

## The epidemiology of preventable adverse drug events: A review of the literature

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### Die Epidemiologie vermeidbarer unerwünschter Arzneimittelgeschehen

**Zusammenfassung.** *Hintergrund:* Eine zunehmende Anzahl an Studien berichten, dass unerwünschte Arzneimittelgeschehen (UAGs) in der stationären Versorgung häufig sind und erheblichen Schaden verursachen. Obwohl der Fokus auf der Vermeidung liegen müsste, untersuchen nur wenige Studien die Vermeidbarkeit von UAGs. Ziel dieses Literaturüberblicks ist, die Studien über UAGs und ihre Vermeidbarkeit zusammenzufassen und die Inzidenzen, Eigenschaften, Risikofaktoren, Kosten und Präventionsmöglichkeiten darzustellen.

*Methoden:* Wir durchsuchten systematisch die Datenbanken Medline und Embase nach Literatur, die im Zeitraum zwischen 1980 und Juni 2002 publiziert wurde. Alle Artikel, die Primärdaten über die Inzidenz und Vermeidbarkeit von UAGs in Krankenhauseinrichtungen beschrieben, wurden einbezogen.

*Ergebnisse:* In den 8 gefundenen Artikeln betrug die Inzidenz von UAGs zwischen 0,7% und 6,5% der hospitalisierten Patienten; bei bis zu 56,6% der Fälle wurde die UAG als vermeidbar angesehen. Des Weiteren führten UAGs in 2,4% bis 4,1% zur Einweisung in Krankenhauseinrichtungen, auch hier wurde bei bis zu 69,0% der Fälle die Vermeidbarkeit angenommen. Ein großer Anteil von vermeidbaren UAGs, die sogenannten Medikationsfehler, ereignen sich beim Verschreiben, Transkribieren, Zubereiten und Darreichen von Arzneimitteln. Eine genauere Analyse der Medikationsfehler zeigt, dass diese in bis zu 57,0 Fällen pro 1.000 Verordnungen vorliegen. Zwischen 18,7% und 57,7% dieser Fehler hat das Potential eine Patientenschädigung zu bewirken, letztendlich führen jedoch nur etwa 1% zu vermeidbaren UAGs.

*Folgerung:* Die Erfassung von Fehlern mit nur potentieller Schädigung durch computergestützte Methoden ist eine effektive Möglichkeit, UAGs zu verstehen und zu vermeiden. Neben der Verwendung von Computer-Erfassungsmethoden kann durch die Teilnahme von Pharmazeuten bei der Medikamentenverschreibung ein enormer Anteil an Fehlern vermieden werden. Die größte Herausforderung bei der Veränderung des Gesundheitssystems in ein System, in dem die Patientensicherheit höchste Priorität hat, ist die Entwicklung einer Kultur des perma-

nenten Lernens aus Fehlern unter den Mitarbeitern. Indem Wahrnehmungen und Anregungen der Mitarbeiter genutzt werden und ihre Ideen durch kurze Veränderungszyklen implementiert werden, kann das Mitarbeiterpotential zu einer führenden Kraft bei der Verringerung von Fehlern und Verbesserung des Gesundheitssystems werden.

**Schlüsselwörter:** Unerwünschte Arzneimittelgeschehen, Epidemiologie, Medikationsfehler, medizinische Schädigung, Übersichtsarbeit.

**Summary.** *Background:* A growing amount of data suggests that adverse drug events (ADEs) in hospital settings are frequent and result in substantial harm. Even though prevention is where efforts must be directed, only a few studies have reported on the preventability of these events. The objective of this article is to review the literature of ADEs and their preventability, and to report on their incidences, characteristics, risk factors, costs and prevention strategies.

*Methods:* We systematically searched Medline and Embase for literature published between 1980 and June 2002. All articles reporting primary data on the incidences of ADEs and their preventability in hospital settings were included.

*Results:* In the 8 articles retrieved the incidences of ADEs were between 0.7% and 6.5% of hospitalized patients; in up to 56.6% these events were judged to be preventable. Furthermore, ADEs accounted for 2.4% to 4.1% of admissions to inpatient facilities; preventability was stated in up to 69.0% of these events. A substantial body of preventable ADEs, the so-called medication errors, occur in the process of ordering, transcribing, dispensing and administering the drugs. Further investigations into medication errors at the ordering stage reveal their occurrence in up to 57.0 per 1,000 orders. Between 18.7% and 57.7% of those errors have the potential for harm, but only in about 1% they result in preventable ADEs.

