Eur J Clin Pharmacol (2007) 63:1075–1083
DOI 10.1007/s00228-007-0359-4

PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

Recognition and management of potential drug–drug interactions in patients on internal medicine wards

Priska Vonbach · André Dubied · Jürg H. Beer · Stephan Krähenbühl

Received: 20 May 2007 / Accepted: 27 July 2007 / Published online: 6 September 2007

Abstract
Introduction Our aim was to study and possibly improve the clinical management of potential drug–drug interactions (pDDIs) in hospitalized patients by specific interventions.
Methods During the initial period, inpatients on three medical wards were screened for major and moderate pDDIs using the interaction screening program Pharmavista. During the second period, patients at discharge were screened similarly. After assessment of the detected pDDIs for clinical relevance, written recommendations and/or information about the pDDIs were sent to the treating physicians. Feedback from the physicians and implementation of the recommendations were analyzed.
Results During the initial period, 502 inpatients were exposed to 567 pDDIs, of which 419 (74%) were judged to be clinically relevant. Three hundred and forty-nine substantiated recommendations and 70 simple information leaflets were handed out to the physicians. Eighty percent (278 of 349) of the recommendations were accepted and implemented. During the second period, 792 patients at hospital discharge were exposed to 392 pDDIs, of which 258 (66%) were judged to be clinically relevant. Two hundred and forty-seven substantiated recommendations and 11 simple information leaflets were sent to the physicians. Seventy-three percent (180 of 247) of the recommendations were accepted. At hospital discharge, 47 of 71 interventions recommending checkable medication changes were implemented. One year after hospital discharge, 11 of 13 checked medication changes were still in place.
Conclusions Clinically relevant pDDIs are common in patients on medical wards, and their management can be influenced by providing substantiated recommendations to physicians. Most changes in medication following such recommendations are still in place 1 year after discharge.

Keywords Drug–drug interactions · Drug–drug interaction screening program · Intervention · Medication error · Adverse drug reaction

P. Vonbach · A. Dubied
Hospital Pharmacy, Kantonsspital Baden,
Baden, Switzerland

J. H. Beer
Department of Medicine, Kantonsspital Baden,
Baden, Switzerland

S. Krähenbühl (✉)
Clinical Pharmacology & Toxicology, University Hospital,
4031 Basel, Switzerland
e-mail: kraehenbuehl@uhbs.ch

Introduction

Medication errors, adverse drug events (ADEs), and adverse drug reactions (ADRs) are common and clinically important problems. ADEs and ADRs are associated with considerable morbidity and mortality [1–12]. Potential drug–drug interactions (pDDIs) are important risk factors for ADRs, as shown, for instance, for rhabdomyolysis associated with the use of statins [13]. According to a recently published study, 1% of all hospital admissions were caused by drug–drug interactions (DDIs), corresponding to 16% of all patients admitted with ADRs [8]. In a review of nine studies about ADRs, the authors reported that ADRs due to DDIs caused 2.8% of all hospital admissions [14]. In recent years, major advances in our understanding regarding DDIs could be observed, particularly in the molecular mechanism by which drugs interact. In contrast, our ability to appropriately apply this informa-

tion to specific patients has not progressed with the same velocity, and many patients continue to suffer from ADRs associated with DDIs.

Changes in medication at the transition point from outpatient to inpatient care and vice versa may increase the frequency of drug-related problems such as pDDIs [10, 15–17]. In our own study of the prevalence of pDDIs during hospital stay (Vonbach B, unpublished observation), 47% of all pDDIs at discharge were created by medication changes during hospitalization. Furthermore, several deficiencies were detected regarding the clinical management of pDDIs.

The aims of this study were therefore to analyze pDDIs and to find ways to improve their clinical management by appropriate interventions during hospitalization and at hospital discharge.

Methods

Patients and data collection

The intervention study was conducted at the Cantonal Hospital of Baden. The protocol of the study had previously been approved by the local ethics committee. The hospital is a 400-bed teaching institution serving a population of approximately 250,000 inhabitants. The Clinic of Medicine was not equipped with a computerized physician order entry (CPOE) and, therefore, no automatic DDI order check was available.

Two separate groups of patients were studied at different occasions. Between February and May 2005, patients admitted to three medical wards were included into the first study (intervention study during hospitalization). Information on drugs prescribed during hospitalization was retrieved from clinical records and collected on a fixed day once a week and once per patient. Between June and October 2005, patients to be discharged from three wards were included in the second study (intervention study at hospital discharge). This intervention was performed as soon as the date of discharge was known, when the patients were still in the hospital. Information on drugs prescribed at discharge was obtained from the hospital discharge letters on the day of discharge.

Demographic information (age and sex), length of hospital stay, main diagnosis [according to the International Classification of Diseases (ICD-10)] and the number of additional diagnoses were obtained from clinical records.

