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# Lack of Awareness of Community-Acquired Adverse Drug Reactions Upon Hospital Admission

## Dimensions and Consequences of a Dilemma

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## Abstract

**Objective:** Adverse drug reactions (ADRs) are a well-known cause of hospital admission. Nevertheless a quantitative estimate of the preventability of and physicians' awareness of these reactions is lacking.

**Study Design and Methods:** Using intensive bedside and computer-assisted drug surveillance methods a 13-month prospective pharmacoepidemiological survey was carried out on patients admitted to two medical wards of the Erlangen-Nuremberg University Hospital in Erlangen, Germany. This study aimed to define the incidence of preventable and unavoidable ADRs. In addition we investigated the awareness of the physicians to ADRs at the time of admission and the rate of contraindicated pre-admission prescriptions.

**Results:** In 78 (8.5%) of 915 (10.9%) admissions a total of 102 (42 preventable) community-acquired ADRs were detected on admission. In 45 (3.8%) of the admissions ADRs led directly to hospitalisation. 56.9% of the ADRs were not recognised by the attending physician on admission. Marked correlation was found between the awareness of ADRs and their probability and severity scores ($r = 0.85$ and $r = 0.94$, respectively; $p < 0.05$). The most frequently detected ADRs were due to direct toxicity and secondary pharmacological effects. Idiosyncratic reactions were often missed and 18.6% of all drugs prescribed prior to admission were contraindicated. Leading the list were diuretics, analgesics/NSAIDs and antipsychotics/sedatives.

**Conclusions:** Awareness of existing ADRs on hospital admission and appropriate prescribing prior to hospital admission require attention. Early detection of ADRs on hospital admission can be achieved by the use of computer support systems. Many ADRs could be prevented by adhering to indications and contraindications.

## Background

Adverse drug reactions (ADRs) are amongst the most important causes of iatrogenic illness in terms of morbidity and mortality. They have serious medical-legal and economic consequences.[1-3] Numerous studies have shown that ADR-related hospital admissions comprise up to 10% of the total number of admissions.[4-6] They contribute significantly to the socio-economic burden of healthcare.[1] The number of ADRs that remain unrecognised on admission is unknown. The present study was undertaken to evaluate the incidence of ADRs on admission, the rate of and the causes of missed detections. Special consideration is given to the community physician's ability to comply with drug contraindications. Unrecognised ADRs inflict health damage, costs and cause prolonged hospital stays.[7] A solution may come from the use of computerised support systems.[8-14]

## Methods

### Study Design

A prospective 13-month survey ending in January 1999, was carried out in the Department of Medicine I of the Erlangen-Nuremberg University Hospital in Erlangen, Germany. The two study wards accepted medical patients. One 29-bed ward admitted adult males only while the other 11-bed ward had both male and female patients. Patients readmitted to the study wards within the study period were enrolled into the study and taken into consideration. All patients were monitored by a pharmacoepidemiological team, consisting of a pharmacist, a clinical pharmacologist and a staff physician, supported by a computerised monitoring system described elsewhere, for the occurrence of ADRs at the time of admission.[9,15] Patients aged ≥65 years were considered 'elderly'.

The awareness of physicians to ADRs was rated on the basis of reviewing the chart notes and the actions taken by the attending physicians. The team determined whether the recognised or unrecognised ADRs were the cause of hospital admission. Finally, the medical outcome was defined.

As patients may have several ADRs simultaneously, the total number of ADRs could be larger than the total number of patients having an ADR. For analysis of patient-related factors (e.g. ADR rate) the first observed adverse reaction on hospital admission was analysed. For analysis of ADR-related factors (e.g. probability, severity, mechanism, preventability, outcome) all ADRs were taken into consideration.