*Implications:* The detection of errors having only the potential for harm by means of computerized surveillance has shown to be a useful technique in order to understand and prevent ADEs. Apart from the use of sophisti-

cated computer techniques the participation of pharmacists in the drug prescribing process results in a tremendous error reduction. The greatest task in changing the health care system into a system with safety as its first priority is to create a culture of constant learning from mistakes among health care professionals. The appreciation of the health care teams' ideas and perceptions for improvement, and their implementation through small improvement cycles, may represent the leading strength in error reduction and health care improvement.

**Key words:** Adverse drug events, epidemiology, medication errors, medical injury, literature review.

## Introduction

Drug related errors are the most common single cause of medical errors leading to more than 7,000 US deaths in 1993 [1, 2]. This constitutes a 2.6-fold increase in preventable drug related mortality over ten years [2]. Drug related errors leading to death or serious injury are, however, only the tip of the iceberg. A far higher number of errors evolve in the process of prescribing and administering the drug, where only some have the potential to harm a patient. But the sheer and increasing utilization of medications makes drug related errors a major problem for in- and out-of-hospital patients. In 1998, nearly 2.5 billion prescriptions were dispensed in US pharmacies at an estimated cost of about \$ 92 billion [3]. Furthermore, an estimated 3.7 billion drug administrations were made to patients in hospitals [4].

There has been a growing amount of literature reporting on drug-related injury recently. Unfortunately, studies focusing on the preventability of adverse drug events (ADEs) have been rare, even though prevention is where efforts must be directed to in order to improve patient safety.

This article is the second in a two part series on medical errors. While the first part reviewed the literature on adverse events and their preventability [5], this part focuses on studies reporting the incidence of ADEs and their preventability covering the years 1980 to 2002. The aim of this review is to provide answers to the following three questions. First, what are the reported incidences of preventable ADEs? Second, what are the characteristics of those events? In order to answer this second question we will report on the types of preventable ADEs, the underlying risk factors and the economic consequences of the events. Further, we will also summarize studies on the incidence of medication errors and their relation to ADEs. The third question to be answered is, what fraction of preventable ADEs could actually be prevented?

## Methods

### Literature

We systematically searched Medline and Embase for literature published between 1980 and June 2002. Search terms were: "adverse drug events", "medication errors", "medical injury" and "negligent care". The reference sections of all retrieved articles and monographs connected to the issue were hand searched for further studies. Studies that reported primarily data on the incidences of ADEs and their preventability in the hospital setting were included in this review. Papers report-

ing on "adverse drug reactions" were excluded, as this term does not include therapeutic errors. The data extraction was undertaken by one medical doctor. From a total of 137 articles retrieved, 8 met our criteria and were included in the analyses.

## Results

### Defining the object

ADEs are injuries due to a drug application and they may be classified as preventable or unavoidable. Medication errors are a subset of preventable drug related events. They can occur at any stage of ordering, transcribing, dispensing and administering the drug. Many of the medication errors do not have the potential to harm a patient, e.g. a missed dose of a non-critical medication. However, a ten-fold overdose of a critical medication due to spelling mistakes in the order can lead to an ADE and thus to serious injury or even death.

In the leading report on medical errors, recently published by the Institute of Medicine (IOM), the following terms are recommended to define drug related events uniformly:

- *Adverse drug events (ADEs)* are injuries resulting from medical interventions related to a drug. Adverse drug events may result from medication errors (e.g., rash caused by an allergic response to penicillin with documented allergy) or from adverse drug reactions not involving any error (e.g., rash caused by an antibiotic without known allergy).
- *Potential ADEs* are medication errors with the potential for injury but in which no injury occurred (e.g. wrong dose).
- A *medication error* is an error occurring at any stage in the process of delivering a medication. They include the entire range of severity, from trivial errors, such as orders that necessitated clarification or missing doses, to life-threatening errors, such as a patients receiving a ten-fold overdose of a toxic agent.
- A *preventable adverse drug event* is "an adverse drug event attributable to an error" [6].
- An *error* is defined as "the failure of a planned action to be completed as intended (i.e., error in execution) or the use of a wrong plan to achieve an aim (i.e., error in planning)" [7].

The definition and assessment of preventability remains somehow unclear in most of the reviewed studies. Some of the studies do not even give a definition of preventability but use it in terms of "would the event have been preventable by optimal quality of care" [8, 9]. While interpreting the study results it should be kept in mind that the judgment of "preventability is in the eye of the reviewer" [10] and not a proven fact (see also the paper on medical errors [5]).

