Potential Drug Interactions – Exposure and Management in Hospital and Ambulatory Settings

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To Dorina and my family

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Abbreviations

ABDA	Federal Union of German Pharmacists Associations
ACEI	Angiotensine-converting Enzyme Inhibitor
afssaps	French Health Products Safety Agency
AKA	Medicines Commission of Swiss Pharmacists
AFP	Automated Forms Processing
ARB	Angiotensine Receptor Blocker
CI	Confidence interval
CrCl	Creatinine Clearance
CYP	Cytochrome P450 isoenzyme
DDD	Daily Drug Dose
DRP	Drug-related problem
E.g.	For example
EKBB	Ethics Committee of both Basel
FASS	Pharmaceutical Specialities in Sweden
MAOI	Monoamino Oxidase Inhibitor
NSAID	Non-steroidal Anti-inflammatory Drug
POM	Prescription only Medicine
OR	Odds ratio
ORCA	Operational Classification of Drug Interactions
OTC	Over-the-counter
PCNE	Pharmaceutical Care Network Europe
WHO	World Health Organisation

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Summary

Health care professionals are responsible to ensure safe dispensing and use of drug regimens involving the use of drug combinations that may interact and cause serious adverse events. In the last 40 years an enormous amount of data on drug interactions has been published. But, although potential drug interactions are probably common only few of them manifest serious adverse events and often only in predisposed patients. Therefore, health care professionals feel inundated with hints for potential drug interactions of questionable clinical significance provided by their drug interactions information sources. Computerised alerts systems enable important assistance but their performance is not satisfying.

Simply knowing that two drugs may interact does not offer enough information to health care professional to devise a plan to reduce risk of an adverse outcome. The risk of most drug interactions can be minimised by an accurate management (e.g. by dose adjustment, spacing of dosing times and close monitoring of the therapy) and thus, drug combinations do not have to be avoided. Therefore, drug interaction information sources should directly provide guidelines about the manageability of a drug interaction.

The present thesis aimed to focus on four different aspects of the management of potential drug interactions in hospitalised and ambulatory patients: A) to determine the influence of patient-related risk factors on the development of an adverse outcome, B) to assess the prevalence and patient knowledge of potential drug interactions with over-the-counter (OTC) drugs used for self-medication, C) to assess preoccupation with potential drug interactions, perception of quality of drug interaction information sources, information needs, and how their requirements relate to those expressed by general practitioners, and D) to observe on site the management of potential drug interactions in daily community pharmacy practice.

Drugs have been recognised as a primary or contributing cause of hyperkalaemia, especially when administered to patients with underlying risk factors. The objective of **project A** was to analyze the influence of known risk factors on the velocity to develop hyperkalaemia in 551 hospitalised patients. Compared to the drug treatment at entry, during hospitalisation significantly more patients were treated with drugs associated with hyperkalaemia such as heparins, angiotensin converting enzyme

inhibitors (ACEIs) or angiotensin receptor blockers (ARBs), potassium supplements, potassium-sparing diuretics, and/or NSAIDs or COX-2 selective inhibitors. Risk factors associated with a high velocity to develop hyperkalaemia were in descending order: use of potassium supplements, severe renal impairment, use of potassium-sparing diuretics, use of ACEIs or ARBs, and diabetes mellitus. The velocity to develop hyperkalaemia significantly increased in patients with ≥2 of such risk factors. Dose-effects could be found for potassium supplements and potassium sparing diuretics, but not for ACEIs or ARBs. In contrast, use of kaliuretics (loop diuretics or thiazides) was associated with a decreased velocity to develop hyperkalaemia.
The results of this study have shown that patients with multiple risk factors should be closely monitored and a rapid change in laboratory values should alert health care providers to adequate actions.

Project B focussed on selected potential drug interactions of different clinical relevance between prescription only medicines (POMs) and OTC drugs pharmacy customers purchased for self-medication. In community pharmacies potential drug interactions with self-medication arise mainly in two situations: First, if an OTC drug is purchased by a passer-by customer whose prescribed drug therapy is not known, or second, if a POM or an OTC drug is requested by a regular customer whose prescribed drug therapy is usually recorded. Both customer groups were checked for potential drug interactions. Of 1183 observed passer-by customers, 164 (14.4%) purchased at least one of selected OTC drugs with risk for potential drug interactions. Out of them 102 (62.2%) were interviewed: 43 (42.2%) mentioned taking prescribed drugs, and 3 of them were exposed to potential drug interactions of moderate severity.
Out of 592 regular customers using at least one selected drug with a risk for potential drug interactions, 434 (73.3%) could be interviewed. Of them 69 (15.9%) were exposed to a potential drug interaction between purchased OTC drug for self-medication and their POM. Furthermore, 116 (26.7%) regular customers were exposed to potential drug interactions within their prescribed drugs and in 28 (6.5%) multiple (≥ 2) potential drug interactions were found. Out of 434 regular customers 203 (46.8%) were aware of potential drug interactions between their POM and OTC drugs. Of them 96 (47.3%) were informed by their prescribing physician and 52 (25.6%) by their community pharmacist. Awareness of potential drug interaction was

significantly associated with the age of customers and the potential severity of drug interactions.
Thus, the results of this study support efforts to increase awareness of potential drug interactions with OTC drugs. Although community pharmacies are adequately equipped with computerised drug interaction surveillance systems this is often not applied to self-medication. Vigilance for potential interactions of all drugs, including those sold over the counter, should be increased.

Project C aimed to analyze the current drug interaction management in Swiss community pharmacies with a particular focus on electronic systems and to compare the results with those gathered among German general practitioners in a recent survey. A postal questionnaire was randomly sent to 500 community pharmacies of the German part of Switzerland. The response rate was 57.4%. Only 24.7% pharmacists reported to be confronted less than daily with potential drug interactions. Use of computer software to identify potential drug interactions was widespread in community pharmacies (90.2%) and the software was the primary source of information (81.2 ± 29.6%). The quality of the interaction software was judged sensitive (identifying all dangerous interactions) by 80.5 ± 21.5% but specific (identifying only relevant interactions) by only 38.3 ± 32%. Pharmacists declared a low override rate (14%) of drug interaction alerts although unjustified alerts were reported by 60.6 ± 33.1%. In contrast to general practitioners pharmacists opted less often for information on the mechanism of the interaction and more frequently for details for dose adjustment. Both groups complained about deficient information on non-interacting alternatives. The information needs of community pharmacists differed considerably from general practitioners.
Substantial improvement of drug interaction software systems is thus required at least in two important aspects: the suppression of inappropriate alerts and the tailoring to the needs of the user.

Drug interaction alert systems are commonly used in community pharmacies. They intend to ensure safe medication dispensing and use. But, pharmacists are inundated with alerts and override is possible. In **project D** on-site practice of community pharmacies was observed and the nature and management of drug interaction alerts were analysed. During two days 15 researchers assessed in 15 different pharmacies

data of 600 regular customers with multiple drug therapy (≥ 2 drugs) and interviewed the responsible pharmacists about the management actions in consequence of drug interaction alerts. The median frequency of drug interaction alerts increased from 0.5 to 40 to 76 depending on the settings of the 15 community pharmacies' computer systems to flag only severe (N=4), severe and moderate (N=6) or severe, moderate and minor (N=5) potential drug interactions. Because of these settings out of 787 potential drug interactions detected on new or repeated prescriptions 277 (35.2%) were technically overridden by computer systems. Only 256 (32.5%) of 787 potential drug interactions emerged from a new prescription. The drug interaction alert systems produced 656 alerts of which 146 (22.3%) were invalid because of multiple alerts for the same interaction or alerts for combinations of which one drug was no longer taken. Of the 510 remaining relevant drug interaction alerts 289 (56.7%) were overridden by community pharmacists without any evaluation. The attendance of the patients by the pharmacists themselves was associated with a lower override of alerts. The sum of technical and pharmacist's override results in a rate of 71.9%. Of the remaining 211 potential drug interactions 87 (41.2%) were analysed trough consultation of literature, a physician or the patient himself and of them 55 (63.2%) resulted in an intervention (close monitoring, adjustment of dose or ingestion time, stop of therapy, or alternative therapy). Determinants associated with the analysis of drug interaction alerts were the potential high severity (severe or moderate) and the alert flagged for the first time.

As long as no sophisticated solutions are available it is important to avoid override of clinically relevant potential drug interactions. All of the 10 potential drug interactions classified as severe were detected and adequately managed. Therefore, classification of potential drug interactions is a very strong determinant for detection. Two conclusions are drawn from this study: Firstly, a focus on first-time alerts generated by new prescriptions and the elimination of invalid alerts would result in a substantial improvement in the specificity of drug interaction alert systems, and secondly, the claim to reduce their sensitivity by filtering drug interaction of moderate or minor severity might be reduced.

In **conclusion** this thesis shows that:

- Patients with risk factors (renal impairment, diabetes mellitus) should be closely monitored when adding combinations of risk drugs (potassium supplement, potassium-sparing diuretics, ACEI or ARB) for hyperkalaemia and a rapid change in laboratory values should alert health care providers to action by identifying and possibly removing risk drugs.

- Potential drug interactions between POM and OTC drugs for self-medication are widespread. Efforts for an improved vigilance and an increase of patient awareness are needed. New approaches to assess self-medication like account cards to assess regular customers OTC drugs can be promising.

- Computer-assisted drug interaction surveillance in community pharmacies lacks sensitivity and specificity while producing a high rate of invalid alerts. The information needs of community pharmacies differed considerably compared to those of general practitioners. Hence, substantial improvement of drug interaction software systems is required at least in two important aspects, the suppression of inappropriate alerts and the tailoring to the needs of the user.

- Pharmacists override many drug interaction alerts without any evaluation either by ignoring them or by setting their systems to flag only potential drug interactions of high severity. They are sensitised to analyse first-time alerts and potential drug interactions of high severity. The results of Project D show that focusing on new prescriptions would significantly reduce the number of alerts. Therefore, substantial improvement by new sophisticated options implemented in computer-assisted drug interaction alert systems is required.

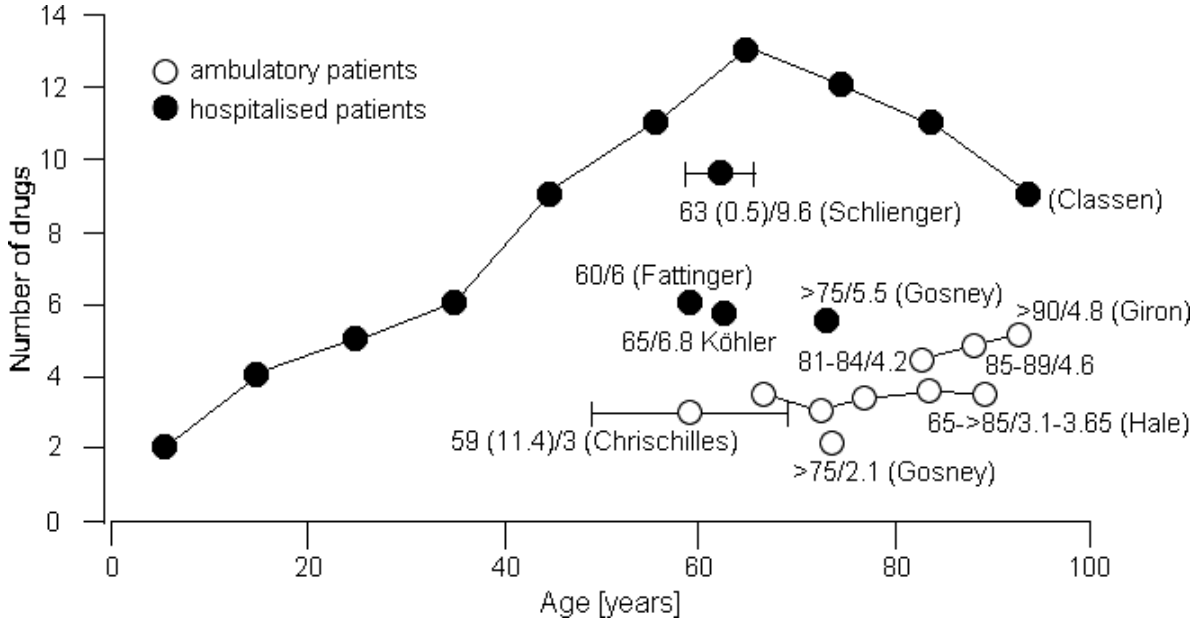
1 General introduction

A multiplicity of outcomes is possible when people use drugs. Most commonly the patient benefits from drug therapy; however, adverse events, ranging from minor side effects to death, may occur. One of the consequences of multiple drug use is the risk of one drug influencing the activity, the availability or the effect of a second drug. This so-called drug interaction can be desired[1] or result in adverse effects like reduced effectiveness or increased toxicity of the involved drugs.[2] There are a number of mechanisms by which drugs interact with each other, and most of them can be divided in two general categories: pharmacokinetic and pharmacodynamic interactions. Pharmacokinetic drug interactions occur when one drug affects the absorption, distribution, metabolism, or excretion of another. Pharmacodynamic drug interactions occur when two drugs have additive or antagonistic pharmacologic effects.[3]

1.1 Epidemiology of drug interactions

The probability of a drug interaction increases exponentially in hospitalised[4-6] and ambulant patients[7, 8] with the number of drugs a patient is taking. Two developments cause an increase of polypharmaceutical combination therapies in highly developed health care systems: First, an increased life expectancy which leads to an increase of chronic diseases and therefore leads to an enhanced demand for drugs, which is associated with the necessity of one individual patient to be treated by multiple practitioners or specialists: Second, due to chronic diseases long-term therapies and preventive actions become more important.[9] The number of drugs taken at the same time is clearly higher in hospitalised patient settings[5, 10-13] than in ambulatory patients[13-16] (Figure 1). Mentioned studies (Figure 1) assume a good compliance which may lead to an overestimation of drug exposure.[9] In general the intake of over-the-counter (OTC) drugs for self-medication is frequent.[17] In ambulatory patients the actual risk of drug interactions with self-medication is often not considered and might therefore be underestimated.

Figure 1: Review of drug use associated with patients age (specified above as age group / number of drugs (author).[9] The number of drugs used per defined period of drug therapy is clearly higher in hospitalised patients[5, 10-13] compared to ambulatory patients[13-16].



Egger et al.[6] showed in a study at the University Hospital Basel that 53.8% of potential drug interactions at discharge resulted from a change of the medication during the hospital stay. Straubhaar et al.[18] observed in a study at the University Hospital Basel that hospitalisation of patients with heart failure results in an increase in the number of drugs prescribed per patient and, thereby, also in the number of potentially interacting drug combinations per patient. During the hospital stay a close medical monitoring combined with continuous nursing and therapeutic care is generally guaranteed. But this may profoundly change after discharge. Therefore, epidemiologic post-marketing surveillance investigations in ambulatory patients are of particular importance for drug safety.[19]

In her thesis Käser[20] assessed 22 potential drug interactions of clinical relevance (major and moderate) and 65 of 'possibly' clinical relevance (major, moderate and minor) per 100 outpatients per year. Reported incidences in outpatients range from 9.2% to 70.3% for drug interactions of any severity and from 1.2% to 23.3% for those considered of major relevance.[21-27] This large ranges may be explained by investigations in different study populations or different definitions used for the clinical relevance of potential drug interactions.[19]

Despite the high incidences of potential drug interactions the number of manifest adverse events is rather low.[28-31] Studies thus far have not provided conclusive data

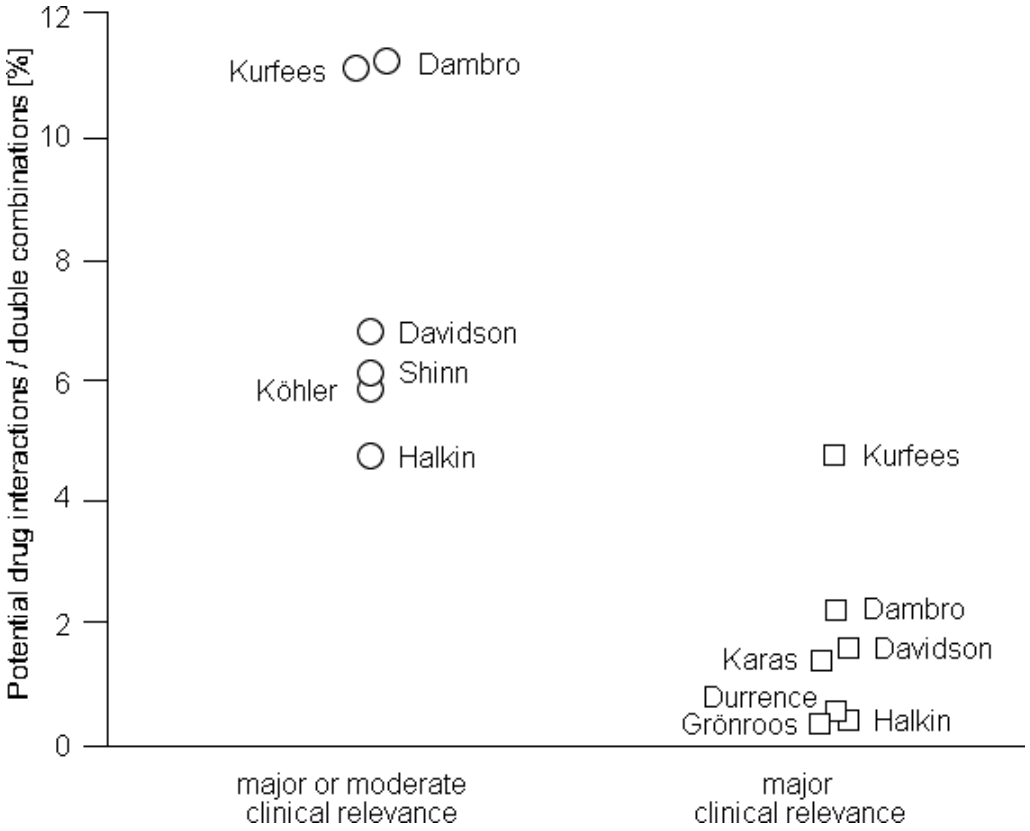
with respect to the frequency of prescribing interacting drugs and the occurrence of manifest adverse events caused by drug interactions in outpatients. Juurlink et al.[32] recognised the need to examine clinical outcomes of drug interactions in a population-based fashion. They delivered data on three drug interactions that involve commonly used medications and that produce specific toxic effects. Elderly patients taking glyburide hospitalised for hypoglykaemia were more than 6 times as likely to be treated with co-trimoxazole, patients admitted with digoxin toxicity about 12 times more likely to be treated with clarithromycin and patients treated with angiotensine-converting enzyme inhibitors (ACEI) admitted with hyperkalaemia were about 20 times more likely to have been treated with a potassium-sparing diuretic.

In the literature, the prevalence of potential drug interactions is often expressed as percentage of exposed patients. This fact does not consider that one patient may be affected by several potential drug interactions and that the prevalence is biased by the number of drugs taken together.[9] Alternatively, the frequency of potential drug interactions can be expressed by the number of potential drug interactions relating to the number of possible double combinations of drugs which can be calculated according to the equation [33].

$$\text{Number of drug pairs} = \frac{n \cdot (n-1)}{2}$$

The frequency of clinical relevant potential drug interactions is about 6% and of highly relevant potential drug interactions below 2% (Figure 2).[9]

Figure 2: Reported frequencies of potential drug interactions of major and moderate[5, 34-38] or only major[7, 34-36, 38-40] clinical relevance relating to the number of possible double combinations of drugs.[9]



1.2 Management of potential drug interactions

The identification of patients at risk and an accurate management of their drug therapy are important challenges for health care professionals to avoid serious clinical consequences caused by adverse drug reactions. This process of maximizing the benefits and minimizing the risks of a drug therapy for individual patients is complex and there are many steps where errors can occur. The mission of health-care providers is to provide systematic pharmaceutical care to reduce preventable drug-related morbidity and mortality.[41] The Pharmaceutical Care Network Europe (PCNE) advanced this systematic approach.[42] They classified drug-related problems (DRPs) according to their possible causes, possible interventions and the outcomes of interventions. The PCNE classification was designed to be used in research, as a process indicator in experimental pharmaceutical care studies and as an instrument to help health care professionals to document DRP-information in the pharmaceutical

care process (Table 1). Amongst possible negative outcomes of drug therapies drug interactions pose an important problem. The possible causes of DRPs lie at prescribers', pharmacists' or patients' level and interventions to prevent adverse outcomes due to DRPs are installed at these levels. Any deviation from the intended beneficial effect of a drug therapy results in a drug-related problem.[43] An optimal therapeutic outcome is only achieved with the absence of DRPs.[41] Drug-related mortality and morbidity pose a major problem to health care. The rates of drug-related hospital admissions found in two meta-analyses[44, 45] were up to 5.3% and Winterstein et al.[46] found a median preventability rate of drug-related hospital admissions of 59%. The newspaper headline 'Once a $76.6 billion headache, now a $177.4 billion migraine' describes the increasing economic load caused by DRPs in the USA between 1995 and 2000 after cost-of-illness analysis by Ernst and Grizzle[47]. There is a need to reduce economic and medical burdens caused by DRPs by their identification, prevention and solution in a process of pharmaceutical care[48]. A study of admissions to an Australian hospital found that drug interactions accounted for 4.4% of DRPs encountered.[49]

According to the definition of PCNE a DRP is an event or circumstance involving drug therapy that 'actually' or 'potentially' interferes with desired health outcomes.[42] According to this definition a drug interaction can be considered to be 'potential' in the constellation of patients' drug therapy or 'manifest' when leading to an adverse event. Drug interactions are often predictable based on an understanding of simple pharmacologic properties because they are caused by the same pharmacokinetic and pharmacodynamic principles that determine the behaviour of drugs in the body.[32, 50] Only few potential drug interactions do lead to 'manifest' outcomes and little information is available about the epidemiology of adverse outcomes. Most evidence is derived from case reports, volunteer studies, or investigations of potential drug interactions in hospitalised patients.[32] It is very difficult for health care providers to predict the manifestation of a drug interaction. Hence, the statement 'Predicting drug interaction outcomes – do we do better than meteorologists?' by Hansten and Horn[51] describes the incertitude in the process of pharmaceutical care to minimise risk resulting from drug interactions.

A drug interaction that is likely to cause an adverse outcome in one patient may have no effect on another patient. Therefore, it gets more and more important to provide

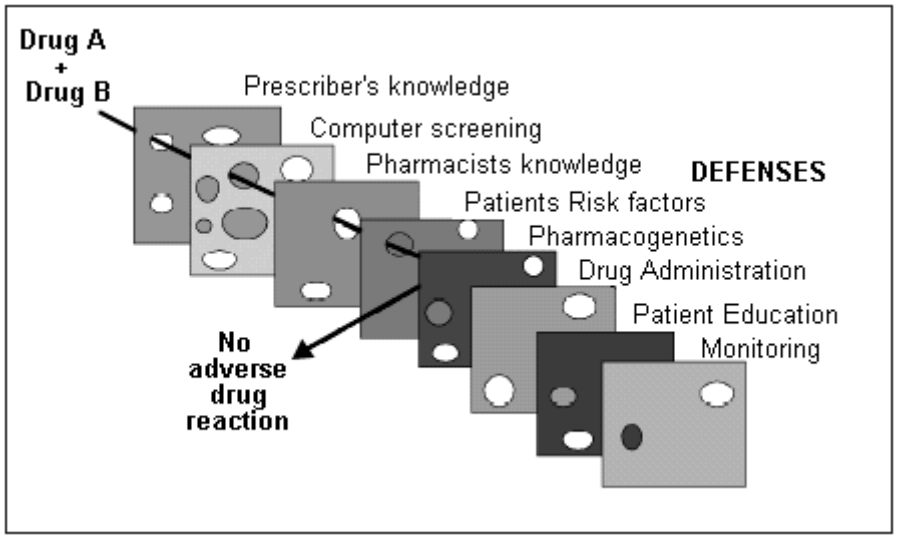
information about patient risk factors. Bergk et al.[33] revealed that 11.6% of major or moderate potential drug interactions are only relevant in predisposed ambulatory patients. The variability among patients can be explained by the influence of a multiplicity of factors like e.g. advanced age, co-morbidities, pharmacogenetic influences. For example, the increased risk of hyperkalaemia in a patient treated with an ACEI and a potassium-sparing diuretic who also is a diabetic with renal impairment is obvious. A patient who is deficient in a cytochrome P450 isoenzyme (CYP) may be less likely to manifest an adverse event caused by a drug interaction. For example, a CYP2D6 deficient patient may have an adequate therapeutic response with a low dose of a drug metabolised by CYP2D6 (e.g. simvastatin) compared with patients with normal or high CYP2D6 activity.[52] When taking a potent CYP2D6 inhibitor (e.g. fluoxetine) there will be no interaction with simvastatin in the CYP2D6 deficient patient but there might be a substantial increase in serum simvastatin in patients with normal or high CYP2D6 activity.[53] It is possible to determine a person's genotype or phenotype for many of the CYP isoenzymes, but this is used primarily in research rather than as clinical tool for predicting drug response. As these procedures become more automated and less expensive, however, it is likely that they will become more widely used for clinical management, at least for selected patients.[53]

Table 1: The basic Pharmaceutical Care Network Europe Classification (PCNE) scheme for drug related problems

	Code	Primary domains
Problems	P1	**Adverse reaction(s)** Patient suffers from an adverse drug event
	P2	**Drug Choice Problem** Patient gets or is going to get a wrong (or no drug) drug for his/her disease and/or condition
	P3	**Dosing problem** Patient gets more or less than the amount of drug he/she requires
	P4	**Drug Use/Administration Problem** Wrong or no drug taken/administered
	P5	**Interactions** There is a manifest or potential drug-drug or drug-food interaction
	P6	**Other**
Causes	C1	**Drug/Dose Selection** The cause of the DRP can be related to the selection of the drug and/or dosage schedule
	C2	**Drug Use Process** The cause of the DRP can be related to the way the patient uses the drug, in spite of proper dosage instructions (on the label)
	C3	**Information** The cause of the DRP can be related to a lack or misinterpretation of information
	C4	**Patient/Psychological** The cause of the DRP can be related to the personality of the patient.
	C5	**(Pharmacy) Logistics** The cause of the DRP can be related to the logistics of the prescribing or dispensing mechanism
	C6	**Other**
Interventions	I0	**No intervention**
	I2	**At prescriber level**
	I2	**At patient (or carer) level**
	I3	**At drug level**
	I4	**Other**

'The Swiss cheese model' by James Reason[54], a British psychologist, has become the dominant paradigm for analysing medical errors and patient safety incidents. It was adapted by Hansten and Horn[55] to the problem of drug interactions which systematically illustrates the avoidance/occurrence of an adverse drug reaction caused by a drug interaction (Figure 3). Because adverse drug reactions resulting from drug interactions are almost completely preventable it is important to identify the steps at which that prevention can take place.[55] Perfect systems do not exist. The holes in the Swiss cheese represent gaps in the defenses (Figure 3).[54]

Figure 3: The Swiss cheese model. Adapted by Hansten and Horn[55] from the 'Swiss cheese model of accident causation' by Reason[56]. The hazard (in this case a drug interaction) must traverse the layers of defense for an adverse drug event to occur. In this case, the patient's pharmacogenetic makeup protects against an adverse event. The holes in the cheese represent the gaps in defenses.



If managed adequately, many drug interactions do not result in clinical manifestations. The risk of drug interactions often can be reduced by close monitoring, dose adjustment and/or coordinated sequence of administration. Bergk et al.[33] revealed that only 25.3% of potential drug interaction of major severity offered no management options and should thus be avoided. Anyhow, Chen et al.[57] found an incidence of 1.9 per 1000 patient years (95% confidence interval (CI) 1.5, 2.3) of prescribed potentially hazardous/contraindicated drug interactions. They identified multiple possible causes (e.g., lack of knowledge of the drug interaction or of the patient medication history) and system failures (e.g., incomplete medication records, communication between primary and secondary care or between the prescriber and the patient) for the dispensing of contraindicated drug combinations.

1.2.1 Drug interaction information sources

In the past 40 years more than 20000 journal articles on drug interactions have been published. This flood of information has overwhelmed even the most dedicated and compulsive of health care providers.[58] No one can possibly memorise all the potential drug interactions that have been identified to date, and new interacting drug pairs are identified every month. To cope with this task drug interaction compendia in the form

of books, computer or personal digital assistant (PDA) software or online databases are offered to health care providers. Studies revealing the prevalence of potential drug interactions often reference the US-database by Thompson Micormedex™[59] or the British Stockley's drug interactions[60], which can be considered as standard referenced information sources. In Austria, Germany and Switzerland a drug interaction database is implemented in the drug information Pharmavista®[61] which is adapted from the German ABDA-Database[62] for the Swiss market and is used in all community pharmacies and also by some physicians. This database is also available online as a subscription-only service.

Simply knowing that two drugs may interact does not provide enough information for the health care provider.[53] It is also important to have information on measures that can be taken to reduce the likelihood of an adverse outcome. Therefore, drug interaction monographs have to contain information about the potential adverse effect, the rating of severity of the potential adverse event, the mechanism of the interaction, and suggestions for the clinical management including dose-adjustment, sequential dosing time, alternative therapies, monitoring or patient related risk factors. Bergk et al.[63] revealed that German practitioners wish more informative support on drug interactions, especially concerning management. In particular, information about non interacting alternative therapies was thought to be lacking.

1.2.2 Drug interaction classification systems

It is often difficult to distinguish clinically important from unimportant drug interactions. It has become unrealistic to expect individual practitioners to read all of the relevant data and determine on their own which drug interactions are the most important clinically.[58] Accordingly, most books and software evaluating drug interactions use classification systems to help the health care provider with this process.