### Cases and Matched Controls

Matched controls were selected among all patients admitted to the study wards during the study period. Matched controls had no evidence of an ADR. Additional matching criteria included the study ward, age (± 5 years), gender and primary discharge diagnosis. One control was matched for each ADR-positive patient. Patients admitted for intentional poisoning, attempted suicide or drug abuse were excluded. The data collected for all cases and controls included age, gender, main diagnosis, drug therapy at the time point of admission, bodyweight in kg, height in cm, body mass index (BMI) in $kg/m^2$ and comorbidities, as assessed by the Charlson Index.[16] This control group was only used to compare the drug prescriptions in patients with no evidence of ADRs.

### Drug Prescriptions and Contraindications

The medication regimens were screened to identify contraindications on the basis of the patients' diagnoses and clinical or laboratory data. The European physicians' drug index, the 'Rote Liste', was used as the reference list for classifying contraindications.[17] Conditions or disease states that prohibited prescribing a particular drug were judged to be absolute contraindications. A relative contraindication was assumed in cases where the particular drug should not be prescribed generally but is allowed only if specific precautions were executed.

## Procedures for Identifying Adverse Drug Reactions (ADRs)

ADRs were defined according to the WHO definition.[18]

Three methods were used for identifying ADRs.

- Patients were evaluated for the occurrence of ADRs by physicians, who were part of the pharmacoepidemiological team, at the time of admission.
- All charts were reviewed by the pharmacoepidemiological team three times weekly.
- A specially developed computer monitoring system (CMS) including patients' data and date of events was used to generate a daily list of alerts (automatically generated laboratory signals) based upon predefined values of laboratory tests that might indicate potential ADRs. The alerts were classified by the pharmacoepidemiological team according to their plausibility of being an ADR.[9,15]

## Classification of ADRs

### *Probability and Severity*

All potential ADRs, detected by the pharmacoepidemiological team were evaluated independently by a physician, a clinical pharmacologist and a pharmacist. The probability that a drug caused an ADR was determined by using the Naranjo algorithm. Nine weighted questions had to be answered to classify a causal association between drugs and ADRs – temporal sequence, pattern of response, withdrawal, re-exposure, alternative causes, placebo response, drug levels in body fluids or tissues, dose response relationship, previous patient experience with the drug, and confirmation by objective evidence.[19] Only possible, probable and definite ADRs were taken into consideration. ADRs which were classified as doubtful were excluded from further analysis.

Additionally, the observers independently assigned a weighted score to the following components used to categorise severity: the ADR impaired the patient's quality of life; the ADR led to or prolonged hospitalisation; the ADR caused temporary or permanent malfunction of an organ system; the ADR caused temporary or permanent inability to work, was dangerous, life threatening or fatal, the ADR led to discontinuance of the drug or substitution of a different.[9] A score of 1–4 indicates a mild, a score of 5–8 a moderate and a score of >8 a severe drug reaction.

If the three reviewers disagreed, they met and reached consensus.

### *Preventability*

To assess the preventability of each ADR the criteria developed by Schumock and Thornton were adapted.[20] The pharmacoepidemiological team, in co-operation with the staff physicians, conducted a retrospective review of all patient charts. To minimise bias, a pharmacist, a clinical pharmacologist and the staff physicians independently reviewed each ADR to determine preventability. If their conclusions differed the staff physician served as arbitrator. Furthermore, ADRs were judged 'tolerable', if a positive benefit-to-risk ratio was assigned for the responsible drug by the physician.

### *Mechanisms*

All ADRs were categorised into one of six groups according to their putative pathogenetic mechanisms: toxicity (e.g. digitoxin-induced PQ-time prolongation); overdose (e.g. theophylline-induced tachycardia); secondary pharmacological effects (e.g. erythromycin-induced pseudomembranous colitis); idiosyncratic reactions (e.g. carbamazepine-induced hepatitis or risperidone-induced jaundice); drug allergies; or drug-drug interactions.