Classification of pDDIs and interventions

Medication was screened for pDDIs by a clinical pharmacist (PV) using the drug interaction screening program Pharmavista [18]. This drug interaction program originates from the ABDA-Datenbank published by the Bundesvereinigung Deutscher Apothekerverbände (Federal Organization of German Pharmacist Associations). The program was chosen based on our own evaluation of nine drug interaction screening programs, revealing that Pharmavista is the most suitable widely available drug–drug interaction program for the Swiss drug market [19]. The program classifies severities of DDIs into five categories: (1) major[1], (2) moderate[2], (3) minor[3], (4) insignificant[4], and (5) unidentified source[5].

After screening, pDDIs classified as major and moderate according to Pharmavista were judged for clinical relevance. Pharmavista provides a judgment for clinical relevance, which was accepted in most cases. If the clinical pharmacist disagreed with this judgment, she had to compare it with the judgment in *Stockley's Dug Interactions* [20]. In the case of an agreement between Stockley's and Pharmavista, this judgment was accepted. In the case of a disagreement, the clinical pharmacist had to discuss the problem with one of the coauthors (AD, JHB, SK) until an agreement had been achieved. For pDDIs judged to be clinically relevant, written recommendations concerning the clinical management of the pDDI were prepared for the treating physicians. In addition to these recommendations, a leaflet based on the information contained in Pharmavista about the mechanism of the pDDI, possible ADRs, and the clinical management of the pDDI and ADRs was prepared and sent to the treating physicians. Physicians were asked to give written feedback regarding acceptance or rejection of the recommendations. In addition, in the second part of the study (intervention at hospital discharge), physicians were asked to assess the clinical relevance of the pDDI themselves.

Implementation of the recommendations during hospitalization was verified by investigating the medication prescribed at hospital discharge, which was checked for changes according to the recommendations. Concerning the interventions at hospital discharge, short-term implementation was verified by investigating the medication prescribed at hospital discharge. Long-term implementation was

[1] Major interactions: May be life threatening, or permanent damage may be induced. Such drugs should not be administered together.

[2] Moderate interactions: Frequently cause therapeutic difficulties and may even cause harm. Combinations may be administered, however, if patients are monitored carefully.

[3] Minor interactions: Are associated with increased or reduced drug effects, but these alterations, in general, do not cause harm and can be tolerated.

[4] Insignificant interactions: Cause mainly no or only unimportant effects, and no special action is required.

[5] Unidentified source: For such interactions, no medical literature is available. Their clinical relevance is therefore unclear.

Table 1 Characteristics of patients included in the two arms of the study

Characteristics		Intervention during hospitalization (n=502)	Intervention at hospital discharge (n=792)
Age - years	Mean	68.4	66.5
	95% confidence interval	67.2–69.7	65.3–67.6
	Median	71	69
	Range	17–96	17–99
Sex - no. (%)	Male	231 (46)	404 (51)
	Female	271 (54)	388 (49)
Length of hospital stay - days	Mean	13.0	9.3
	95% confidence interval	12.1–13.9	8.6–9.9
	Median	10	7
	Range	1–91	1–72
Number of diagnoses	Mean	4.3	4.5
	95% confidence interval	4.1–4.5	4.3–4.6
	Median	4	4
	Range	1–16	1–15
Main diagnoses (according to ICD-10) - no. (%)	Diseases of the circulatory system	137 (27.3)	221 (27.9)
	Diseases of the respiratory system	78 (15.5)	54 (6.8)
	Diseases of the digestive system	52 (10.4)	109 (13.8)
	Neoplasms	42 (8.4)	61 (7.7)
	Symptoms, signs, or abnormal clinical or laboratory findings not classified elsewhere	36 (7.2)	22 (2.8)
	Factors influencing health status and contact with health services	14 (2.8)	45 (5.7)
	Diseases of the nervous system	25 (5.0)	44 (5.6)
	Diseases of the musculoskeletal system and connective tissue	20 (4.0)	42 (5.3)
	Other (<5%)	98 (19.5)	194 (24.5)

investigated by asking the general practitioners of randomly selected patients for details about the current medication 1 year after hospital discharge.

Statistical analysis

Descriptive data were expressed as means with corresponding 95% confidence intervals (CIs), as medians with ranges, or as proportions. Data were analyzed with R for Windows version 2.2.0 (R Development Core Team, 2005, R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient characteristics and dropouts

Between February and May 2005, 539 patients were enrolled for the intervention study during hospitalization. Of these, 37 (7%) patients were excluded (31 patients died during hospitalization, and six patients were excluded due to gaps in their medical history). The median time between hospital admission and registration of the drugs prescribed was 5 days (mean 5.1 days, 95% CI 4.7–5.6 days). Between June and October 2005, data concerning 826 patients were recorded at the end of hospitalization for the intervention study at hospital discharge. Patient characteristics are displayed in Table 1.