In the database Pharmavista® potential drug interactions are classified into 'severe' (life-threat / intoxication / permanent harm), 'moderate' (frequent therapeutic problems / combination can be administered but close monitoring required), 'minor' (increased or decreased drug effect / only specific subgroups affected), 'negligible' (Usually induces no or limited clinical effects / generally no modification of therapy required) and 'external specifications' (only assumed or described in particular cases / clinical consequences unclear). Studies using the Pharmaceutical Specialities in

Sweden (FASS) classification divided major drug interactions into those that could be managed by dose adjustment (category C) and combinations that should be avoided (category D).[8, 22] However, category D still includes drug combinations that can be therapeutically useful and safely administered under certain circumstances.[33] Apart from dosage, there are further factors modulating the risk arising from drug interactions: Some are only relevant in predisposed persons; others are blunted if the interacting pair is combined with further co-medication (e.g., potassium substitution in patients receiving digoxin and a potassium-sparing diuretic), and yet others only occur when the combination is administered strict concurrently and can be avoided by temporally separated administration interval of sufficient length (e.g., aluminium or magnesium antacids combined with ciprofloxacin[64]).[33]

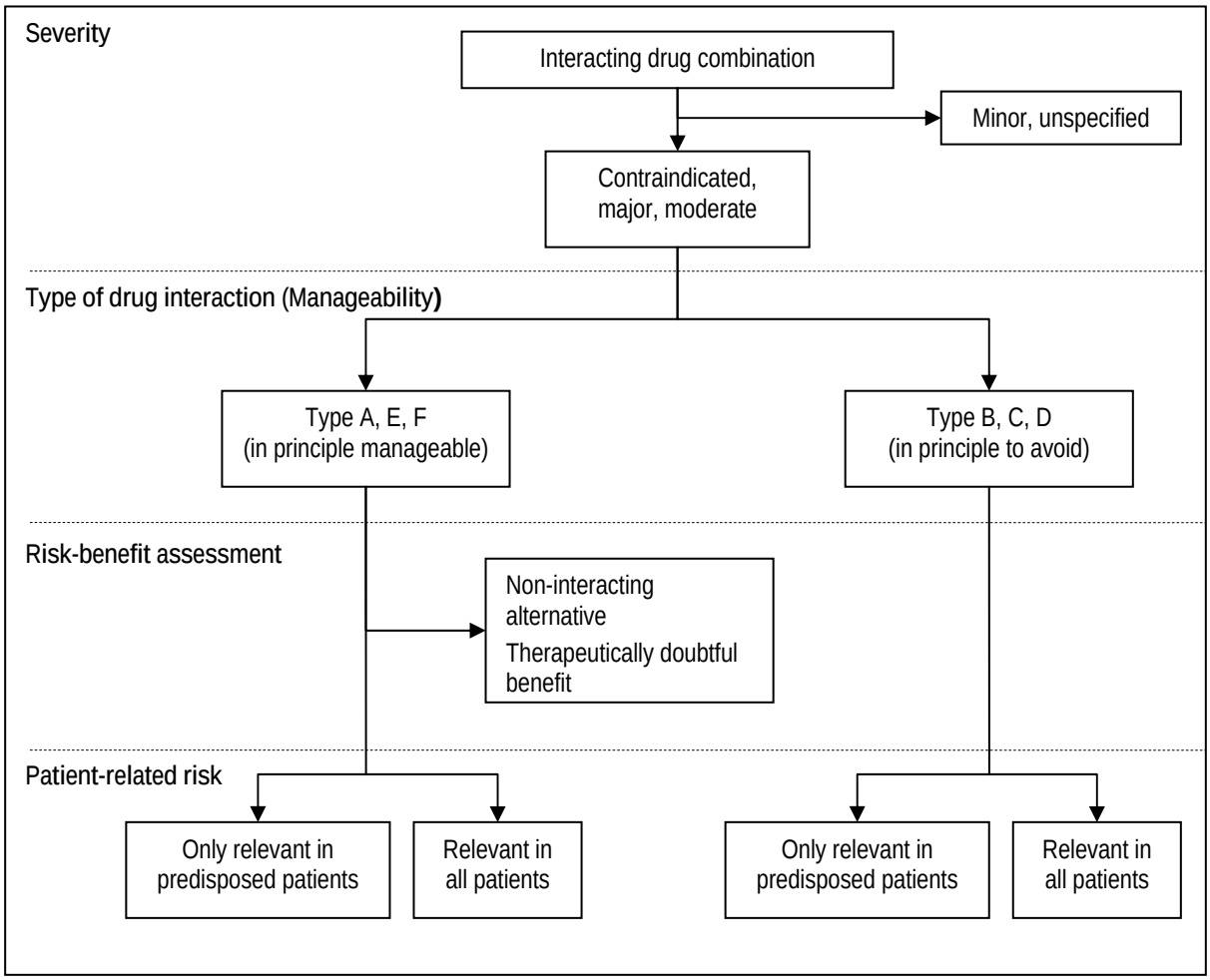
Earlier studies reported frequencies of drug interactions and classified them according to their potential severity (e.g., major, moderate, minor). Bergk et al.[33] used the classification of adverse effects by Edwards and Aronson[65] (Table 2) which incorporates grading of the clinical relevance together with management options to estimate the risk arising from drug interactions. They developed an algorithm (Figure 4) to differentiate between drug combinations that require specific management efforts and those that should be avoided by all means.

Table 2: Classification of adverse effects induced by drug interactions modified after Edwards' and Aronson's classification of adverse drug reactions[65] by Bergk et al.[33]

Type of drug interaction	Characteristics	Management options*	Examples
A: Augmented (dose-related)	Related to pharmacologic action of drugs Extent: Gradual or dose-dependent change mostly indicated by a clinical surrogate Management possible Mechanism: Pharmakokinetic or pharmacodynamic (additive effect of both drug on same target system)	Any or all of the following: Reduce dose, substitute or compensate by third compound, or change route of administration or separate	cimetidine + theophylline acarbose + glibenclamide digoxin + potassium-sparing diuretics calcium + digoxin
B: Bizarre (not dose-related)	Not related to pharmacologic action of drugs and any or all of the following: Extent: Nongradual or dose-independent change, mostly no clinical surrogate indicating the extent Management impossible Mechanism: Unknown or pharmacodynamic with a nongradual or dose-independent or sudden effect.	Avoid	sotalol + tricyclic antidepressant (QT prolongation) paroxetine + St. John's wort (serotonine syndrome) allopurinol + captopril (hypertensitivity reactions)
C: Chronic (dose- and time-related)	Dependent on cumulative dose or continuous long-tem use	Avoid long-term use	acetaminophen + carbamazepine (induced hepatotoxity)
D: Delayed (time-related)	Usually dose-related Occurs or becomes apparent sometime after use of combination	Avoid	L-Asparaginase + epipodophyllotoxin (treatment-related leukaemia)
E: End of use (withdrawal)	Occurs after withdrawal of one drug because of adaptive effects after long-term exposure	Withdraw slowly	Beta-blocker + clonidine
F: Failure (failure of therapy)	Reduced pharmacologic action of one or both drugs Extent: Gradual or dose-dependent change mostly indicated by a clinical surrogate Management possible Mechanism: Pharmacokinetic or pharmacodynamic	Either increase dose or change route of administration or separate or both	alprazolam + St. John's wort carbamazepine + theophylline levothyroxine + iron

* Different possibilities of how drug interactions can be managed; but not every option applies to all examples.

Figure 4: Management-oriented algorithm according to 4 decision layers for systematic evaluation of drug interactions by Bergk et al.[33] The type of drug interaction is classified according to Edward and Aronson[65] as exemplified in Table 2.



Hansten and Horn[58] used a similar management-oriented approach to innovate a new drug interaction classification system. They applied this classification into their drug interaction compendium 'Drug Interactions: Analysis and Management'[50] and the booklet 'The top 100 Drug Interactions – A Guide to Patient Management'[66]. The so called 'OpeRational ClassificAtion for drug interactions' (ORCA) (Table 3) was developed by the Drug Interaction Foundation with input from an international group of physicians. They perceived the deficiencies of the drug interaction classification systems used in the United States and Europe and aimed to improve the clinical utility of classification systems. This classification enables health care providers to decide ultimately on a course of action (or inaction) for each potential drug interaction giving them information on management options that can reduce patient risk.[58]

Table 3: Operational Classification of Drug Interactions (ORCA) innovated by Hansten and Horn[50, 58, 66]

Class	Definition	Characterisation
1	**Avoid Combination**	Risk of combination outweighs benefit
2	**Usually avoid combination**	Use only under special circumstances - Interactions for which there are preferably alternatives for one or both drugs - Interactions to avoid unless the benefit is judged to outweigh the increased risk
3	**Minimise Risk**	Assess risk and take one or more of the following actions if needed: - Consider alternatives: Alternatives may be available that are less likely to interact - Circumvent: Take action to minimise the interaction (without avoiding combination) - Monitor: Early detection can minimise the risk of an adverse outcome.
4	**No Special Precautions**	Risk of adverse outcome appears small
5	**Ignore**	Evidence suggests that the drugs do not interact

1.2.3 Computerised drug interaction screening systems

One of the responsibilities of pharmacists is to prevent patients from unsafe or non-effective drug regimens. In particular they should avoid the dispensing of interacting combinations of drugs that may cause hazardous adverse effects. In Switzerland and in other countries, every community pharmacy is obliged to use a computerised screening system for this task. Computerised drug interaction screening software analyses prescriptions prospectively for potential drug interactions. There is good evidence that electronic decision support by drug interaction surveillance software in the prescription fulfilment process can reduce the number of potentially hazardous drug interactions.[38, 67-69] Halkin et al.[38] revealed that drug interaction surveillance software in community pharmacies and physician offices can reduce the dispensing of prescriptions with severe interactions up to 67.5 %. Malone et al.[69] reported that between 20% and 46% of prescription drug claims with 25 clinically important potential drug interactions were reversed when pharmacies were alerted. On the other hand, available systems have been shown to have significant deficiencies.[70]

Hazlet et al.[58] showed that the performance (sensitivity, specificity, and positive and negative predictive value) (Table 4) of most tested drug interaction screening programs was suboptimal.

Table 4: Factors to evaluate the performance of drug interaction screening programs adapted by Hazlet et al.[71]

Factor	Definition
Sensitivity	Ability of the software program to correctly identify those drug interaction pairs that were defined as clinically important (number of true positives / [number of true positives + number of false negatives])
Specificity	Ability of the software to ignore drug interaction pairs that were not define as clinically important (number of true negatives / [number of true negatives + number of false positives])
Positive predictive value	Probability that when a warning was issued by the computer, it was for a DDI defined as clinically important (number of true positives / [number of true positives + number of false positives])
Negative predictive value	Probability that the absence of a computer alert reflected the determination that no clinically important drug interaction existed (number of true negatives / [number of true negatives + number of false negatives])

Barrons[72] evaluated these factors for PDA software products for drug interactions and found a greater than 90% ability to detect important and to ignore unimportant interactions for 4 of 9 software products whereas 2 of them were evaluated to be more comprehensive and easier to use than the others. Vonbach et al.[73] compared four drug interaction screening programs and found for Pharmavista®[61] the highest sensitivity with an acceptable positive predictive value and specificity. Furthermore, they evaluated the drug interaction monographs of Pharmavista®[61] positively as comprehensive due to very useful descriptions regarding the effect, mechanism, clinical management and discussion of evidence and negatively because the literature is not clearly referenced. German general practitioners were unsatisfied with the contents of drug interaction information sources. [63] In particular they missed information about the mechanism of a drug interaction and the management guidelines including the advice for dose adjustment and about alternative therapies. Hansten[53] complains that management guidelines in the current drug interaction

information sources are often inadequate. He recommends inclusion of information on measures that can be taken to reduce the likelihood of an adverse outcome.[58, 74]

1.2.3.1 Computerised drug interaction alerts

Too many alerts complicate the medication surveillance because the identification of relevant signals becomes more difficult.[2] Thus, knowing that most of the time the patient will not suffer from an adverse outcome, health care providers ignore most drug interaction alerts provided in ambulatory care.[53] Several recent studies have focussed on computerised drug interaction alerts and how health care providers perceive them. Weingart et al.[75] revealed that general practitioners overrode 89% of level 1 (severe) and 96% of level 2 (moderate) drug interaction alerts. Chui and Rupp[76] and Murphy et al.[77] found comparable results for community pharmacists' responses to drug interaction alerts. In these studies override was defined as the absence of any intervention by the health care provider. Reasons given for overriding alerts are[78]:

- The patient was no longer taking the interacting medication
- The interaction was not clinically significant
- The patient was stable on the combination
- The benefit of the treatment outweighed the risk of the interaction

In a questionnaire survey by Magnus et al.[79] 22% of general practitioners admitted that they frequently override drug interaction alerts without properly checking them. Abarca et al.[80] examined community pharmacists' attitudes towards computerised drug interaction alerts; despite a large proportion of clinically unimportant alerts, community pharmacy managers did not believe these alerts were meaningless or a waste of time. However, they were not completely confident that their computer systems provided them with meaningful drug interaction alerts.

1.2.3.2 Determinants for interventions by pharmacists because of drug interaction alerts

A diploma thesis completed in our group Kurth[81] analysed 277 drug interaction alerts in 5 Swiss community pharmacies. He revealed that 45% of the drug combinations with potential to interact were first time prescriptions, 26% were prescribed by different physicians. Furthermore, 10% of drug combinations at risk to interact showed less than 10 days of potential overlap. A bigger study by Buurma et al.[82] analysed 2572 drug interaction alerts in 63 Dutch community pharmacies and revealed that different prescribers were involved in 21% of alerts and 31% of all alerts occurred for the first time. Pharmacies intervened (= modification of the prescription, communication with the prescriber, or communication with the patient) after first time alerts with a 7.3-fold, for highest severe potential drug interaction with a 2.1-fold, and for elderly patients with a 1.7-fold higher likelihood. Prescribing by different prescribers was a negligible determinant. In contrast, Tamblyn et al.[83] assessed that patients who had a single primary-care physician or a single dispensing pharmacy were less likely to be prescribed potential drug interactions.

Many pharmacists find that computerised drug interaction screening systems detect a large number of drug interactions of questionable clinical significance.[53] Buurma et al. [82] found a high frequency of 17 drug interaction alerts per pharmacy per day. Kurth[81] revealed in his diploma thesis that the number of drug interaction alerts per prescription is dependent to the software configurations of Swiss community pharmacies which can be configured to flag only potential drug interactions of moderate and/or high severity. Depending on the level of these filters he observed 2 (level 1 = ‘severe’) to 180 (level 1 = ‘severe’, ‘moderate’ and ‘minor’) drug interaction alerts per pharmacy per day.

1.2.3.3 Recommendations for improving the management of potential drug interactions

Community pharmacists are a critical component in the medication use process since they are often the last line of defense against potentially harmful drug interactions. However, several gaps in the community pharmacy drug interaction screening processes have been identified. These include failure to properly screen for potential drug interactions, inadequate drug interaction surveillance software and information sources, and an overwhelming number of clinically irrelevant or insignificant alerts.[80]

To improve the drug interaction management by health care providers Hansten[53] makes the following recommendations:

- Improve the drug interaction knowledge of health care providers
- Improve computerised drug interaction screening systems
- Provide information on patient risk factors that increase the chance of an adverse outcome
- Incorporate pharmacogenetic information into risk assessment
- Provide information on drug administration risk factors that increase the chance of an adverse outcome
- Improve patient education on drug interaction

Discussions led to optimisation of the current drug interaction management in community pharmacies in Switzerland and Germany. The Medicines Commission of Swiss Pharmacists (AKA) launched a debate to adapt the currently used drug interaction softwares and the classification system of the drug interaction database. To enrich and stimulate this debate we aimed to explore the current situation in community pharmacies. In particular, we projected to examine community pharmacists' use of, satisfaction with and expectations towards drug interaction information sources and their management of drug interaction alerts provided by drug interaction surveillance systems.

The consideration of additional risk factors and patients' self-medication pose often a problem in the management of potential drug interactions. Therefore, we aimed to analyse the influence of risk drug and different risk factors and their combinations on the development of a specific adverse outcome (hyperkalaemia). Furthermore, we analysed drug interactions with drugs purchase for self-medication and surveyed patient knowledge.

2 Aims of the thesis

Project A: Potential drug interactions rarely manifest adverse effects. Hyperkalaemia belongs to the most frequent electrolyte abnormalities in clinical practice. Drugs have been recognised as a primary or contributing cause of hyperkalaemia, especially when combined and/or administered to patients with underlying risk factors. The prevalence of potentially interacting drug combinations among potassium supplements, potassium sparing diuretics and ACEI or ARB is very high in ambulatory as well as in hospital settings. The objective of this project was to analyze the influence of the known risk factors for hyperkalaemia on the velocity to develop hyperkalaemia in hospitalised patients.

Project B: OTC drugs can be used for self medication without advice of a pharmacist or a physician. Freely available, its use is often perceived as safe by the customers. The lack of professional supervision may carry an increased risk of adverse drug effects including those caused by drug interactions.
It was the aim of this project to asses the prevalence of potential drug interactions with selected prescription only medicines (POM) and OTC drugs in passer-by and regular customers as well as their awareness of these potential drug interactions.

Project C: In some countries, including Switzerland, community pharmacies are obliged to keep a medication history of all dispensed prescription drugs and to check prescriptions to prevent the use of unsafe drug regimens including those caused by potentially interacting drugs. To comply with these statutory requirements, almost all pharmacies use computer software systems for the quality assurance of pharmacotherapy. These systems identify potential drug interactions, alert the pharmacy team to intervene before dispensing potentially interacting drugs, and serve as a drug interaction information source.
The objective of this postal questionnaire survey was to analyze the current drug interaction management in Swiss community pharmacies

with a particular focus on electronic systems and to compare the results with those expressed by German general practitioners in a recent survey.

Project D: It has been revealed that physicians and pharmacists ignore the majority of computerised drug interaction alerts in primary care. In project C pharmacists reported to consider drug interaction alerts, but they were overwhelmed by inappropriate alerts because of a lack of specificity of their drug interaction systems.

The purpose of this study was to explore the process of identification, analysis and management of drug interaction alerts generated by community pharmacies' computer systems.

3 Project A: The influence of risk factors on the velocity to develop hyperkalaemia

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Drug Safety (in press)

Abstract

Background/objective:

Drugs have been recognised as a primary or contributing cause of hyperkalaemia, especially when administered to patients with underlying risk factors. The objective of this study was to analyse the influence of the known risk factors for hyperkalaemia on the velocity to develop hyperkalaemia.

Study design/methods:

Clinical characteristics, laboratory data and medication profiles of patients developing hyperkalaemia (serum potassium ≥ 5.0mmol/L) hospitalised between 2000 and 2004 in the University Hospital Basel were recorded. Factors associated with a high velocity to develop hyperkalaemia were detected using a multiple logistic regression model. Subsequently, the velocity to develop hyperkalaemia during a defined observation period was compared between patients with one and patients with ≥2 risk factors. Finally, the dose effects of drugs identified as risk factors for a high velocity to develop hyperkalaemia were analysed using two sample comparisons.

Results:

A random sample of 551 hospitalised patients was analysed. Compared to the drug treatment at entry, during the hospitalization significantly more patients were treated with drugs associated with hyperkalaemia such as heparins ($p<0.001$), angiotensin converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB) ($p=0.002$), potassium supplements ($p<0.001$), potassium-sparing diuretics ($p<0.001$) and/or NSAIDs or COX-2 selective inhibitors ($p<0.001$). Risk factor associated with a high velocity to develop hyperkalaemia were use of potassium supplements (adjusted odds ratio = OR 3.386, 95% CI 2.251, 5.091), severe renal impairment (OR 3.119, 95% CI 2.007, 4.850), use of ACEI or ARB (OR 2.642, 95% CI 1.742, .4.006), use of potassium-sparing diuretics (OR 2.065, 95% CI 1.310, 3.254), and diabetes mellitus (OR 1.525, 95% CI 1.005, 2.313). The velocity to develop hyperkalaemia significantly increased in patients with ≥2 of such risk factors. Dose-effects could be

found for potassium supplements (p=0.006) and potassium sparing diuretics (p=0.007), but not for ACEI or ARB (p=0.289). In contrast, the use of kaliuretics (loop diuretics or thiazides) was associated with a decreased velocity to develop hyperkalaemia in patients with serious renal impairment (p=0.016) and in patients treated with ≥2 drug classes associated with a high velocity to develop hyperkalaemia (p=0.001).

Conclusions:

Risk factors associated with a high velocity to develop hyperkalaemia are use of potassium supplements > severe renal impairment > use of ACEI or ARB > use of potassium-sparing diuretics > diabetes mellitus. Coincidence of two or more of these risk factors is associated with an even faster development of hyperkalaemia. Clinicians should be aware of these risk factors in order to avoid a rapid development of potentially life-threatening hyperkalaemia.

Background

Potassium disorders belong to the most frequent electrolyte abnormalities in clinical practice. Hyperkalaemia is less common than hypokalaemia but potentially more serious, especially if potassium levels are rising rapidly. [1] In hospital settings, drugs have been recognised as a major cause of hyperkalaemia in up to 75% patients presenting with this electrolyte abnormality. [2] Reported incidences of hyperkalaemia vary from 1.1% to 10%, depending on the threshold used for hyperkalaemia, which ranges from 5.0 mmol/L to 6.0 mmol/L. [2, 3]
Several drugs have been identified as a primary or contributing cause of hyperkalaemia. [2, 4, 5] Especially when administered to patients with underlying disturbances in potassium homeostasis, hyperkalaemia induced by these drugs can occasionally become life-threatening. [2] Juurlink et al. recognised increasing rates of hyperkalaemia due to the widespread use of spironolactone after the publication of the Randomised Aldactone Evaluation Study (RALES). [6, 7] Use in patients with pre-existing risk factors for hyperkalaemia, inappropriately high doses of spironolactone, additional medications contributing to hyperkalaemia, inadequate clinical or laboratory monitoring and no clear indication for critical drugs were considered to be major causes for the increasing occurrence of hyperkalaemia. [8, 9] The reality is, however, that spironolactone is often prescribed to patients with additional drug and non-drug related risk factors for hyperkalaemia [9]. Most patients, who developed life threatening hyperkalaemia while being treated with angiotensin converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB) and spironolactone, had additional risk factors including renal failure, diabetes mellitus and/or treatment with non-steroidal anti-inflammatory drugs (NSAID). [10, 11]

Combinations of potassium-sparing diuretics, potassium supplements and ACEI or ARB interact with each other due to their additive pharmacodynamic effects. [12] In a study performed at the University Hospital of Basel, potential drug interactions between potassium-sparing diuretics, potassium supplements and ACEI were most prevalent compared with other potentially severe drug interactions in patients at discharge. [13] Furthermore, besides drug interactions with statins, the combination of ACEI and potassium-sparing diuretics was the most prevalent potentially severe drug interaction in ambulatory dyslipidaemic patients. [14] Additional drugs, for

instance NSAIDs, cyclooxygenase (COX) -2 selective inhibitors, non-selective beta-blockers, cyclosporine, digoxin, drospirenone, heparins, lithium, pentamidine, succinylcholine, tacrolimus, trimethoprim and drugs administered as a potassium salt as well as potassium-containing salt substitutes have been reported to be associated with hyperkalaemia. [2, 4, 12] Furthermore, case-control studies with multivariate analysis revealed that diabetes mellitus, renal impairment and use of spironolactone or use of ACEI are independent risk factors for hyperkalaemia in hospitalised patients with congestive heart failure. [15, 16]

Although the velocity of the increase in serum potassium levels appears to be a risk factor for the development of adverse effects associated with hyperkalaemia, [1] the risk factors associated with a high speed for the development of hyperkalaemia have so far not been investigated. The objective of this study was therefore to analyse the influence of single and multiple drug and non-drug related risk factors on the velocity to develop hyperkalaemia in hospitalised patients.

Methods

Study design, Patients and Data Collection

A random sample of patients developing hyperkalaemia (serum potassium levels ≥ 5.0 mmol/L [5]) during their hospitalisation between January 2000 and March 2004 in four general medical wards of the University Hospital of Basel was retrospectively identified using electronic clinical laboratory records. The University Hospital Basel is a medical-surgical teaching institution covering an urban area of approximately 300'000 inhabitants in the Northwest of Switzerland.

Laboratory data, drug and non-drug related risk factors for hyperkalaemia (identified as described below) were assessed for a period of minimally 2 days and maximally 10 days, beginning at the date, when the patient's serum potassium level began to rise until the date when the maximal value was measured (observation period). Information on drugs, demographic characteristics (age, sex, size and weight), major diagnoses and treatments were retrieved from the patient records. Since it was assumed that the risk factors associated with a high velocity for hyperkalaemia were among the risk factors associated with hyperkalaemia itself, such risk factors were identified in recent publications. Non-drug related risk factors were obtained from the review of Evans and Greenberg [5] and drugs potentially interfering with potassium homeostasis were retrieved from recent reviews of Perazella [2], Palmer [4] and Evans and Greenberg [5]. In addition, all drugs stopped or added within two days prior to the observation period were also included in the analysis.

Patients on chronic haemodialysis, surgical patients and patients with hyperkalaemia on hospital admission were not included in the study. The minimal increase in serum potassium levels had to be 0.5 mmol/L, and at least two serum potassium levels (in addition to the level obtained at entrance) had to be measured during one admission. Patients with serum potassium levels > 4.5 mmol/L at the beginning of the observation period were also not included in the study. Pseudohyperkalaemic patients were recognised based on comments of the chemical laboratory mentioning haemolysed samples and could therefore be excluded from the analysis. Patient's creatinine clearance (CrCl) was estimated by the Cockroft-Gault formula. [17] Severe renal impairment was defined as CrCl < 30 mL/min. The velocity to develop

hyperkalaemia was calculated as the mean daily increase in serum potassium over the observation period in mmol/L per day, and is given as]:

$$\frac{\text{maximal serum potassium level} - \text{minimal serum potassium level}}{\text{number of days between these two measurements}}$$

For the majority of patients, more than two potassium serum levels were obtained during the observation period. To analyse the influence of the daily dose of drugs associated with a higher velocity to develop hyperkalaemia, high and low daily doses were defined for each drug. These definitions were based on the defined daily doses (DDD) by the WHO Collaborating Centre for Drug Statistics Methodology. A 'high dose' was defined as a daily dose > DDD. For spironolactone daily doses > 25 mg were considered to be a 'high dose'. [4] The study protocol was approved and accepted by the regional ethics committee.

Statistical analysis

Results are expressed as proportions and as medians with the corresponding interquartile range (IQR). Numerical variables were tested for normal distribution using the Kolmogorov-Smirnov test. The non-parametric Mann-Whitney-U test was used for unpaired two-sample comparisons. Statistical significance was defined as a p-value <0.05. Statistical analyses were performed using SPSS for Windows version 13.0 (SPSS Inc., Chicago, USA). To test for a correlation between the velocity to develop hyperkalaemia and the extent of hyperkalaemia, patients were grouped into quartiles according to their velocity to develop hyperkalaemia. The mean maximal serum potassium levels of these groups were then compared among each other using analysis of variance followed by Tukey-HSD post-hoc analysis. To compare risk factors that changed during the observation period, McNemar's chi-square test was used. For the analysis of potential risk factors for hyperkalaemia, continuous variables were dichotomised. Known risk factors from the literature (see above) were included in a multiple logistic regression model to analyze the independent association of these risk factors with a higher velocity to develop hyperkalaemia. The

median was used as cut-point to dichotomise the velocity to develop hyperkalaemia. Variables independently associated with a higher velocity to develop hyperkalaemia in this multiple logistic regression analysis were defined as ‘major risk factors’. Comparison of patients with no, one and multiple risk factors were performed using Tukey-HSD post-hoc test.

Results

Patients Characteristics

A random sample of 600 patients hospitalised in the University Hospital of Basel developing hyperkalaemic serum potassium levels (≥ 5.0mmol/L) between January 2000 and January 2004 was extracted from the electronic laboratory database, taking into account the inclusion and exclusion criteria described above. Of them, 49 (8.1%) had to be excluded from the analysis due to pseudohyperkalaemia. Demographic and clinical characteristics of the remaining study sample containing 551 patients are summarised in Table 1.

At the beginning of the observation period 144 (26.1%) patients were hypokalaemic (serum potassium < 3.5mmol/L). These patients showed a significantly higher median of the velocity to develop hyperkalaemia (0.42 vs. 0.35 mmol/L per day; $p<0.001$) than initially normokalaemic patients, but the median of their serum potassium level at the end of the observation period was not significantly different compared to patients being normokalaemic at the beginning of the observation period (5.37 vs. 5.41 mmol/L per day; $p=0.405$). The number of patients with severe renal impairment (CrCl < 30mL/min) significantly increased from 121 (22.0%) at the beginning to 152 (27.5%) at the end of the observation period ($p=0.031$). Importantly, the velocity to develop hyperkalaemia was positively correlated with the extent of hyperkalaemia (Figure 1).

None of the 81 deaths (14.7%) was directly attributable to hyperkalaemia. However, patients who died reached a significantly higher median of serum potassium level at the end of the observation period compared with the surviving patients (5.38 vs. 5.53 mmol/L; $p=0.025$). Of 30 (5.4%) patients developing severe hyperkalaemia (serum potassium levels > 6.5 mmol/L), 8 died. Heart failure (37%), pneumonia (13.5%) and myocardial infarction (11.1%) were the most frequent causes of death.

Risk factors for a high velocity to develop hyperkalaemia

Known potential non drug-related risk factors for hyperkalaemia were obtained from the literature and are listed in Table 2. The most prevalent risk factors in our patients were advanced age, diabetes mellitus and congestive heart failure. During the observation period, the mean drug use significantly increased from 8 (IQR 5-10)

before to 10 (IQR 7-12) different drugs per patient (p<0.001). Exposure to drugs associated with hyperkalaemia before and during hospitalization is shown in Table 3. As could be expected, the drugs associated with hyperkalaemia used most often in our patients were heparin, ACEI/ARB, potassium supplements, potassium-sparing diuretics and NSAIDs. For all of these drug classes, the exposure of patients increased during hospitalization as compared to entry. Accordingly, the number of patients treated with drugs potentially causing hyperkalaemia increased from 351 (63.7%) to 508 (92.1%) (p<0.001). Of the 144 patients that were hypokalaemic (serum potassium < 3.5mmol/L) at the beginning of the observation period, 133 (92.4%) were treated with potassium supplements. The number of patients with more than one drug potentially causing hyperkalaemia significantly increased (p<0.001) from 226 (40.7%) to 315 (63.2%) during the observation period. Of the 160 patients with a diagnosis of congestive heart failure, 138 (86.3%) were treated with an ACEI or an ARB, and a potassium-sparing diuretic or a potassium supplement.

In the multiple logistic regression model, drug related risk factors (Table 3) and non-drug risk factors (Table 2) for the development of hyperkalaemia were included and tested for their influence on the velocity to develop hyperkalaemia. Risk factors independently associated with a high velocity to develop hyperkalaemia are listed in Table 4. The identified risk factors increased the velocity to develop hyperkalaemia in the following order: use of potassium supplements > severe renal impairment > use of ACEI or ARB > use of potassium-sparing diuretics > diabetes mellitus. Figure 2 shows that the velocity to develop hyperkalaemia increased with a rising number of risk factors. Pair wise comparison by Tukey-HSD post-hoc analysis showed that the velocity to develop hyperkalaemia is significantly higher for patients with ≥2 as compared to patients with one or zero risk factors (Figure 2).

Dose of drugs identified as risk factors (risk drugs)

In an additional analysis, we focussed on the daily dose of risk drugs as a risk factor for the velocity to develop hyperkalaemia. Patients treated with ‘high-dose’ (daily doses > 3000 mg potassium chloride) potassium supplements showed a significantly higher median of the velocity of the daily increase in serum potassium levels (n= 99) than patients (n=101) treated with ‘low-dose’ potassium supplements (0.48 vs. 0.40

mmol/L per day; p=0.006). The median of the velocity of the daily increase in serum potassium levels was significantly higher in patients (n=63) treated with 'high-dose' potassium-sparing diuretics (daily doses of amiloride > 10mg or spironolactone > 25 mg) compared with those (n=74) treated with 'low-dose' potassium sparing diuretics (0.52 vs. 0.40 mmol/L per day; p=0.007). On the other hand, there was no significant higher median of the velocity in the daily increase of serum potassium levels between patients (n=129) treated with 'high-dose' ACEI or ARB (daily doses > DDD) vs. those treated with 'low-dose' (n=139) ACEI or ARB (0.47 vs. 0.43 mmol/L per day; p=0.289). Fifty-seven (53.8%) of the 106 patients treated with spironolactone were treated with daily doses > 25 mg.

Combinations of risk drugs

In another analysis, we focused on combinations among the drugs associated with a high risk to develop rapid hyperkalaemia (potassium supplements, potassium-sparing diuretics and ACEI or ARB). At the end of the observation period, 410 (74.4%) patients obtained at least one of these drugs. Of them, 138 were treated with a double and 28 with a triple combination. Patients with double or triple combinations were compared with patients with only single drug use. The median of the velocity to develop hyperkalaemia was significantly lower in patients treated with an ACEI or ARB (n=120) versus patients treated with an ACEI or ARB combined with potassium sparing diuretics (n=60) (0.39 vs. 0.53 mmol/L per day; p=0.002). Furthermore, a significantly lower median of the velocity to develop hyperkalaemia was found in patients treated with an ACEI or ARB versus patients treated with the combination of ACEI or ARB and potassium supplements (n=60) (0.39 vs. 0.52 mmol/L per day; p=0.002). On the other hand, in patients treated with potassium supplements or potassium-sparing diuretics, the median of the velocity to develop hyperkalaemia was not lower than in patients treated with potassium supplements or potassium-sparing diuretics combined with an ACEI or ARB. The velocity to develop hyperkalaemia in patients with triple combinations (potassium supplements, ACEI or ARB and potassium-sparing diuretics, n=28) equaled 0.50 (IQR 0.37-0.94) mmol/L This velocity is significantly higher ($p<0.05$) compared to patients using only one of these drug classes, but not significantly different as compared to patients with double combinations.