In the long term it is even likely that many ADEs currently judged nonpreventable may become preventable with new approaches.

In the following text we will use the definitions as recommended by the IOM but maintain the study-specific terms when presenting the literature.

Table 1 gives examples of a medication error, an ADE and a potential ADE. The conceptual relation between

**Table 1.** Definition and example of medication error, adverse drug event (ADE) and potential ADE

Incident	Definition	Example
Medication error	Any error at any stage of ordering, transcribing, dispensing, administering or monitoring	A missed-dose of a non-critical medication
Potential ADE	A medication error with potential for injury	An order for an antibiotic was written for a patient with known allergy, but the mistake was intercepted by the nurse
Adverse drug event (ADE)	Injury due to a drug application	Drug rash
– Preventable ADE	Injury due to an error	Allergic reaction in a patient known to be an allergic
– Non-preventable ADE (adverse drug reaction)	Injury, with no error involved	Allergic reaction in a patient not known to be an allergic

medication errors, potential ADEs and ADEs is presented in Fig. 1. The “pyramid” represents the preventable part of events, which includes all medication errors and potential ADEs and a fraction of ADEs. Medication errors make up the biggest part of all errors and only a small proportion of medication errors represent a potential ADE or an ADE. Furthermore it can be seen that potential ADEs are always medication errors while only the minority of ADEs have medication errors as origin.

*Methods used to detect ADEs*

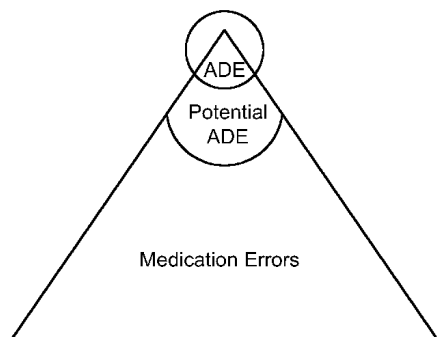
The methods used to collect data on ADEs and medical injury vary considerably, and include non-stimulated or stimulated self-report, record review, computerized monitoring, pharmacist participation on clinical rounds, direct observation, or a combination of methods. Every method detects a somewhat different subset of adverse events and the detection rates vary remarkably between the methods. In a comparison of methods using adjusted rates of ADEs, Leape points out that while the yield by non-stimulated self-report was only 0.2 ADEs per 100 patients, incidences of 0.7% and 3.8% were identified by record review and computerized screening respectively. A combination of chart review and self-report identifies an incidence of 6.5% and chart review combined with computerized screening an incidence of 10% [11]. The main

limitation of self-report – which used to be the method of choice for permanent error detection in hospitals – is the high fraction of underreporting [12]. However, while detection sensitivity is lower as compared to other methods, these are more costly, time consuming and need more personal involvement which limits their use in routine care.

*Incidence of ADEs and their preventability*

We found 8 studies reporting the incidence of ADEs and their preventability in hospital settings. They can be divided into three categories: studies reporting on (1) the incidence of ADEs in hospitalized patients; (2) hospital related ambulatory settings and (3) incidence of ADEs leading to hospitalization. Table 2 gives an overview of the incidences of ADEs and their preventability.

The three most extensive population-based studies on medical injury focused on all kinds of adverse events, and ADEs were, therefore, only one part of all reported events. In two of the three benchmark-studies [13, 14], ADEs were the most common single cause of injury accounting for more than 19% of the total events (see also our article on medical errors [5]). In the Harvard Medical Practice Study (HMPS), 19.4% of all serious adverse events with disability at discharge or prolongation of hospital stay were related to the use of medication. Applied to the overall incidence of adverse events of 3.7%, the rate of serious ADEs was 0.7%. In 17.7% the ADE was judged to be due to negligence, i.e., they failed “to meet the standard of practice of an average qualified physician practicing in the specialty in question” [14]. Originally, the HMPS investigated “negligent” ADEs, which is at the peak of the spectrum of preventable ADEs meeting the legal criteria for malpractice claims. A broader spectrum of preventable AEs are due to relatively minor errors, not fulfilling the criteria for malpractice suits, still having the potential for serious injury of the patient. Because the majority of errors, though preventable, are not due to negligence, Leape et al. re-evaluated the HMPS data in 1993 in order to get insight into the preventability of all ADEs [15]. In this analysis, 45.2% of drug related events were judged as preventable. ADEs were more likely to be unpreventable than other types of AEs (preventability was on average 70%), mainly because many of them were caused by