Prescribed drugs and prevalence of pDDIs

The number of drugs prescribed per patient, the drug pairs analyzed, and the prevalence of major and moderate pDDIs are presented in Table 2. Fewer patients (n=502) were analyzed in the intervention study during hospitalization than in the study at hospital discharge (n=792). Due to a higher number of drugs prescribed to inpatients than at hospital discharge (median n=11 vs. n=6 drugs per patient, respectively), the total number of major and moderate pDDIs and the number of pDDIs per patient was nevertheless higher during hospitalization (567 pDDIs, 1.13 pDDIs per patient) than at hospital discharge (392 pDDIs, 0.49 pDDIs per patient).

Interventions performed

During the intervention period for inpatients, 419 pDDIs (74% out of the 567 major and moderate pDDIs) were

Table 2 Number of drugs and drug pairs analyzed per patient and prevalence of major and moderate potential drug–drug interactions (pDDIs) [95% confidence interval (CI)]

	Parameters	Intervention during hospitalization (n=502)	Intervention at hospital discharge (n=792)
Number of drugs (drugs prescribed "as required" excluded)	Mean (95% CI)	7.8 (7.5–8.1)	5.7 (5.5–5.9)
	Median (range)	7 (0–21)	5 (0–18)
Number of drugs prescribed "as required"	Mean (95% CI)	3.7 (3.6–3.8)	0.4 (0.4–0.3)
	Median (range)	3 (0–12)	0 (0–5)
Total number of drugs ("as required" included)	Mean (95% CI)	11. (11.1–11.9)	6.1 (5.9–6.3)
	Median (range)	11 (1–26)	6 (0–18)
Number of drug pairs ("as required" included)	Mean (95% CI)	70.1 (65.3–74.9)	20.8 (19.3–22.4)
	Median (range)	55 (0–325)	15 (0–153)
Number of patients with ≥1 major pDDI	No. (%)	22 (4.4)	6 (0.8)
	95% CI (%)	2.6–6.2	0.15–1.36
Number of patients with ≥1 major or moderate pDDI	No. (%)	284 (56.6)	243 (30.7)
	95% CI (%)	52.2–61.0	27.5–33.9
Number of major pDDIs per patient	Mean (95% CI)	0.05 (0.03–0.08)	0.01 (0.00–0.01)
	Median (range)	0 (0–3)	0 (0–1)
Number of major or moderate pDDIs per patient	Mean (95% CI)	1.13 (0.98–1.27)	0.49 (0.43–0.56)
	Median (range)	1 (0–13)	0 (0–7)

Drugs prescribed "as required" are included in the analysis

judged to be clinically relevant (see Fig. 1). For 349 pDDIs, recommendations including an information leaflet about the pDDI were provided. For 70 additional cases, simply the respective Pharmavista general information leaflet was handed out to the treating physicians.

Regarding the intervention period at hospital discharge, 258 pDDIs were judged to be clinically relevant (66% out of 392 major and moderate pDDIs; see Fig. 1). For 247 pDDIs, recommendations including information about the pDDI and for 11 pDDIs, Pharmavista information leaflets only were delivered to the treating physicians.

Table 3 shows a summary of the recommendations. Among the 419 interventions during hospital stay, 48 (11%) implied withdrawal or replacement of a drug. Four recommendations (1%) implied temporal withdrawal (pausing) of a drug and three (0.7%) the prescription of an additional drug. At hospital discharge, withdrawal or replacement of a drug was recommended in 29 (11%) of the 258 interventions. During the hospitalization intervention period, 130 additional recommendations concerning the pDDI and possible ADRs were provided directly to the general practitioners treating the patients (111) and/or to certain patients themselves (25). During the intervention period at hospital discharge, the hospital physicians were asked to transmit the recommendations to the general practitioners. In addition, 17 advices about pDDIs and possible ADRs were given directly to the patients during this period of the study.

In 218 (38% of 567) cases of pDDIs during hospitalization and 145 (37% of 392) instances of pDDIs at hospital discharge, no specific recommendation was provided. In 148 (68% of 218) pDDIs during hospitalization and in 63 (43% of 145) pDDIs at hospital discharge, the reason to omit a recommendation was due to a difference in judgment regarding clinical relevance of the pDDI between the intervention team and Pharmavista. In such cases, this drug–drug interaction had to be listed as clinically not relevant in Stockley [20]. For example, the combinations insulin and cardioselective beta-blockers, topical β_2-sympathomimetics and cardioselective beta-blockers, low molecular weight heparin and low dose aspirin, or topical corticosteroids and diuretics are all classified as moderate pDDIs by Pharmavista, but they were not considered to be clinically relevant by the intervention team. Other reasons for omitting recommendations were the existence of specific patient variables (e.g., time-limited therapy), or the management of the pDDI had already been initiated by the treating physician.