Kaliuretics

At the end of the observation period, significantly ($p<0.001$) more patients were treated with a kaliuretic (thiazide or loop diuretic) than before the observation period (288 or 52.3% vs. 178 or 32.1% of the patients). Patients with severe renal impairment (CrCl≤ 30 mL/min) treated with kaliuretics (n=85) showed a significantly lower) velocity of the increase in serum potassium than patients with severe renal impairment without kaliuretics (n=67) (0.44 vs. 0.52 mmol/L per day; $p=0.016$). Out of 167 patients treated with at least 2 of the 3 drug classes identified as risk drugs associated with a higher velocity to develop hyperkalaemia, 138 (82.6%) were treated with a kaliuretic. These 138 patients showed a significantly lower median of the velocity to develop hyperkalaemia compared with the remaining 29 patients of this group without kaliuretics (0.45 vs. 0.63 mmol/L per day; $p= 0.001$).

Discussion

Hyperkalaemia is a life-threatening electrolyte disturbance associated with different drug or non-drug related risk factors. The current study reveals that several risk factors can contribute to a fast development of hyperkalaemia. By multivariate analysis, the risk factors significantly associated with a high velocity to develop hyperkalaemia were identified in the order: use of potassium supplements > severe renal impairment > use of potassium-sparing diuretics > use of ACEI or ARB > diabetes mellitus (Table 4). Importantly, the velocity to develop hyperkalaemia correlated with the extent of hyperkalaemia that was reached and was higher in the presence of more than one of these risk factors.

Except for the use of potassium supplements, the order of the risk factors (as expressed by the adjusted odds ratios) is comparable with the corresponding odds ratios for the development of hyperkalaemia identified in a recent case-control study in hospitalised patients with congestive heart failure. [15] In our study, potassium supplements contribute most strongly to the velocity to develop hyperkalaemia in the multivariate model. This may be explained by the facts that in our study 144 (26.4%) of the patients were hypokalaemic at the beginning of the observation period and that most of these patients were treated quite aggressively with potassium supplements. These patients showed a significantly ($p=0.001$) higher velocity of the daily increase of serum potassium levels. However, in a study of 4921 outpatients treated with potassium supplements, only 3.6% developed hyperkalaemia. [2, 18] In comparison, hospitalised patients treated with potassium supplements appear to have a higher risk for hyperkalaemia, since hyperkalaemia was found in 15% to 40% of these patients. [2] This difference in the frequency of hyperkalaemia between hospitalised and ambulant patients treated with potassium supplements may be explained by a more aggressive potassium supplementation and by a higher prevalence of other risk factors for hyperkalaemia in hospitalised patients.

In our study, the majority (142 or 71%) of the 200 patients treated with potassium supplements had an additional ‘major risk factor’ for hyperkalaemia such as severe renal impairment, use of potassium-sparing diuretics, use of ACEI or ARB and/or diabetes mellitus.

Several studies about hyperkalaemia highlight the risk of the potential drug interaction between spironolactone and ACEI or ARB. [10, 19] Palmer recommends that the dose of spironolactone should not exceed 25 mg per day when used in combination with an ACEI or ARB. [4] In agreement with this recommendation, the use of high-dose potassium-sparing diuretics (daily doses of spironolactone > 25mg or of amiloride > 10mg) significantly accelerated the velocity to develop hyperkalaemia in our study, whereas no such effect was observed for high-dose ACEI or ARB. Our study therefore supports the statements of Palmer et al. that the dose of spironolactone should not exceed 25mg day when used in patients with heart failure, in particular in patients with other risk factors for hyperkalaemia such as treatment with ACEI, ARB or potassium supplements and in patients with renal failure. [4] In our study, 20.5 % of the patients (n=60) treated with an ACEI or ARB in combination with potassium-sparing diuretics had severe renal impairment at the beginning of the observation period and of the 106 patients treated with spironolactone, 57 (53.8%) were treated with daily doses > 25mg. In this context, it is important to realise that in the RALES study spironolactone was investigated in a daily dose of 25mg and not at higher doses. [4]

Although not identified as risk factors for a fast development of hyperkalaemia in this study, drugs associated with hyperkalaemia including NSAIDs (Table 3) could contribute to the development of hyperkalaemia, especially when combined with Although not identified as risk factors for a fast development of hyperkalaemia in this study, drugs associated with hyperkalaemia including NSAIDs (Table 3) could contribute to the development of hyperkalaemia, especially when combined with

Kaliuretics (loop diuretics or thiazides) are effective in reducing the risk for hyperkalaemia. Patients at risk for hyperkalaemia could therefore be treated with kaliuretics. In our study, the potassium-lowering effect of kaliuretics could be confirmed in patients with severe renal impairment and in patients treated with ACEI, ARB, potassium-sparing diuretics and/or potassium supplements. The velocity to develop hyperkalaemia in these patients was significantly lower, if they were treated also with kaliuretics. However, the risk of hyponatraemia should be taken into consideration and the patients should be monitored closely when loop diuretics or thiazides are prescribed. [20]

The strength of this study is the analysis of the velocity to develop hyperkalaemia. Therefore we used an observational study design without a control group. This is different to the other studies in this field, which assessed only the occurrence of hyperkalaemia with the objective to identify risk factors for hyperkalaemia [15, 16]. Our study reveals that the velocity to develop hyperkalaemia is influenced almost by the same risk factors as the occurrence of hyperkalaemia. The only exception is the treatment with potassium supplements, which is a more pronounced risk factor for the velocity to develop hyperkalaemia than for the occurrence of hyperkalaemia. The exposure to ≥2 risk factors further enhances the velocity to develop hyperkalaemia. Since the velocity to develop hyperkalaemia is correlated with the extent of hyperkalaemia, patients with ≥2 risk factors should be monitored very closely for the development of potentially life-threatening hyperkalaemia.

Some limitations of this study merit discussion. First, the study sample was recruited on four general wards in one university hospital, representing patients of one single community with long hospitalisation stay (18 days). The findings may therefore not be generalised and be transferred to other hospital or ambulatory settings. Second, the Cockroft-Gault formula [17] may overestimate the CrCl. A comparison with other methods estimating the CrCl reveals, however, that the differences are small, suggesting that other methods would not change our findings. [21] Third, the study was retrospective and the way we calculated the velocity to develop hyperkalaemia did assume a linear rise of serum potassium. We did not judge the linearity of the increase, even in patients where multiple serum potassium determinations were available in the observation period. Fourth, hospitalised patients are closely monitored and hyperkalaemia is normally quickly detected and can therefore be treated immediately. Similar to previous in-hospital studies, [16] only a small number of patients (5.4%) developed severe hyperkalaemia (serum potassium levels > 6.5mmol/L) and more than half of the subjects developed only mild hyperkalaemia (serum potassium levels < 5.5mmol/L). The situation for outpatients might be different. In these patients, less intense monitoring may result in an increased risk of hyperkalaemia, which can be fatal. [22]

The relatively high mortality (14.7%) of patients in this study is comparable to other in-hospital studies. [16] This may be explained by the polymorbidity (7.diagnoses per patient) of the patients studied and their advanced age (72.2 years). None of the deaths could directly be attributed to hyperkalaemia. Nevertheless, patients who died showed a significantly higher maximal serum potassium level as compared to the entire study population, and cardiac diseases were the most frequently reported cause of death.

Conclusions

Risk factors associated with a high velocity to develop hyperkalaemia are use of potassium supplements > severe renal impairment > use of ACEI or ARB > use of potassium-sparing diuretics > diabetes mellitus. Coincidence of two or more of these risk factors is associated with an even faster development of hyperkalaemia. Since the velocity to develop hyperkalaemia is correlated with the extent of hyperkalaemia, the serum potassium levels in patients with ≥2 risk factors should be monitored closely to avoid life-threatening hyperkalaemia. A rapid increase in serum potassium (>0.5mmol/L per day) should alert clinicians to identify and possibly remove risk factors for hyperkalaemia.

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Tables

Table 1: Demographic and clinical characteristics of the patients (n=551)

Characteristic	
Age in years, [median (IQR)]	72.2 (63.5-80.3)
Sex (male) [no. (%)]	270 (49)
Length of hospital stay in days [median (IQR)]	18 (11-30)
Observation period in days [median (IQR)]	5 (3-6)
Number of diagnoses for each patient [median (IQR)]	7 (6-9)
Number of drugs [median (IQR)]	10 (7-12)
New drugs added 2 days before or during observation period [median (IQR)]	3 (2-5)
Drugs stopped 2 days before or during observation period [median (IQR)]	2. (0-3)
Maximal serum potassium level in mmol/L [median (IQR)],	5.4 (5.1-5.8)
Serum potassium level at the beginning of the observation period in mmol/L [median (IQR)],	3.8 (3.4-4.1)
Daily increase in serum potassium in mmol/L [median (IQR)],	0.38 (0.26-0.57)
Creatinine clearance[a] in mL/min [median (IQR)],	43.3 (28.9-63.6)
Creatinine clearance[a] at the beginning of the observation period in mL/min [median (IQR)],	46.9 (31.9-67.9)

IQR = interquartile range

a Creatinine Clearance estimated by the Cockroft and Gault formula [17].

Table 2: Prevalence of non-drug related risk factors for hyperkalaemia

Non-drug related risk factor[a]	no. (%)
Advanced age (≥ 65 years)	388 (70.4)
Diabetes mellitus	166 (30.1)
Congestive heart failure	160 (29.0)
Severe renal impairment[b]	152 (27.5)
Chronic kidney disease	31 (5.6)
Acute kidney failure	36 (6.5)
Blood transfusions	41 (7.4)
Tubulointerstitial nephritis	14 (2.5)
Renal sclerosis	5 (0.9)
Obstructive uropathy	4 (0.7)
Volume depletion	3 (0.5)
Primary adrenal insufficiency	2 (0.4)
Metabolic Acidosis	2 (0.4)
Haemolysis	1 (0.2)
Hyperglycaemia	1 (0.2)
Acute tumor lysis, amyloidosis, amyloidosis, congenital adrenal hyperplasia, fluoride poisoning, gastrointestinal bleeding, Gordon syndrome, hyperkalaemic periodic paralysis, hyporeninaemic hypoaldosteronism (type IV Renal tubular acidosis), papillary necrosis, post kidney transplantation, primary hyporeninism, rhabdomyolysis, systemic lupus erythematosus, sickle cell disease, surgery, tissue trauma	0
Catabolic states, geophagia, vigorous exercise	Data not available

a Risk factors to develop hyperkalaemia according to Palmer [4], Evans and Greenberg [5].

b Creatinine Clearance (< 30 mL/min) estimated by the Cockroft and Gault formula [17].

Table 3: The study populations (n = 551) exposure to drugs associated with risk for hyperkalaemia before during and at the end of the observation period

McNemar's Chi-square test was performed to compare exposure to risk drugs for hyperkalaemia before and at the end of observation period.

Drug exposure	Before observation period, no. (%)	At the end of observation period, no. (%)	P-value
Heparin	174 (31.6)	320 (58.1)	<0.001
ACEI/ARB	217 (39.4)	268 (48.6)	0.002
Potassium supplement	139 (25.2)	200 (36.3)	<0.001
Potassium-sparing diuretic :	80 (14.5)	137 (24.9)	<0.001
Spironolactone		106 (19.2)	
Amiloride		31 (5.6)	
NSAID/COX-2 selective inhibitor	32 (5.8)	76 (13.8)	<0.001
Digoxin	38 (6.9)	44 (8.0)	0.491
Trimethoprim	14 (2.5)	25 (4.5)	0.073
Calcineurin-antagonist:	15 (2.7)	16 (2.9)	0.855
Ciclosporine		13 (2.4)	
Tacrolimus		3 (0.5)	
Antineoplastic drugs	3 (0.5)	12 (2.2)	0.019
Nonselective beta-blocker	5 (0.9)	8 (1.5)	0.403
Intravenous amino acids (arginine, lysine, epsilon-aminocaproic acid)	4 (0.7)	4 (0.7)	1.000
Lithium	2 (0.4)	2 (0.4)	1.000
Drospirenone, mannitol, metyrapone, penicillin G potassium, pentamidine, post kidney transplantation, somastatin, succinylcholine	0	0	-
Herbal medications, high potassium containing food	data not available		

ACEI = Angiotensin converting enzyme inhibitor; **ARB** = Angiotensin receptor blocker; **NSAID** = non-steroidal anti-inflammatory drug; **COX-2** = Cyclooxygenase type 2

Table 4: Independent risk factors significantly associated with a high velocity to develop hyperkalaemia

In a multiple logistic regression analysis, all drugs associated with hyperkalaemia (Table 3) and non-drug related risk factors for hyperkalaemia (Table 2) were included to identify independent risk factors significantly associated with a high velocity to develop hyperkalaemia.

Major risk factor	B	OR	95% CI	P-value
Use of Potassium supplements	1.220	3.386	2.251-5.091	<0.001
Severe renal impairment[a]	1.138	3.119	2.007-4.850	<0.001
Use of ACEI or ARB	0.971	2.642	1.742-4.006	<0.001
Use of Potassium-sparing diuretics	0.725	2.065	1.310-3.254	0.002
Diabetes mellitus	0.442	1.525	1.005-2.313	0.047

a Creatinine Clearance (< 30 mL/min) estimated by the Cockroft and Gault formula [17].

B = Regression coefficient; **OR** = adjusted odds ratio; **95% CI**= 95% confidence interval; **ACEI** = Angiotensin converting enzyme inhibitor; **ARB** = Angiotensin receptor blocker

Figure 1: Correlation of the velocity to develop hyperkalaemia (mean daily increase in serum potassium) with the extent of hyperkalaemia.

Patients were grouped into quartiles regarding their velocity to develop hyperkalaemia. A high velocity to develop hyperkalaemia was associated with high maximal serum potassium levels (analysis of variance followed by Tukey-HSD posthoc analysis).

Boxes represent interquartile range (25%-75%) with mean (□) and median (_); whisker = standard deviation

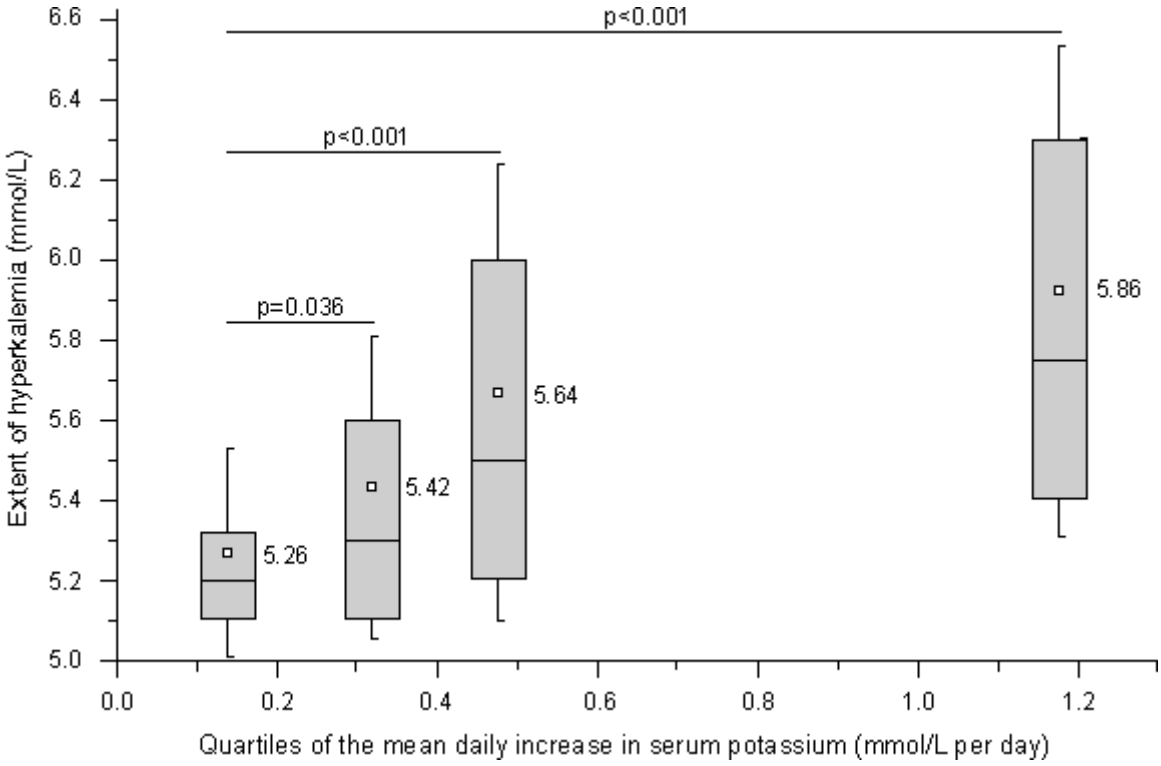
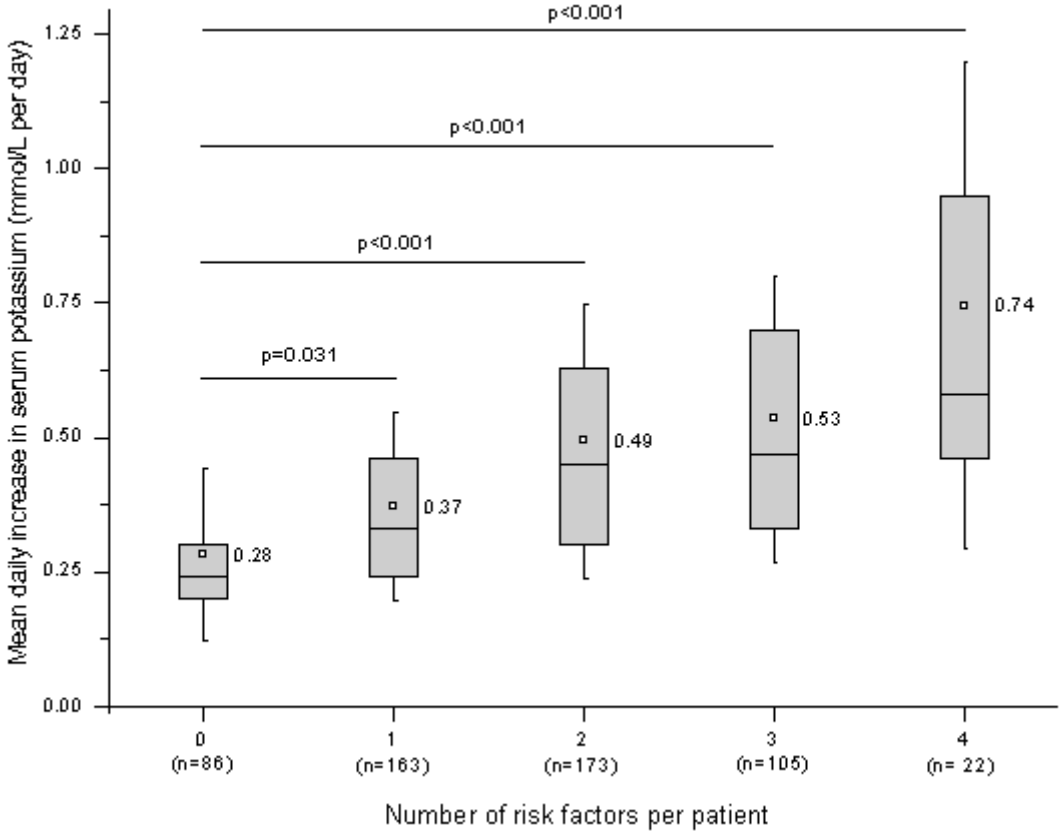


Figure 2: The velocity to develop hyperkalaemia (mean daily increase in serum potassium) according to the number of risk factors.

The risk factors included for the calculation were severe renal impairment, diabetes mellitus and treatment with potassium-sparing diuretics, angiotensin converting enzyme inhibitors angiotensin receptor blockers or potassium supplements. The velocity to develop hyperkalaemia is higher with an increasing number of these risk factors. In comparison to patients without such risk factors, patients with one or more risk factor show a significantly higher velocity to develop hyperkalaemia ($p>0.05$) (analysis of variance followed by Tukey-HSD post-hoc analysis).

Boxes represent interquartile range (25%-75%) with mean (□) and median (_); whisker = standard deviation



4 Project B: Prevalence and patient knowledge of potential drug interaction with self-medication

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Summary

Background and Objective

In community pharmacies potential drug interactions between prescription only medicines (POM) and OTC drugs purchased for self-medication arise mainly in two situations: (A) if an OTC drug is purchased by a passer-by customer whose prescribed drug therapy is not known, or (B) if a POM or an OTC drug is requested by a regular customer whose prescribed drug therapy is usually recorded. With this study we aimed to assess the prevalence of potential drug interactions with selected POM and OTC drugs in passer-by and regular customers as well as their awareness of these potential drug interactions.

Methods

Data were collected in 14 community pharmacies in the region of Basel, Switzerland by observation of customer contacts and interviews with passer-by customers purchasing selected OTC drugs, and telephone-interviews with regular customers treated with selected POMs identified in community pharmacies' databases. The selected POMs and OTC drugs are drugs which could lead to clinically relevant drug interactions of varying severity but manageable through different interventions such as adjustment of dose and its timing and/or monitoring of the therapy, and avoidance of the combination by choosing an alternative treatment.

Results

Of 1183 passer-by customers observed, 164 (14.4%) purchased at least one of the selected OTC drugs. 102 (62.2%) of those subjects were interviewed. 43 (42.2%) mentioned taking prescribed drugs, and 3 of them were exposed to potential drug interactions of moderate severity.

Out of 592 regular customers selected from the community pharmacy database, 434 (73.3%) could be interviewed. 69 (15.9%) of them were exposed to a potential drug interaction between purchased OTC drug for self-medication and their POM. Furthermore, 116 (26.7%) regular customers were exposed to potential drug interactions within their prescribed drugs and in 28 (6.5%) multiple (≥ 2) potential drug interactions were found.

203 (46.8%) regular customers were aware of potential drug interactions between their POM and OTC drugs. 96 (47.3%) of them were informed by their prescribing physician and 52 (25.6%) by their community pharmacist. Awareness of potential drug interaction was higher in younger customers [odds ratio (OR) 0.95; 95% confidence intervals (CI) 0.93, 0.97, p<0.0001] and higher for drug interactions classified as ‘severe’ [OR 1.79; 95% CI 1.16, 2.77, P = 0.009].

Conclusion

Efforts to increase awareness of potential drug interactions are needed. Although community pharmacies are adequately equipped with computerised drug interaction surveillance systems this is often not applied to self-medication. Vigilance for potential interactions of all drugs, including those sold over the counter, should be increased.

Background

Over-the-counter (OTC) drugs can be used for self-medication without advice of a pharmacist or a physician. Freely available, their use is often perceived as safe by customers [1]. The lack of professional supervision may increase the risk of adverse drug effects including those caused by drug interactions. Availability and use of OTC drugs vary among different countries [2-6]. In Switzerland OTC drugs are classified as 'pharmacist only' (e.g. Levonorgestrel), 'pharmacy only' (e.g. Ranitidine), 'drug store only' (e.g. Paracetamol) or freely available (e.g. low-dose vitamins and minerals). In 2004 OTC drugs amounted to 41.9% of accredited drugs. In ambulatory care 72.1% of OTC dugs are sold by community pharmacies [7], 34.1% of customers visit Swiss community pharmacies to purchase an OTC drug [8].

In recent years, health authorities have encouraged self-care for minor ailments to reduce the cost of medical care [9]. Advertisement for OTC drugs is allowed in all media including television and their availability and use have increased. More and more drugs are switched from prescription only to non-prescription status [84]. Even drugs such as statins and triptans, with a considerable risk of interaction have been switched. OTC drugs interacting with POMs like non steroidal anti-inflammatory drugs (NSAIDs), pseudoephedrine and dextromethorphan are commonly used by ambulatory patients [10]. Certain segments of the population like the elderly, children, organ transplant or HIV infected patients are at elevated risk of adverse drug effects from significant drug interactions between prescribed and OTC drugs [11, 12].

Some pharmacokinetic drug interactions like those between antacids and tetracyclines or quinolones can be managed by adjusting dose regimens or spacing dosing times. Other potential interactions such as that between monoamino oxidase (MAO) inhibitors and dextromethorphan or indirect acting sympathomimetics present in cough or cold medications are best avoided by choosing an alternative treatment [13].

The first step before any intervention by a pharmacist is the identification of the potential drug interaction. In Switzerland community pharmacies electronically record all prescribed drugs for mandatory health insurance claims and this recording is automatically computer-checked for potential drug interactions. So far, self-medication drugs are checked less systematically. They are often not recorded in the

individual medication history. The need to treat OTC drugs like all other medications and to monitor patients' self-medication is more and more recognised [11]. Some Swiss community pharmacies have started to collect data of their regular customers' self-medication using a record card.

Recent studies of potential drug interactions in ambulatory care have focused only on prescribed drugs [14]. Little is known about the prevalence of potential drug interactions between prescription only and OTC drugs. In a Finnish national health care study clinically relevant potential drug interaction were identified among 68 (4%) of OTC drug users, but only 10 were at constant risk of clinically relevant drug interactions from continuous OTC drug use [3].

In community pharmacies potential drug interactions between POM and OTC drugs for self-medication arise mainly in two situations (A) if an OTC drug is purchased by a passer-by customer whose prescribed drug therapy is not known or (B) if a POM or an OTC drug is requested by a regular customer whose prescribed drug therapy is usually recorded. Our study addresses both of these situations. We aimed to assess the prevalence of potential drug interaction with selected POMs and OTC drugs in passer-by and regular customers as well as their awareness of these potential drug interactions.

Methods

POMs and OTC drugs were selected for their potential to cause clinically relevant drug interactions (Table 1). An important consideration was the possibility to handle the potential interactions by dose regimen adjustment, spacing dosing times, alternative choice of therapy, or closer monitoring (Table 1). All drug interactions had to be contained in the database Pharmavista® [15] which is implemented in the drug interaction surveillance softwares of all Swiss community pharmacies. Pharmavista® [15] is adapted from the German ABDA-Datenbank [16] for the Swiss market. In this database drug interactions are classified into 'severe' (the interaction can be life-threatening for the patient or intoxications or permanent harms for the patient can occur), 'moderate' (the interaction often induces therapeutic problems, but if the patient is closely monitored the combination can be administered), 'minor' (the interaction can lead to increased or decreased drug effects or only specific person subgroups are considered'), 'negligible' (the interaction mostly induces no or limited clinical effects and generally no alterations in therapy are required) and 'external specifications' (the interaction is only assumed or described in particular cases and its clinical consequences are unclear).

Passer-by customers purchasing selected OTC drugs were observed in community pharmacy and interviewed for their prescribed medicines. Regular customers with selected POMs were selected from the community pharmacies database and interviewed over the phone for their self-medication, their awareness of potential drug interaction and their source of information.

Data collection

Data were collected over a 4-week period in April 2005 in 14 out of 99 community pharmacies randomly selected in the region of Basel, an urban area of approximately 450,000 inhabitants in the Northwest of Switzerland. Pharmacy patrons signed a letter of informed consent and all included pharmacy customers gave their consent to be interviewed. The study protocol was approved and accepted by the regional ethics committee.

A pharmacist trained as observant researcher spent one regular working-day in each study pharmacy. He observed contacts with passer-by customers at the counter and he approached those who purchased one of the selected OTC-drugs for an interview.

He asked for their age and any prescribed drugs. Customers younger than 18 years were excluded from the study. Of customers refusing the interview, their gender and their reason of refusal were assessed and their age group was estimated.
In the database of the study pharmacies the observant researcher identified regular customers with at least one of selected POMs (Table 1) in their medication history of the last 100 days. The first 12 regular customers treated with the selected POM of each pharmacy's database, aged between 18 and 75 years, were included and demographic characteristics and medication profiles were recorded. Telephone interviews were performed by a structured questionnaire by one trained pharmacist. Interview questions referred to the awareness of potential drug interactions of the prescribed drug with OTC drugs and actual OTC use including frequency and dose (Table 2). If a potential drug interaction was detected, questions about awareness, management as well as adverse events were asked. At the end of the interview the regular customer was informed about possible potential drug interactions of its POM with OTC drugs. For customers that could not be interviewed demographic data, prescribed drugs and the reason of refusal or non-respondence were assessed.

Statistical analysis

Results are expressed as proportions and as means ± standard deviations (SD) or medians with the corresponding range. Independent two-sample comparison of single continuous variables was performed using Students' t-test. Chi-square statistics were used for categorical comparisons. To analyse the association of covariates with regular customers' awareness of potential drug interactions with self-medication drugs, logistic regression analysis was performed. Covariates in a simultaneous model were gender, age as a continuous variable, number of prescribed drugs as a continuous variable, the collection of self-medication data by community pharmacies, the occurrence of potential drug interactions between the POM and other prescribed drugs, the occurrence of potential drug interactions between the POM and an OTC drug purchased for self-medication and treatment with POMs that can lead to potentially 'severe' drug interactions with OTC-drugs (Table 1). Odds ratios (OR) are presented with 95% confidence intervals (CI). Statistical significance was defined as p-value <0.05. Statistical analysis was performed using SPSS for Windows version 13.0 (SPSS, Inc., Chicago, IL 60606).

Results

Observation of passer-by customers

In 14 community pharmacies, 1183 passer-by customers were observed during 112 hours. 164 (14.4 %) requested at least one of the selected potentially interacting OTC drugs (Table 1) and 102 (Age 55.2 ± 16.2 years, 62.7% female) were interviewed. Reasons for refusal of the interview were purchase of an OTC drug for another person (n=25), refusal due to lack of time or interest (n=21), poor knowledge of drugs prescribed (n=14) and escape (n=2). Of the interviewed regular customers, 43 (42.2%) mentioned being on 2.2 ± 1.3 prescribed drugs. For 3 customers one of the selected potential drug interactions (Table 1) was found: Two potential drug interactions between ibuprofen and low-dose ASA and one potential drug interaction between ibuprofen and spironolactone.

Telephone interviews with regular customers

Of the 592 regular customers selected from the community pharmacy database 434 (73.3%) agreed to be interviewed (Age 69.9 ± 13.1 years, 56.4% female, meanly 5.0 ± 2.1 prescribed drugs). Responders were significantly older ($P < 0.001$), more frequently female ($P < 0.001$) and more frequently treated with prescribed drugs than non-responders ($P < 0.001$). Main reasons for non-response (n=158) were no contact due to absence (44.9%) or no known telephone number (39.2%) and refusal of the interview due to lack of time or interest (10.8%).

Of the 14 community pharmacies included in this study 8 (57.8%) had partial records of the self-medication of their regular customers and this allowed detection of some potential drug interactions with OTC drugs. No differences in prevalence of potential drug interactions between purchased OTC drugs and POMs (chi-square, $P = 0.524$) and in prevalence of drug interactions between the selected POMs and other prescribed drugs ($P = 0.329$) were found between regular customers of the two types of pharmacies.

Prevalence of selected potential drug interactions in regular customers

In 69 (15.9%) regular customers potential drug interactions between OTC drugs purchased for self-medication and POMs were found (Figure 1). In 116 (26.7%)

regular customers additional potential drug interactions between other prescribed drugs and in 28 (6.5%) multiple (≥2) potential drug interactions were found (Figure 1).

MAO-inhibitors

Of 29 customers treated with a MAO-inhibitor 17 (58.6%) could be interviewed and in 4 of them a potential drug interactions with purchased OTC drugs were found. All were treated with moclobemide and purchased cold and cough medications containing a combination of paracetamol and the potentially interacting agents pseudoephedrine, phenylephrine or dextromethorphan. However, all customers indicated taking these drugs less than 2 to 3 times per week. None of these potential drug interactions were identified by their physician or pharmacist. Two of these customers reported warmth and dizziness after taking the cold and cough medications. Two customers were treated with the POM tramadol, one with the POM mirtazapine and one with prescribed dextromethorphan. Overall in 6 (35.3%) out of 17 interviewed customers potential drug interactions were found.