## Physicians Awareness to ADRs

The awareness of physicians to verified ADRs was classified into two main categories by the pharmacoepidemiological team:

- if no evidence that the physician recognised an ADR (possible, probable or definite) existed in the chart it was categorised as 'not recognised'
- if reactions such as chart notes, dose reductions, discontinuation of a drug, additional laboratory studies or other diagnostic measures could be

detected in the context of the ADR, the ADR was categorised as 'recognised'.

### Medical Outcome

The medical outcomes of the ADRs were grouped into five categories:

- the ADR led to irreversible injury
- the ADR necessitated aggressive therapy (e.g. critical care unit)
- the ADR necessitated another drug or antidote treatment
- *restitutio ad integrum*, i.e. complete return to health occurred after withdrawal of the medication
- the ADR had no effect on outcome.

### Ethics

The study was approved by the institutional Ethics Review Board.

### Statistics

For continuous variables the arithmetic mean, standard deviation, median, upper and lower quartile and for discrete variables frequency tables were calculated. Statistical dependence of discrete variables and differences of continuous variables were explored using the $\chi^2$-test and the t-test where appropriate. The association of 'recognised' ADRs with the probability and severity score was assessed through Spearman correlations.

## Results

### Characteristics of the Study Population

Nine hundred and fifteen admissions of 711 patients to the department of medicine were observed. Of the admissions, 55.6% were elective, 11.9% of the patients were assigned to the study wards by other departments or hospitals and 32.5% of the patients were hospitalised as emergencies. Fifteen percent (n = 133) of all patients were women. Mean age was 54 years, with a range of 17–97 years and mean duration of hospitalisation was 8.7 days, with a range of 1–81 days.

### ADR Rate

In 78 (8.5%) of the 915 admissions (10.9% of all patients) 102 ADRs were detected at the time of hospitalisation. The absolute number of ADRs in each ADR-positive patient varied from 1 to 3 (mean = 1.3 SD ± 0.57). In 45 of the admissions (3.8%) involving 35 patients ADRs were the direct cause of hospitalisation. No repeated admission for any ADR was observed. In those hospitalised due to an ADR the mean duration of stay was 14.6 days (SD ± 10.1) whereas ADR-negative patients spent an average of 6.3 days (range 1–78 days, $p < 0.0001$) in hospital. The rate of elderly patients (aged ≥65 years) among those admitted due to ADRs (67.9%) was similar to the rate of elderly patients among those with community acquired ADRs not leading to hospitalisation (65.7%).

### Probability and Severity

Causality for 47 (46.1%) of the 102 community-acquired ADRs was judged as 'possible', 44 (43.1%) as 'probable' and 11 (10.8%) as 'definite'. Severity of 46 (45.1%) of all the ADRs was classified as mild, 47 (46.1%) as moderate and nine (8.8%) as severe. One patient died as a result of sepsis secondary to pancytopenia induced by chemotherapy. The median severity score for the ADRs was 5. It was 7 (SD ± 2.0) in community-acquired ADRs leading to hospitalisation and 4 (SD ± 1.8) in those not leading to hospitalisation.

### Mechanisms of ADRs

Toxicity, overdose (n = 40; 39.2%) and secondary pharmacological effects (n = 32; 31.4%) were the leading causes of ADRs. Idiosyncratic reactions were observed 18 times (17.7%). Drug allergies (n = 5; 4.9%) or drug-drug interactions (n = 5; 4.9%) were seen less frequently. No differences were noted in the distribution of ADRs between patients, who were or were not hospitalised due to community-acquired ADRs.

Comparing elderly patients (aged ≥65 years) with younger patients revealed that more secondary pharmacological effects (n = 15, 42.9% vs n = 17,

25.4%, $p < 0.07$) and more drug-drug interactions (n = 4, 11.4% vs n = 1, 1.5%, $p < 0.05$) were observed. On the other hand, fewer toxic drug effects (n = 8, 22.6% vs n = 27, 40.3% $p < 0.08$) and idiosyncratic reactions (n = 3, 8.6% vs n = 15, 22.4%, $p < 0.1$) were seen in the elderly.