Acceptance of the interventions and assessment of the clinical relevance of pDDIs by treating physicians

As shown in Fig. 1, 80% (278 of 349) of the recommendations provided during the intervention period for inpatients and 73% (180 of 247) of the recommendations during the intervention period at hospital discharge were accepted and executed by the hospital physicians. No feedback was obtained for 12% (42) and 13% (32), respectively, of the recommendations provided. Eight percent (29) and 14% (35) of the recommendations, respectively, were not accepted by the treating physicians. Specifically, three recommendations concerning major pDDIs were not accepted during hospitalization. All three recommendations concerned the prescription of a noncardioselective beta-blocker and β_2-sympathomimetics as inhalative antiasthmatic drugs. At hospital discharge, two major pDDIs (a noncardioselective beta-blocker combined with an inhalative β_2-sympathomimetic antiasthmatic drug and an α_2-sympathomimetic drug—

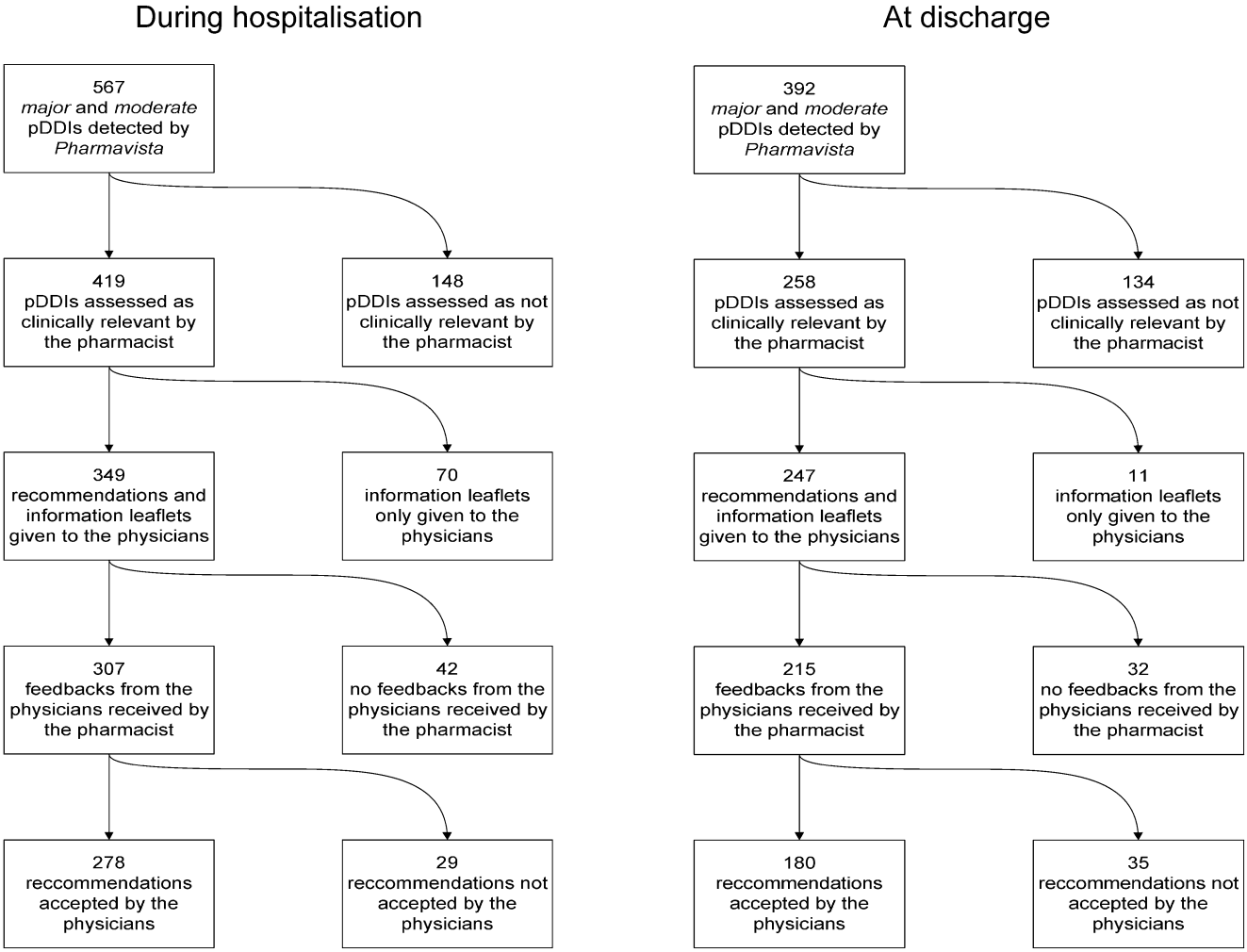

Fig. 1 Interventions in patients with major or moderate potential drug–drug interactions (pDDIs) and feedback concerning acceptance and implementation of the recommendations by the treating physicians. Intervention periods are (*1*) during hospitalization and (*2*) at hospital discharge

clonidine—combined with a noncardioselective beta-blocker) were not accepted.