Immunosuppressants

Out of 35 regular customers treated with immunosuppressants (cyclosporine or tacrolimus) 23 (65.7%) could be interviewed. One of them purchased a St. John's wort preparation and 2 customers consumed grapefruit juice. None of these potential drug interactions were identified by their physician or pharmacist and no closer monitoring of immunosuppressants serum levels was carried out. None of these customers reported abnormal drug concentrations, toxic effect or allergic reactions. We found 3 other customers that were treated with prescribed St. John's wort preparations. Overall in 6 (26.1%) out of 23 interviewed customers, potential drug interactions were found.

Oral anticoagulants

Out of 168 regular customers treated with oral anticoagulants, 134 (79.8%) were interviewed. 8 of them purchased NSAIDs or high-dose ASA (single dose ≥ 500mg) for self-medication. Five customers purchasing NSAID (diclofenac, ibuprofen or naproxen) reported having informed the physician and took precautions such as closer monitoring and dose-adjustment. All of them reported taking NSAID 2 to 3

times per week or less. The three customers purchasing ASA were not aware of the potential drug interaction and no precautions were taken. All of them reported taking ASA, 2 to 3 times per week or less and additionally they were treated with further prescribed NSAIDs (diclofenac or ibuprofen). None of the 8 customers reported a change in hypoprothrombinemic response or even bleedings. Furthermore, we found other 54 customers with potential drug interactions with prescribed ASA (single dose ≥ 500 mg), diclofenac or ibuprofen. Overall in 62 (46.3%) out of 134 interviewed customers potential drug interactions were found.

Potassium-sparing diuretics

Of 81 regular customers treated with potassium-sparing diuretics 61 (75.3%) were interviewed and in 11 of them potential drug interactions between spironolactone and OTC drugs were found. Nine of them purchased NSAIDs (ibuprofen or diclofenac) and 2 of them potassium supplements. One customer using an OTC-NSAID was additionally treated with an angiotensine converting enzyme (ACE) inhibitor. This customer took a daily dose of 25mg spironolactone and mentioned that his serum potassium level is regularly monitored. Four customers that purchased OTC-NSAIDs were additionally treated with diclofenac in a POM dose. In 6 of 9 customers that purchased OTC-NSAIDs the potential drug interaction was recognised by their physician. Of the 2 customers that purchased potassium supplements one customer was additionally treated with prescribed diclofenac. All of them reported taking the NSAIDs for self-medication 2 to 3 times per week or more seldom. Regular customers that purchased potassium supplements reported that the potential drug interaction was recognised by a physician and that their serum potassium levels are regularly monitored. Both were treated with the combination because of hypokalaemia. No customer reported a hyperkalaemic serum potassium level, an adverse event due to hyperkalaemia or renal impairment. Furthermore, we found other 26 customers with potential drug interactions with other prescribed drugs. They were treated with ACE inhibitors, angiotensin receptor blockers and potassium supplements. Overall in 38 (62.3%) out of 61 interviewed customers potential drug interactions were found.

Tetracyclines

Out of 132 regular customers treated with tetracyclines (doxycycline or minocycline) 82 (62.1%) could be interviewed and 41 of them reported consumption of products containing polyvalent cations during their antibiotic therapy. Of them 4 took antacids containing magnesium and aluminium, 8 multiminerals, 4 magnesium supplements, 4 calcium supplements and one customer an iron supplement. Furthermore, 13 customers mentioned to take calcium containing food (milk or dairy products) at the same time than tetracyclines. To avoid the potential drug interactions 8 of 41 customers ingested products containing polyvalent cations 2 to 3 hours before or after taking tetracyclines. Out of 36 customers with potential drug interactions a total of 19 mentioned to take products containing polyvalent cations daily. One customer reported of a therapy failure potentially caused by an interaction with calcium containing food. None of these potential drug interactions was recognised by their pharmacist or physician. Furthermore, 8 patients were treated with other prescribed supplements containing calcium, iron or magnesium. Overall in 40 (48.8%) out of 82 interviewed customers potential drug interactions were found.

Low-dose ASA

Of 147 regular customers treated with low-dose ASA (≤ 300mg) 117 (79.6%) could be interviewed. Of them 7 purchased OTC ibuprofen. None of the potential drug interactions were recognised by their physician or pharmacist. All customers mentioned to take ibuprofen in single doses of 200mg to 600mg. None of them purchasing OTC drugs took daily doses of ibuprofen > 1200mg. All of them reported taking ibuprofen 2 to 3 times per week or less. None of them considered to take ibuprofen 2 hours after low-dose ASA to minimise risk. No customer reported of an adverse cardiovascular event. Furthermore, we found 8 other customers that were treated with prescribed POM ibuprofen in single doses of 400 to 600 mg. Overall in 15 (12.8%) out of 117 interviewed customers potential drug interactions were found.

Awareness of potential drug interactions in regular customers

Of the interviewed regular customers 203 (46.8%) were aware about potential drug interactions between their POM and OTC drugs for self-medication or food (Figure 2). Of them 96 (47.3%) were informed by the prescribing physician and 52 (25.6%)

by the community pharmacy. Further information sources were package inserts (24; 11.8%), hospital (7; 3.4%), home care nurses (2), magazines (2), friends (2) and television (1). In two cases the customers themselves were health care professionals. The remaining 17 patients could not remember of whom they were informed about potential drug interactions.

The level of information varied between customers with different POM therapies: 22 of 23 (95.6%) immunosuppressed, 88 of 134 (65.7%) anticoagulated customers, 9 of 17 (52.9%) treated with MAO-inhibitors, 51 of 82 (62.2%) customers treated with tetracyclines, 12 of 61 (19.7%) treated with potassium-sparing diuretics and 21 of 117 (17.9%) treated with low-dose ASA reported having been informed about the problem (Figure 2).

The awareness was significantly higher for potential drug interactions classified as 'severe' [OR 1.79; 95% CI 1.16, 2.77, P = 0.009]. Furthermore, regular customers aware of potential drug interactions were significantly younger [OR 0.95; 95% CI 0.93, 0.97, p<0.0001]. For regular customers, no association between awareness and gender [OR 1.05; 95% CI 0.70, 1.57, P = 0.818], recording of self-medication data by community pharmacies [OR 1.06; 95% CI 0.71, 1.59, P = 0.778], number of prescribed drugs [OR 1.03; 95% CI 0.92, 1.15, P = 0.599], occurrence of a potential drug interaction with an OTC drug purchased for self-medication [OR 0.92; 95% CI 0.52, 1.61, P = 0.669] or occurrence of a potential drug interaction with another prescribed drug [OR 1.11; 95% CI 0.68, 1.81, P = 0.763] was found.

In the pharmacies that partially recorded customers' self-medication more patients were informed about potential drug interactions but the difference compared with customers of other pharmacies was not significant (chi-square, P = 0.534).

Of the 69 regular customers with potential drug interactions between POMs and OTC-drugs for self-medication, 33 (47.8%) reported knowing about the potential drug interactions.15 of them specified that their physician or pharmacist alerted them and precautions were taken.

Discussion

This study focuses on selected potential drug interactions of varying clinical relevance and with different management options (Table 1) in two different groups of pharmacy customers: (A) passer-by customers whose prescribed drug therapy is not known and (B) regular customers whose prescribed drug therapy is usually recorded. This reflects the daily practice in community pharmacies. However, only a selection of potential drug interactions was investigated. Therefore, the overall prevalence of potential drug interactions with self-medication is certainly higher.

Of 102 passer-by customers purchasing one of the selected OTC drugs (Table 1) only 3 reported receiving treatment with a potentially interacting POM. All of the potential interactions were of moderate severity. A study in Finland revealed similar results with a low prevalence of 4% of harmful potential drug interactions in OTC drug users [3]. In contrast, the prevalence of selected potential drug interactions in the population of regular customers treated with selected POMs with a risk for potential drug interactions with OTC drugs was relatively higher (15.9%). A reason for the low prevalence of potential drug interactions in passer-by customers might be that they do not regularly consume drugs. It is difficult for community pharmacists to identify and manage potential drug interactions in passer-by customers because of a lack of information about their medication profile and their purchase of drugs for self-medication in different pharmacies. Focus on regular customers treated with selected POMs known to interact with OTC drugs may be a helpful strategy in community pharmacies. Honig and Gillespie [12] proposed useful strategies for avoiding potential drug interactions between OTC-drugs and POMs on both individual and societal levels. They suggested better labeling of drugs and highlighted the need to enquire about OTC-drug use. Of the regular customers, more than half (53.2%) had no information on potential drug interactions between their POMs and OTC-drugs. As expected, poor awareness was particularly marked for potential drug interactions of moderate severity.

In 8 of the 14 participating community pharmacies partial self-medication records were held for their regular customers. This service is recent and currently only few customers are covered. Wider implementation of this service would be useful. A precondition is the customer’s acceptance of surveillance by his pharmacy. Therefore customers have to be motivated to participate more fully in their healthcare [17].

The severity of a potential drug interaction can have a significant effect on identification and its management. Hansten, Horn and Hazlet suggested a new classification of potential drug interactions based on management options [18]. The implementation of this classification in computerised drug interaction systems could reduce the override of alerts of less severe potential drug interactions and improve their management by health-care professionals. Our results suggest the need for optimised tools and approaches for the identification and management of potential drug interactions in community pharmacies, the only place where a check for both POM and OTC drugs can be systematically performed.

Regular customers reported taking OTC drugs infrequently. Those taking analgetics (NSAIDs or ASA) for self-medications were particularly likely to mention use of their drugs only in case of need and therefore less than ‘daily’. Another study supports our results suggesting that participants took OTC analgetics mainly temporary: Only 7% of the study population used OTC drugs daily [3]. This occasional ingestion of OTC drugs for self-medication reduced the risk of dose-or time-related interactions [19] such as interactions between low-dose ASA with ibuprofen or interactions between tetracyclines and polyvalent cations. For other dose- or time-related potential drug interactions the situation is different: Patients treated with POMs such as oral anticoagulants or immunosuppressants that require regular monitoring, even the occasional ingestion of potentially interacting OTC drugs should be avoided because of an unfavorable risk benefit ratio. For drug interactions such as between MAO-inhibitors and dextromethorphan or sympathomimetics (Table 1) an infrequent intake still present a substantial risk.

Conclusion

In conclusion, this study reveals that potential drug interactions between POMs and OTC drugs for self-medication are widespread. Efforts to increase awareness of potential drug interactions are needed. Although community pharmacies are equipped with a computerised check system for potential drug interactions this is often not applied to self-medication. Vigilance for all drugs, including those sold over the counter should be improved. There is a particular need for improved checking for drug interactions. Customers should be asked regularly about their self-medication to prevent serious interactions with prescribed medication.

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Tables

Table 1: Selected potential drug interactions between prescription only medicines and over-the-counter drugs or food

Potential drug interaction				
Prescription only medicine	Over-the-counter drug or food	Class[1]	Possible adverse outcome[2]	Management options[2]
Orally-administered tetracycline (Doxycyline, Lymecycline, Minocycline)[3]	Polyvalent Cations (e.g. Aluminium, Calcium, Iron, Magnesium, Zinc)	moderate	Impaired absorption of the tetracycline can reduce the serum concentration and the antibacterial efficacy of the tetracycline	Minimise risk by coordinated sequence of administration (take tetracyclines 2 hours before or 6 hours after polyvalent cations) or consider an alternative antibiotic
Low-dose ASA[4]	Ibuprofen	minor	Inhibition of the antiplatelet effect of ASA and possible decrease of its cardioprotective effects	Minimise risk by coordinated sequence of administration (ibuprofen ingestion 2 hours after ASA) or consider an alternative to ibuprofen
Potassium-sparing diuretic (Eplerenone, Potassium canreonate, Spironolactone, Triamteren)[3]	Potassium salts	severe	severe hyperkalaemia	Avoid unless benefit outweighs risk in cases of severe or refractory hypokalaemia and minimise risk by carefully monitoring serum potassium levels
	NSAIDs[5]	moderate	Hyperkalaemia, renal impairment, renal failure	Minimise risk by monitoring serum potassium levels and renal function
Oral Anticoagulant (Acenocoumarol, Phenprocoumon)[2]	NSAIDs[5]	moderate	Bleeding due to inhibition of platelet function and gastric erosions	Avoid unless benefit outweighs risk, monitor the prothrombin time carefully and watch for evidence of bleeding especially from the gastrointestinal tract
	Salicylates	severe		
Immunosuppressant[1] (Cyclosporine, Sirolimus, Tacrolimus)[3]	St. John‘s wort	moderate	Decreased effect of immunosuppressant, rejection reaction	Usually avoid and use antidepressant other than St. John‘s wort, if used together monitor for altered immunosuppressant effect by initiation, discontinuation or changes in dosage of St. John‘s wort preparations
	Grapefruit	minor	Increased blood concentration of the immunosuppressant, nephrotoxicity	Avoid drinking grapefruit juice. If grapefruit juice is taken concurrently carefully monitor for altered immunosuppressant effect especially by initiation, discontinuation of grapefruit juice
Monoamino oxidase inhibitors (Moclobemide, Selegiline)[3]	Dextromethorphan	severe	Serotonin syndrome (agitation, confusion, hypomania, myoclonus, rigidity, hyperreflexia, tremor, incoordination, sweating, shivering, seizures, coma)	Dextromethorphan is contraindicated in patients receiving nonselective or MAO-A inhibitors (Moclobemide)
	Indirect-acting Sympathomimetics (e.g. Phenylephrine, Pseudoephedrine)	severe	Hypertension, palpitations, headache and lightheadedness	Avoid combinations and use alternative therapies

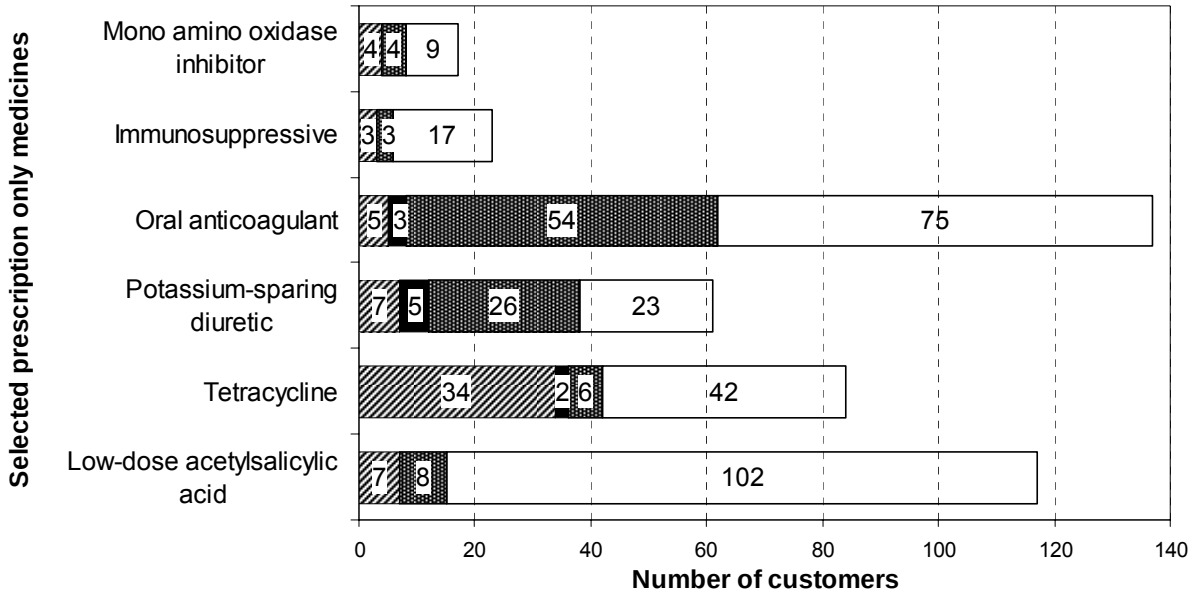
[1]Classification according to the database Pharmavista® [51], which is used by Swiss community pharmacies drug interaction surveillance software
[2]Retrieved from Drug Interactions: Analysis and Management [85] and the database Pharmavista® [51]
[3]Drugs available in Switzerland
[4]ASA = Acetyl salicylic acid, [5]NSAID = Non-steroidal anti-inflammatory drug

Table 2: Questions asked in the structured telephone interview with regular customers

Question	Possible Answers
Are you informed about possible drug interactions[4] of your POM[3] with OTC-drugs?	Yes / No
If yes, who did inform you?	My pharmacist / my physician / the drug information prospect / further possibilities
Did you take one of following[1] OTC[2] drugs or foods during therapy with the POM[3]?	Yes / No
How often do you take the potentially interacting OTC drug?	Several times per day / daily / several times per week / less often
Was the potential drug interaction detected?	Yes / No
If yes, by whom?	My pharmacist / my physician / the customer himself / further possibilities
Was one of the following actions[5] taken to minimise the risk of an adverse event?	Choice of an alternative therapy, stop of one drug, time or dose adjustment, laboratory monitoring, further actions
Did one of following possible outcomes (listed in Table 1) occur?	Yes / No

1: Potentially interacting OTC drugs are listed in Table 1
2: OTC = Over-the-counter
3: POM = Prescription only medicine
4: Potential drug interaction = potential drug-drug or drug-food interaction
5: Management actions to minimise risk an adverse effect retrieved from Drug Interactions: Analysis and Management [85]

Figure 1: Prevalence of potential drug interactions in regular customers of community pharmacies treated with selected prescription only medicines



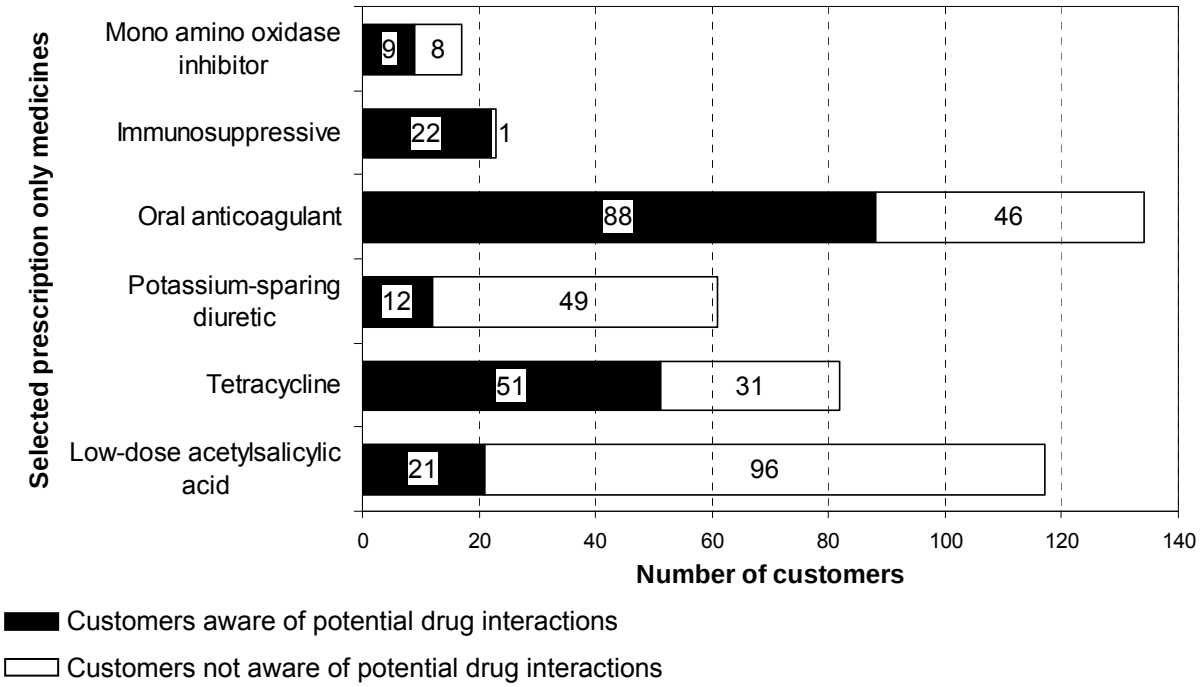
Potential drug interaction caused by drugs purchased for self-medication

Multiple (≥2) potential drug interactions caused by a drug purchased for self-medication and another prescribed drug

Potential drug interaction between prescribed drugs

No potential drug interaction

Figure 2: Awareness of potential drug interactions of regular customers of community pharmacies treated with selected prescription only medicines



5 Project C: Management of drug interactions in community pharmacies: A questionnaire based survey in Switzerland

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Abstract

Objective:

To analyze the current drug interaction management in Swiss community pharmacies with a particular focus on electronic systems and to compare the results with those expressed by German general practitioners in a recent survey.

Methods:

Data were collected with a postal questionnaire which was randomly sent to 500 out of 833 community pharmacies of the German part of Switzerland.

Results:

The response rate was 57.4% and only 24.7% pharmacists reported to be confronted less than daily with potential drug interactions. Use of computer software to identify potential drug interactions was widespread in community pharmacies (90.2%) and the software was the primary source of information (81.2 ± 29.6%). The quality of the interaction software was judged sensitive (identifying all dangerous interactions) by 80.5 ± 21.5% but specific (identifying only relevant interactions) by only 38.3 ± 32%. Pharmacists declared a low override rate (14%) of drug interaction alerts although unjustified alerts were reported by 60.6 ± 33.1%. In contrast to general practitioners pharmacists opted less often for information on the mechanism of the interaction and more frequently for details for dose adjustment. Both groups complained about deficient information on non-interacting alternatives.

Conclusion:

The information needs of community pharmacists differed considerably from general practitioners and pharmacists were overwhelmed by inappropriate alerts because of a lack of specificity of their drug interaction systems. Substantial improvement of drug interaction software systems is thus required at least in two important aspects, the suppression of inappropriate alerts and the tailoring to the needs of the user.

Introduction

Potential drug interactions are highly prevalent, but the number of adverse drug reactions caused by drug interactions is probably low [1-4]. Reported incidences in outpatients range from 9.2% to 70.3% for drug interactions of any severity and from 1.2% to 23.3% for those considered of major relevance [5-11]. A German primary care study showed that of all observed major or moderate potential drug interactions only 11.7 % offered no management options and such drug combinations should thus be avoided [12]. The majority of the potential drug interactions do not result in clinical manifestations if they are managed adequately e.g. by dose adjustment or a coordinated sequence of administration [12]. However, given the frequency of combination treatment even a low penetrance of complications caused by drug interactions will substantially impact drug safety. Indeed drug interactions are responsible for up to 3.8% of hospital admissions [2, 13-15].

In some countries, including Switzerland, community pharmacies are obliged to keep a medication history of all dispensed prescription drugs and to check prescriptions to prevent the use of unsafe drug regimens including those caused by potentially interacting drugs. To comply with these statutory requirements, almost all pharmacies use computer software systems for the quality assurance of pharmacotherapy. These systems identify potential drug interactions, alert the pharmacy team to intervene before dispensing potentially interacting drugs, and serve as a drug interaction information source.

Thus far, only very few epidemiologic studies on the adverse outcomes of drug interactions have been performed. Therefore drug interaction information sources generally lack data on clinical importance of potential drug interactions and information on risk factors that contribute to their adverse outcomes. Indeed the majority of general practitioners were dissatisfied with the information on therapeutic alternatives, severity, mechanism, and dose adjustment in the drug interaction information sources they used [16]. Consequently electronic drug interaction information sources should include management guidelines for dose adjustment and spacing of administration times and should help to avoid contraindicated drug combinations. Moreover, they should also provide monitoring information for an early detection of adverse events.

Drug interaction information is required on different levels of drug therapy. First, the prescription of drug combinations should be supported by appropriate information technology to maintain high quality standards already at the point of care. In addition to the support of physicians in drug selection and dosing also the dispensing pharmacies should have access to comprehensive information on drug interactions in order to assess combinations prescribed by several independent physicians in charge of a patient and also to detect risks arising from combinations with drugs dispensed without prescription. Obviously, safety concerns detected in a pharmacy should be resolved in communication with the treating physician who ideally has access to the same knowledge bases. Because pharmacists and physicians have different duties in pharmacotherapy and also different training, their information needs may also differ. We therefore aimed to assess how pharmacists deal with drug interactions in daily practice, which information sources they use and wish to have, and how their requirements relate to those expressed by general practitioners.

Methods

Study population

From the 833 pharmacies in the German speaking part of Switzerland a random sample of 500 community pharmacies was invited to participate in this cross-sectional survey. Pharmacies were selected by use of the freeware Research Randomizer (http://www.randomizer.org/form.htm). No stratification or any other selection procedures were applied.

In Switzerland community pharmacies dispense 68.9% of all over-the-counter drugs and 57.2% of all prescription drugs. The remaining drugs are dispensed by physicians (27.8%), hospitals (13.9%), and drug stores (1.2%) [17]. If not limited by regional legislation, physicians are allowed to store drugs in their practice and dispense drugs to their patients.

All Swiss community pharmacies have electronic drug management systems. The knowledge base on drug interactions integrated in these systems is originally developed by ABDATA (Eschborn, Germany) [18] to be used in all Austrian, German, and Swiss community pharmacies. The knowledge base is adapted by E-mediat AG (Schönbühl, Switzerland) to the Swiss market and sold to pharmacy software providers. Furthermore, it is published as an integrated part of Pharmavista® [19], a drug information service which is available on the Internet or on CD-ROM as subscription-only service for Swiss health care professionals. Each drug interaction monograph is fully referenced and monthly updated. Potential drug interactions are classified into ‘severe’ (life-threat / intoxication / permanent harm), ‘moderate’ (frequent therapeutic problems / combination can be administered but close monitoring required), ‘minor’ (increased or decreased drug effect / only specific subgroups affected), ‘negligible’ (no or limited clinical effects / generally no modification of therapy required) and ‘external specifications’ (only occurring in particular cases / clinical consequences unclear). The majority of electronic drug interaction systems used in Swiss community pharmacies can be set up to flag only potential drug interactions of moderate and/or high severity. Such alerts can either be ‘ignored’ (overridden); ‘considered’ (deliberate response to the alert), or in some cases have to be ‘analysed’ more precisely through consideration of additional

parameters (e.g. patient related risk factors) and consultation of drug interaction information sources.

Data collection

The questionnaire included 28 items grouped in four sections. The first part of the questionnaire contained three questions to clarify pharmacists' perceptions of drug interactions and the preoccupation with this problem in daily practice. The second part focused on management of interaction alerts in pharmacy practice with three questions on the configuration of the drug interaction surveillance software, three questions on the quality of their drug interaction surveillance software to be 'sensitive' (software identifies % of cases of dangerous potential drug interactions) and to be 'specific' (software identifies % of cases of really clinically relevant potential drug interactions) and to flag 'false' alerts (e.g. multiple or repeated alerts for the same patient, the patient was no longer taking the interacting drug, in % of cases) and four questions on the actions taken by pharmacy teams after drug interaction alerts. A third part contained five questions on the usage (frequency and type) of drug interaction information sources and the pharmacists' satisfaction with the provided information. Eight questions in the fourth part addressed the communication with physicians. Additionally, characteristics of the pharmacists (gender, professional experience, working hours, postgraduate education) and their community pharmacies (location, profile of customers, and implementation of quality management system) were assessed. We used multiple choice questions or visual
analogue scales ranging from never (coded as 0%) to always (coded as 100%).

Questions on pharmacists' perception of the risk arising from potential drug interactions, the preoccupation with potential drug interactions in daily practice, the usage (frequency and type) of drug interaction information sources, and their satisfaction with the information provided were retrieved from a recent structured questionnaire-based survey among German general practitioners [16].

The study was carried out between June 2005 and August 2005. The questionnaire was sent together with a letter explaining the rationale of the study and a prestamped return envelope. Questionnaires had to be filled in by the pharmacy manager or his substitute. Comprehensibility of the questionnaire was evaluated in a pre-test among

10 community pharmacists. To increase the response rate, responders could win one of five annual subscriptions to an educational community pharmacy drug information service (value = 40 EUR). Four weeks later, a reminder was sent together with a second questionnaire to non-responders of the survey to further boost response rates [20]. To characterise non-responders, gender, age, professional experience, configuration of the drug interaction surveillance software settings, and reason for non-response were assessed in a telephone interview with 50 randomly selected non-responding pharmacy managers.

All returned questionnaires were processed with the automated forms processing software Teleform® version 7.0 from Cardiff Software Inc., Vista, USA. Automated forms processing software was validated by Jorgensen et al. [21] who showed an improved quality of the data while reducing the processing time. To avoid potential errors, all numeric and letter recognitions were verified visually on data sheets and on screen.

Data analysis

Results are expressed as proportions and as means ± standard deviation (SD) or medians with the 25% to 75% interquartile range (IQR). Main descriptive results are expressed as absolute numbers and percentages. Independent two-sample comparison of single variables was analysed using Students' t-test. Chi-square statistics was used for categorical comparisons. In a multiple logistic regression analysis the daily preoccupation with potential drug interactions or the frequency of using drug interaction information sources as dependent variables were dichotomised into ''daily'' (for each prescription, several times daily, daily) versus all other categories (once a week, once a month, less than once a month, never). Covariates were gender, professional experience, working hours [%], pharmacy certified for quality management, pharmacy location at countryside or village, predominantly change customers, postgraduate education as community pharmacist, the pharmacies` software configuration to flag only 'severe' potential drug interactions, and software configuration of the length of the period a patient's past medication history was screened for potential drug interactions. Odds ratios (OR) are presented with 95% confidence intervals (CI). Statistical significance was defined as

a p-value <0.05. All statistical analyses were performed using SPSS for Windows version 13.0 (SPSS, Inc, Chicago, IL, USA).

Results

Characteristics of the study sample

Of 500 invited community pharmacies 57.4% (287) returned the questionnaire. Most questionnaires (87.1%, 250/287) were filled in by the pharmacy manager. More than 95% of the questions were answered by all responders. Characteristics of the responding pharmacists and their community pharmacies are presented in Table 1. Comparison of responding pharmacy managers with 50 non-responding pharmacy managers showed no significant differences with respect to gender (p=0.54), mean age (p=0.56), professional experience (p=0.47), and the location of their community pharmacies (p=0.36). The main reasons for non-response were lack of time or interest (34%) and personal absence during the survey period (26%).

Perception of the risk arising from drug interactions and preoccupation with potential drug interactions

For the majority of the responding pharmacists [91% (261/287)] drug interactions were an important safety hazard in pharmacotherapy. Of these, 19.5% (51/261) judged the clinical relevance of drug interactions to be an outstanding problem, 76.2% (199/261) to be equally important, and only 4.2% (11) to be subordinate compared with other safety hazards in pharmacotherapy. Neither a significant association with gender or postgraduate specialisation in community pharmacy nor a trend with age, workload, or years of professional experience was found (p>0.05). The majority (75.3%; 216/287) of the responding pharmacists mentioned to deal at least daily with potential drug interactions.

Configuration and perception of the quality of drug interaction surveillance software

The community pharmacies' computers were equipped with pharmacy software of 6 different providers and most of them (90.2%; 259/287) used their software to identify potential drug interactions. In contrast, 9.8% (28/287) had inactivated this option in their computer system. Those pharmacies were less frequently certified with a quality management system (p=0.032) and felt less frequently confronted with potential drug interactions (p<0.001). In 18.5% (48/259) of the community pharmacies the drug interaction surveillance software was set to flag only 'severe', in 39.8% (103/259) to

flag ‘severe’ and ‘moderate’, and in 41.7% (108/259) to flag all potential drug interactions. In pharmacies in which the software was set to flag only ‘severe’ potential drug interactions, pharmacists less frequently dealt with potential drug interactions (p<0.001). The median length of the period a patient’s past medication history was screened for potential drug interactions was 120 days (IQR 90-180 days). Pharmacists estimated the quality of their drug interaction surveillance software to be ‘sensitive’ in 80.5 ± 21.5%, to be ‘specific’ in 38.3 ± 32%, and to flag ‘false’ alerts (e.g. multiple or repeated alerts for the same patient, the patient was no longer taking the interacting drug) in 60.6 ± 33.1% of drug interaction alerts. If the software was set to flag only ‘severe’ potential drug interactions, pharmacists (n = 259) rated their drug interaction surveillance software to be less ‘sensitive’ (72.1 ± 27.0% vs. 82.6 ± 19.5%; p=0.018) but more ‘specific’ (54.7 ± 36.7% vs. 34.8 ± 29.8%; p=0.002). When pharmacists estimated the software to produce ‘false’ alerts in ≥ 50% (n=169) of alerts their software was configured to observe a significantly longer period of the medication history (170.5 ± 97.8 days vs. 133.1 ± 82.3 days; p=0.007). Multiple logistic regression analysis confirmed these results: Configuration of the pharmacy software to flag only ‘severe’ potential drug interactions (OR 0.009, 95% CI 0.003, 0.028; p<0.001) and the configuration of the length of the period a patient’s past medication history was screened for potential drug interactions (OR 1.014, 95% CI 1.003, 1.025; p=0.014) were associated with the daily preoccupation with potential drug interactions, while no effect was observed with all other defined covariates (see Methods).