**Fig. 1.** The relationship between medication errors, potential adverse drug events (ADEs) and ADEs. The “pyramid” represents the preventable part of events which includes all medication errors and potential ADEs and a fraction of ADEs

**Table 2.** Incidence of ADEs and rate of preventability

Reference	Setting	Detection method	Sample (n)	Incidence (%)	Preventability (%)
<i>Hospitalized patients</i>					
Leape et al. 1991 (USA) [13]	51 hospitals	Record review	30,195	0.7 (19.4 of 3.7)	17.7
Wilson et al. 1995 (Australia) [15]	28 hospitals	Record review	14,000	1.6 (10.8 of 16.6)	43.0
Classen et al. 1997 (USA) [7]	1 hospital	Computerized monitoring	1,580	2.4	48.1
Bates et al. 1993 (USA) [17]	Medicine	Self-report and chart review	420	6.0	56.0
Bates et al. 1995 (USA) [18]	11 med. and surg. units	Self-report and chart review	4,031	6.5	28.0
<i>Ambulance</i>					
Honigman et al. 2001 (USA) [19]	Ambulance	Computerized monitoring	23,064	5.5	38.0
<i>Leading to admission</i>					
Rougheard et al. 1998 (Australia) [8]	–	Review of 14 articles	–	2.4–3.6	32.0–69.0
Hallas et al. 1990 (USA) [22]	Cardiology	Written and verbal histories	366	4.1	33.3

*med* medicine; *surg* surgery.

unpredictable allergic reactions or unpreventable effects of chemotherapy. Hospitals should still target their efforts at reducing preventable ADEs despite their relatively low preventability because of their sheer number. In absolute numbers, the group of preventable ADE ranged third after preventable technical complications of surgery and wound infections.

The study from Utah and Colorado, using the same methods and definitions as the HMPS, presents comparable figures: 19.3% of total events were attributable to drugs and in 35.1% the ADEs were attributable to negligent care [13]. The nonnegligent fraction of preventable errors has not been investigated in this study. Unfortunately, this study does not report numbers necessary to calculate the rate of ADEs in relation to the total incidence of adverse events. In the Quality of Australian Health Care Study (QAHCS) ADEs accounted only for 10.8% of the total adverse events [16]. The ADEs were judged as preventable – which means that they were an “error in management due to failure to follow accepted practice at an individual or system level” – in 43% of cases. Applied to the overall ADE incidence of 16.6% the estimated rate of serious ADEs was 1.7%. The fraction of negligent ADEs was not investigated in the QAHCS.

The incidences of ADEs in these retrospective benchmark studies on medical injury are comparatively low (0.7% to 1.6%) as opposed to prospective studies on ADEs (2.4% up to 6.5%). This is mainly due to the detection method used, and to the strict inclusion criteria that capture only events that produce disability at discharge or prolonged hospitalization.

In a tertiary care institution in Salt Lake City, a hospital-wide computerized surveillance program for the continuous detection and characterization of ADEs was developed and implemented in 1987. The incidence of ADEs was 1.7% during an 18-month period [17]. The overall incidence of ADEs after three years of monitoring turned out to be 2.4%, of which 48.0% were judged to be potentially preventable [8]. This method, though detecting a rather low rate of ADE, proved very useful for the continuous monitoring of ADE.

Other studies used combinations of more time consuming methods, and found a higher rate of ADEs. In a pilot study over 37 days in seven units in an urban tertiary care hospital, ADEs were identified using a combination of incidence reporting, solicited reporting by research nurses and chart review [18]. The incidence of ADEs was approximately 6.0% per hospitalization. In 56% the ADEs were judged to be definitely or probably preventable.

In a prospective cohort study, Bates observed ADEs in 11 medical and surgical units over a 6-month period [19]. Using simulated self-report (nurses and pharmacists were asked to report incidents) and daily chart review the author identified an ADE-incidence of 6.5% [19]. In 28% the event was judged to be preventable (incidence of preventable ADEs 2%). In an additional 5.5% of patients, a potential ADE was averted by chance or interception of the error. Taking only the ADEs into account that led to prolonged hospitalization or disability at discharge the incidence revealed to be 0.5%, close to the HMPS estimate (0.7%).

Honigman detected ADEs at an incidence of 5.5 per 100 admitted patients in the ambulatory setting by using a

computer program [20]. In 38% of cases the ADE was judged to be preventable. Patients required hospitalization because of the ADE at a rate of 3.4 per 1,000.