Out of 258 major and moderate pDDIs at hospital discharge, 209 (81%) were assessed as clinically relevant by the treating physicians, 15 (6%) as not clinically relevant, and for 34 (13%) pDDIs, no feedback was obtained. Two major pDDIs (a non-cardioselective beta-blocker combined with a β_2-sympathomimetic as an inhalative antiasthmatic drug, and a potassium salt combined with a potassium-sparing diuretic) were assessed as clinically not relevant by the physicians.

Verification of the implementation by the treating physicians

Verification of the implementation of the recommendations at hospital discharge was only possible in cases where drug regimen changes (withdrawal, replacement, or pausing of a drug or prescription of an additional drug) had been recommended. Drugs prescribed "as required" were excluded from this analysis. Eighty-five percent of such recommendations (60 of 71) had initially been accepted (no feedback: four; refusal of the recommendation: seven). Of those, 47 recommendations had been implemented at discharge, corresponding to 66% of all recommendations and to 78% of the accepted recommendations. The second verification, 1 year after hospital discharge, was performed in 16 randomly selected patients. Two patients died during the year after discharge, and one patient had changed his general practitioner and could therefore not be located. In 85% (11 of 13 recommendations that could be judged), the medication changes according to the recommendation were still in place.

Discussion

Several studies have shown that appropriate interventions by health professionals can reduce prescribing errors [21–23]. According to Leape et al. [22], the presence of a

Table 3 Type of recommendation to avoid major and moderate potential drug–drug interactions (pDDIs)

	Intervention during hospitalization (total number of interventions 419)	Intervention at hospital discharge (total number of interventions 258)
Withdrawal of a drug – no. (%)	5 (1.2)	5 (1.9)
Withdrawal of a drug prescribed "as required" - no. (%)	13 (3.1)	0 (0.0)
Replacement of a drug by another drug – no. (%)	30 (7.2)	24 (9.3)
Replacement of a drug by another drug or to pause a drug - no. (%)	4 (1.0)	0 (0.0)
Prescription of an additional drug – no. (%)	3 (0.7)	0 (0.0)
Change of the drug application time – no. (%)	18 (4.5)	35 (13.6)
Fixation of the end of therapy - no. (%)	6 (1.4)	1 (0.4)
Fixation of the maximal dose - no. (%)	10 (2.4)	1 (0.4)
Monitoring of possible adverse drug reactions - no. (%)	24 (5.7)	38 (14.7)
Monitoring of the renal function - no. (%)	22 (5.3)	12 (4.6)
Monitoring of the blood pressure - no. (%)	17 (4.1)	18 (7.0)
Monitoring of the international normalized ratio value - no. (%)	62 (14.8)	42 (16.3)
Monitoring of the potassium serum level - no. (%)	77 (18.4)	39 (15.1)
Monitoring of the drug blood or serum level - no. (%)	6 (1.4)	15 (5.8)
Monitoring of the glucose blood level - no. (%)	24 (5.7)	6 (2.3)
Verification of the indication for a drug - no. (%)	5 (1.2)	4 (1.6)
Information provided about the pDDI only - no. (%)	70 (16.7)	11 (4.3)
Other measures (<1.0%) - no. (%)	6 (1.0)	6 (2.3)

pharmacist on rounds in a medical intensive care unit is associated with a substantially lower rate of ADEs associated with prescribing errors. In this study, the rate of ADEs associated with wrong prescription decreased by 66%: from 10.4 per 1,000 patient-days (95% CI 7–14) before to 3.5 (95% CI 1–5) after the intervention [22]. Furthermore, a direct association between the availability of clinical pharmacy services with the frequency of medication errors was demonstrated by the evaluation of almost half a million medication errors in 1,081 US hospitals [23]. An analysis of the causes of preventable prescribing errors revealed that clinical pharmacists could play an important role in the prevention of prescribing errors; for instance, in supplying appropriate information and in monitoring prescriptions to detect errors at this stage [24]. Potential DDIs should be identified and dealt with by a close collaboration between treating physicians and clinical pharmacists, preferably at the moment of drug prescription [25]. On the other hand, a recent study revealed that systematic review of medications by a clinical pharmacol-

ogist with special knowledge in DDIs and ADRs did not reduce drug-related morbidity or mortality [26]. One explanation for this finding is that pDDIs only rarely result in ADRs [11]. Nevertheless, ADRs associated with DDIs can be of high clinical importance [8, 13], justifying close monitoring of medications for pDDIs.