Management of drug interaction alerts by community pharmacy teams

Written directives for the management of flagged drug interaction alerts were available in 18.5% (48/259) of the community pharmacies while 78.4% (203/259) reported to have only verbal instructions. Pharmacists estimated that drug interaction alerts are always ‘considered’ in 86 ± 18.6% of cases by their pharmacy teams. This proportion was not higher if the drug interaction surveillance software was configured to flag only ‘severe’ potential drug interactions (p=0.19). Pharmacists estimated that a more thorough follow-up ‘analysis’ of drug interaction alerts through consultation of further information sources was required in 63.8 ± 32.7% of the alerts. This frequency was higher if the drug interaction surveillance software was configured to flag only ‘severe’ potential drug interactions (p<0.001).

Of all community pharmacies 79.8% (229/287) documented activities triggered by the detection of potential drug interactions. Of them 36.2% (83/229) stated to document their activities only if a 'severe' potential drug interaction was flagged, 20.1% (46/229) only if a physician was contacted, 30.1% (69/229) only if the therapy was modified (e.g. closer monitoring, dose adjustment, or alternative therapy), and 11.8% (27/229) in any situation. Furthermore, pharmacists estimated that in their pharmacies 70.8 ± 28.1% of the customers are informed about potentially interacting drugs.

Perception of use and quality of drug interaction information sources

In case of consultation of drug interaction information sources to analyse more precisely an alert or to answer a specific question, pharmacists indicated to favour drug interaction information provided by their electronic drug interaction system in 81.2 ± 29.6% and the published national drug formulary [22] in 67.2 ± 32% of the cases. More male pharmacists reported to use preferentially (i.e. in ≥ 50% of cases) electronic drug interaction information sources (community pharmacies drug interaction surveillance software, the drug interaction knowledge base of Pharmavista® [19], or further specific electronic drug interaction information sources available via internet or from their local computer or personal digital assistant software (e.g. DRUGREAX© Thompson Micromedex™, Greenwood Village or Stockley's Drug Interactions, Electronic Version 2006 © The Pharmaceutical Press, London, etc.) (p=0.05). In general, 70.3% of the pharmacists (199/283) reported to use their drug interaction information sources 'daily'.

Multiple logistic regression analysis did not show an association between the 'daily' use of drug interaction information sources and defined covariates (see methods). Figure 1 and Figure 2 show satisfaction with the content provided by the drug interaction information sources currently used and the expectations with respect to the content of future drug interaction information sources. The use of the same questions asked in a recent survey in general practitioners [16] enabled direct comparison of responses of community pharmacists with those of general practitioners. Congruently, community pharmacists and general practitioners were most dissatisfied with the content of their drug interaction sources about non-interacting alternative therapies. Both equally considered the severity of the outcome to be an essential information, but all other comparisons of pharmacists' and general

practitioners' satisfaction and future expectations differed significantly ($p<0.001$) (Figure 1 and Figure 2).

Communication between pharmacists and prescribing physicians concerning potential drug interactions

Pharmacists reported a median of 25 (IQR 10-30) overall contacts to prescribing physicians and a median of 3 (IQR 1-6) due to potential drug interactions during the three months preceding the survey. A total of 56.8% (163/287) pharmacists reported to contact physicians in general exclusively by telephone, the remaining 43.2% (124/287) by telephone or fax, video conferencing, email, mail, or via the patient. If the contact was induced by a potential drug interaction most of the pharmacists (72.5%, 208/287) chose the direct communication by telephone.

Pharmacists' perception of the frequency of causes to contact a physician is presented in Figure 3. The majority of pharmacists (62.7%; 180/282) reported to contact physicians 'rarely' or 'never' due to potential drug interactions. Pharmacists working in pharmacies whose drug interaction surveillance software is configured to flag only 'severe' potential drug interactions reported similar frequencies (72.9%; 35/48) to contact a physician 'never' or 'rarely' compared with the other pharmacists (61.2%; 126/208) ($p=0.128$).

Discussion

The use of computer software for prospective medication surveillance is a very common approach to avoid medication errors [1]. In our study all community pharmacies were equipped with drug interaction surveillance software and most of them (90.2%) used it to identify potential drug interactions. Electronic drug interaction checks in community pharmacies and physician offices can reduce the dispensing of prescriptions with severe interactions up to 67.5 % [23]. Although immediate impact on prescription and dispensing has been demonstrated, there is only limited and inconclusive evidence whether the computer software is effective enough to prevent medication errors [24-26]. Evaluation of the performance of pharmacies' electronic drug interaction systems in the USA showed that they largely varied in specificity and sensitivity to identify clinically important potential drug interactions in daily practice [27].

In our survey pharmacists reported to consider 86% of interaction alerts and hereby admit to in fact ignore 14% of them. This override is comparable with 22% of physicians who admitted to ignore alerts without considering more information on the drug interaction [28]. With respect to other studies revealing that physicians and pharmacists override the majority of electronic alerts in primary care [29, 30] this rate seems small. A major reason for ignoring such alerts may be that too many alerts considered irrelevant are provided [31, 32]. Consequently, electronic drug interaction systems can be configured to flag only 'severe' potential drug interactions. Such a configuration was used by 18.5% of responding pharmacists. As expected, in these pharmacies the preoccupation with drug interactions was reduced, drug interactions were more frequently further evaluated, and the pharmacists acknowledged that their electronic drug interaction system may be less 'sensitive' while being more 'specific'.

The approach to filter potential drug interactions by computer systems is indispensable and a promising way to reduce the overwhelming fraction of meaningless alerts. Indeed, Bergk and co-workers [12] showed that their incidence could be reduced by 28% when filtering the fraction of minor and unspecified potential drug interactions. However, the resulting prescription quality strongly depends on the classification of the severity of potential drug interactions and still ignores patient characteristics which could render a 'severe' interaction 'minor' for an

individual patient. Moreover, the very high number of 60% ‘false’ alerts (e.g. multiple or repeated alerts for the same patient, the patient was no longer taking the interacting drug) reported in our survey indicates that also the timing of drug therapy needs to be considered by the interaction software in more detail. Moreover, because many drug interactions are concentration-dependent and can be avoided by appropriately adjusting doses [12] optimised drug interaction systems should also include an alert suppression if an interacting combination is prescribed in adjusted doses. Hence, more sophisticated filters instead of unjustified filters to flag only potential drug interaction of highest severity are needed. Indeed, Peng and coworkers [33] reported that sophisticated filters (assessment of time overlapping of drug therapies, of duration of drug therapy, and of total drug dose) could reduce the incidence of potential drug interaction alerts by 71% and in combination with clinical pharmacists’ review even by 94%. Consequently, software providers should be challenged to revise and optimise the current drug interaction surveillance software and also include an alerting history in their software because many alerts are caused by already checked repeat prescriptions and therefore are likely overridden [29, 30, 34].

Pharmacists most frequently sought information on drug interactions in their electronic surveillance system even though it did not meet their expectations in most important aspects. Particularly, most pharmacists complained about a lack of information about non-interacting alternative therapies and the specific advice for dose adjustment. General practitioners expressed the same criticism [16]. In agreement, Hansten et al. [27, 31] noticed that management guidelines provided by drug interaction information sources are often inadequate and should be considered in the classification of potential drug interactions.

With regard to the content of future drug interaction information sources community pharmacists and general practitioners expressed very different expectations with the largest difference seen in the valuation of information components on advice for dose adjustment and non-interacting alternatives which were less essential for community pharmacists. This result reflects the different situations and needs of the two professions in daily practice.

In comparison with further reasons to contact a physician potential drug interactions play an inferior role (Figure 2). The relatively low frequency of contacts (one per month) with respect to the high frequency of alerts and the statement that the majority of their patients is informed about the detected drug interactions indicates that in the process of prescribing and dispensing community pharmacies manage drug interaction alerts mainly themselves. This raises the question on relevance and quality of this management.

Some limitations of this survey merit discussion. First, the overall response rate was only 57.4% making a non-response bias possible. However, this figure compares well with a recent survey in German general practitioners [16] and the fact that nonresponding pharmacists did not differ from responders suggests that such a bias will not be critical. Second, our study was conducted in the German-speaking part of Switzerland and represents the health care situation in this region in the year 2005. However, there are many reasons justifying extrapolation of its results to other European health care systems. Indeed, drug interaction software in community pharmacies from all German speaking countries (Switzerland, Germany, and Austria) is based on the same drug interaction database and in these countries also many of the software systems used by the physicians have integrated this database. Because of the numerous similarities in drug prescription and dispensing in Switzerland and Germany it appears likely that the differences observed between the two professions rather relate to differences in their tasks and needs than differences between countries. It therefore supports the notion that for each profession specific tools should be developed.

In conclusion, our study revealed that the drug interaction software supporting community pharmacists lacks sensitivity and specificity while producing a high rate of ‘false’ alerts. The study also showed that the information needs of community pharmacies differed considerably from those of general practitioners. Hence, substantial improvement of drug interaction software systems is required at least in two important aspects, the suppression of inappropriate alerts and the tailoring to the needs of the user.

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Table 1: Characteristics of the participating pharmacists and their pharmacies (N=287)

Characteristics of pharmacists	
Mean age ± SD	45.0 ± 9.4 years
Female gender	147 (54.8%)
Mean years of professional experience ± SD	18.5 ± 9.5 years
Mean working hours ± SD [%]	90 ± 15%
Pharmacy manager	250 (87.1%)
Postgraduate specialisation as community pharmacist	215 (74.9%)
Characteristics of community pharmacies	
Location	
City or urban agglomeration	200 (70%)
Countryside or village	86 (30%)
Predominantly regular customers (versus change customers)	212 (74.4%)
Implementation of quality management system	
Implemented	27 (9.4%)
Submitted for certification	83 (28.9%)
No quality management system	176 (61.3%)

Figure 1: Swiss pharmacists' and German general practitioners' satisfaction with the content provided by the drug interaction information sources they currently use.

Comparison of the results of two questionnaire surveys in 287 pharmacists and 1216 general practitioners.

N = Number of responding pharmacists and general practitioners

P-value: Chi-square analysis of differences between responses of pharmacists and general practitioners who answered that the content provides insufficient information.

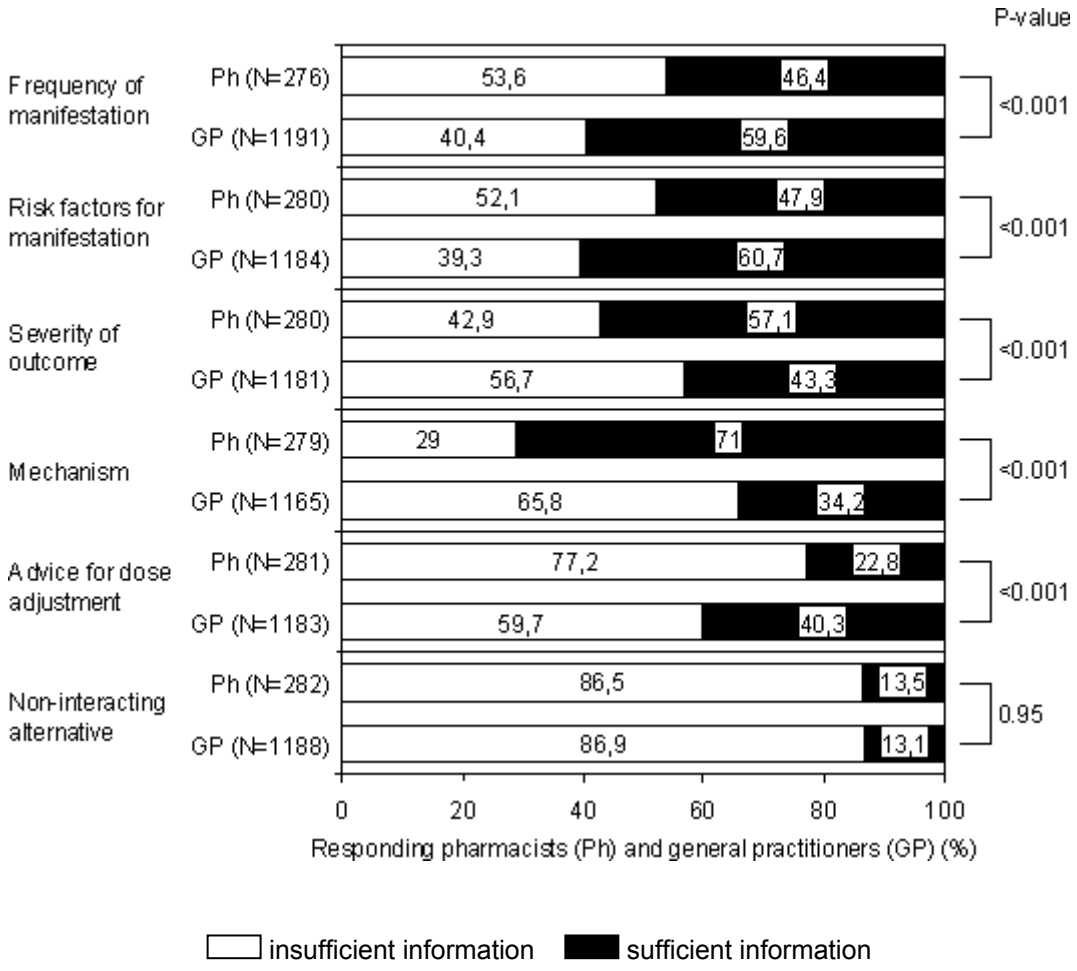


Figure 2: Swiss pharmacists' and German general practitioners' expectations with respect to the content of future drug interaction information sources.

Comparison of the results of two questionnaire surveys in 287 pharmacists and 1216 general practitioners by chi-square analysis.

N = Number of responding pharmacists and general practitioners

P-value: Chi-square analysis of differences between responses of pharmacists and general practitioners who expected that the content is essential.

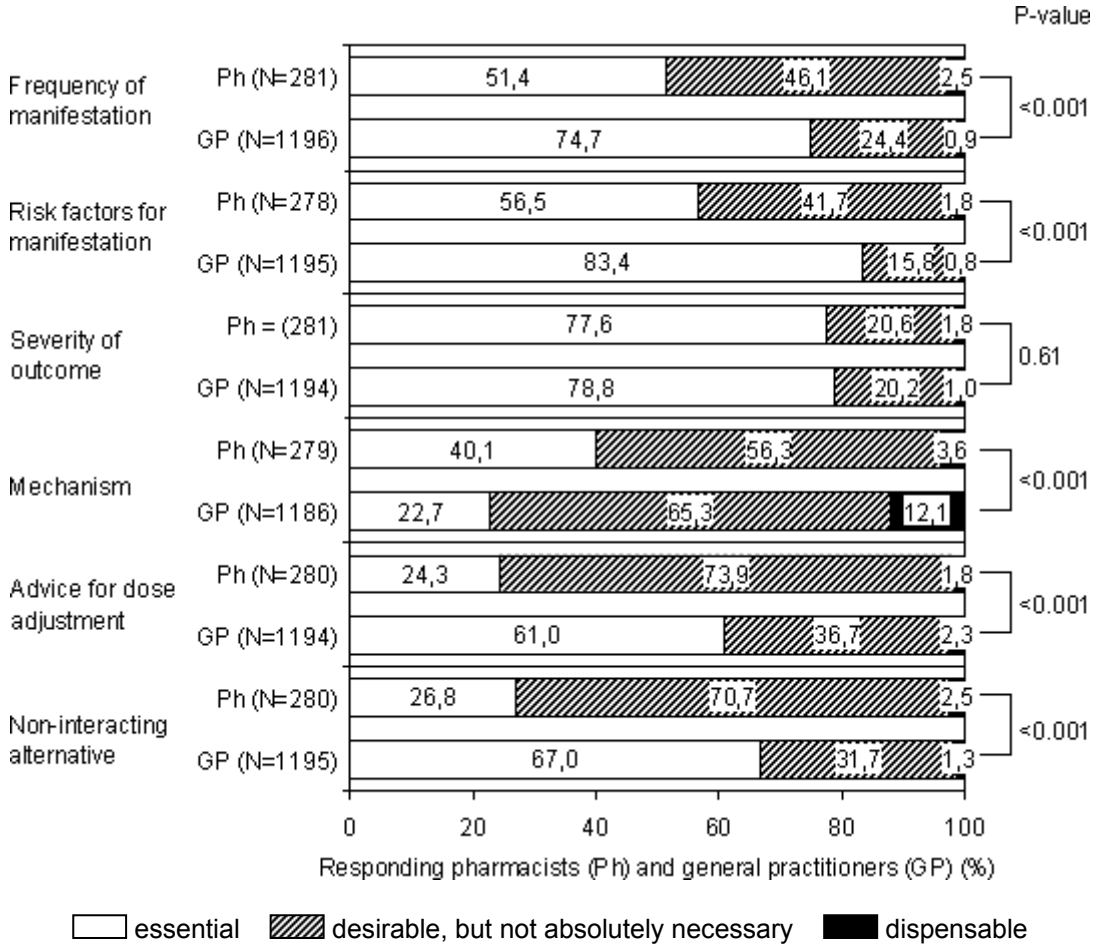
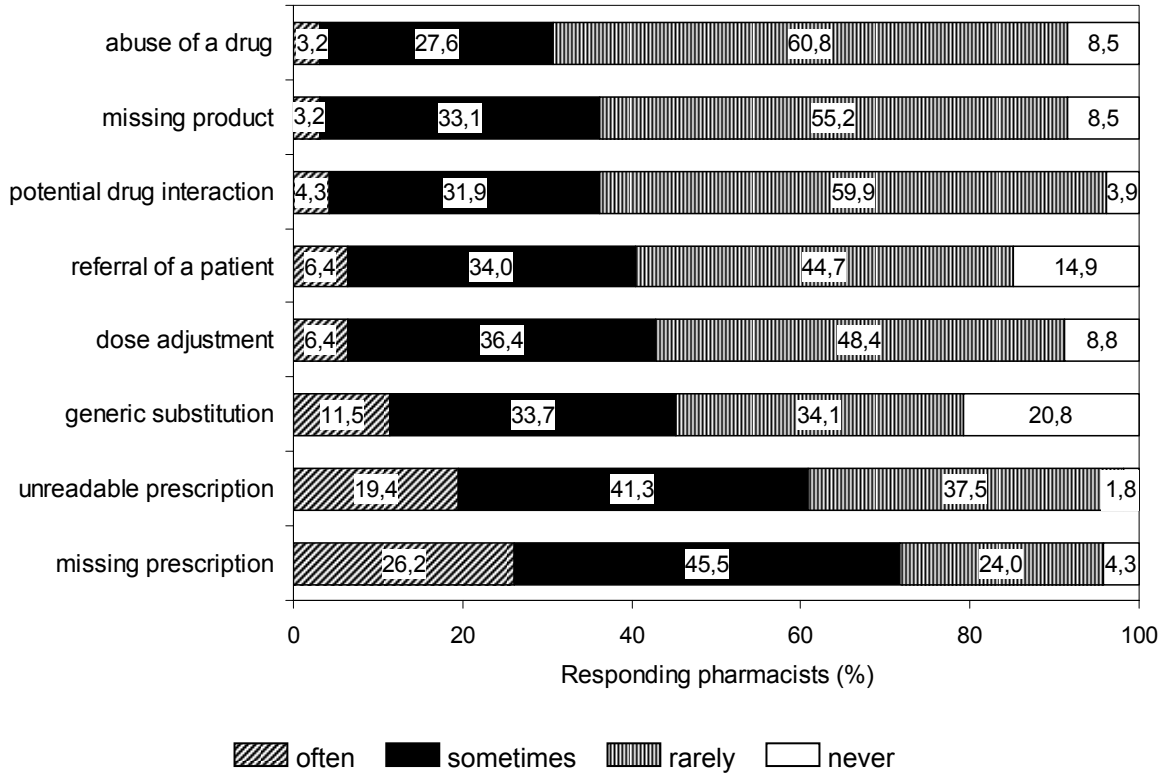


Figure 3: Reasons to contact a physician as indicated by 287 Swiss pharmacists in a questionnaire survey.



6 Project D: Management of drug interaction alerts in community pharmacies

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Summary

Background and objective:

Drug interaction alert systems are commonly used in community pharmacies to identify potential drug-drug interactions. However, depending on the software default setting, pharmacists may override alerts because they are too numerous. We explored the handling of drug interaction alerts by community pharmacies in Switzerland.

Methods:

Data were collected by 15 pharmacy students in 15 Swiss community pharmacies. The medication history and the drug interaction alerts of 600 patients who had ≥ 2 drugs on prescription were assessed, and the pharmacists in charge were interviewed about their management of drug interaction alerts.

Results:

In the 15 study pharmacies, the computer systems were programmed to flag only 'severe' drug interactions in 4, 'severe or moderate' in 6, or 'severe, moderate or minor' in 5 pharmacies. The median frequency of drug interaction alerts increased with decreasing default severity level from 0.5 to 40 respectively to 76 per 40 patient visits and pharmacy. Due to these default settings, 277 (35.2%) of 787 potential drug interaction alerts on new or repeated prescriptions were overridden by computer systems. Only 256 (32.5%) of 787 potential drug interactions emerged from new prescriptions. The alert systems produced 656 alerts of which 146 were irrelevant due to multiple alerting of the same interaction or of drug combinations currently no longer taken. Of the 510 remaining relevant drug interaction alerts, 289 (56.7%) were overridden by community pharmacists without any action taken. If the pharmacist took care of a patients' prescription him- or herself (as opposed to just controlling a prescription after a technician took care of the patient), fewer drug interaction alerts were overridden by the pharmacist (Odds ratio [OR] 0.6, 95% confidence interval [CI] 0.42 – 0.98; p=0.042). Both technical override (by default settings) and pharmacists' decision to override alerts summed up to a total of 71.9% overrides (566 of 787 potential drug interactions). Of the remaining 211 interactions alerts, 87 (41.2%) were checked more closely by consulting literature, contacting the prescribing physician or

discussing the issue with the patient. This led to 55 (63.2%) interventions (close monitoring, adjustment of dose or ingestion time, therapy stop, or switching to alternative therapy). Determinants associated with action taken after an interaction alert were the potential high severity (severe or moderate) (OR 3.34, 95% CI 1.77-6.31; p<0.001) as well as the alert flagged for the first time (OR 3.76, 95% CI 1.98-7.14; p<0.001). All severe potential drug interactions (N=10) generated an alert and all caused an intervention.

Conclusions:

Pharmacists override a substantial proportion of drug interaction alerts of minor or moderate potential severity by ignoring them or by programming the system to only flag drug interactions of potentially high severity. More sophisticated systems with improved sensitivity and specificity are required. As long as they are not available, it is important to ensure that at least potentially severe drug interactions are not missed, a goal that seems to be largely achieved.

Background

Community pharmacists can play an important role in improving drug therapy by preventing the use of unsafe or non-effective drug regimens and by avoiding drug interactions with potentially harmful effects on patients [1]. To comply with this responsibility, community pharmacies in various countries, including Switzerland, fulfil the patients' prescriptions, store an electronic medication history and use computer-assisted review tools.

Drug interaction alert systems have already been proven to be effective in community pharmacies and in physician offices in reducing the number of potential drug interactions [2, 3[. A recent study revealed that between 20% and 46% of prescription drug claims were reversed when pharmacies were alerted for important potential drug interactions [4]. However, drug interaction alert systems in pharmacies have been shown to be too unsophisticated [5], leading to an excessive number of alerts which pharmacists or physicians find to be trivial or inappropriate for the current situation [6]. As a result, physicians and pharmacists override the majority of drug interaction alerts in primary care [7-9]. In a questionnaire survey among physicians, 22% admitted to frequently override drug interactions alerts without properly checking them [10]. A common way to reduce the perceived excess number of interaction alerts is to activate by default only a subset of the entire drug interaction database, for example only drug interactions flagged with the highest level of potential severity.

In a recent questionnaire survey most Swiss community pharmacists (90.2% of those who responded) reported to regularly use drug interaction alert systems [11]. A majority (58.3%) configured their system to flag only moderate to severe potential drug interactions thought to be clinically relevant. Nevertheless, they reported a lack of specificity of their drug interaction alert systems, and they reported to override only a low rate (14%) of drug interaction alerts.

With the present study we aimed at further exploring the self reported drug interaction alert management of a sample of community pharmacies in Switzerland. In particular, we focused on the nature of drug interaction alerts and on pharmacists' handling them in daily routine.

Methods

Study design, patients and data collection

We recruited 15 pharmacy students who were in their 5th study year and who attended their externship in a Swiss community pharmacy. They received written instructions and specific training. Each student collected data from patients who presented a new or a repeat prescription which was delivered or at least double checked by the pharmacist on duty. Inclusion criteria of patients were age ≥ 18 years, multiple (>2) drugs prescribed and at least one prior visit at this pharmacy to pick up prescription drugs during the last 3 months.

Patient records contained the patients' age and gender, the drug history of the previous 3 months, and data on drug interaction alerts; potential drug interactions were identified if drugs were prescribed on the same or on separate prescriptions, and issued by the same or by separate physicians.

After consecutive collection of 20 cases, the students interviewed the pharmacist on duty using a structured questionnaire (Figure 1). During this interview he confronted the pharmacist with all potential drug interaction alerts produced by the electronic system, and the student recorded the pharmacists' management of these drug interaction alerts. In addition, the students assessed the default configuration of the drug interaction alert systems.

The students were instructed to collect data, and the community pharmacists gave informed consent. All data were anonymised in the pharmacy prior to being analysed. Each student repeated data collection on another day when another pharmacist was on duty, aiming at collecting a sample of 40 records per pharmacy.

The study was carried out in May 2005. All data (patient records and structured interviews) were processed with the automated forms processing (AFP) software Teleform® version 7.0 from Cardiff Software, Inc, Vista, CA, USA. AFP was validated by Jorgensen et al. [12] who showed that AFP software reduced processing time. Due to possible errors, all numbers and letters which were recorded were verified visually on data sheets and on screen.

Classification of potential drug interactions

All contributing Swiss community pharmacies work with electronic drug management systems. The knowledge base on drug interactions integrated in these systems is Pharmavista® [13], a system from the German ABDA-Database [14] adapted to the Swiss market. Potential drug interactions are classified into 'severe' (life-threatening / intoxication / permanent harm), 'moderate' (frequent therapeutic problems / combination can be administered but close monitoring required), 'minor' (increased or decreased drug effect / only specific subgroups affected), 'negligible' (no or limited clinical effects / generally no modification of therapy required), and 'external specifications' (only occurring in particular cases / clinical consequences unclear). The majority of drug interaction alert systems used in Swiss community pharmacies can be set to flag only potential drug interactions of moderate and/or high severity. In this study, all potential drug interactions of severe, moderate or minor clinical relevance according to the interaction database in Pharmavista® were investigated.

Statistical analysis

Descriptive results are expressed as medians with the corresponding 25% to 75% interquartile range (IQR), or as proportions. Main descriptive results are expressed as absolute numbers and percentages. Numerical variables were tested for normal distribution using the Kolmogorov-Smirnov test. The non-parametric Mann-Whitney-U test was used for unpaired two-sample comparisons. Nominal data in independent groups were compared with Pearson chi-square analysis. Covariates associated with the override of drug interaction alerts were detected with multiple logistic regression analysis. Odds ratios (OR) are presented with 95% confidence intervals (CI). Statistical significance was defined as p-value <0.05. Statistical analysis was performed using SPSS for Windows version 13.0 (SPSS, Inc, Chicago, IL, USA).

Results

Patient characteristics

The study encompassed data on 600 outpatients recruited in 15 community pharmacies operating with the same drug interaction database. Of those, 324 (54.4%) were female, their median age was 63 (IQR 50-75) years, and 275 (45.8%) were ≥ 65 years. They were treated with a total of 3522 drugs which corresponded to 10,556 possible drug pairs. For each patient a median of 5 (IQR 4-8) drugs and a median of 10 (IQR 6-28) possible drug pairs were identified. The number of drugs did not differ between male and female patients (p=0.76).

Potential drug interactions in general

The analysis of the medication histories yielded a total of 961 potential drug interactions (9.1% of 10,556 possible drug pairs), affecting 375 (62.5%) patients. Of those, 413 (43.0%) were classified as minor, 538 (56.0%) as moderate, and 10 (1.0%) as severe. These potential drug interactions were described in 151 separate monographs of the drug interaction database Pharmavista®. Per patient, a median of 1 (IQR 0-2) potential drug interaction was found. Most prevalent drug classes involved were drugs affecting the cardiovascular system (30.8%), the nervous system (17.6%), the alimentary tract and metabolism (15.4%), and the musculoskeletal system (15.0%). Patients with one or more potential drug interaction were treated with significantly more drugs than those without (6 versus 4; p<0.001).
Of the 961 potential drug interactions detected in the medication history, 174 (18.1%) were interactions between drugs previously picked up by the patient at a prior visit at the pharmacy. Thus, the remaining 787 (81.9%) potential drug interactions were detected upon issuing a new or a repeat prescription.

Frequency and nature of drug interaction alerts

Individual configuration of the drug interaction alert systems in the 15 community pharmacies generated a total of 656 drug interaction alerts. Of those, 146 alerts were irrelevant due to multiple alerting for the same drug interaction (N=103; 69.9%) or due to alerting of drug combinations of which one drug was no longer taken (N=43; 30.1%). Thus, out of 787 potential drug interactions caused by a new or repeat

prescription, 510 (64.8%) generated a relevant alert affecting 312 (52%) patients. The remaining 277 (35.2%) potential drug interactions were systematically overridden because of the default configuration of the drug interaction alert systems which flagged only distinct categories of potential drug interactions (Figure 2). In four of the 15 community pharmacies, the system was set to flag only severe, in 6 to flag severe or moderate, and in 5 to flag severe, moderate or minor potential drug interactions. Depending on these settings, the median number of alerts per pharmacy and per 40 patient visits increased from 0.5 (IQR 0-1) when only severe interactions were flagged, to 40 (IQR 35-48) when severe or moderate, and to 76 (IQR 73-91) when severe, moderate or minor potential drug interactions were flagged. Overall, the median number of alerts per pharmacy and per 40 patient visits was 43 (IQR 2-73).

Of 787 potential drug interactions, 256 (32.5%) emerged from a new prescription and were observed for the first time. Of those, 147 (57.4%) generated an alert and 109 (42.6%) were overridden because of the default software setting. The time period a patients' past medication history was screened for potential drug interactions can also be programmed by the pharmacy. The median number of days set as default was 100 (IQR 90-120 days). In pharmacies with a longer prior observation period (≥ 100 days; N=7), the number of irrelevant alerts was statistically significantly higher compared to those with a prior screening period below 100 days (11.5 versus 4; p=0.001). The majority (369, 72.4%) of the 510 potential drug interactions causing alerts were the result of a prescription by the same physician, and 261 (51.2%) were detected on the same prescription.
Table 1 displays characteristics and pharmacist's management of drug interaction alerts generated by the 10 most prevalent of 787 potential drug interactions detected on new or repeat prescriptions.