There is also evidence suggesting that ADEs account for a sizable number of admissions to inpatient facilities, but it is unknown what fraction of these ADE-related admissions are actually attributable to error. In a meta-analysis of drug related hospital admissions between 1966 and 1989, Einarson summarized 36 articles and found that drug-induced hospitalization accounted for approximately 5% of admissions [21]. A review of 14 Australian studies published between 1988 and 1996 reported that 2.4% to 3.6% of all hospital admissions were drug related, and between 32% and 69% of these were definitely or possibly preventable [9]. ADEs also result in an increased number of visits to emergency departments: An analysis of 62,216 visits to an emergency department by patients enrolled in a health maintenance organization (HMO) revealed that 1.7% emergency department visits were due to medication misadventures. Of these misadventures, 14.1% resulted in hospital admission [22]. Hallas and colleagues investigated drug related admissions to a cardiology department. Of the 366 consecutive hospitalizations, 4.1% were "definite" or "probable" drug related. One quarter (26.6%) was judged to be definitely avoidable [23].

#### *Characterization of preventable ADEs*

The studies reporting incidences of ADEs report rates of preventability at up to 56.6% for events occurring in hospitals and of almost 70% for events leading to hospital admission.

In the HMPS the following types of drug related error (including negligent errors) occurred in descending frequency: inadequate follow-up of therapy (45%), errors in dose or method of use (42%), use of inappropriate drugs (22%), avoidable delay in treatment (14%), failure to recognize possible antagonistic or complementary drug-drug interactions (8%) [14]. In the QAHCS, the most common reasons for drug related injury (including preventable errors) were: error in the method of use or dose (18%), drug used inappropriately (14%) and inadequate monitoring of drug levels or other follow-up (12%) [16]. The drug types most often related to ADEs with high preventability were: Cardiovascular drugs (74%), anticoagulant drugs (40%), antibiotics (30%), antihypertensive drugs (16%) and antineoplastic drugs (9%). In the prospective study of Classen et al. using computerized ADE-detection, excessive drug dosage in relation to the patient's weight and calculated renal function accounted for 42% of all ADEs and was judged to be potentially preventable [8]. Drug interactions accounted for 4.6% and known allergies for 1.5% of all ADEs; both categories were judged to be preventable. In 1% preventable ADEs were caused by medication errors, including giving the correct drug to the wrong patient, giving the wrong drug to the correct patient, giving the wrong dose to the correct patient, and giving the wrong dosage frequency to the correct patient.

Bates and colleagues categorized preventable events by stage of drug flow and found that in 49% the primary error occurred in the ordering stage, 11% occurred in the

transcription, 14% in the dispensing stage and 26% occurred in the administration stage [19]. Errors that occurred early in the process were significantly more likely to be intercepted ( $p < 0.001$ ). Of the ordering errors, 48% could be intercepted; the same applied for 23% of the transcription, and 37% of dispensing errors, but 0% of the administration error. Among the drug classes associated with preventable ADEs the most common were: analgetics (29%), sedatives (10%), antibiotics (9%), antipsychotics (7%) and diabetes drugs (6%).

Investigation into the underlying causes of preventable ADEs revealed that errors leading to death or serious injury are only the tip of the iceberg. A far higher number of errors evolve in the process of prescribing and administering the drug where only some have the potential to harm a patient. These so called "medication errors" can be seen as the base of the iceberg and as such as starting point for understanding and improving ADEs. This perception has led to a number of investigations focusing on medication errors and their potential to cause patient injury.

#### *Medication errors*

Errors in the process of ordering or delivering a medication are a major contribution to the overall problem of ADEs (Table 3). All medication errors are – by definition – potentially preventable. The theoretical preventability of those errors makes a deeper investigation therefore interesting, regardless of whether an injury actually occurred or the potential for injury is present. Less than 1% of medication errors result in ADEs, but nearly 60% of these errors have the potential for adverse consequences [24, 25].

Lesar et al. conducted a study to quantify medication prescribing errors written by physicians practicing in a tertiary-care teaching hospital [25]. Medication errors were detected by medication orders being reviewed by a centralized staff of pharmacists and prescribing physicians. From a total of 289,000 medication orders written during a one-year study period, 905 prescribing errors were detected and averted, of which 57.7% were rated as having potential for adverse consequences. The overall error rate was estimated to be 3.13 errors per 1,000 orders written, and 1.81 significant errors. The error rate (4.01 per 1,000 orders) was highest between 12 pm and 3: 59 pm. First-year postgraduate residents were found to have a higher error rate than other prescribers. Services with the highest error rate were obstetrics/gynecology and surgery/anesthesia. Nearly the same error rate was found in a one-year study conducted in a 631-bed tertiary-care teaching hospital. The estimated overall error rate was 3.99 per 1,000 medication orders [26]. The most common factors associated with errors were related to knowledge and the application of knowledge regarding drug therapy (30%), patient factors that effected drug therapy (29.2%), dosing calculations (17.5%) and nomenclature factors (13.4%).