Acceptance of recommendations regarding management of pDDIs by treating physicians in our study (80% during the intervention period in inpatients and 73% during the intervention period at discharge) is comparable to the degree of acceptance of 63% reported in an intervention study in which written advice was provided [26]. Acceptance of more than 90% of the interventions was reported when direct (oral) communication between treating physicians and clinical pharmacists was possible [22, 27]. We assume that improvements regarding the degree of acceptance of well-documented and easily manageable pDDIs are possible. For example, three of 23 recommendations concerning interactions between statins and cytochrome P450-3A4-inhibiting drugs to replace the statin by a noninteracting statin or to pause statin therapy during an anti-infectious therapy with clarithromycin were rejected by treating physicians. Reasons mentioned for these refusals were either the absence of clinical relevance and/or the rarity of clinical ADRs associated with this pDDI. The frequency of rhabdomyolysis in patients treated with a statin without a DDI is in the range of 1:10,000 patient years [28]. In patients treated with a statin and with a pDDI associated with an increase in the statin serum concentration, the frequency of rhabdomyolysis is estimated to increase by a factor of ten, reaching 1:1,000 patient years [29]. Although rhabdomyolysis is still a rare event even in the presence of a pDDI, it is our opinion that such pDDIs should be avoided due to the severity of rhabdomyolysis, which can be fatal [13].

Similarly, three of eight recommendations concerning the interaction between polyvalent cations and quinolone antibacterials to postpone application time of the polyvalent cation were also refused by treating physicians. It is well established that concomitant administration of a polyvalent cation can dramatically impair the absorption of quinolones [30]. Such combinations should therefore be avoided.

Clinical management of pDDIs mostly implies monitoring of either symptoms of a possible ADR or of laboratory parameters. Only in 11% of the cases was modification of the prescription recommended. These findings concur with the results of a study analyzing the nature and management of pDDI alerts in Dutch community pharmacies, where 9% of all actions contained prescription modification [31].

Drug interaction screening programs may be helpful tools to check prescriptions for DDIs. Although automated order checks offer possible benefits for patient care, the effect of such real-time warnings remains to be comprehensively assessed [32]. Previous research suggests that above a certain threshold, more warnings are ignored or overridden rather than followed [33, 34]. A reduction in overrides was achieved by displaying only critical to high-severity alerts [35].

In our study, about one third of all moderate pDDIs detected by Pharmavista were judged to be not clinically relevant. This corresponds well with our evaluation study [19], which revealed a positive predictive value of 0.67 for Pharmavista using *Stockley's Drug Interactions* as the gold standard [20]. Other approaches to classify pDDIs, e.g., by considering not only the severity of possible ADRs, may possibly increase acceptance by treating physicians. An interesting approach was proposed by a Dutch working group [36], which defined four core parameters, namely, degree of evidence for the existence of a pDDI, clinical relevance and incidence of ADRs associated with the pDDI, and presence of additional risk factors associated with the development of an ADR. A management-orientated algorithm containing four decision layers (severity, manageability, risk/benefit assessment, and patient-related risk factors associated with a given pDDI) was proposed by another group [37]. Similarly, the OpeRational ClassificAtion (ORCA) system [38] takes into account the potential severity of the ADR due to a DDI, the factors known to increase or decrease the risk for the development of an ADR, and the existence of management alternatives to avoid the pDDI or to reduce the risk for an ADR by other means.

Despite the fact that we could show positive effects in terms of recognition of pDDIs and implementation of recommendations, we are convinced that in hospitalized patients, interventions regarding pDDIs should ideally be provided at the point of prescription. In clinical practice, DDI alert programs should be integrated into the CPOE system. Health professionals with specific knowledge in recognition and management of pDDIs and other medication errors should survey the overriding of alerts, and interventions should be executed if overridden alerts are deemed to be clinically relevant [27, 39]. As modifications in medication shortly before hospital discharge are common, a pDDI check at discharge can also be recommended. The importance of a DDI check at discharge is also given by the fact that checks for DDIs are much more difficult to perform in ambulatory patients [10, 17].

Limitations

Clinically manifest DDIs were not investigated in this study. Therefore, we use the expression "potential" DDI. Data about negative clinical outcomes caused by DDIs are rare, but some retrospective studies have been published [40, 41] showing increased risks for ADRs for patients with drug prescriptions containing pDDIs. Intervention studies

should be performed to investigate whether good clinical management of pDDIs can reduce drug-related morbidity and/or mortality.