### Physicians Awareness

Only 44 of the 102 ADRs were noted in the charts by the attending physicians. As judged from the measures taken on admission, ADRs that led to hospitalisation were more often recognised (n = 29) as compared with ADRs that were not the reason for hospitalisation (n = 15: $p < 0.002$). A significant correlation was found between the awareness to ADRs and the probability and severity score ($r = 0.85$, $r = 0.94$; respectively, $p < 0.05$) [figure 1 and figure 2]. If an ADR was judged to be definite or severe, the awareness of the attending physicians increased up to 100%. On the other hand, mild or possible ADRs were mostly not recognised by them.

Physician awareness of ADRs varied with their putative pathogenetic mechanism. Idiosyncratic ADRs or those of unknown mechanism were unlikely to be detected by the attending physicians (2 of 18 idiosyncratic ADRs), whereas ADRs that were secondary pharmacological effects were recognised in 19 of 32 cases and toxic reactions and overdosage were recognised in 18 of 40 cases; however, this still only amounts to a detection rate of about a 51% ($p < 0.003$).

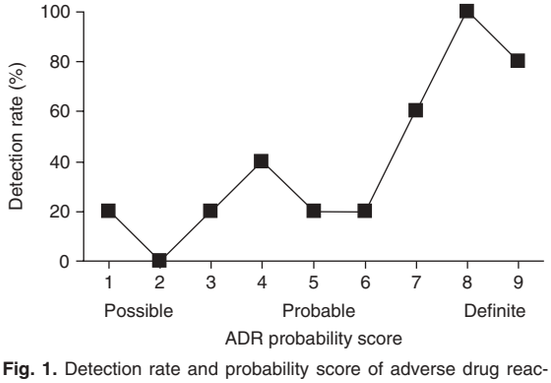


**Fig. 1.** Detection rate and probability score of adverse drug reactions (ADRs).

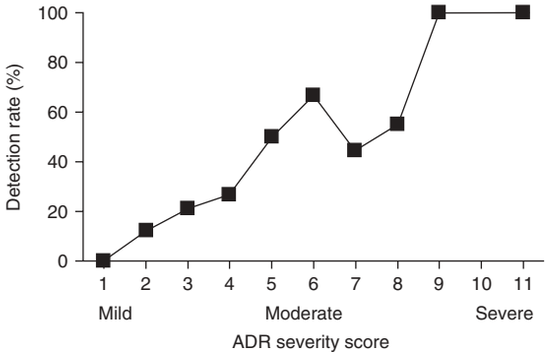


**Fig. 2.** Detection rate and severity score of adverse drug reactions (ADRs).

### ADR Outcome

In recognised ADRs (44 patients) the most likely responsible drug was withdrawn in 20 cases, an additional drug was prescribed in 20 others. In the others dose adjustment prevailed. Most of these ADRs resolved, except one (see below). Out of the total of 102 ADRs, 16 (15.7%) caused an irreversible injury necessitating aggressive therapy. One death was associated with an ADR despite adequate treatment. In 12 patients changes in therapy had no obvious scientific basis.

In patients hospitalised due to an ADR there was more need for immediate aggressive therapy and more irreversible drug injuries were observed (28 out of 45 vs 7 out of 56; $p < 0.0001$). On the other hand, medication was withdrawn in these patients less often (6 vs 15; $p < 0.1$). No difference in outcome of ADRs could be detected between the two age groups. The organ systems involved in the ADRs are shown in figure 3.