Management of drug interaction alerts in community pharmacies

The handling of drug interaction alerts by community pharmacists is displayed in Figure 2. Pharmacists reported that 289 of 510 alerts (36.7%) were overridden without checking them (Figure 2). When the pharmacist took care of the prescription him- or herself (as opposed to having a pharmacy technician taking care of it), significantly fewer drug interaction alerts were overridden (Table 2) (410 [80.4%] of

potential drug interactions generating alerts were only double checked by the pharmacist, but the prescription was taken care of by a pharmacy technician in the pharmacy).

Pharmacists stated that 87 (11.1%) alerts of potential drug interactions were analysed in more detail by consulting literature, contacting the prescribing physician or discussing the issue with the patient (Figure 2). The main reasons for exploring a drug interaction in more detail were higher severity (severe or moderate) of the potential drug interaction, or the detection of a potential drug interaction for the first time (Table 3). Out of 87 alerts which were explored in more detail, 55 (63.2%) prompted an intervention (e.g. close monitoring of the therapy, adjustment of dose or ingestion time, termination of a therapy or switching to an alternative therapy) (Figure 2).

All severe potential drug interactions (N=10) generated an alert and all caused an intervention. These were the combination of a nitrate and a phosphodiesterase-5 inhibitor (N=3), a monoamono oxidase inhibitor and a sympathomimetic drug (N=1), the combination of an HMG-CoA reductase inhibitor and a macrolid antibiotic (N=2), an oral anticoagulant and a salicylate (N=3), or combining potassium with a potassium-sparing diuretic (N=1).

According to the pharmacists, they decided to inform 34 (15.9%) of 204 patients with drug interaction alerts about the potential risk of 42 (5.3%) of 787 potential drug interactions.

Discussion

We found a substantial proportion (71.9%) of overriding potential drug interactions in daily pharmacy practice. In our analysis we distinguished between systematic override of potential drug interactions via configuration of the drug interaction alert systems (35.2%), and overriding potential drug interactions generated by computer alerts without taking further action (36.7%). Previous studies exploring the management of drug interaction alerts reported even higher frequencies of overriding alerts [7-9].

In our study, pharmacies were free to configure the system as they liked. Thus, they decided to set the default for alerts for various severities of potential drug interactions, and they could choose the period of previous medication history in a patient record covered by the drug interaction check. We set as a standard a time period of 3 months because most drug packages are designed to cover a therapy of 3 months, and therefore potential drug interactions during chronic therapies should be identified. We defined any potential drug interaction described in the drug interaction database (severe, moderate or minor) as relevant for drug interaction check without any filtering. The same drug interaction database was used in all study pharmacies. Thus, the frequency of detecting and overriding drug interaction alerts depends on all these parameters, and they are rarely comparable. In our study we found by on-site observation a 56.7% override of drug interaction alerts, as compared to self-reported override of 14% in a previous study with similar pharmacies using the same drug interaction database [11].

To reduce the frequency of clinically irrelevant interaction alerts, most pharmacies in our study set their systems to flag only potential drug interactions of high severity. Consequently, they tolerated the computerised override of 35.2% of potential drug interactions of only minor or even both, moderate or minor severity, including 109 first-time potential drug interactions. Bergk and co-workers [15] showed that the frequency of alerts could be reduced by 28% when filtering the fraction of minor and unspecified potential drug interactions. A panel of pharmacists concluded that the sensitivity of the computer systems should be adjustable [8]. However, there is no good data basis to support an arbitrary delineation of drug interaction alerts, and

there is a risk of patients being harmed by drug interactions rated as being low risk drug interaction [16]. In a study of potential drug interactions with transplant medications, it was noted that, if the system was set to alert only for contraindicated pairs, 90% of clinically significant interactions would be missed [17]. Therefore, the override of drug interaction alerts of moderate or minor severity may be a questionable step.

Various reasons may contribute to the remarkable proportion of overridden interaction alerts. A main reason for overriding alerts may be that pharmacists are desensitised to check drug interaction alerts because they are inundated with too many inappropriate or even invalid alerts [6, 18]. Hansten and Horn referred to this effect as ‘alert fatigue’ [19]. On the other hand, community pharmacists considered drug interaction alerts to be useful and did not state that a high alert frequency decreases the ability to spot clinically relevant drug interactions [20].
This study further suggest that pharmacists were more likely to override potential drug interactions if a technician handled the prescription and the pharmacist only double-checked it for control purposes, as opposed to handling the prescription him or herself. In Switzerland, the pharmacists on duty is required to check all drugs dispensed on prescription by a technician, but this findings indicates that the pharmacist may still be less aware of a possible interaction alert on computer if someone else handles the prescription.

In our study, only a small part of the interaction alerts were flagged for the first time. A high rate (71.2 %) of alerts was probably useless. They were caused by the renewal of drug combinations that might already have been checked before, by invalid alerts due to previous discontinuation of interacting drugs, or by multiple alerts for the same potential drug interaction (Figure 2). The high frequency of alerts caused by renewals was already reported by previous studies [7, 8]. Hence, intelligent computer systems allowing the documentation and thereby specific inactivation of previously evaluated drug interaction alerts on an individual patient record level to reduce or eliminate duplication alerts would be desirable [8]. Indeed, Peng and co-workers [21] reported that sophisticated filters (e.g. assessment of time overlapping of drug therapies, of duration of drug therapy, and of total drug dose) could reduce the incidence of potential drug interaction alerts by 71% and in

combination with pharmacists' review even by 94%. Our results further underline the need for such sophisticated software filters.

Another reason for overriding drug interaction alerts without further evaluation might be the attitude of pharmacists who may consider most drug interactions to be clinically irrelevant for their patients based on personal experience. Indeed, although in theory potential drug interactions are common, only few have serious clinical consequences [22-24]. Furthermore, the computer systems produce a high number of alerts, but they do in fact overestimate the risk of drug interactions since by far not all alerts would lead to clinical consequences in all patients [25]. Thus, as revealed in this study, pharmacists tend to focus on potentially relevant potential drug interactions according to the classification provided by the drug interaction database. A similar reasoning was reported by physicians who admitted to override drug interaction alerts; 98% believed that the potential drug interaction was not serious, and 87% thought that it was not relevant to their patient [10]. However, decision based on personal experience alone may not be good enough to manage risks, because the number of observations made by an individual heath care provider is not sufficient to predict the likelihood of an individual patient to suffer from a drug interaction [26].

A majority (61%) of 221 alerts not overridden by pharmacists did not lead to specific action, and pharmacists often did not further evaluate an alert because it was already evaluated in the past (Figure 2). However, when they analysed an alert more precisely by consultation of the literature, by contacting the prescribing physician or by discussing the problem with the patient, an intervention frequently occurred. Consequently, both the decision whether a more in depth analysis of an alert is required, as well the decision what to do about it, are important intellectual services provided by pharmacists. Further studies are needed to investigate if these decisions and interventions were adequate and whether they had indeed beneficial clinical consequences for the patients.

The majority of potential drug interactions alerts were caused by a prescription issued by the same physician (72.4%), and in 52.4% of alerts the potentially drugs were on the same prescription. The likelihood of overriding interaction alerts or of evaluating them in more detail was neither associated with drugs being prescribed by

separate physicians (versus same physician), nor with drugs being prescribed on separate prescriptions. However, a possible approach for community pharmacies to reduce the workload induced by potentially irrelevant alerts may be to focus only on patients getting drugs prescribed by different prescribers. Tamblyn and co-workers [27] revealed that patients who had a single primary-care physician were less likely to be prescribed drugs potentially causing a drug interaction compared with patients with more than one prescriber.

Of the potential drug interactions classified as severe, none was overridden by the pharmacists and all were managed by intervention in our study. Thus, the classification of a potential drug interaction as being potentially severe is a strong predictor for a subsequent work-up of the alert by the pharmacist. This emphasised the need for a drug interaction classification used by commercially available databases which is indeed based on pharmacologically correct, timely and appropriate information. Most potential drug interactions do not have to be regarded as absolute contraindications but can be managed adequately e.g. by close monitoring, dose adjustment or a coordinated sequence of drug administration (15). However, most of these manageable potential drug interactions are classified as ‘moderate’ or ‘minor’ in drug interaction databases and are therefore often ignored *a priori* by default. Computer programs producing interaction alerts and at the same time providing also management options to health care providers may be highly welcome [6, 28].

Several strengths and limitations of this study merit further discussion. In our study we have chosen to conduct an on-site observation using trained students shortly before getting their pharmacy diploma. Even though the data prescriptions issued and the number and nature of all potential drug interactions in the medication history with all flagged alerts are likely to be valid, and even though structured interviews with the pharmacist on duty were conducted on the same day to reliably reflect the management and overriding habits of such alerts, we still rely on subjective data from interviews. There is a possibility of some sort of bias because the student and the pharmacist on duty are part of the same pharmacy team. However, this was not considered to be a major problem, according to a self-evaluation of the students. The study was conducted in the German-speaking part of Switzerland and may only represent the health care situation in this region. However, a main reason to

extrapolate the findings to other European health care systems is the fact that the drug interaction alert systems in community pharmacies from all study pharmacies is the same as used in all other parts of German-speaking countries (Switzerland, Germany, and Austria). Another limitation of this study is the relatively small sample sise of 15 community pharmacies. Therefore, the study may in theory reflect a chance finding not generalisable to other populations. Furthermore, we did not assess clinical outcomes on a patient level, and we don't know whether patients actually suffered from clinical consequences of drug interactions or whether drug interactions were prevented by pharmacists' interventions. Another point to keep in mind is that, even though most community pharmacies are adequately equipped with drug interaction alert systems, this often does not apply to over-the-counter drug use. There is a potential for drug interactions with over-the-counter medication, but few pharmacies record over-the-counter drug use in electronic patient records. Efforts to increase the identification and awareness of potential drug interactions in this area may be needed [29].

In summary, this study indicates that overriding alerts for potential drug interactions of minor to moderate severity is quite frequent. Pharmacists sometimes override drug interaction alerts without further evaluation either by ignoring them after an alert came up, or by setting their systems to flag only potential drug interactions of high severity. Nevertheless, although drug interaction alert systems have several limitations, they may help to improve drug safety and to provide information for an adequate management of potential drug interactions by community pharmacists. Improved systems are required with higher sensitivity and specificity and lower numbers of inappropriate alerts. As long as no more sophisticated filters are available, it is important to avoid the override of severe potential drug interactions, a goal that seems to be largely accomplished based on the findings of this study.

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Tables

Table 1: The 10 most prevalent potential drug interactions detected on new or refill prescriptions of regular pharmacy customers and management of drug interaction alerts by community pharmacists.

Drug combination	Severity	Potential adverse effect	Patients [N (%)]; (N=600)	Potential drug interactions[1] [N (%)]; (N=787)	Alerts [N (%)]; (N=510)	Override[2] [N (%)]; (N=289)	Precise Analysis[3] [N (%)]; (N=87)	Intervention[4] [N (%)]; (N=55)
Diuretic (loop or thiazide) + NSAID	moderate	Decreased diuretic and antihypertensive effectiveness	45 (7.5)	52 (6.6)	42 (8.2)	20 (6.9)	5 (5.7)	1 (1.8)
ACEI + diuretic (loop or thiazide)	minor	Postural hypotension	44 (7.3)	50 (6.4)	36 (7.1)	26 (9)	3 (3.4)	1 (1.8)
Antidiabetes agent + ACEI	minor	Hypoglycemia	37 (6.2)	49 (6.2)	42 (8.2)	28 (9.7)	4 (4.6)	1 (1.8)
ACEI + NSAID	moderate	Decreased antihypertensive effectiveness and/or renal function	32 (5.3)	34 (4.3)	25 (4.9)	12 (4.2)	4 (4.6)	2 (3.6)
NSAID + glucocorticoid	moderate	Gastro intestinal ulcers and/or bleedings	25 (4.2)	28 (3.6)	25 (4.9)	15 (5.2)	3 (3.4)	0 (0)
Antidiabetes agent + thiazide diuretic or analogue	minor	Decreased antihyperglycemic effectiveness	22 (3.7)	33 (4.2)	24 (4.7)	18 (6.2)	2 (2.3)	1 (1.8)
Beta blocker + NSAID	moderate	Decreased antihypertensive effectiveness	21 (3.5)	24 (3.1)	20 (3.9)	11 (3.8)	3 (3.4)	1 (1.8)
Biphosphonates + polyvalent cations[5]	moderate	Decreased biphosphonate effectiveness	20 (3.3)	28 (3.6)	20 (3.9)	8 (2.8)	6 (6.9)	6 (10.9)
Neuroleptic agent + SRI	moderate	Increased plasma levels or QT-time prolongation	20 (3.3)	20 (2.5)	13 (2.5)	7 (2.4)	4 (4.6)	3 (5.5)
Antidiabetes agent + beta blocker	minor	Decreased diabetic control	18 (3.0)	25 (3.2)	18 (3.5)	14 (4.8)	3 (3.4)	2 (3.6)

[1]In one patient the same potential drug interaction could be de detected several times, e.g. when treated with two antidiabetic agents metformin and glimepiride + ACEI

[2]Override by pharmacist without any evaluation = The drug interaction was neither mentioned nor considered during the fulfilment of the prescription

[3]Precise analysis= Consultation of e.g., literature, prescriber(s), or patient himself

[4]Intervention = E.g., close monitoring, adjustment of dose or ingestion time, stop of therapy, or alternative therapy

[5]Polyvalent cations= Drugs containing e.g. aluminium, calcium, magnesium, iron, etc. (E.g., antacids, mineral nutrients)

NSAID = non-steroidal anti-inflammatory drug; ACEI = angiotensine converting enzyme inhibitor; SRI = serotonin reuptake inhibitor

Table 2: Determinants associated with the override (N=289) of drug interaction alerts (N=510) in community pharmacies.

Determinant	N (%)	P-value	Adjusted OR	95% CI
Gender (female)	162 (56.1)	0.749	0.94	0.66-1.35
Age (≥ 65 years)	141 (48.8)	0.495	1.13	0.79-1.63
Fulfilment of prescription by pharmacist himself	48 (16.6)	0.042	0.63	0.40-0.98
Different prescribers	78 (27.0)	0.722	0.92	0.60-1.43
Different prescriptions	157 (54.4)	0.710	0.93	0.63-1.37
Potential severity (severe or moderate)	144 (49.8)	0.067	0.71	0.50-1.02
Period a patient's past medication history was screened for potential drug interactions (≥100 days)	155 (53.6)	0.075	1.39	0.97-1.99
First time alert	69 (23.9)	0.191	0.76	0.51-1.14

OR = Odds ratio; CI = Confidence interval

Table 3: Determinants associated with the more precise analysis (N=87) of drug interaction alerts (N=221) in community pharmacies.

Determinant	N (%)	P-value	Adjusted OR	95% CI
Gender (female)	49 (56.3)	0.500	0.81	0.44-1.49
Age (≥65 years)	38 (43.7)	0.797	1.08	0.58-1.98
Fulfilment of prescription by pharmacist himself	23 (26.4)	0.640	1.18	0.59-2.36
Different prescribers	28 (32.2)	0.994	1.00	0.49-2.05
Different prescriptions	54 (62.1)	0.410	1.32	0.68-2.53
Potential severity (severe or moderate)	67 (77.0)	< 0,001	3.34	1.77-6.31
Period a patient's past medication history was screened for potential drug interactions (≥100 days)	43 (49.4)	0.333	1.35	0.74-2.48
First time alert	42 (48.3)	< 0.001	3.76	1.98-7.14

OR = Odds ratio; CI = Confidence interval

Figures

Figure 1: Question scheme used in the structured interview with pharmacists on duty to assess the actions taken due to drug-drug interaction alerts 1:

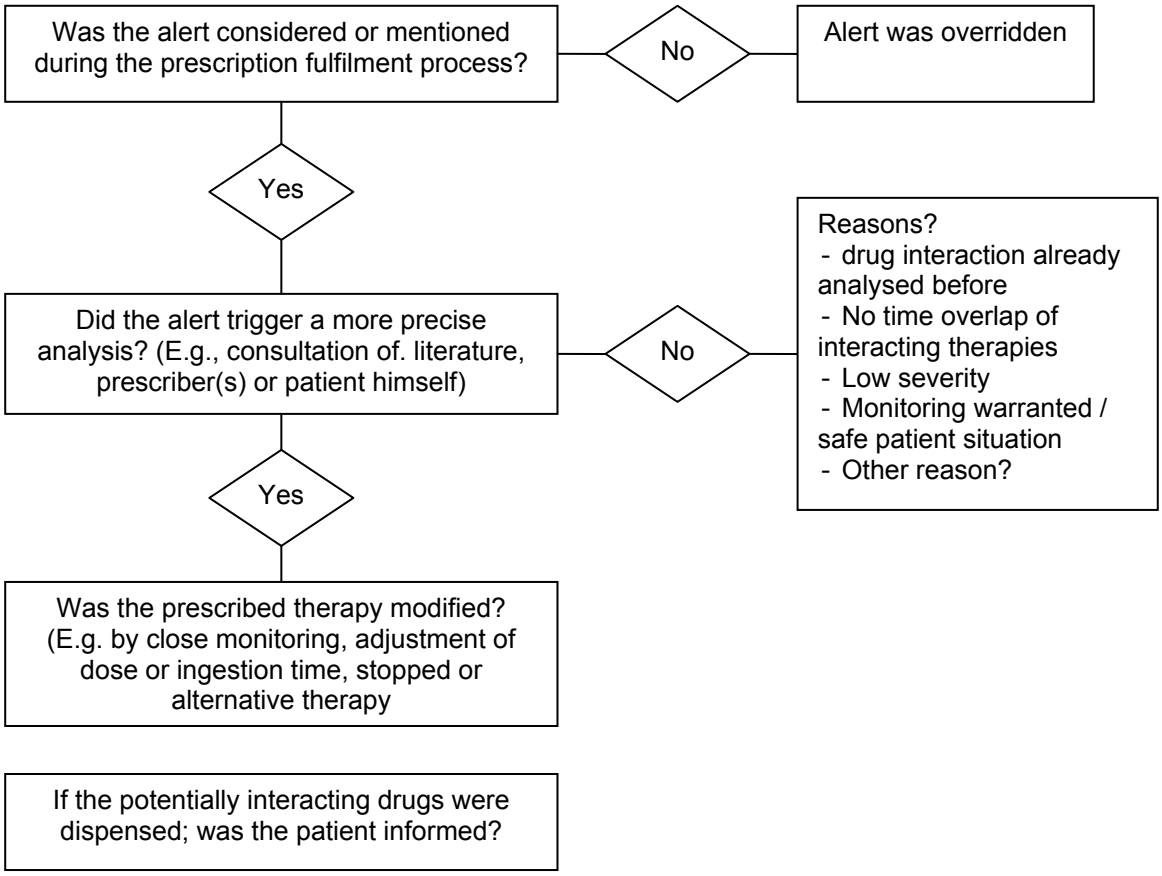
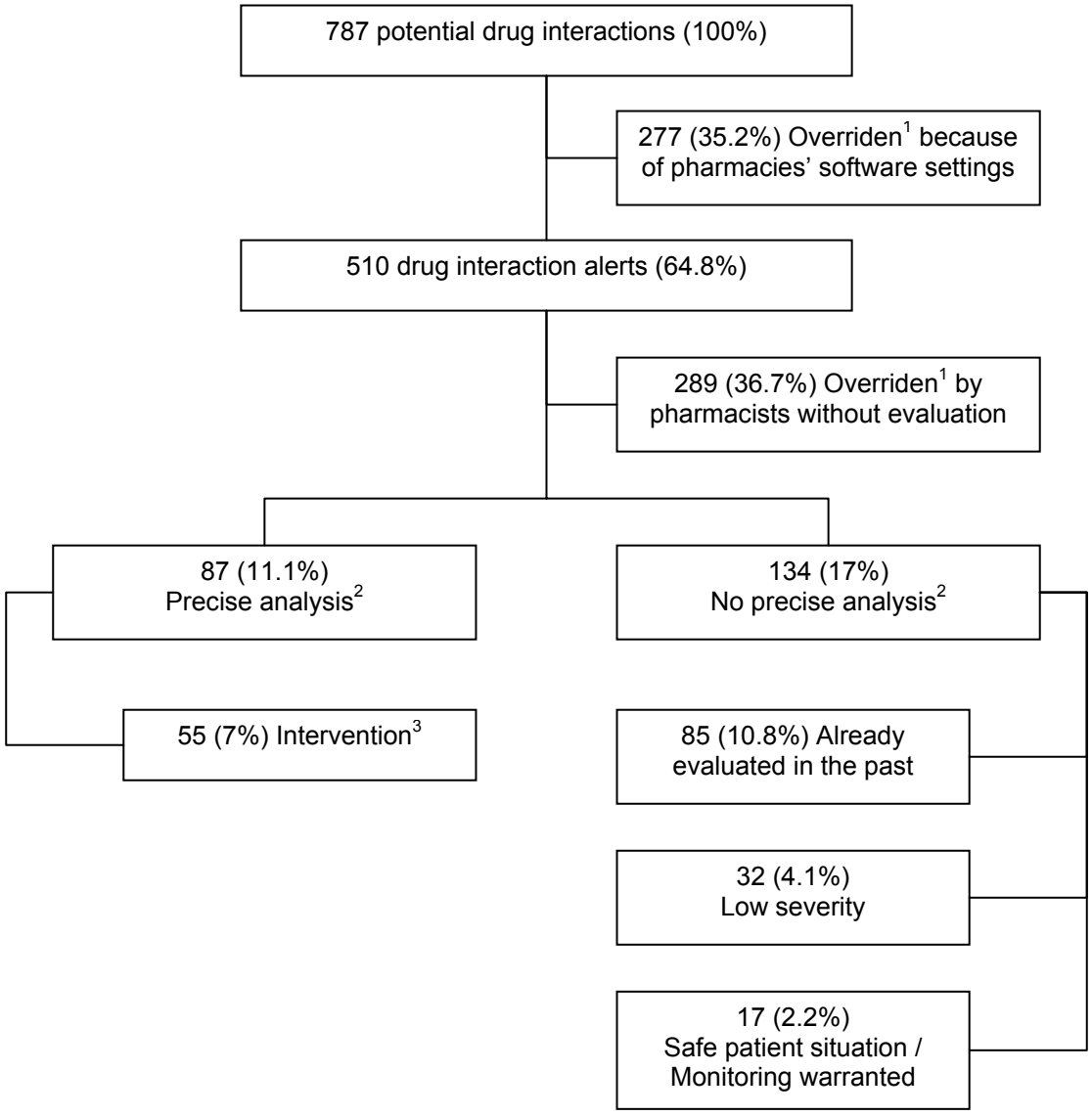


Figure 2: Management of drug interaction alerts assessed in an interview with the pharmacist on duty (510 potential drug interaction alerts among 204 patients).

[1] Override = The drug interaction was neither mentioned nor considered during fulfilment of the prescription

[2] Precise analysis = Consultation of e.g., literature, prescriber(s), or patient himself

[3] Intervention = E.g., close monitoring, adjustment of dose or ingestion time, stop of therapy, or alternative therapy



7 General discussion, conclusions and outlook

7.1 General discussion

In the present thesis different aspects of the management of potential drug interactions in the process of pharmaceutical care were evaluated.

In **project A** we researched additive effects of different risk factors on the development of hyperkalaemia which can lead to life-threatening adverse effects. Hospitalised patients with multiple risk factors including risk drugs (potassium supplements, potassium-sparing diuretics, ACEI or ARB) and comorbidities (severe renal impairment, diabetes mellitus) developed faster and higher hyperkaelemic serum potassium levels (≥ 5.0 mmol/L) than patients without or only few of these risks. Furthermore, the study showed that the use of risk drugs significantly increased during hospital stay. Two other studies, also conducted at the University Hospital Basel, revealed that the number of potential drug interactions increased significantly during hospital stay whereas the combinations between ACEI + potassium-sparing diuretics, ACEI + potassium supplements, and potassium supplements + potassium-sparing diuretics were among the most prevalent.[6, 18] Hyperkalaemia is a common electrolyte disturbance in hospitalised patients despite close monitoring of potassium levels and renal function. But, similar to other studies[86, 87] only few patients developed severe hyperkalaemia (>6.5 mmol/L). The situation might be different in outpatients because less intense monitoring could result in an increased risk of fatal outcomes. Juurlink et al.[88] revealed increased rates of hyperkalaemia-induced hospitalisations after the publication of the RALES study, which provoked a wide use of spironolactone combined with ACEI without caution. Patients with multiple risk factors for hyperkalaemia should be closely monitored and a rapid change in laboratory values should alert health care providers to action by identifying and possibly removing risk drugs. With regard to medical and pharmaceutical care, health care professionals prescribing and dispensing such risk drugs must consider both, potential drug interactions and patient-related risk factors.[89, 90] In ambulatory settings the linkage between laboratory and pharmacy systems would be a promising approach for a closer monitoring of drug therapies.[91]

Project B focussed on selected potential drug interactions of different clinical relevance between POMs and OTC drugs pharmacy customers purchased for self-medication. Even though, only a selection of potential drug interactions was investigated, we observed a high prevalence of potential drug interactions between POMs and self-medication drugs. In particular among regular customers treated with selected POMs, the prevalence of potential drug interactions was high. Whereas passer-by customers seldom reported to take POMs potentially interacting with the OTC-drugs they purchased. Therefore, to focus on regular pharmacy customers might be a helpful strategy to identify and manage potential drug interactions with self-medication. Although the impact of account cards for purchased self-medication drugs could not have been shown, this might be a promising approach in community pharmacies to improve drug safety by assessing entire medications profiles. This service is recent and currently only few customers are covered. Wider implementation of this service would be useful. A precondition is the customer's acceptance of surveillance by his pharmacy. Therefore, customers have to be motivated to participate more fully in their healthcare.[92] Establishing a caring relationship with the patient involving information provision and communication is a basic step of the pharmaceutical care process[93]. Thereby pharmacists can play an important role in reducing the risk of some drug interactions. Although most regular customers reported an infrequent intake of their OTC drugs, self-medication still presents a substantial risk for drug interactions. In the present project only 46.8% of regular customers were aware about potential drug interactions of their POM with self-medication and of them 47.3% admitted to be informed by the physician and 25.6% by the pharmacist. The level of information varied among customers with different drug therapies and the awareness was significantly higher for 'severe' potential drug interactions.

Potential drug interactions between POM and OTC drugs for self-medication are widespread. Efforts for an improved vigilance and an increase of awareness are needed. New approaches such as account cards to assess regular customers OTC drugs can be promising. Other actions include a better labeling of risky OTC drugs and the need to query patients' self-medication.[94]

Project C aimed to assess how pharmacists deal with drug interactions in daily practice, which information sources they use and wish to have, and how their

requirements relate to those expressed by general practitioners. Pharmacists admitted that computerised drug interaction alert systems supporting their fulfilment of prescriptions lacks sensitivity and specificity in identification of patients at risk while producing a high rate of possibly clinically irrelevant and invalid alerts. Such deficiencies of computerised drug interaction surveillance systems have already been shown in other countries.[71, 82] There is insufficient information to determine whether these systems are actually helpful in the community pharmacy settings.[70] Despite deficiencies of the drug interaction alert systems pharmacists admitted that they consider the majority of the provided alerts and override only a small amount (14%) of them.

It is not enough information for the health care provider to be informed, that two drugs may interact. It is also important to have access to information on measures that can be taken to reduce the likelihood of an adverse outcome.[58] In the present study pharmacists reported to be unsatisfied with the information about non-interacting alternative therapies and the specific advice for dose adjustment in the drug interaction information sources they use. General practitioners expressed the same criticism.[63] With regard to the content of future drug interaction information sources community pharmacists and general practitioners expressed very different expectations with the largest difference seen in the valuation of information components on advice for dose adjustment and non-interacting alternatives which were less essential for community pharmacists. This result reflects the different situations and needs of the two professions in daily practice. Substantial improvement of drug interaction software systems is thus required at least in two important aspects, the suppression of inappropriate alerts and the tailoring to the needs of the user.

The findings in Project C launched a discussion on optimisation of the currently used drug interaction softwares and the classification of the drug interaction database. The AKA (Medicines Commission of Swiss Pharmacists) debated about the need of a **new management-based classification** of potential drug interactions according to ORCA[58] (Table 3). An adjustment of the classification was already effected by other database providers: The US-database by Thompson Micormedex™[59] newly implemented in 2004 a fourth class of contraindicated next to major, moderate and minor drug combinations and the French Health Products Safety Agency (afssaps)

introduced in 2005 the new ‘Thesaurus des interactions medicamenteuses’ a new management-based classification with four categories (contraindication, combination disadvised, caution of use, intake possible) similar to ORCA[58] (Table 3). Table 5 displays the classification recommendation of AKA. When adopting the classification according to ORCA most drug interaction monographs will be disposed in category III ‘Monitoring respectively adjustment of the therapy necessary’. Therefore, the suggestion is to subdivide this category considering that some drug interactions only harm predisposed patients. This approach would simplify the management because the user obtains direct information about patient related risk factors. Future approaches e.g. electronic patient-held record cards containing information of comorbidities or pharmacogenetics, could directly be linked with the drug interaction database. Furthermore, the AKA suggested to consider the management options in community pharmacies and to provide specific information to community pharmacies that potential drug interactions can be managed under their own direction or that the consultation of the prescriber is needed. This information would reduce the workload of analysing potential drug interactions in the prescription fulfilment process. For example, the potential drug interaction between antacids and quinolones can easily be managed in community pharmacies by giving the quinolone 2 hours before or 6 hours after the antacid.

The AKA recommends to include categories **I** to **III** in the drug interaction check in community pharmacies. Category **IV** should contain clinically irrelevant potential drug interactions of minor or unspecified clinical relevance that do not demand any management action. Category **V** contains drug pairs with evidence that no interaction between two drugs exists (Table 5).

Table 5: Recommendations of the Medicines Commission of Swiss Pharmacists (AKA) for a new management-based classification of potential drug interactions in community pharmacies according to the operational classification by Hansten, Horn and Hazlet[58].

Categories	Characterisation	Management
I: Contraindicated	The risk of the combination always outweighs benefit	- Medication error - Avoid and if possible consider alternative after consultation of prescriber(s)
II: Usually contraindicated	Under special circumstances the benefit of the combination outweighs the risk	- Use only after consultation of prescriber(s) - If possible consider alternative - Monitoring and/or adjustment of the therapy - Inform patient
IIIa: Minimise risk by adjustment or monitoring of the therapy - **IIIb: Minimise risk only in predisposed patients**	The benefit of the combination of therapy outweighs the risk	- Use **after consultation of prescriber(s)** or **in pharmacists' direction** 1. If possible consider alternative (only after consultation of prescriber(s)) 2. Monitoring and/or adjustment of the therapy (If possible in pharmacists' direction) 3. Inform patient
IV: No special precautions	Risk of adverse outcome appears small	- Use recommended - Eventually inform patient
V: Ignore	Evidence suggests that the drugs do not interact	- Ignore

In **Project D** we focussed on community pharmacies management of drug interaction alerts in regular customers. Pharmacists overrode 71% of drug interactions without any evaluation either by ignoring them or by setting their systems to flag only potential drug interactions of high severity. This is a much higher percentage than that reported by the pharmacists in project C (14%). Pharmacists were sensitised to analyse first-time alerts and potential drug interactions of high severity. Most alerts were caused by repeated drug combinations and might therefore already have been verified. This result has already been found in studies in community pharmacies in other countries.[77, 82] Hence, substantial improvement of sensitivity and specificity of drug interaction alert systems is required. A more sophisticated approach for drug interaction alert systems to focus only on new prescriptions would significantly reduce the number of alerts and consequentially the inundation with irrelevant alerts. When pharmacists limit their drug interaction alerts systems to a subset of the total database, they are assuming that none of the ignored interactions will cause an adverse outcome in a patient.[95] A lot of pharmacists may believe that most drug interactions are clinically irrelevant for their patients according to the experience they

gained over years. But there would be a medicolegal risk if a patient is harmed by a 'low risk' drug interaction.[96] Peng et al.[97] revealed that some sophisticated filters (e.g. regarding drugs dose and time overlap of the therapies) would reduce the amount of potential drug interactions by 71% and together with pharmacists review by > 94%.
Use of sophisticated filters would significantly reduce the override. While such improvements are essential, no computer program can replace pharmacists' informed evaluation to recognise the factors that alter a patient's risk for an adverse event and to consider the risk against the benefit of administering the drugs. Therefore, pharmacists should be sensitised to manage drug interaction alerts adequately.

