Adverse drug reactions in a department of systemic diseases-oriented internal medicine: prevalence, incidence, direct costs and avoidability. Eur J Clin Pharmacol 2000 May; 56 (2): 181-6
46. Thomas EJ, Brennan TA. Incidence and types of preventable adverse events in elderly patients: population based review of medical records. BMJ 2000; 320 (7237): 741-4
47. Kaushal R, Bates DW, Landrigan C, et al. Medication errors and adverse drug events in pediatric inpatients. JAMA 2001 Apr 25; 285 (16): 2114-20
48. Cox AR, Anton C, Goh CH, et al. Adverse drug reactions in patients admitted to hospital identified by discharge ICD-10 codes and by spontaneous reports. Br J Clin Pharmacol 2001 Sep; 52 (3): 337-9
49. Senst BL, Achusim LE, Genest RP, et al. Practical approach to determining costs and frequency of adverse drug events in a health care network. Am J Health Syst Pharm 2001; 58 (12): 1126-32
50. Thuermann PA, Windecker R, Steffen J, et al. Detection of adverse drug reactions in a neurological department: comparison between intensified surveillance and a computer-assisted approach. Drug Saf 2002; 25 (10): 713-24
51. Vargas E, Terleira A, Hernando F, et al. Effect of adverse drug reactions on length of stay in surgical intensive care units. Crit Care Med 2003 Mar; 31 (3): 694-8
52. Egger T, Dormann H, Ahne G, et al. Identification of adverse drug reactions in geriatric inpatients using a computerised drug database. Drugs Aging 2003; 20 (10): 769-76
53. Somers A, Petrovic M, Robays H, et al. Reporting adverse drug reactions on a geriatric ward: a pilot project. Eur J Clin Pharmacol 2003 Feb; 58 (10): 707-14
54. Briant R, Ali W, Lay-Yee R, et al. Representative case series from public hospital admissions 1998, I: drug and related therapeutic adverse events. N Z Med J 2004; 117 (1188): U747
55. Rothschild JM, Landrigan CP, Cronin JW, et al. The Critical Care Safety Study: the incidence and nature of adverse events and serious medical errors in intensive care. Crit Care Med 2005; 33 (8): 1694-700
56. Nebeker JR, Hoffman JM, Weir CR, et al. High rates of adverse drug events in a highly computerized hospital. Arch Intern Med 2005; 165 (10): 1111-6
57. Gurwitz JH, Field TS, Judge J, et al. The incidence of adverse drug events in two large academic long-term care facilities. Am J Med 2005; 118 (3): 251-8
58. Hartwig SC, Denger SD, Schneider PJ. Severity-indexed, incident report-based medication error-reporting program. Am J Hosp Pharm 1991 Dec; 48 (12): 2611-6
59. Bates DW, Leape LL, Petrycki S. Incidence and preventability of adverse drug events in hospitalized adults. J Gen Intern Med. 1993 Jun; 8 (6): 289-94
60. Schumock GT, Guenette AJ, Keys TV, et al. Prescribing errors for patients about to be discharged from a university teaching hospital. Am J Hosp Pharm 1994 Sep 15; 51 (18): 2288, 90
61. Shaughnessy AF, D'Amico F. Long-term experience with a program to improve prescription-writing skills. Fam Med 1994 Mar; 26 (3): 168-71
62. Nettleman MD, Nelson AP. Adverse occurrences during hospitalization on a general medicine service. Clin Perform Qual Health Care 1994 Apr-Jun; 2 (2): 67-72
63. Dean BS, Allan EL, Barber ND, et al. Comparison of medication errors in an American and a British hospital. Am J Health Syst Pharm 1995 Nov 15; 52 (22): 2543-9
64. Borel JM, Rascati KL. Effect of an automated, nursing unit-based drug-dispensing device on medication errors. Am J Health Syst Pharm 1995; 52 (17): 1875-9
65. Ridge KW, Jenkins DB, Noyce PR, et al. Medication errors during hospital drug rounds. Qual Health Care 1995; 4 (4): 240-3
66. Lesar TS, Briceland L, Stein DS. Factors related to errors in medication prescribing. JAMA 1997 Jan 22-29; 277 (4): 312-7
67. Mehrtens T, Carstens G. Medikationsfehler auf einer Station. Krankenhaus Pharmazie 1997; 18: 168-70
68. Lacasa C, Cot R, Roure C, et al. Medication errors in a general hospital. Eur J Hosp Pharm 1998; 4: 35-40
69. McNally KM, Sunderland BV. No-blame medication administration error reporting by nursing staff at a teaching hospital in Australia. Int J Pharm Pract 1998; 6: 67-71
70. Raschke RA, Gollihare B, Wunderlich TA, et al. A computer alert system to prevent injury from adverse drug events: development and evaluation in a community teaching hospital. JAMA 1998 Oct 21; 280 (15): 1317-20
71. Bates DW, Leape LL, Cullen DJ, et al. Effect of computerized physician order entry and a team intervention on prevention of serious medication errors. JAMA 1998; 280 (15): 1311-6