Conclusions

The management of clinically relevant pDDIs can be improved by a good collaboration between health professionals involved in drug therapy. Providing substantiated recommendations to the treating physicians appears to be rewarding in the case of pDDIs, as most recommendations are accepted and implemented and are still in place 1 year after hospital discharge.

Acknowledgements We thank Sanofi Aventis, Meyrin/Switzerland, for financial support. The study was also supported by a grant from the Swiss National Science Foundation to SK (310000-112483/1). Furthermore, we thank e-Mediat, Schönbühl/Switzerland, for providing us the drug interaction screening program Pharmavista. The authors declare no conflict of interest directly relevant to the content of this manuscript.

References

1. Einarson TR (1993) Drug-related hospital admissions. Ann Pharmacother 27(7–8):832–840
2. Bates DW, Cullen DJ, Laird N, Petersen LA, Small SD, Servi D, Laffel G, Sweitzer BJ, Shea BF, Hallisey R et al (1995) Incidence of adverse drug events and potential adverse drug events. Implications for prevention. ADE Prevention Study Group. JAMA 274(1):29–34
3. Classen DC, Pestotnik SL, Evans RS, Lloyd JF, Burke JP (1997) Adverse drug events in hospitalized patients. Excess length of stay, extra costs, and attributable mortality. JAMA 277(4):301–306
4. Lesar TS, Lomaestro BM, Pohl H (1997) Medication-prescribing errors in a teaching hospital. A 9-year experience. Arch Intern Med 157(14):1569–1576
5. Lazarou J, Pomeranz BH, Corey PN (1998) Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. JAMA 279(15):1200–1205
6. Fattinger K, Roos M, Vergeres P, Holenstein C, Kind B, Masche U, Stocker DN, Braunschweig S, Kullak-Ublick GA, Galeazzi RL, Follath F, Gasser T, Meier PJ (2000) Epidemiology of drug exposure and adverse drug reactions in two swiss departments of internal medicine. Br J Clin Pharmacol 49(2):158–167
7. van den Bemt PM, Egberts TC, de Jong-van den Berg LT, Brouwers JR (2000) Drug-related problems in hospitalised patients. Drug Saf 22(4):321–333
8. Pirmohamed M, James S, Meakin S, Green C, Scott AK, Walley TJ, Farrar K, Park BK, Breckenridge AM (2004) Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients. BMJ 329(7456):15–19
9. Mjorndal T, Boman MD, Hagg S, Backstrom M, Wiholm BE, Wahlin A, Dahlqvist R (2002) Adverse drug reactions as a cause for admissions to a department of internal medicine. Pharmacoepidemiol Drug Saf 11(1):65–72
10. Forster AJ, Murff HJ, Peterson JF, Gandhi TK, Bates DW (2005) Adverse drug events occurring following hospital discharge. J Gen Intern Med 20(4):317–323
11. Krahenbuhl-Melcher A, Schlienger R, Lampert M, Haschke M, Drewe J, Krahenbuhl S (2007) Drug-related problems in hospitals : a review of the recent literature. Drug Saf 30(5):379–407
12. van der Hooft CS, Sturkenboom MC, van Grootheest K, Kingma HJ, Stricker BH (2006) Adverse drug reaction-related hospitalisations: a nationwide study in The Netherlands. Drug Saf 29(2):161–168
13. Omar MA, Wilson JP (2002) FDA adverse event reports on statin-associated rhabdomyolysis. Ann Pharmacother 36(2):288–295
14. Jankel CA, Fitterman LK (1993) Epidemiology of drug–drug interactions as a cause of hospital admissions. Drug Saf 9(1):51–59
15. Smith L, McGowan L, Moss-Barclay C, Wheater J, Knass D, Chrystyn H (1997) An investigation of hospital generated pharmaceutical care when patients are discharged home from hospital. Br J Clin Pharmacol 44(2):163–165
16. Himmel W, Tabache M, Kochen MM (1996) What happens to long-term medication when general practice patients are referred to hospital? Eur J Clin Pharmacol 50(4):253–257
17. Cook RI, Render M, Woods DD (2000) Gaps in the continuity of care and progress on patient safety. BMJ 320(7237):791–794
18. e-mediat. Pharmavista - information for healthcare professionals. Version February 2005 ed: e-mediat AG, Schönbühl, Switzerland 2005
19. Vonbach P, Dubied A, Krahenbuhl S, Beer JH (2005) Evaluation of drug interaction screening programs. Forum Med Suisse 8S(Suppl 23):P15
20. Stockley IH (2002) Stockley's drug interactions, 6th edn. The Pharmaceutical Press, London, Chicago
21. Hanlon JT, Weinberger M, Samsa GP, Schmader KE, Uttech KM, Lewis IK, Cowper PA, Landsman PB, Cohen HJ, Feussner JR (1996) A randomized, controlled trial of a clinical pharmacist intervention to improve inappropriate prescribing in elderly outpatients with polypharmacy. Am J Med 100(4):428–437
22. Leape LL, Cullen DJ, Clapp MD, Burdick E, Demonaco HJ, Erickson JI, Bates DW (1999) Pharmacist participation on physician rounds and adverse drug events in the intensive care unit. JAMA 282(3):267–270
23. Bond CA, Raehl CL, Franke T (2002) Clinical pharmacy services, hospital pharmacy staffing, and medication errors in United States hospitals. Pharmacotherapy 22(2):134–147
24. Dean B, Schachter M, Vincent C, Barber N (2002) Causes of prescribing errors in hospital inpatients: a prospective study. Lancet 359(9315):1373–1378
25. Wiltink EH (1998) Medication control in hospitals: a practical approach to the problem of drug–drug interactions. Pharm World Sci 20(4):173–177
26. Mannheimer B, Ulfvarson J, Eklof S, Bergqvist M, Andersen-Karlsson E, Pettersson H, von Bahr C (2006) Drug-related problems and pharmacotherapeutic advisory intervention at a medicine clinic. Eur J Clin Pharmacol 62(12):1075–1081
27. Chan AL (2005) Pharmacist intervention when interacting drugs are prescribed despite alerts. Am J Health Syst Pharm 62(17): 1760–1763
28. Graham DJ, Staffa JA, Shatin D, Andrade SE, Schech SD, La Grenade L, Gurwitz JH, Chan KA, Goodman MJ, Platt R (2004) Incidence of hospitalized rhabdomyolysis in patients treated with lipid-lowering drugs. JAMA 292(21):2585–2590
29. Ratz Bravo AE, Tchambaz L, Krahenbuhl-Melcher A, Hess L, Schlienger RG, Krahenbuhl S (2005) Prevalence of potentially severe drug–drug interactions in ambulatory patients with dyslipidaemia receiving HMG-CoA reductase inhibitor therapy. Drug Saf 28(3):263–275
30. Kays MB, Overholser BR, Mueller BA, Moe SM, Sowinski KM (2003) Effects of sevelamer hydrochloride and calcium acetate on the oral bioavailability of ciprofloxacin. Am J Kidney Dis 42(6): 1253–1259