7.2 Conclusions

In **conclusion** this thesis shows that:

- Project A revealed that patients with risk factors for hyperkalaemia (renal impairment, diabetes mellitus) should be closely monitored when adding combinations of risk drugs for hyperkalaemia (potassium supplement, potassium-sparing diuretics, ACEI or ARB). And, a rapid change in laboratory values should alert health care providers to action by identifying and possibly removing risk drugs.

- OTC-drugs purchased for self-medication may often not be considered in the management of potential drug interactions. Freely available, their use is often perceived as safe by customers. Project B shows that potential drug interactions between POM and OTC drugs for self-medication are widespread. Efforts for an improved vigilance and an increase of patient awareness are needed. New approaches like patient-held account cards would enable to document self-medication in the medication history of a patient. Thus, they would be covered by the automatic drug interaction check.

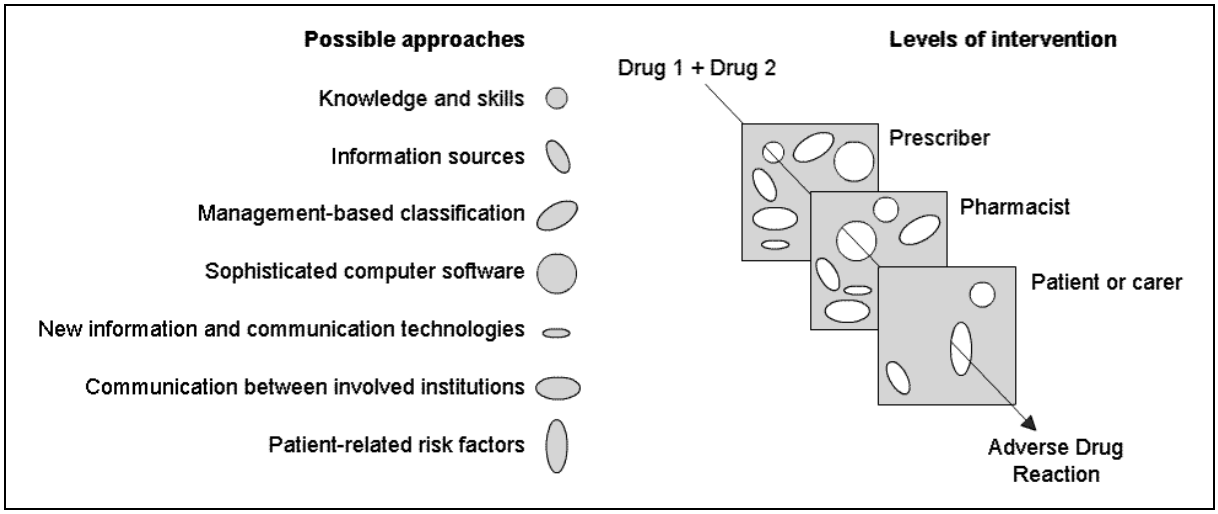
- In Project C pharmacists admitted that computer-assisted drug interaction surveillance in community pharmacies lacks sensitivity and specificity while producing a high rate of invalid alerts. The study also showed that the information needs of community pharmacies differed considerably compared to those of general practitioners. Hence, substantial improvement of drug interaction software systems is required at least in two important aspects, the suppression of inappropriate alerts and the tailoring to the needs of the user.

- In project D we revealed that pharmacists override many drug interaction alerts without any evaluation either by ignoring them or by setting their systems to flag only potential drug interactions of high severity. They are sensitised to analyse first-time alerts and potential drug interactions of high severity. The results show that focusing on new prescriptions would

significantly reduce the number of alerts. Substantial improvement of computer-assisted drug interaction surveillance is required. But finally no computer program can replace the informed evaluation of potential drug interactions and therefore pharmacists should be sensitised to manage the alerts adequately.

7.3 Outlook

Figure 5: Possible approaches to darn the present gaps in defenses on prescriber's, pharmacist's, patient's or carer's level to prevent adverse drug reactions resulting from a drug interaction according to the Swiss cheese model by Reason[56].



Recapitulating the present thesis, numerous problems in the management of potential drug interactions were revealed. These gaps in defense have to be darned to avoid adverse drug reactions resulting from drug interactions (Figure 5). Therefore, the impact of new approaches should be evaluated in future projects:

- An important factor for an accurate management of potential drug interactions is the knowledge of potential drug interactions by health care providers. Pharmacists often override drug interaction alerts because they are desensitised to manage them. Currie et al.[98] showed that training programs proved to be an effective way to increase the number of DRPs including potential drug interactions identified and addressed by pharmacists. Therefore, **knowledge and skills** of the pharmacist in managing drug interactions, including how to judge the risk of a drug interaction, should be improved through basic and continuing education. In most community pharmacies drug interaction alerts will be noticed first by technicians. They should be instructed and supervised on how to judge and, if possible, how to manage these alerts.[2]

- For health care providers it is important to acquire directly information on measures that can be taken to reduce the likelihood of an adverse outcome. Pharmacists are unsatisfied with the current information contents their drug interaction **information sources** provide (project C). A new **management-based classification** based on ORCA[58] should be implemented in the currently used drug interaction database (Pharmavista®[61]). Pharmacists assume that none of the ignored interactions will cause an adverse outcome when checking only potential drug interactions of high severity. Significant drug interactions might be missed and medicolegal risk exists if a patient is harmed by a low risk interaction.[95] Therefore, the current classes of potential drug interactions should be reviewed, compared with standard information sources and classified according to their management options (Table 5).

- Project C and D revealed that pharmacists are inundated with invalid alerts (multiple alerts for the same potential drug interaction or for combinations of which one drug already had been stopped) and alerts for renewal prescriptions that might already have been approved. Project D showed that in regular customers only 32.5% of potential drug interactions occurred for the first time. Therefore, before setting pharmacies computer software to flag only potential drug interactions of high severity it would be obvious to improve drug interaction software ability to recognise first time alerts and to filter already evaluated potential drug interactions. Furthermore, with this new approach the stop of interacting drug combinations could be identified. This is important for several potentially interacting drugs. For example the dose of digoxin has to be readapted when the therapy with a p-Glycoprotein Inhibitor like itraconazol is discontinued. Current computer software in community pharmacies needs substantial improvement. Adding new **sophisticated computer settings** would lead to a re-engineering of the prescription fulfilment process. Therefore, community pharmacies have to debate with computer software providers to achieve desired improvements of their computer software.

- The **communication between involved institutions** in ambulatory care, hospital and perihospital institutions is a critical issue. The access to clinical relevant informations (complete medication, patient history and laboratory

data) has still to be optimised. **New information and communication technologies** would facilitate the surveillance of drug-related problems including those caused by drug interactions. New approaches like electronic prescribing and data management by computer health care networks are planned or are partially implemented. Their impact in pharmaceutical care and particularly in the management of potential drug interactions has still to be investigated.

For the management of potential drug interactions it is important to be informed about the medication history, **patient-related risk factors**, patients' laboratory data and patients' self-medication. Electronic patient-held records might improve the current situation. With patients electronic insurance card a valuable instrument to record these data would be available.

Overall, recent developments in e-health to support health decision-making processes may have multiple potential benefits. This asks for intensified research, including the impact on pharmaceutical care and in particular on the prevention of drug related problems.

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9 Appendix

Project B:

Project C:

Project D:

B.1 Recruitment of community pharmacies

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UNI BASEL

Kantonsspital Basel
Universitätskliniken

Basel, 09.03.2005

Apotheken Beobachtungsstudie 2005
Potentielle Arzneimittelinteraktionen in der Selbstmedikation

Sehr geehrte Damen und Herren,
Liebe Kolleginnen und Kollegen

Im Rahmen der Diplomarbeit „Potentielle Arzneimittelinteraktionen in der Selbstmedikation" möchten wir die tägliche Apothekenpraxis beobachten und Patienten interviewen. Als Fortsetzung der 95, 97, 99 und 02 durchgeführten Basler-Apothekenbeobachtungsstudie (BABS) in 30 Apotheken der Region Basel wird die Häufigkeit von Nachfragen durch Kunden analysiert. Der Fokus liegt auf Nachfrage und Empfehlung von Analgetika, sowie neu auf potentiellen Wechselwirkungen.

Zusätzlich interessieren uns Risikopatienten mit ausgewählten Dauertherapien, die wir telefonisch befragen würden.

Die Studie wird von Daniela Reber, Diplomandin des 5. Jahreskurses Pharmazie, in den Wochen vom 4. April bis 6. Mai durchgeführt. **Es wird für Sie und Ihr Team kein Arbeitsaufwand anfallen und der normale Tagesablauf wird nicht gestört**.

Die Studie wurde von der Ethikkommission beider Basel (EKBB) Nr. 10/2005 bewilligt. Die Anonymität der teilnehmenden Personen und Apotheken ist gewährleistet. In der Beilage finden Sie einen Auszug aus der Eingabe an die EKBB.

Es würde uns freuen, wenn Sie uns ermöglichen, in Ihrer Apotheke Daten für unsere Studie zu erheben.

Frau Daniela Reber wird Sie bezüglich Teilnahme an der Studie in den nächsten Tagen kontaktieren, um das schriftliche Einverständnis einzuholen.

Vielen Dank im Voraus für Ihr Interesse.

Mit freundlichen Grüssen

Prof. Dr. S. Krähenbühl Dr. K. Hersberger

J. Indermitte D. Reber

B.2 Formularies for data collection

13047

INSTITUT FÜR KLINISCHE PHARMAZIE
Departement Pharmazie der Universität Basel

Code

Basler Apothekenbeobachtungsstudie: Arzneimittelwechselwirkungen in der Selbstmedikation 2005

Bedienung ☐ ApothekerIn ☐ Pharma-Assistentin ☐ andere ☐ Kombination

Alter ☐ 18-30 ☐ 31-60 ☐ 61-++

Geschlecht ☐ W ☐ M

Rezept ☐ ohne Dossier ☐ R ☐ DR ☐ V ☐ AoR	**Wunsch**	**Beratung**	**Varia**
Analgetika **Anzahl** ☐ ☐ Para ☐ COX-2 ☐ Ibu ☐ Mef ☐ ASS ☐ Diclo ☐ Napr ☐ ASS-LD ☐ Opi ☐ andere ☐ Kombi Andere	**Analgetika** **Anzahl** ☐ ☐ Para ☐ Diclo ☐ Ibu ☐ Napr ☐ ASS ☐ andere Kombi ☐ coff ☐ Vit C ☐ andere Andere	**Analgetika** **Anzahl** ☐ ☐ Para ☐ Dicl ☐ Ibu ☐ Napr ☐ ASS ☐ andere ☐ Para/Ass Kombi ☐ coff ☐ Vit C ☐ andere Andere	☐ Varia
Erkältung/Grippe/Schnupfen Kombi ☐ Neo ☐ Pre ☐ Vi ☐ andere: **Sympa** ☐ Pseudo ☐ Phenpropa ☐ Phenyleph ☐ Ephedrin ☐ andere **Nas/Aug** ☐ Vibr ☐ Spir ☐ Arb ☐ Rexo	**Erkältung/Grippe/Schnupfen** Kombi ☐ Neo ☐ Pre ☐ Vi ☐ andere: **Sympa** ☐ Pseudo ☐ Phenpropa ☐ Phenyleph ☐ Ephedrin ☐ andere **Nas/Aug** ☐ Vibr ☐ Spir ☐ Arb ☐ Rexo	**Erkältung/Grippe/Schnupfen** Kombi ☐ Neo ☐ Pre ☐ Vi ☐ and **Sympa** ☐ Pseudo ☐ Phenpropa ☐ Phenyleph ☐ Ephedrin ☐ andere **Nas/Aug** ☐ Vibr ☐ Spir ☐ Arb ☐ Rexo	
Antituss ☐ Dextro ☐ Codein ☐ Nosc **Alk/Kompl** ☐ Antacida ☐ Multi ☐ Mg ☐ And ☐ Ca ☐ Rani ☐ Fe **Johannis** ☐ stand ☐ nicht stand	**Antituss** ☐ Dextro ☐ Codein ☐ Nosc **Alk/Kompl** ☐ Antacida ☐ Multi ☐ Mg ☐ And ☐ Ca ☐ Rani ☐ Fe **Johannis** ☐ stand ☐ nicht stand	**Antituss** ☐ Dextro ☐ Cod ☐ Nosc **Alk/Komp** ☐ Antacida ☐ Multi ☐ Mg ☐ And ☐ Ca ☐ Rani ☐ Fe **Johannis** ☐ stand ☐ nicht stand	
PDE5-I ☐ Silde ☐ Varde ☐ Tada			
Buprop ☐ **Antiadi** ☐ Regenon ☐ X112 ☐ Reductil ☐ andere	Jahrgang		

Dauertherapie ☐ Dossier vorhanden ☐☐ **IC-Nr.** _____

Interaktion erkannt
☐ Ja ☐ Nein

Intervention von Beobachter aufgrund kontraindizierter IA nötig
☐ Ja ☐ Nein

Management
☐ Abgabeverweigerung ☐ Weiterleitung an Arzt ☐ Information an Patienten

INSTITUT FÜR KLINISCHE PHARMAZIE

Departement Pharmazie für klinische Pharmazie

18946

Arzneimittelwechselwirkungen in der Selbstmedikation 2005: Befragung von Risikopatienten

Low Dose Aspirin

Erfassungsdatum d ☐☐ m ☐☐ y 2005 Code ☐☐

Name: Adresse: Geschlecht ☐ W ☐ M

Vorname: Tel: Geburtsdatum d ☐☐ m ☐☐ y ☐☐☐☐

ASS-low dose ☐ Asprin Cardio 100 ☐ Asprin Cardio 300 ☐ Tiatral 100 SR

Patientendossier: DT auf Rezept

Selbstmedikation durch System erfasst

Wissen Sie, dass es Medikamente gibt, die Sie nicht zusammen mit Aspirin Cardio einnehmen sollten?

☐ nein ☐ ja,... ☐ Schmerzmittel ☐ Ginkgopräparate ☐ NSAID ☐ Ibuprofen

Woher haben Sie diese Informationen?

☐ Apotheke ☐ Arzt ☐ Packungsbeilage ☐ Spitex/Hauspflege ☐ Andere, welche?

Haben Sie während Ihrer Aspirin Cardio-Therapie Arzneimittel ...

...gegen Schmerzen eingenommen?

☐ nein ☐ weiss nicht ☐ ASS ☐ Ibuprofen ☐ Paracetamol ☐ Naproxen ☐ Diclofenac ☐ andere

☐ 30d _____

Dosierung ☐ mehrmals täglich ☐ täglich ☐ 2-3 mal pro Woche ☐ seltener ☐ weiss nicht

☐ 1 mal/d ☐ 3 mal/d

☐ 2 mal/d ☐ 4 mal/d

Einnahmezeit 2h nach ASS-LD

Falls Einnahme von Ibuprofen:

Durchschnittliche ED

☐ Nein ☐ Packungsbeilage

☐ Apotheke ☐ Spital

☐ 200 mg ☐ 400 mg ☐ 600 mg ☐ 800 mg ☐ Arzt ☐ Andere_____

...zur Konzentrationsförderung (Ginkgo) eingenommen? ☐ nein ☐ weiss nicht ☐ Ginkgo

☐ 30d _____

Dosierung ☐ mehrmals täglich ☐ täglich ☐ 2-3 mal pro Woche ☐ seltener ☐ weiss nicht

Interaktion erkannt	**UAW**	**UAW Selbstanamnese**	**UAW abgeklärt**
☐ ja ☐ nein	☐ Ja	☐ vermehrte Blutungsneigung	☐ Nein ☐ Arzt
☐ Apo ☐ Spital	☐ nein		☐ Apo ☐ Andere
☐ Arzt ☐ Pat			☐ Spital _____

32440

INSTITUT FÜR KLINISCHE PHARMAZIE

Departement Pharmazie für klinische Pharmazie

Arzneimittelwechselwirkungen in der Selbstmedikation 2005: Befragung von Risikopatienten

Kaliumsparende Diuretika

Erfassungsdatum d ☐☐ m ☐☐ y 2005 Code ☐☐

Name: Adresse: Geschlecht ☐ W ☐ M

Vorname: Tel: Geburtsdatum d ☐☐ m ☐☐ y ☐☐☐☐

Spironolacton ☐ Aldactone ☐ Primacton ☐ Xenalon ED ☐ 25 mg ☐ 50 mg ☐ 100 mg

Erfassung aus Patientendossier

DT auf Rezept

Selbstmedikation durch System erfasst

Wissen Sie, dass es Medikamente gibt, die Sie nicht zusammen mit Aldactone einnehmen sollten?

☐ ja,... ☐ nein ☐ ACE-Hemmer ☐ Kaliumpräparate ☐ NSAID ☐ Andere

Woher haben Sie diese Informationen?

☐ Apotheke ☐ Arzt ☐ Packungsbeilage ☐ Spitex/Hauspflege ☐ Andere, welche?_____

Haben Sie während Ihrer Aldactone -Therapie Arzneimittel ...

...gegen Schmerzen eingenommen?

☐ nein ☐ weiss nicht ☐ Paracetamol ☐ Diclofenac ☐ Naproxen ☐ ASS ☐ Ibuprofen ☐ andere

_____

☐ 30d Dosierung ☐ mehrmals täglich ☐ täglich ☐ 2-3 mal pro Woche ☐ seltener ☐ weiss nicht

...Kaliumpräparate eingenommen? ☐ Kaliumsupplemente ☐ Andere

☐ 30d Dosierung ☐ mehrmals täglich ☐ täglich ☐ 2-3 mal pro Woche ☐ seltener ☐ weiss nicht

Interaktion erkannt

☐ ja ☐ nein

☐ Apo ☐ Spital

☐ Arzt ☐ Pat

Monitoring

☐ Kaliumspiegelmessung

☐ EKG-Messung

☐ Kreatininmessung

UAW

☐ Ja

☐ nein

UAW Selbstanamnese

☐ Muskelschwäche

☐ Kribbeln, Ameisenlaufen

☐ Herzrhytmusstörungen

☐ Konfusion

☐ andere

_____

UAW gemessen

☐ EKG- Veränderungen

☐ Kaliumspiegel erhöht

☐ Herzrhytmusstörungen

UAW abgeklärt

☐ Nein

☐ Apo

☐ Spital

☐ Arzt

☐ Andere

_____

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28501
Arzneimittelwechselwirkungen in der Selbstmedikation 2005: Befragung von Risikopatienten

Erfassungsblatt MAO-Hemmer

Erfassungsdatum d ☐☐ m ☐☐ y 2005 **Code** ☐☐

Name: **Adresse:** **Geschlecht** ☐ W ☐ M

Vorname: **Tel:** **Geburtsdatum** d ☐☐ m ☐☐ y ☐☐☐☐

Moclobemid ☐ Aurorix ☐ Moclo A ED ☐ 150 ☐ 300 Selegilin, 5 mg ☐ Jumexal ☐ Generikum

Zyvoxid ☐ Tabl ☐ Susp

Patientendossier: DT auf Rezept

Selbstmedikation durch System erfasst

Wissen Sie, dass es Medikamente gibt, die Sie nicht zusammen mit Moclobemid/Selegilin einnehmen dürfen?
☐ ja,... ☐ Husten ☐ Grippe ☐ Schnupfen ☐ Appetitzügler ☐ Bupropion ☐ Andere, welche?
☐ nein _____

Woher haben Sie diese Informationen?
☐ Apotheke ☐ Arzt ☐ Packungsbeilage ☐ Spitex/Hauspflege ☐ Andere, welche?_____

Haben Sie während Ihrer Moclobemid/Selegilin-Therapie Arzneimittel ...

...gegen Reizhusten eingenommen? ☐ nein ☐ weiss nicht ☐ Dex ☐ Cod ☐ Nosc _____
☐ 30d Dosierung ☐ mehrmals täglich ☐ täglich ☐ 2-3 mal pro Woche ☐ seltener ☐ weiss nicht

Kombinationen ☐ Neo ☐ Pre ☐ Vi ☐ And

...gegen Gri/Schnupf/Erk... eingenommen? ☐ nein ☐ weiss nicht ☐ Pseudo ☐ Phenpro ☐ Ephe ☐ Phenyleph
☐ 30d _____
Dosierung ☐ mehrmals täglich ☐ täglich ☐ 2-3 mal pro Woche ☐ seltener ☐ weiss nicht

...Augentropfen oder Nasensprays angewendet? ☐ nein ☐ weiss nicht ☐ Vibroc ☐ Spirig ☐ Arbid ☐ Rexopht
☐ 30d _____
Dosierung ☐ mehrmals täglich ☐ täglich ☐ 2-3 mal pro Woche ☐ seltener ☐ weiss nicht

...Appetitzügler eingenommen? ☐ nein ☐ weiss nicht ☐ Regenon ☐ Reductil ☐ X112 ☐ Andere
☐ 30d _____
Dosierung ☐ mehrmals täglich ☐ täglich ☐ 2-3 mal pro Woche ☐ seltener ☐ weiss nicht

...zur Raucherentwöhnung (Zyban) eingenommen? ☐ ja ☐ nein ☐ weiss nicht
☐ 30d _____
Dosierung ☐ mehrmals täglich ☐ täglich ☐ 2-3 mal pro Woche ☐ seltener ☐ weiss nicht

Interaktion erkannt
☐ ja ☐ nein
☐ Apo ☐ Spital
☐ Arzt ☐ Pat

UAW
☐ Ja
☐ nein

UAW Selbstan
☐ Erregung, Verwirrheit, Angst
☐ Krämpfe
☐ Durchfall
☐ Schwitzen, Überhitzung
☐ Zittern
☐ Andere, welche _____
☐ keine

UAW gem.
☐ instabiler Blutdruck
☐ erhöhter Blutdruck
☐ erhöhte Herzfrequenz

UAW abgeklärt
☐ Nein
☐ Apo
☐ Spital
☐ Arzt
☐ Andere

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Departement Pharmazie für klinische Pharmazie
25319
Arzneimittelwechselwirkungen in der Selbstmedikation 2005: Befragung von Risikopatienten

Antibiotika(Tetracycline)

Erfassungsdatum d ☐☐ m ☐☐ y 2005 Code ☐☐

Name: Adresse: Geschlecht ☐ W ☐ M

Vorname: Tel: Geburtsdatum d ☐☐ m ☐☐ y ☐☐☐☐

Tetracycline ☐ Doxycyclin ☐ Minocyclin

mg ☐ 20 ☐ 42.5 ☐ 50 ☐ 100 ☐ 200

_____

Erfassung aus Patientendossier

DT auf Rezept

Selbstmedikation durch System erfasst

Wissen Sie, dass es Medikamente/Lebensmittel gibt, die Sie nicht zusammen mit Antibiotika einnehmen dürfen? ☐ nein ☐ ja,... ☐ Antacida ☐ Mineralien ☐ CO2 Getränke ☐ Ca- haltige Lebensmittel ☐ andere

Woher haben Sie diese Informationen?
☐ Apotheke ☐ Arzt ☐ Packungsbeilage ☐ Spitex/Hauspflege ☐ Andere, welche?

Haben Sie während Ihrer Antibtiotika -Therapie Arzneimittel ...

...zur Nahrungsergänzung (Mineralien)/Lebensmittel eingenommen?
☐ nein ☐ weiss nicht ☐ Mg ☐ Ca ☐ Fe ☐ Multimineralien ☐ Ca-haltige LM _____
☐ 30d
Dosierung ☐ mehrmals täglich ☐ täglich ☐ 2-3 mal pro Woche ☐ seltener ☐ weiss nicht
Einnahmezeit ☐ Einnahme des Antibiotikums 1-2 h vor oder 4 h nach diesen Präp

...gegen Magenbrennen eingenommen? ☐ nein ☐ weiss nicht ☐ Antacida
☐ 30d
Dosierung ☐ mehrmals täglich ☐ täglich ☐ 2-3 mal pro Woche ☐ seltener ☐ weiss nicht
Einnahmezeit ☐ Einnahme des Antibiotikums 1-2 h vor oder 4 h nach diesen Präp

Interaktion erkannt	**UAW**	**UAW Selbstanamnese**	**UAW abgeklärt**
☐ ja ☐ nein	☐ Ja	☐ Krämpfe	☐ Nein ☐ Arzt
☐ Apo ☐ Spital	☐ nein	☐ Therapieversager	☐ Apo ☐ Andere
☐ Arzt ☐ Pat			☐ Spital _____

INSTITUT FÜR KLINISCHE PHARMAZIE

5581

Departement Pharmazie für klinische Pharmazie

Arzneimittelwechselwirkungen in der Selbstmedikation 2005: Befragung von Risikopatienten

Immunsuppressiva

Erfassungsdatum d ☐☐ m ☐☐ y 2005 Code ☐☐

Name: Adresse: Geschlecht ☐ W ☐ M

Vorname: Tel: Geburtsdatum d ☐☐ m ☐☐ y ☐☐☐☐

Ciclosporin ☐ Sandimmune ☐ Ciclosol ED ☐ 10 mg ☐ 25 mg ☐ 50 mg ☐ 100 mg

Rapamune ☐ Lsg ☐ 1 mg, Tabl ☐ 2 mg, Tabl.

Prograf ☐ 0.5 mg ☐ 1 mg ☐ 2 mg

Erfassung aus Patientendossier

DT auf Rezept

Selbstmedikation durch System erfasst

Wissen Sie, dass es Medikamente gibt, die Sie nicht zusammen mit Immunsuppressiva einnehmen sollten?

☐ ja,... ☐ NSAID ☐ Johanniskraut

☐ nein

Woher haben Sie diese Informationen?

☐ Apotheke ☐ Arzt ☐ Packungsbeilage ☐ Spitex/Hauspflege ☐ Andere, welche?_____

Haben Sie während Ihrer Immunsuppressiva -Therapie Arzneimittel ...

(nur bei Tacrolimus)...gegen Schmerzen eingenommen?

☐ nein ☐ weiss nicht ☐ Paracetamol ☐ Diclofenac ☐ Naproxen ☐ ASS ☐ Ibuprofen ☐ andere _____

☐ 30d Dosierung ☐ mehrmals täglich ☐ täglich ☐ 2-3 mal pro Woche ☐ seltener ☐ weiss nicht

..., die Johanniskraut enthalten, eingenommen? ☐ nein ☐ weiss nicht ☐ Johanniskraut

☐ 30d Dosierung ☐ mehrmals täglich ☐ täglich ☐ 2-3 mal pro Woche ☐ seltener ☐ weiss nicht

Interaktion erkannt

☐ ja ☐ nein

☐ Apo ☐ Spital

☐ Arzt ☐ Pat

UAW

☐ Ja

☐ nein

UAW Selbstanamnese

☐ Abstossungsreaktion

☐ andere _____

UAW gemessen

☐ subtherapeutische Konz (< 80 -100 ng/ml)

☐ andere _____

Monitoring

☐ Kreatininmessung

☐ Serumspiegelmessung des Immunsupp

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12866
Arzneimittelwechselwirkungen in der Selbstmedikation 2005: Befragung von Risikopatienten

Orale Antikoagulantien

Erfassungsdatum d m y 2005 Code

Name: Adresse: Geschlecht: ☐ W ☐ M

Vorname: Tel: Geburtsdatum: d m y

Acenocoumarol ☐ Sintrom mitis, 1mg ☐ Sintrom, 4 mg | **Phenprocoumon** ☐ Marcoumar, 3 mg

Patientendossier : DT auf Rezept

Selbstmedikation durch System erfasst

Wissen Sie, dass es Medikamente gibt, die Sie nicht zusammen mit Marcoumar/ Sintrom einnehmen dürfen?
☐ nein ☐ ja,...
☐ Schmerzmittel ☐ pflanzliche Arzneimittel ☐ Lebensmittel ☐ NSAID ☐ Ibuprofen ☐ ASS

Woher haben Sie diese Informationen?
☐ Apotheke ☐ Arzt ☐ Packungsbeilage ☐ Spitex/Hauspflege ☐ Andere, welche?

Haben Sie während Ihrer Marcoumar/Sintrom-Therapie Arzneimittel ...

...gegen Schmerzen eingenommen? ☐ nein ☐ weiss nicht ☐ ASS ☐ NSAID ☐ Paracetamol
☐ 30d _____
Dosierung ☐ mehrmals täglich ☐ täglich ☐ 2-3 mal pro Woche ☐ seltener ☐ weiss nicht

...auf pflanzlicher Basis eingenommen? ☐ nein ☐ weiss nicht ☐ Johanniskraut ☐ Ginkgo
☐ 30d _____
Dosierung ☐ mehrmals täglich ☐ täglich ☐ 2-3 mal pro Woche ☐ seltener ☐ weiss nicht

Interaktion erkannt
☐ ja ☐ nein
☐ Apo ☐ Spital
☐ Arzt ☐ Pat

UAW
☐ Ja
☐ nein

UAW Selbstanamnese
☐ vermehrtes Nasenbluten
☐ Hämaturie

UAW gemessen
☐ Thrombose
☐ Darmblutungen
☐ Veränderungen Quick

UAW abgeklärt
☐ Apo
☐ Spital
☐ Arzt
☐ nein

Massnahmen
☐ Häufigere Quick- Messung
☐ Dosisanpassung
☐ anderes _____

C.1 Covering letter

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UNI BASEL

Basel, Freitag 3. Juni 2005

Befragung von öffentlichen Apotheken in der Deutschschweiz

Sehr geehrte Dame, sehr geehrter Herr

Die vorliegende Apothekenbefragung ist Teil der Diplomarbeit in Pharmazeutischen Wissenschaften von Laura Erba und erfolgt in Zusammenarbeit mit der Arzneimittelkommission der Schweizer Apotheker (AKA).

Die Umfrage soll Aspekte der Zusammenarbeit zwischen Apotheke und Arzt untersuchen und Hinweise geben, wie in öffentlichen Apotheken mit potentiellen Arzneimittelwechselwirkungen (DDIs) umgegangen wird.

Ihre Apotheke wurde aus Deutschschweizer Apotheken zur Teilnahme an dieser Studie ausgewählt.
Die Teilnahme an der vorliegenden Befragung ist selbstverständlich freiwillig, bedenken Sie aber bitte, dass das Ergebnis dieser Studie wiederum allen Offizinapotheken zu Gute kommt.

Unter allen Teilnehmern an der Studie werden zudem 5 Jahres-Gratis-Abonnements von im@il-Offizin (www.imail-offizin.ch) verlost.
Die Auswertung des Fragebogens geschieht strikt anonym. Die Nummerierung der Fragebogen dient nur zur Identifizierung von Apotheken, falls eine Erinnerung nötig sein sollte. Nach Auswertung der Studie wird keine Identifizierung der einzelnen Apotheken mehr möglich sein.

Bitte schicken Sie den ausgefüllten Fragebogen nach Möglichkeit bis **Montag, den 4. Juli 2005** mittels beiliegedendem Antwortcouvert an uns zurück oder faxen Sie das Ganze an obenstehende Faxnummer.

Für Ihre wertvolle Mitarbeit bedanken wir uns schon jetzt recht herzlich und hoffen, dass das Ergebnis dieser Befragung auch für Ihre Apotheke eine Bereicherung wird. Die Ergebnisse dieser Studie werden im Herbst 2005 publiziert.