Children are at particular risk of medication errors for a number of reasons. One cause is that a high fraction of medications used in pediatrics have never been tested in children. A European study has shown that almost half (46.0%) of medications are prescribed either unlicensed or off-label. In German pediatrics 4.0% of medications were prescribed unlicensed and 26.0% off-label [27]. Another

reason is the need to calculate each dose based on the child's weight. Folli et al. showed that errors occurring in children are primarily attributable to incorrect dosage [28]. In an analysis of 101,000 medication orders in two children's teaching hospitals during a six-month period in 1985, a total of 479 errant medication orders were identified. 27 of these were determined as potentially lethal. The frequencies of errors were similar at both institutions, and were estimated at 4.9 and 4.5 errors per 1,000 medication orders.

In the above studies, pharmacists were employed to identify errant orders. Far higher rates were found in a study using a multidisciplinary detection approach with self-report by pharmacists, nurse review of patient charts, and the review of medication sheets. Bates et al. conducted the study in three medical units over a 51-day period. Over the study period, 10,070 medication orders were written, and 530 medication errors were identified (53 errors/1,000 orders) [24]. Of the medication errors, 53% involved at least one missing dose and 15% involved other dose errors. Of the 530 medication errors 35 resulted in potential ADEs (6.6%) and 25 in ADEs (4.7%). Of the 25 ADEs 5 resulted in preventable ADEs (0.9%). Physician computer order entry could have prevented 86% of the potential ADEs, and 60% of preventable ADEs. Using the same detection methods in two pediatric institutions (n=10,778 medication orders) an error rate of 57 per 1,000 orders was revealed [29]. Of the 616 medication errors 115 were leading to potential ADEs (18.7%), and 26 to ADEs (4.2%). Of the ADEs 5 were judged to have been preventable (0.8%). Most of the potential ADEs occurred at the stage of drug ordering (79%) and involved incorrect medication doses (34%), anti-infective drugs (28%), and intravenous medications (54%). Physician reviewers judged that computerized physician order entry could potentially have prevented 93% and ward-based clinical pharmacists 94% of potential ADEs.

#### *Risk factors for injury*

Patients are at risk of injury regardless of their age, sex, or health status. However, some factors even increase the overall risk of harm in medical care.

The HMPS and the QAHCS showed that patients aged 65 and older encounter more adverse events than others, even though the percentage of preventable adverse events seems to be independent of age [14, 16]. In a subsequent analysis of 15,000 patients discharged in 1992, Thomas et al. showed that the higher rate of adverse events among the elderly is most likely related to the higher clinical complexity of their care, rather than directly related to age [30]. In this multivariate analysis, which adjusted for comorbid illnesses and case mix, age was not found to be an independent predictor of preventable adverse events.

The intensity of care also affects the risk of injury. Bates et al found that ADEs occurred more often among adult patients in intensive care units (ICU) than in medical or surgical wards [31]. However, when the number of doses dispensed in the different units was adjusted for, the differences were no longer significant. Cullen et al. compared a medical unit (non-ICU) with an ICU and reports that the number of ADEs increases with the number of drugs ordered [32]. The rate of preventable ADEs and

potential ADEs in ICUs was nearly twice as high as in non-ICUs. But again after adjusting for the number of drugs ordered, there was a similar likelihood for ADEs to occur in ICUs than in non-ICUs.

Leape and colleagues explain the relation between the numbers of administered medications and the increase of ADEs as follows: "In average a hospitalized patient receives 10 different medications during a hospitalization. In a teaching hospital the number is even 20 or 30. Even a very small error rate can have serious consequences in a modern hospital if the rate of administered medications is that high. An average-sized (600 beds) teaching hospital administers more than 4 million doses of drugs a year. Every single dose offers several opportunities for errors and even if the drug ordering and dispensing system is 99.9% error free, there will still be more than 4,000 errors annually in a hospital. If only 1% of these result in an adverse event, this commendably low error rate will cause 40 adverse events from medication alone" [15].