31. Buurma H, De Smet PA, Egberts AC (2006) Clinical risk management in Dutch community pharmacies : the case of drug–drug interactions. Drug Saf 29(8):723–732
32. Kaushal R, Shojania KG, Bates DW (2003) Effects of computerized physician order entry and clinical decision support systems on medication safety: a systematic review. Arch Intern Med 163 (12):1409–1416
33. Weingart SN, Toth M, Sands DZ, Aronson MD, Davis RB, Phillips RS (2003) Physicians' decisions to override computerized drug alerts in primary care. Arch Intern Med 163(21):2625–2631
34. Payne TH, Nichol WP, Hoey P, Savarino J (2002) Characteristics and override rates of order checks in a practitioner order entry system. Proc AMIA Symp 602–606
35. Shah NR, Seger AC, Seger DL, Fiskio JM, Kuperman GJ, Blumenfeld B, Recklet EG, Bates DW, Gandhi TK (2006) Improving acceptance of computerized prescribing alerts in ambulatory care. J Am Med Inform Assoc 13(1):5–11
36. van Roon EN, Flikweert S, le Comte M, Langendijk PN, Kwee-Zuiderwijk WJ, Smits P, Brouwers JR (2005) Clinical relevance of drug–drug interactions : a structured assessment procedure. Drug Saf 28(12):1131–1139
37. Bergk V, Gasse C, Rothenbacher D, Loew M, Brenner H, Haefeli WE (2004) Drug interactions in primary care: impact of a new algorithm on risk determination. Clin Pharmacol Ther 76 (1):85–96
38. Hansten PD, Horn JR, Hazlet TK (2001) ORCA: OpeRational ClassificAtion of drug interactions. J Am Pharm Assoc 41 (2):161–165
39. Bobb A, Gleason K, Husch M, Feinglass J, Yarnold PR, Noskin GA (2004) The epidemiology of prescribing errors: the potential impact of computerized prescriber order entry. Arch Intern Med 164(7):785–792
40. Ray WA, Murray KT, Meredith S, Narasimhulu SS, Hall K, Stein CM (2004) Oral erythromycin and the risk of sudden death from cardiac causes. N Engl J Med 351(11):1089–1096
41. Juurlink DN, Mamdani M, Kopp A, Laupacis A, Redelmeier DA (2003) drug–drug interactions among elderly patients hospitalized for drug toxicity. Jama 289(13):1652–1658