Mit freundlichen Grüssen

Prof. Dr. Rudolf Bruppacher — Dr. Kurt Hersberger, Projektleiter

Jörg Indermitte, Betreuer — Laura Erba, Diplomandin

C.2 Questionnaire

48792

Umfrage in öffentlichen Apotheken der Deutschschweiz

Diplomarbeit Pharmazie 2005 **Seite 1**

UNI BASEL

Zum Umgang mit potentiellen Arzneimittelwechselwirkungen (DDIs) in öffentlichen Apotheken

1. Stellen unerwünschte Arzneimittelwechselwirkungen (DDIs) aus Ihrer Erfahrung ein wichtiges Sicherheitsrisiko in der Arzneimitteltherapie dar? ☐ ja ☐ nein

2.1 Welche Bedeutung haben DDIs aus Ihrer Erfahrung im Vergleich zu anderen Sicherheitsrisiken in der Arzneimitteltherapie?
☐ es ist ein herausragendes Problem
☐ es ist eines von vielen Problemen
☐ es ist ein untergeordnetes Problem

2.2 Wie häufig beschäftigen Sie sich in Ihrer Apotheke mit potentiellen DDIs?
☐ bei jeder Verordnung ☐ einmal pro Monat
☐ mehrmals täglich ☐ weniger als einmal pro Monat
☐ täglich ☐ nie
☐ einmal pro Woche

Bei der Rezeptvalidierung kann die Apothekensoftware automatisch potentielle DDIs erkennen.

3. Ist in Ihrer Apotheke die automatische Erkennung von potentiellen DDIs durch die Apothekensoftware aktiviert? ☐ ja ☐ nein (weiter mit Frage 7)

4.1 Einstellungen der Apothekensoftware: Auf welcher Stufe ist der "Filter" Ihres Systems eingestellt?
☐ Es können keine Filtereinstellungen gewählt werden
☐ 1 = nur schwere DDIs werden angezeigt
☐ 2 = mittlere und schwere werden angezeigt
☐ 3 = schwache, mittlere und schwere werden angezeigt
☐ 4 = unbedeutende, schwache, mittlere und schwere werden angezeigt
☐ 5 = Alle DDIs (inkl. Fremdangaben) werden angezeigt

4.2 Für welchen Beobachtungszeitraum wurde die automatische Erkennung von DDIs eingestellt?
☐ 1 Monat ☐ 2 Monate ☐ 3 Monate ☐ 4 Monate ☐ 5 Monate ☐ 6 Monate
☐ Anderer Zeitraum: ☐☐☐ Tage ☐ Es ist kein Beobachtungszeitraum wählbar

5. Wie beurteilen Sie die Qualität Ihrer Software zur Erkennung potentieller DDIs?

Ich verpasse keine für den Patienten gefährlichen potentiellen DDIs:	nie	0% ○	10% ○	20% ○	30% ○	40% ○	50% ○	60% ○	70% ○	80% ○	90% ○	100% ○	immer
Die Software zeigt auch klinisch nicht relevante potentielle DDIs an:	nie	0% ○	10% ○	20% ○	30% ○	40% ○	50% ○	60% ○	70% ○	80% ○	90% ○	100% ○	immer
Die Software präsentiert auch Fehlanzeigen : (z.B. Mehrfach dieselbe Anzeige bei einem Patienten, Anzeigen mit Arzneimitteln bereits abgesetzter Therapien)	nie	0% ○	10% ○	20% ○	30% ○	40% ○	50% ○	60% ○	70% ○	80% ○	90% ○	100% ○	immer

Die folgenden Fragen beziehen sich auf den Umgang mit Anzeigen potentieller DDIs durch die Apothekensoftware: Diese Anzeigen können Sie entweder "übergehen", "beachten" (=die Entscheidung, ob eine genauere Überprüfung einer potentiellen DDI nötig ist, wird aktiv gefällt), "überprüfen" (=zusätzliche Konsultation von Informationsquellen).

6.1 Bestehen in Ihrer Apotheke klare Anweisungen im Umgang mit diesen Anzeigen? ☐ keine Anweisungen ☐ mündliche ☐ schriftliche

6.2 Schätzen Sie, wie häufig diese Anzeigen in Ihrer Apotheke "beachtet" werden:

	nie	0% ○	10% ○	20% ○	30% ○	40% ○	50% ○	60% ○	70% ○	80% ○	90% ○	100% ○	immer

6.3 Wer entscheidet in Ihrer Apotheke, ob nach solchen Anzeigen zusätzlich eine genauere "Überprüfung" erfolgen muss? (Nur eine Antwort)
☐ Es entscheidet immer der Apotheker
☐ Der Apotheker entscheidet nur in bestimmten Fällen
☐ Die Pharmaassistentin kann selbstständig entscheiden
☐ Anderer Umgang mit potentiellen DDIs

6.4 Schätzen Sie, wie häufig diese Anzeigen in Ihrer Apotheke "überprüft" werden:

	nie	0% ○	10% ○	20% ○	30% ○	40% ○	50% ○	60% ○	70% ○	80% ○	90% ○	100% ○	immer

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7.1 Werden Therapien mit potentiellen DDIs in Ihrer Apotheke dokumentiert?

- ☐ Nein
- ☐ Ja, alle
- ☐ Ja, nur "überprüfte" Interaktionsanzeigen
- ☐ Ja, nur schwerwiegende
- ☐ Ja, nur nach Rücksprache mit dem Arzt
- ☐ Andere, welche? _____

7.2 Wie dokumentieren Sie diese? _____

- ☐ Schriftlicher Kommentar
- ☐ Ausdruck der Monographie der Apothekensoftware zur pot. DDI
- ☐ Kommentar im elektronischen Dossier
- ☐ Andere Art der Dokumentation, welche? _____

8.1 Welche der folgenden Informationsquellen konsultieren Sie, um potentielle DDIs zu "überprüfen" (Mehrfachantworten möglich)?

Arzneimittelkompendium:	nie	0% ○	10% ○	20% ○	30% ○	40% ○	50% ○	60% ○	70% ○	80% ○	90% ○	100% ○	immer
Informationen der Apothekensoftware:	nie	0% ○	10% ○	20% ○	30% ○	40% ○	50% ○	60% ○	70% ○	80% ○	90% ○	100% ○	immer
Weiterführende Literatur (z.B Ammon: Arzneimittelneben- und Wechselwirkungen; Hansten&Horn's: Drug Interactions and Management, Stockley: Drug interactions, etc.):	nie	0% ○	10% ○	20% ○	30% ○	40% ○	50% ○	60% ○	70% ○	80% ○	90% ○	100% ○	immer
Pharmavista:	nie	0% ○	10% ○	20% ○	30% ○	40% ○	50% ○	60% ○	70% ○	80% ○	90% ○	100% ○	immer
Andere elektronische Quellen (z.B Pubmed, Thompson Micromedex, etc.):	nie	0% ○	10% ○	20% ○	30% ○	40% ○	50% ○	60% ○	70% ○	80% ○	90% ○	100% ○	immer

8.2 Wenn Sie alle diese Informationsquellen zusammen betrachten: wie häufig benutzen Sie diese?

☐ mehrmals täglich ☐ täglich ☐ einmal pro Woche ☐ einmal pro Monat ☐ weniger als einmal pro Monat ☐ nie

9. Wie beurteilen Sie insgesamt die Qualität Ihrer Informationsquellen zu potentiellen DDIs?

Möglicher unerwünschter Effekt:	☐ Ausreichende Information	☐ Zu wenig Information
Häufigkeit des Auftretens klinisch relevanter Folgen:	☐ Ausreichende Information	☐ Zu wenig Information
Mechanismus der potentiellen DDI:	☐ Ausreichende Information	☐ Zu wenig Information
Risikofaktoren für das Auftreten einer DDI:	☐ Ausreichende Information	☐ Zu wenig Information
Einschätzung des Schweregrads:	☐ Ausreichende Information	☐ Zu wenig Information
Hinweis auf ein nicht-wechselwirkendes Ausweichpräparat:	☐ Ausreichende Information	☐ Zu wenig Information
Vorschlag zur Dosisanpassung:	☐ Ausreichende Information	☐ Zu wenig Information
Hinweis, den Arzt zu kontaktieren:	☐ Ausreichende Information	☐ Zu wenig Information

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10. Wie wichtig sind für Sie die folgenden Informationen zu DDIs in der täglichen Praxis?

Möglicher unerwünschter Effekt	☐ Unverzichtbar	☐ Wünschenswert	☐ Entbehrlich
Häufigkeit des Auftretens klinisch relevanter Folgen	☐ Unverzichtbar	☐ Wünschenswert	☐ Entbehrlich
Mechanismus der potentiellen DDIs	☐ Unverzichtbar	☐ Wünschenswert	☐ Entbehrlich
Risikofaktoren für das Auftreten einer potentiellen DDI	☐ Unverzichtbar	☐ Wünschenswert	☐ Entbehrlich
Einschätzung des Schweregrads	☐ Unverzichtbar	☐ Wünschenswert	☐ Entbehrlich
Hinweis auf ein nicht-wechselwirkendes Ausweichpräparat	☐ Unverzichtbar	☐ Wünschenswert	☐ Entbehrlich
Vorschlag zur Dosisanpassung	☐ Unverzichtbar	☐ Wünschenswert	☐ Entbehrlich
Hinweis, den Arzt zu kontaktieren	☐ Unverzichtbar	☐ Wünschenswert	☐ Entbehrlich

11. Wenn Sie potentiell wechselwirkende Medikamente abgeben, wie häufig informieren Sie den Patienten?

nie ○ 0% ○ 10% ○ 20% ○ 30% ○ 40% ○ 50% ○ 60% ○ 70% ○ 80% ○ 90% ○ 100% immer

Zur Kommunikation des Apothekers mit dem behandelnden Arzt

12. Schätzen Sie, wie oft Sie in den letzten 3 Monaten den Arzt kontaktiert haben:

Total: ☐☐☐ mal

Aufgrund potentieller DDIs: ☐☐☐ mal

13. Wie kommunizieren Sie mit dem Arzt?:
(Mehrfachantworten möglich)

Allgemein: ☐ Telefonisch ☐ Fax ☐ Videokonferenz ☐ E-mail ☐ Über den Patienten

☐ Andere, welche? _____

Wegen potentieller DDIs:

☐ Telefonisch ☐ Fax ☐ Videokonferenz ☐ E-mail ☐ Über den Patienten

☐ Andere, welche? _____

14. Wie beurteilen Sie die Reaktion des Arztes auf Ihre Kontakte wegen potentieller DDIs?

Er antwortete auf meine Kontakte: nie ○ 0% ○ 10% ○ 20% ○ 30% ○ 40% ○ 50% ○ 60% ○ 70% ○ 80% ○ 90% ○ 100% immer

Der Kontakt war für den Arzt relevant: nie ○ 0% ○ 10% ○ 20% ○ 30% ○ 40% ○ 50% ○ 60% ○ 70% ○ 80% ○ 90% ○ 100% immer

Wie häufig wurde die Therapie geändert (z.B Absetzen, Alternativtherapie, Dosisanpassung)? nie ○ 0% ○ 10% ○ 20% ○ 30% ○ 40% ○ 50% ○ 60% ○ 70% ○ 80% ○ 90% ○ 100% immer

Wie häufig wurde eine zusätzliche intensivere Überwachung der Therapie angeordnet? nie ○ 0% ○ 10% ○ 20% ○ 30% ○ 40% ○ 50% ○ 60% ○ 70% ○ 80% ○ 90% ○ 100% immer

Die Reaktionen auf meine Kontakte waren insgesamt: ☐ schwierig ☐ problemlos ☐ sehr angenehm

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15. Grund für den Kontakt: Wenn Sie an alle Kontakte mit Ärzten der letzten 3 Monaten denken. Wie häufig kontaktierten Sie diese wegen folgender Ursachen?	nie	selten	manchmal	häufig
Rezept unlesbar	☐	☐	☐	☐
Arzneimittel nicht verfügbar	☐	☐	☐	☐
Überweisung eines Patienten	☐	☐	☐	☐
Fehlende Verordnung	☐	☐	☐	☐
Abklärung der Patientensituation	☐	☐	☐	☐
Arzneimittelmissbrauch	☐	☐	☐	☐
Potentielle Arzneimittelwechselwirkungen	☐	☐	☐	☐
Generikasubstitution	☐	☐	☐	☐
Dosisanpassung	☐	☐	☐	☐

Neue Möglichkeiten der Zusammenarbeit zwischen Apotheke und Arzt:

16.1 Wie beurteilen Sie "telemedizinische Konsultationen"* (Möglichkeit eines Beratungsgesprächs, in dem der Arzt mittels Videokonferenz bzw. Webcam in die Apotheke geschaltet wird). (* Heutige Anbieter: Dr. Online, DirectCare, Medicopharm)

☐ Ich nutze bereits diese Möglichkeit

☐ Ich könnte mir vorstellen, diese Möglichkeit zu nutzen innerhalb der nächsten:

☐ 6 Monate ☐ 12 Monate ☐ später

☐ ich warte zur Zeit noch ab und beobachte den Markt

☐ Diese Möglichkeit kommt für mich nicht in Frage. Grund: _____

_____

_____

16.2 Einige Stunden pro Woche ist ein Arzt persönlich in der Apotheke anwesend (z.B. zur Grippeimpfung, Alternativmedizin, Tierarzt):

☐ Ich nutze bereits diese Möglichkeit: ☐ Grippeimpfung ☐ Alternativmedizin ☐ Tiermedizin

☐ Andere, welche? _____

☐ Ich könnte mir vorstellen, diese Möglichkeit zu nutzen ☐ Grippeimpfung ☐ Alternativmedizin ☐ Tiermedizin

innerhalb der nächsten:

☐ 6 Monate ☐ 12 Monate ☐ später ☐ Andere, welche? _____

☐ ich warte zur Zeit noch ab und beobachte den Markt

☐ Diese Möglichkeit kommt für mich nicht in Frage. Grund: _____

_____

_____

16.3 Sehen Sie andere Möglichkeiten für eine intensivere Zusammenarbeit zwischen Arzt und Apotheker? Welche?

_____

_____

_____

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Angaben zur Apothekerin /zum Apotheker

Geschlecht ☐ W ☐ M **Jahrgang** ☐☐☐☐ **Jahr des Staatsexamens** ☐☐☐☐

Ihre Position: ☐ Angestellt ☐ Verwaltung ☐ BesitzerIn

Ihr Arbeitspensum: ☐☐ %

FachapothekerIn FPH-Offizinpharmazie: ☐ Ja ☐ In Ausbildung ☐ Nein

Angaben zur Apotheke

Wo liegt Ihre Apotheke? *Orte mit Zentrumsfunktion und mehr als 10000 Einwohner gelten als Stadt. Ortschaften, die an eine Grossstadt angrenzen, gelten als Agglomerationen (z.B Köniz bei Bern):*

☐ Stadt (City, Passantenlage) ☐ Stadt (Quartierlage) ☐ Agglomeration ☐ Land oder Dorf

Kundschaft: ☐ Vorwiegend Stammkunden ☐ Vorwiegend Passanten ☐ In etwa ausgeglichen

Überwiegende Form der Medikamentenabgabe in Ihrem Einzugsgebiet: ☐ Rezeptur ☐ Selbstdispensation ☐ Mischform

Qualitätsmanagement: ☐ QMS ☐ QMS beantragt ☐ Kein QMS

Welche Apothekensoftware haben Sie installiert ?

☐ CSE ☐ Golden Gate (Pharmatic) ☐ Inpha ☐ Pharmacy (PMS) ☐ ProPharma ☐ Andere, welche? ----------

Herzlichen Dank für Ihre Mitarbeit !

Bitte senden Sie uns den Fragebogen bis am 4. Juli 2005 im beiliegendem Rückantwort-couvert zurück oder faxen Sie ihn an die Faxnummer 0612671428. Bei allfälligen Fragen können Sie uns gerne unter der Telefonnummer 0612671426 kontaktieren.

Unter allen Teilnehmern werden 5 Jahres-Abonnements von im@il-Offizin verlost.

i.m@il Offizin

www.imail-offizin.ch

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C.2 Reminder

Institut für Klinische Pharmazie
Universität Basel

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Klingelbergstrasse 50
4056 Basel

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laura.erba@stud.unibas.ch

Basel, Freitag, 23. Juni 2005

Befragung von öffentlichen Apotheken in der Deutschschweiz

Sehr geehrte Dame, sehr geehrter Herr,

Vor rund vier Wochen erhielten Sie von uns den Fragebogen „**.**
Da ein möglichst hoher Rücklauf wichtig für eine aussagekräftige Auswertung ist, wären wir sehr froh, wenn Sie uns den Fragebogen baldmöglichst zurücksenden könnten. Bei etwaigen Fragen rufen Sie uns bitte an (0612611426).

Herzlichen Dank

Dr. Kurt Hersberger, Projektleiter

Jörg Indermitte, Betreuer

Laura Erba, Diplomandin

C.4 Recordation of non-responders

Erfassung der Non-Responder

Guten Tag,

Im Rahmen einer Diplomarbeit an der Universität Basel haben wir ihrem Chef /Ihnen vor etwa 2 Monaten einen Fragebogen gesendet

Wir haben dazu keine Antwort erhalten, und damit wir zumindest einige charakteristische Merkmale erhalten, erlaube ich mir, Sie auf diesem Weg anzufragen, ob Sie mir kurz einige Informationen geben könnten (5 Kurze Fragen):

□ Ja □ Nein

Geschlecht des verantwortlichen Apothekers

□ Männlich

□ Weiblich

Alter des verantwortlichen Apothekers:

□ weniger als 30 Jahre alt
□ zwischen 30 - 40 Jahre alt
□ zwischen 40 - 50 Jahre alt
□ mehr als 50 Jahre alt

Ist Ihre Apotheke in einem SD-Gebiet?

□ Ja □ Nein

Wieso haben Sie nicht geantwortet?

□ Abwesenheit
□ Zeitgründe
□ Keine Umfragen
□ Weiss nicht

Ist die automatische Erkennung durch die Apothekensoftware in ihrer Apotheke aktiviert?

□ Ja □ Nein

D.1 Informed consent

Institut für Klinische Pharmazie
Universität Basel

Studienleitung:
Dr. Kurt Hersberger
(Projektleiter)

Jörg Indermitte
(Betreuer)

Adresse:
Pharmazentrum 0059
Klingelbergstrasse 50
4056 Basel

Tel. 0612671426
Fax. 0612671428

Email:
kurt.hersberger@unibas.ch
joerg.indermitte@unibas.ch

Basel, 15.04.2005

Informed Consent

Liebe Kolleginnen und Kollegen

Im Rahmen einer Portfolioarbeit führen wir mit den Studenten im Praktikumsjahr eine kleine Studie durch. Ihr Einverständnis vorausgesetzt, werden Die Studenten die tägliche Apothekenpraxis beobachten. Der Student erfasst die Besuche von je 20 Stammkunden und beobachtet und erfragt an zwei normalen Arbeitstagen den jeweils verantwortlichen Apotheker während ca. einer halben Stunde zum Umgang mit Arzneimittelinteraktions-Alarmen in Ihrem Computersystem. Die Apotheker und das Apothekenteam sollen über den Inhalt der Untersuchung nicht informier werden. Es wird, mit Ausnahme der kurzen Befragung, kein zusätzlicher Arbeitsaufwand entstehen und der tägliche Arbeitablauf wird nicht gestört. Alle erfassten Daten werden vom Studenten noch in der Apotheke anonymisiert. Erfasst werden neben dem Umgang mit den Interaktionsalarmen Alter und Geschlecht des Kunden und Medikamente die in den letzten 3 Monaten bezogen wurden.

Wir bitten Sie um das schriftliche Einverständnis zur Durchführung der beschriebenen Studie in Ihrer Apotheke

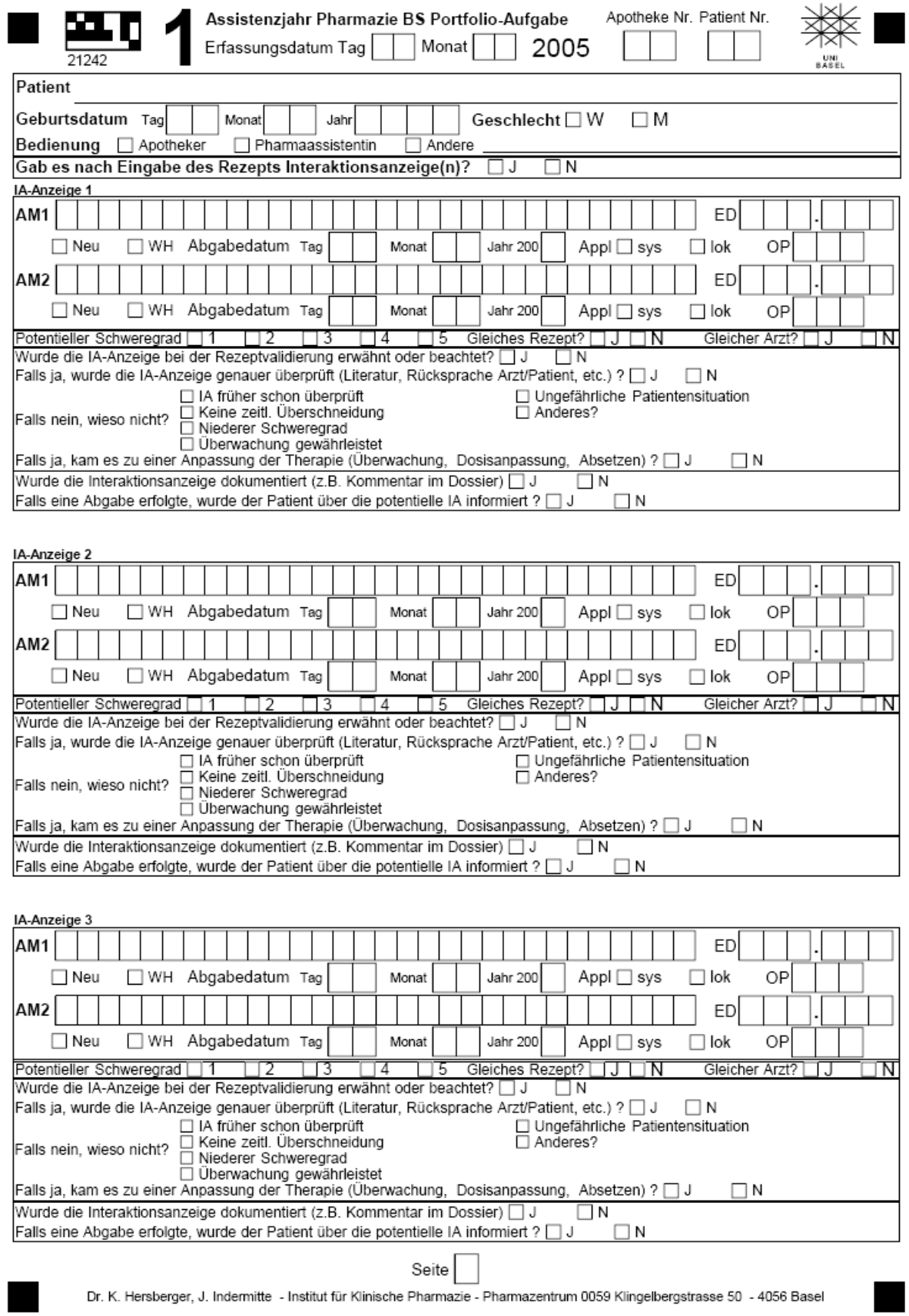
Ort:_____Datum:_____Unterschrift:_____

Vielen Dank und freundliche Grüssen

Dr. K. Hersberger

J. Indermitte

D.2 Formulary for data collection



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1 **Assistenzjahr Pharmazie BS Portfolio-Aufgabe** Apotheke Nr. Patient Nr.

Erfassungsdatum Tag ☐☐ Monat ☐☐ 2005 ☐☐ ☐☐

UNI BASEL

Patient

Geburtsdatum Tag ☐☐ Monat ☐☐ Jahr ☐☐☐☐ **Geschlecht** ☐ W ☐ M

Bedienung ☐ Apotheker ☐ Pharmaassistentin ☐ Andere _____

Gab es nach Eingabe des Rezepts Interaktionsanzeige(n)? ☐ J ☐ N

IA-Anzeige 1

AM1 ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐ ED ☐☐☐.☐☐☐

☐ Neu ☐ WH Abgabedatum Tag ☐☐ Monat ☐☐ Jahr 200☐ Appl ☐ sys ☐ lok OP ☐☐☐

AM2 ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐ ED ☐☐☐.☐☐☐

☐ Neu ☐ WH Abgabedatum Tag ☐☐ Monat ☐☐ Jahr 200☐ Appl ☐ sys ☐ lok OP ☐☐☐

Potentieller Schweregrad ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 Gleiches Rezept? ☐ J ☐ N Gleicher Arzt? ☐ J ☐ N

Wurde die IA-Anzeige bei der Rezeptvalidierung erwähnt oder beachtet? ☐ J ☐ N

Falls ja, wurde die IA-Anzeige genauer überprüft (Literatur, Rücksprache Arzt/Patient, etc.) ? ☐ J ☐ N

Falls nein, wieso nicht? ☐ IA früher schon überprüft ☐ Keine zeitl. Überschneidung ☐ Niederer Schweregrad ☐ Überwachung gewährleistet ☐ Ungefährliche Patientensituation ☐ Anderes?

Falls ja, kam es zu einer Anpassung der Therapie (Überwachung, Dosisanpassung, Absetzen) ? ☐ J ☐ N

Wurde die Interaktionsanzeige dokumentiert (z.B. Kommentar im Dossier) ☐ J ☐ N

Falls eine Abgabe erfolgte, wurde der Patient über die potentielle IA informiert ? ☐ J ☐ N

IA-Anzeige 2

AM1 ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐ ED ☐☐☐.☐☐☐

☐ Neu ☐ WH Abgabedatum Tag ☐☐ Monat ☐☐ Jahr 200☐ Appl ☐ sys ☐ lok OP ☐☐☐

AM2 ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐ ED ☐☐☐.☐☐☐

☐ Neu ☐ WH Abgabedatum Tag ☐☐ Monat ☐☐ Jahr 200☐ Appl ☐ sys ☐ lok OP ☐☐☐

Potentieller Schweregrad ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 Gleiches Rezept? ☐ J ☐ N Gleicher Arzt? ☐ J ☐ N

Wurde die IA-Anzeige bei der Rezeptvalidierung erwähnt oder beachtet? ☐ J ☐ N

Falls ja, wurde die IA-Anzeige genauer überprüft (Literatur, Rücksprache Arzt/Patient, etc.) ? ☐ J ☐ N

Falls nein, wieso nicht? ☐ IA früher schon überprüft ☐ Keine zeitl. Überschneidung ☐ Niederer Schweregrad ☐ Überwachung gewährleistet ☐ Ungefährliche Patientensituation ☐ Anderes?

Falls ja, kam es zu einer Anpassung der Therapie (Überwachung, Dosisanpassung, Absetzen) ? ☐ J ☐ N

Wurde die Interaktionsanzeige dokumentiert (z.B. Kommentar im Dossier) ☐ J ☐ N

Falls eine Abgabe erfolgte, wurde der Patient über die potentielle IA informiert ? ☐ J ☐ N

IA-Anzeige 3

AM1 ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐ ED ☐☐☐.☐☐☐

☐ Neu ☐ WH Abgabedatum Tag ☐☐ Monat ☐☐ Jahr 200☐ Appl ☐ sys ☐ lok OP ☐☐☐

AM2 ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐ ED ☐☐☐.☐☐☐

☐ Neu ☐ WH Abgabedatum Tag ☐☐ Monat ☐☐ Jahr 200☐ Appl ☐ sys ☐ lok OP ☐☐☐

Potentieller Schweregrad ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 Gleiches Rezept? ☐ J ☐ N Gleicher Arzt? ☐ J ☐ N

Wurde die IA-Anzeige bei der Rezeptvalidierung erwähnt oder beachtet? ☐ J ☐ N

Falls ja, wurde die IA-Anzeige genauer überprüft (Literatur, Rücksprache Arzt/Patient, etc.) ? ☐ J ☐ N

Falls nein, wieso nicht? ☐ IA früher schon überprüft ☐ Keine zeitl. Überschneidung ☐ Niederer Schweregrad ☐ Überwachung gewährleistet ☐ Ungefährliche Patientensituation ☐ Anderes?

Falls ja, kam es zu einer Anpassung der Therapie (Überwachung, Dosisanpassung, Absetzen) ? ☐ J ☐ N

Wurde die Interaktionsanzeige dokumentiert (z.B. Kommentar im Dossier) ☐ J ☐ N

Falls eine Abgabe erfolgte, wurde der Patient über die potentielle IA informiert ? ☐ J ☐ N

Seite ☐

Dr. K. Hersberger, J. Indermitte - Institut für Klinische Pharmazie - Pharmazentrum 0059 Klingelbergstrasse 50 - 4056 Basel

10 Curriculum vitae

Personal data

Forenames	Jörg Lorenz
Surname	Indermitte
Date of Birth	December 23rd 1975
Place of Origin	Steg and Hohtenn (VS)

Education and Professional Life

1982 – 1991	Basic education
1991 - 1996	High school at the 'Kollegium Spiritus Sanctus', Brig
June 1996	Matura, main subject science (maturity type C)
1996 - 2000	Studies in pharmacy at the University of Bern
1999 - 2000	Practical year at the community pharmacy 'Central Apotheke', Naters and at the 'Institut Central des Hôpitaux Valaisans', Sion
2000-2002	Studies in pharmacy at the University of Basel
2002	Diploma thesis 'Web based interactive E-learning module enzymes for pharmacy students' under the supervision of Prof. Dr. B. Ernst at the University of Basel, Basel
November 2002	Swiss federal diploma in pharmacy
January 2003 - March 2003	Employed as deputy pharmacist at the pharmacy 'Apotheke Marty', Brig
April 2004 – September 2006	Employed as deputy pharmacist at the pharmacy 'Notfall Apotheke Basel', Basel
May 2003 - September 2006	PhD thesis at the Institute of Clinical Pharmacy, University of Basel under the supervision of Dr. Kurt E. Hersberger and Prof. Dr. Stephan Krähenbühl.
	Thesis topic: 'Potential drug interactions - Exposure and management in ambulatory and hospital settings'
	Assistant in university courses of Clinical Pharmacy
	Author in the framework of 'i.m@il-Offizin'

Additional Courses

2003	'Pharmacoepidemiology and Drug Safety' Symposium, University of Basel
2003	Web Development Course and Certificate, University of Basel
2004	ESCP Congress in Paris, France
2005	Symposium of the Swiss Society of Pharmacology and Toxicology 'Fortschritte in der Pharmakologie' in Bern
2005	'European Symposium on Clinical Pharmacy Congress' in Amsterdam, The Netherlands

Scientific Publications

Indermitte J, Burkolter S, Drewe J, Krähenbühl S, Hersberger KE. The influence of risk factors on the velocity to develop hyperkalaemia. Drug Saf; in press

Indermitte J, Reber D, Beutler M, Bruppacher R, Hersberger KE. Prevalence and patient knowledge of potential drug interactions with self-medication. J Clin Pharm Ther; in press

Indermitte J, Erba L, Beutler M, Bruppacher R, Haefeli WE, Hersberger KE. Management of drug interactions in community pharmacies: A questionnaire based survey in Switzerland. Eur J Clin Pharmacol; in press

Indermitte J, Meier C, Beutler M, Hersberger KE. Management of drug interaction alerts in community pharmacies; submitted

Hersberger KE, Indermitte J, Bruppacher R. Applikationshilfen aus der Apotheke. Ther Umschau 2006; 6: 433-9

Posters and Oral Presentations

Indermitte J, Reber D, Bruppacher R, Krähenbühl S, Hersberger K. Prevalence and patient knowledge of potential drug interactions with self-medication. 26 - 29th October 2005; 34th European Symposium on Clinical Pharmacy, Amsterdam, The Netherlands

Lectures

During my studies I followed courses of the following lecturers: Berger KA, Bruppacher R, Drewe J, Ernst B, Folkers G, Guentert T, Gutmann H, Haschke M, Hersberger KE, Imanidis G, Krähenbühl S, Lampert ML, Leuenberger H, Meier CR, Meier B, Mühlebach S, Schaffner W, Schlienger RG, Scholer A, Surber C, Vedani A, Wolf P, Zaugg CE