### Preventability of ADRs and Preventable Admissions

Forty-two (41.2%) ADRs out of 102 were considered preventable. In four patients (3.9%) the benefit of the drug was judged to be clinically more important than the adverse effect. Twenty ADRs (44.4% of the ADRs in those patients hospitalised due to ADRs) were classified as 'preventable'. In patients younger than 65 years, 46 ADRs (31.4% of all ADRs) were judged not to be preventable, where-

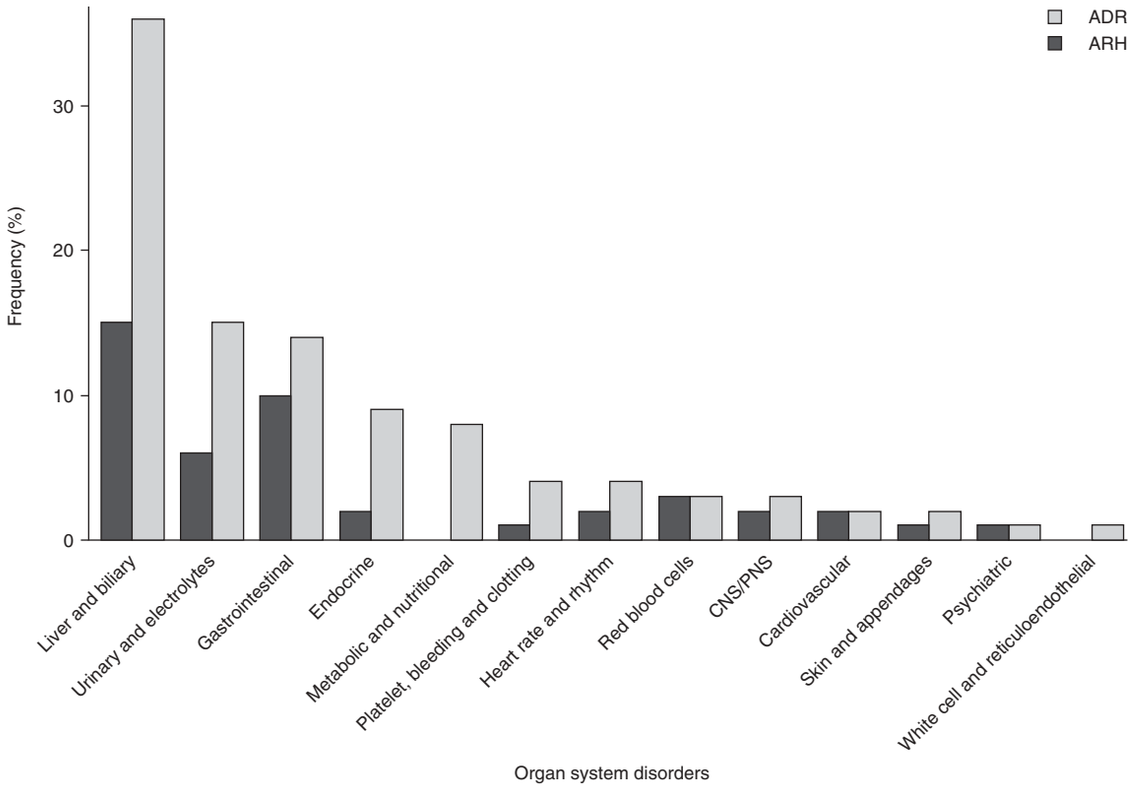


**Fig. 3.** Frequency of organ system disorders associated with adverse drug reactions recognised on admission (ADR) and adverse drug reactions that were the cause of hospitalisation (ARH). **PNS** = peripheral nervous system.

as in the elderly only ten ADRs (28.6%) were considered not to be preventable, two were tolerated and 23 ADRs (65.7%) were judged to be preventable. Compared with the younger patients, in the elderly significantly more ADRs were considered to be preventable ($p < 0.001$).

### Drug Prescriptions Prior to Admission, Violations of Contraindications

The 78 ADR-positive patients were compared with the same number of matched controls. Patients admitted with ADRs received 333 drugs (mean 4.3) and the controls 249 (mean 3.2) on admission.