Besides the number of drugs prescribed, the duration of care seems to be more important in explaining the risk of injury than the characteristics of individual patients. Andrews et al. reported that the likelihood of an adverse event (including ADEs) increases by 6% for each hospital day [33]. This study confirmed that age, ethnicity, sex and payer class of patients experiencing a serious adverse event were broadly similar to those of patients without adverse events.

#### *Economic consequences of ADE*

The additional resource utilization associated with ADEs in hospitalized patients was investigated by Bates et al. [34]. The average increase in length of stay was 2.2 days for patients with ADEs and 4.6 days for patients with preventable ADEs. The post event hospital costs attributable to ADEs were calculated to be on average \$ 2,595 for patients with ADEs and \$ 4,685 for patients with preventable ADEs. This amounts to about \$ 2.8 million annually for a 700-bed teaching hospital. Extrapolated to the US nation as a whole, the increased hospital costs for all ADEs is \$ 5.6 billion and for preventable ADEs \$ 2 billion. In a matched case-control study Classen and colleagues found that the occurrence of an ADE was associated with an increased length of stay of 1.91 days and an increased cost of \$ 2,262. The risk of death among patients experiencing an ADE increased nearly 2-fold. To estimate the cost of drug-related morbidity and mortality in the US ambulatory setting Johnson et al. developed a probability pathway model [35]. Drug-related morbidity and mortality were estimated to cost \$ 76.6 billion in the United States. Costs associated with drug-related hospitalizations contributed the largest part to total costs. Applying the same model for the year 2000 the overall costs of drug-related morbidity and mortality even exceeded \$ 177.4. [36] Hospital admissions accounted again for nearly 70% (\$ 121.5 billion) of total costs, followed by long-term-care admissions (18%; \$ 32.8 billion).

#### *Interventions to reduce error*

Errors leading to ADEs are often due to restricted availability of information at the time of physician order

entry. Making the information available at the time and place where it is needed has thus been one of the strategies in reducing ADEs. Computer-based medical records have shown to be a powerful tool not only in detecting, but also in reducing ADEs.

Raschke et al. evaluated the effects of a computer alert system designed to correct errors that might lead to ADEs and to detect ADEs before maximum injury occurs in a 650-bed community hospital in 1997 [37]. During the six-month study period 596 true positive alerts were found. The alert system detected opportunities to prevent patient injury secondary to ADEs at a rate of 6.4 per 100 admissions. Of the true positive alerts, 44% had been unrecognized by the physicians prior to alert notification. In a prospective study of 79,719 hospitalized patients during a 44-month period Evans and colleagues demonstrated that surveillance of computer-based medical records for known drug allergies and appropriate drug administration rates can reduce the number of ADEs significantly [38]. Early reporting of all confirmed computer-detected ADEs to physicians resulted in a 65% reduction of severe ADEs compared with historic controls. Over the study periods ADEs classified as severe fell from 41 during 113,859 patient days to 15 during 108,320 patient days.

In a pre/post design Bates et al. found that physician computer order entry (POE) decreased the rate of nonintercepted serious medication errors by more than half (55%), from 10.7 to 4.86 events per 1,000 patient-days [39]. Another study showed after additional refinements of the same POE system even an 88% reduction for serious medication errors [39]. The total error rate (missed-doses errors excluded) fell by 81%, from 142.0 to 26.6 per 1,000 patient days. The author stated that the difference in effect size between the two studies is probably due to the additional refinements of the POE system. Order entry results in improvement both because of additional structuring of orders and because it allows checking of orders for problems such as allergies and drug interactions. However, sophisticated technology is not the only option: in-

volving pharmacists in reviewing drug orders significantly reduces the potential harm resulting from errant medication orders [40]. Studies have shown that nearly half of preventable ADEs result from errors in the prescribing process [19]. As prescribing errors frequently have a cascade effect, causing errors downstream in dispensing or administration, error prevention at the prescribing level could have a major impact on overall error reduction. Leape et al. conducted a pre/post interventional study to determine, whether the participation of pharmacists in the ICU at the time of drug prescribing reduces adverse events and compared outcomes to a control unit [41]. The rate of preventable ADEs due to ordering decreased by 66% from 10.4 per 1,000 patient days before to 3.5 per 1,000 patient days after the intervention. In the control unit the rate increased slightly during the same time period from 10.9 and 12.4 per 1,000 patient days.