72. Taxis K, Dean B, Barber N. Hospital drug distribution systems in the UK and Germany: a study of medication errors. Pharm World Sci 1999 Feb; 21 (1): 25-31
73. Flaatten H, Hevroy O. Errors in the intensive care unit (ICU): experiences with an anonymous registration. Acta Anaesthesiol Scand 1999 Jul; 43 (6): 614-7
74. Leape LL, Cullen DJ, Clapp MD, et al. Pharmacist participation on physician rounds and adverse drug events in the intensive care unit. JAMA 1999 Jul 21; 282 (3): 267-70
75. Tissot E, Cornette C, Demoly P, et al. Medication errors at the administration stage in an intensive care unit. Intensive Care Med 1999 Apr; 25 (4): 353-9
76. Bates DW, Teich JM, Lee J, et al. The impact of computerized physician order entry on medication error prevention. J Am Med Inform Assoc 1999; 6 (4): 313-21
77. Calabrese AD, Erstad BL, Brandl K, et al. Medication administration errors in adult patients in the ICU. Intensive Care Med 2001 Oct; 27 (10): 1592-8

78. Barker KN, Flynn EA, Pepper GA, et al. Medication errors observed in 36 health care facilities. Arch Intern Med 2002 Sep 9; 162 (16): 1897-903
79. van den Bemt PM, Fijn R, van der Voort PH, et al. Frequency and determinants of drug administration errors in the intensive care unit. Crit Care Med 2002; 30 (4): 846-50
80. LaPointe NM, Jollis JG. Medication errors in hospitalized cardiovascular patients. Arch Intern Med 2003 Jun 23; 163 (12): 1461-6
81. Taxis K, Barber N. Ethnographic study of incidence and severity of intravenous drug errors. BMJ 2003 Mar 29; 326 (7391): 684-7
82. Greengold NL, Shane R, Schneider P, et al. The impact of dedicated medication nurses on the medication administration error rate: a randomized controlled trial. Arch Intern Med 2003; 163 (19): 2359-67
83. Tissot E, Cornette C, Limat S, et al. Observational study of potential risk factors of medication administration errors. Pharm World Sci 2003; 25 (6): 264-8
84. Wirtz V, Taxis K, Barber ND. An observational study of intravenous medication errors in the United Kingdom and in Germany. Pharm World Sci 2003; 25 (3): 104-11
85. Herout PM, Erstad BL. Medication errors involving continuously infused medications in a surgical intensive care unit. Crit Care Med 2004; 32 (2): 428-32
86. Taxis K, Barber N. Incidence and severity of intravenous drug errors in a German hospital. Eur J Clin Pharmacol. Epub 2003 Oct 29 2004; 59 (11): 815-7
87. van Gijssel-Wiersma DG, van den Bemt PM, Walenbergh-van Veen MC. Influence of computerised medication charts on medication errors in a hospital. Drug Saf. 2005; 28 (12): 1119-29
88. Egger SS, Drewe J, Schlienger RG. Potential drug-drug interactions in the medication of medical patients at hospital discharge. Eur J Clin Pharmacol 2003; 58 (11): 773-778 Epub 2003 Feb 21
89. Dormann H, Criegee-Rieck M, Neubert A, et al. Implementation of a computer-assisted monitoring system for the detection of adverse drug reactions in gastroenterology. Aliment Pharmacol Ther 2004 Feb 1; 19 (3): 303-9
90. Svensson M, Gustafsson F, Galatius S, et al. Hyperkalaemia and impaired renal function in patients taking spironolactone for congestive heart failure: retrospective study. BMJ 2003; 327 (7424): 1141-2
91. Rätz Bravo AE, Tchambaz L, Krähenbühl-Melcher A, et al. Incidence of potential drug-drug interactions in dyslipidaemic patients treated with a statin. Drug Saf 2005; 28 (3): 263-75
92. Schneider MP, Cotting J, Pannatier A. Evaluation of nurses' errors associated in the preparation and administration of medication in a pediatric intensive care unit. Pharm World Sci 1998 Aug; 20 (4): 178-82
93. American Society of Hospital Pharmacy. ASHP guidelines on preventing medication errors in hospitals. Am J Hosp Pharm 1993; 50 (2): 305-14
94. Dean B, Schachter M, Vincent C, et al. Causes of prescribing errors in hospital inpatients: a prospective study. Lancet 2002 Apr 20; 359 (9315): 1373-8
95. Schneider PJ, Gift MG, Lee YP, et al. Cost of medication-related problems at a university hospital. Am J Health Syst Pharm 1995 Nov 1; 52 (21): 2415-8
96. Wu AW, Pronovost P, Morlock L. ICU incident reporting systems. J Crit Care 2002; 17 (2): 86-94
97. Gurwitz JH. Polypharmacy: a new paradigm for quality drug therapy in the elderly? Arch Intern Med 2004 Oct 11; 164 (18): 1957-9
98. Hanlon JT, Lindblad CI, Hajjar ER, et al. Update on drug-related problems in the elderly. Am J Geriatr Pharmacother 2003; 1 (1): 38-43

Correspondence: Dr *Stephan Krähenbühl*, Clinical Pharmacology and Toxicology, University Hospital, Basel, 4031, Switzerland.
E-mail: Kraehenbuehl@uhbs.ch