The most frequently prescribed drugs among our study patients were cardiovascular agents (16.8%) and gastrointestinal drugs (16.2%) followed by diuretics (9.5%), analgesics/NSAIDs (6.2%) and respiratory medications (6.0%). In this patient group (n = 156) 102 (17.5%) prescriptions were considered to be contraindicated on the basis of the patient's diagnosis and the laboratory data. In 38 (24.4%) admissions, 41 absolute contraindications were observed. They involved predominantly diuretics, analgesics/NSAIDs, antipsychotics/sedatives and corticosteroids. Relatively few contraindications to gastrointestinal drugs, anticoagulants and anti-infective agents were detected. The nature of the absolute contraindications and their importance in ADR-positive patients are shown in table I.

The rate of ADR-positive patients (n = 40) with a prescription for at least one contraindicated drug prior to admission was significantly higher as compared with controls (n = 26; $p < 0.04$).

## Discussion

During a recent analysis of patients' records we observed that ADRs had not been recognised on admission. They turned out to persist and to cause secondary illnesses, prolonged hospital stay and in some instances eventually require aggressive treatment. We therefore set out to define the rate of ADRs present on admission to a medical ward and the proportion recognised by the attending physician.

In line with former publications we observed that about 4% of all admissions to the hospital were due to ADRs.[2,6,7,12,21-23] In addition, in another 4.5% of the admissions ADRs were present. More importantly, we could show that more than half of the pre-existing ADRs were not recognised by either the admitting nor the attending physician. If we assume that this finding is not the exception but the rule we can generalise that one in ten patients admitted to a medical department is already experiencing an ADR and that the majority go on unrecognised. A similar failure of recognition has been described in the outpatient setting.[24] Obviously this would be a sizeable burden to the healthcare system in terms of disease load and costs.[1,7,9]

In order to define the dimensions of the problem one has to evaluate to what extent these ADRs were preventable. Indeed, many studies dealing with ADR outcome attempt to define the ratio of predictable or unpredictable, avoidable or unavoidable, preventable or non-preventable, type A (e.g. adverse effects, interactions, secondary effects, etc.) or B (e.g. allergic, intolerance, etc.) situations.[5,8,20,25-27] However, such classifications appear meaningful only in the context of clinical reality. Mild or moderate reactions to antineoplastic therapy often have to be tolerated due to the benefit of therapy and/or the lack of alternatives. In order to come up with a more meaningful estimate we used the classification system of Schumock and Thornton[20] and divided the potentially preventable ADRs into preventable and

**Table I.** Prescription of (absolutely) contraindicated drugs prior to admission in patients with an adverse drug reaction at the time of admission

| Drug group | Drug | Contraindication | No. |
|---|---|---|---|
| Analgesics/NSAIDs | Aspirin (acetylsalicylic acid), diclofenac | Known ulcer | 4 |
| Antipsychotics/sedatives | Flunitrazepam | Renal failure (creatinine 1.1–1.4 mg/dL) | 1 |
| | Zotepine | Alcohol intoxication | 1 |
| Antidiabetics | Gliquidone | Renal failure (creatinine >1.4 mg/dL) | 1 |
| | Metformin | Peripheral occlusive disease | 1 |
| Anti-infectives | Cotrimoxazole (trimethoprin-sulfamethoaxole) | Thrombopenia | 1 |
| Anticoagulants | Phenprocoumon | Advanced atherosclerosis | 1 |
| Cardiovascular | Clonidine, moxonidine | Renal failure (creatinine >1.8 mg/dL) | 1 |
| | Etilefrine | Atherosclerosis | 1 |
| Corticosteroids | Prednisolone | Ulcer | 1 |
| | | Glaucoma | 1 |
| Diuretics | Spironolactone | Hypercalcaemia | 2 |
| | | Renal failure (creatinine >1.8 mg/dL) | 3 |
| | Spironolactone/furosemide | Hypotension | 1 |
| | Xipamide | Severe hyponatraemia | 1 |
| Lipid-lowering drugs | Simvastatin | Increase in transaminase levels | 1 |
| **Total** | | | **22** |

tolerable reactions. Mild ADRs are tolerated in many cases because of the positive element of the risk to benefit ratio. An intervention by the physicians is not necessary in such cases and indeed was not observed in most. Unlike other preventability classifications, which do not exclude tolerable ADRs, our data allow for defining the ADRs which could and should have been prevented. Under these premises 41.2% of all ADRs were judged to be preventable. In reality, however, only a small fraction of these ADRs 'could' have been prevented as only 43.1% of all ADRs were recognised. Consequently, we have to accept that early recognition of an ADR is the predominant factor of preventability.