### Discussion

In this review we found 8 articles reporting on the incidence of ADEs and their preventability. The reviewed articles showed that ADEs occur with high frequency: at least 6% of hospitalized patients experience an ADE. Many of these ADEs, such as unpredictable allergic reactions, are not preventable. However, between 17.7% and 69.0% of ADEs are due to errors and are therefore preventable [15, 19]. Medication errors are 50–100 times more common than ADE, and they are all preventable [24]. Fortunately, most medication errors are harmless, but 1% cause injury, and an additional 5% are potential ADEs that fail to cause injury by chance or because they are intercepted before the medication is administered to the patient. A shortcoming of this review is that it is not a proper systematic review but only a systematic search of Medline and Embase. We did neither search all major databases nor the grey literature. Another limit of our work is that the search strategy did not include all the terms used to describe medical errors. Furthermore data were extracted by one single person and this was not replicated.

**Table 3.** Incidence of medication errors per 1,000 written orders

Reference	Setting	Detection method	Orders (n)	Errors per 1,000 orders	Consequences (%)
Lesar et al. 1990 (USA) [25]	Medicine	Pharmacist	289,411	3.1	pot. ADE 57.7
Lesar et al. 1997 (USA) [26]	Medicine	Pharmacist	–	4.0	
Folli et al. 1987 (USA) [28]	Pediatrics	Pharmacist	101,022	4.5–4.9	
Blum et al. 1988 (USA) [40]	Medicine	Pharmacist	123,367	18.6	
Kaushal et al. 2001 (USA) [29]	Pediatrics	Clinical staff	10,778	57.2	ADE 0.8
Bates et al. 1995 (USA) [24]	Medicine	Multidisciplinary	10,070	53.0	ADE 0.9

ADE adverse drug event; *pot. ADE* potential adverse drug event.

Medicine has a long tradition of examining past practice to understand how things might have been done differently. However, conferences on morbidity and mortality, grand rounds, and peer review all currently share the same shortcomings: a narrow focus on individual performance on error reduction, a tendency to search for errors as opposed to the multiple causes of error induction, and a lack of multidisciplinary integration into an organization-wide safety culture.

Changing the health care system into a system with safety as its first priority needs to take place at least at three interacting levels. The first is the political level, which can give direction and supply a framework for diverse activities. Some of the ongoing political activities have already been described in our first paper on adverse events. The second level is the implementation of certain safety-tools into the organizational working processes and the third, the creation of a culture of learning from mistakes among the health care professionals. Concrete ideas and experiences on building a safety and learning culture originate from other high-risk industries such as aviation or nuclear power and have been refined by human factors engineers and psychologist over the years.

In order to create safer structures organizations should aim to reduce complexity, optimize information processing and using automation and constrain in order to make it difficult for errors to happen [42]. Leape et al. found that seven system failures produced 78% of errors. All of them are preventable through better information systems [43]. The implementation of sophisticated computer-technologies is still very costly. Today, only few hospitals, mainly in the US, have the equipment already implemented required for detecting and preventing errors in daily routine. But the broader use of computer technology in the hospital information flow is an emerging concept in most western countries.

For building a culture of constant learning from mistakes rather than a culture of blaming individuals for making errors concepts like the so called "Model for Improvement" have been useful [44]. This plan-do-study-act cycle describes, in essence, inductive learning – the growth of knowledge through making changes and then reflecting on the consequences of those changes. Such inductive learning is familiar to scientists, but the formal cycles of action and reflection are still unusual in routine health care. Led by the Institute of Healthcare Improvement there have been a series of collaborative efforts to reduce ADEs by using "Models for Improvement" [45]. Teams from 40 US hospitals participated over a 15-month period. As a result, 8 types of changes were implemented by at least seven hospitals, with a success rate of 70%. These changes included nonpunitive reporting of ADEs, ensuring documentation of allergy information, standardizing medication administration times, and implementing chemotherapy protocols. Changes that were most successful were those that attempted to change processes, not people.

### Implications

In summary, ADEs in hospitalized patients are countable, dangerous, and evaluable events, not just a collection of unhappy accidents that strike us in ways that we cannot

predict or understand. Computing systems can bring enormous power in measuring ADEs, understanding where and why they happen and help prevent them. The experiences and perceptions of people working in the health care system are the most valuable source needed to create a culture of constant learning and improvement. Whatever the precise measure of impact of ADEs is, their toll in human and fiscal terms is clearly large enough to justify commitment of hospital resources to programs designed to reduce preventable ADEs to the lowest possible incidence.

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(Received November 12, 2002, accepted after revision April 8, 2003)