Different approaches to reducing and preventing ADRs have been proposed, amongst them screening for specific drugs or defining susceptible populations.[8,13,27-29] We have analysed these options. Indeed we found that patients aged ≥65 years show a significantly higher rate of ADRs (62.9%) judged preventable. In addition, a higher rate of secondary pharmacological effects (42.9%) and drug-drug interactions (11.4%) resulted from multiple illnesses.[30] The higher rate of drug-drug interactions in the elderly can also be explained by increasing polypharmacy (mean number of drugs 5.6 SD ± 2.1 vs 4.3 SD ± 3.1). Drug toxicity and secondary pharmacological effects were responsible for more than 70.6% of all ADRs. No differences were seen in the types of ADRs identified in patients hospitalised due to ADRs as opposed to patients with other ADRs. This observation is not surprising. It suggests, that factors influencing the pharmacodynamic and pharmacokinetic characteristics of the patient, as e.g. organ insufficiency (age) or multiple drug use should increase alertness in order to prevent ADRs.

The most important factor in recognising preexisting ADRs appears to be the awareness of the physician and his/her pharmacological competence. In ADR-related hospitalisations the recognition rate of the physicians was somewhat higher at 65%, but still far from complete. Action by the attending physician was taken in most cases only in severe ADRs (e.g. transfer to an intensive care unit). Not unexpectedly the identification of idiosyncratic and mild ADRs represented the greatest problem.

We also found that 17.5% of the prescriptions prior to admission were inappropriate – many of them plainly violated clear contraindications. In diuretics and analgesics the highest number of contraindications was found in a cohort of patients who predominantly had hepato-gastroenterological diseases.

As long as one out of ten patients admitted has at least one ADR which is most likely not detected on admission, implementing evidence-based therapy appears difficult. To achieve this goal all medications have to be reviewed carefully on admission in order to detect drugs that should have been avoided in view of existing contraindications and ADRs.[7,13,27,31,32] This drug screening is particularly important on admission since inappropriate prescriptions are more likely to occur in outpatients as opposed to drug treatment in hospitals.[31] Because of the plethora of drug information and the distracting circumstances in which the admission often takes place, these goals can be partly achieved by better education of the physicians or an improved work atmosphere.[33,34] In addition, computerised (on-line) surveillance of drug prescriptions in the context of patient-specific risk factors could improve the situation in a cost-efficient way.[8,9,11,32] Such programs have to be integrated into clinical and general practice. They have already been shown to actively help the attending physicians by increasing ADR detection and prevention.[10,14] If the majority of ADRs are already detected on hospital admission a substantial improvement of the quality of therapy and outcome would result as physicians would then be able to react instantaneously and prevent further deterioration of ADRs.

This study has several limitations. First, data presented were obtained only from two units from one medical department. Caution should thus be exercised in the extrapolation of these results to other populations, e.g. surgical and paediatric patients.

Second, although intensive drug surveillance methods for identifying ADRs were used, a com-

plete ADR coverage during the study period could not be achieved.

Third, ADRs were characterised as not recognised if no evidence existed in the patient chart. On the other hand if reactions like chart notes or laboratory studies were detected ADRs were categorised as recognised, but physicians caring for the patients were not asked prospectively whether they were aware of them or not.

## Conclusion

Awareness of existing community-acquired ADRs and appropriate prescribing prior to hospital admission require attention and can be supported by the use of computer programs. Many ADRs could be prevented by adhering to indications and contraindications.

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