ORIGINAL RESEARCH ARTICLE

Drug Safety 2006; 29 (8): 723-732
0114-5916/06/0008-0723/$39.95/0



# Clinical Risk Management in Dutch Community Pharmacies

## The Case of Drug-Drug Interactions

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## Abstract

**Background:** The prevention of drug-drug interactions requires a systematic approach for which the concept of clinical risk management can be used. The objective of our study was to measure the frequency, nature and management of drug-drug interaction alerts as these occur in daily practice of Dutch community pharmacies.

**Methods:** In total, 63 Dutch pharmacies collected all drug-drug interaction alerts during 153 research days (on average 2.4 days/pharmacy), as well as variables related to these alerts, such as involved medicines, first time or recurrent drug-drug interaction, same or different prescribers, patient data (age, sex) and information about the management of drug-drug interactions by the pharmacy. The latter was discriminated into internal procedures only and external action, such as communication with the patient, the prescriber or the anticoagulation clinic and prescription modification. All drug-drug interactions were classified into categories of clinical relevance (A–F) and available evidence (0–4).

**Results:** A total of 43 129 prescription-only medicines were dispensed during the study period. On average, 16.8 interaction alerts per day per pharmacy were collected. Approximately 6% of all prescriptions generated a drug-drug interaction alert. Of all alerts (n = 2572), 31.1% occurred for the first time and with 21% two different prescribers were involved. The 20 most frequently occurring drug-drug interaction alerts accounted for approximately 76% of all alerts. Cardiovascular drugs, NSAIDs, oral contraceptives and antibacterials were most frequently involved. External action was taken in response to 27.3% of the alerts, meaning either a modification of one of the concerned prescriptions (n = 65; 9.3%), communication with the prescriber or anticoagulation clinic (n = 90; 12.8%) or communication with the patient or a relative (n = 547; 77.9%). Where there was no external action (n = 1860; 72.3%), pharmacists concluded in about two-thirds of cases that the drug-drug interaction had been managed in the past. Other reasons not to intervene externally were for instance: incorrect alert; acceptable drug-drug interaction; or outcome of the interaction considered irrelevant. Adjusted for several variables, a first alert was found to be a main determinant for external action. After stratifying for first alerts no other significant determinants were found.

**Conclusions:** A high frequency of drug-drug interaction alerts was found. Most concerned recurrent alerts, which were the main reason not to act externally. Concerning the assessment phase in the risk-management process, drug-drug interactions with no or low evidence/relevance should be reconsidered. Concerning the management of drug-drug interactions in pharmacies, the opportunity to actively suppress alerts for a certain period of time should be studied in more detail. There are indicators that the management of patient-orientated advice could be improved and a greater degree of consistency developed for the management of first and recurrent interaction alerts.

## Background

According to the literature, medical errors do not occur from individual recklessness but rather from basic flaws in the organisation of the healthcare system.[1] Therefore, effective prevention of medical errors requires a systematic approach towards the healthcare system. Clinical risk management aims to change the organisation from organisational vulnerability towards organisational integrity.[2] The clinical risk-management process consists of three main phases, i.e. (i) risk assessment, (ii) risk management and (iii) evaluation of strategies. During the risk-assessment phase, potential hazards are identified and stratified in terms of evidence, probability and clinical significance. The risk-management phase tries to define the operational strategies needed to minimise these hazards, the identification of resources and the execution of those strategies, which includes the recognition, analysis and management of (potential) health hazards in daily clinical practice. A final and crucial part of clinical risk management is the performance evaluation of risk-management strategies, i.e. to determine whether these strategies have actually been effective and efficient.[3]

Prescription errors have been reported to occur in up to 11% of all prescriptions; the majority of which are dose-related errors.[4,5] The occurrence of such errors has been the subject of several studies and is part of the public debate about patient safety.[6] Pharmacists can play a major role in the detection and prevention of drug-related problems and medication errors.[7-13] The impact of drug-drug interactions on drug-related morbidity, including unnecessary hospital admissions, has been demonstrated.[14-17] In addition, during recent years, drug-drug interactions have become a major reason for withdrawal of drugs from the marketplace and labelling changes, partly because adequate risk management could not be established in daily clinical practice.[18]

Several steps of the clinical risk-management process can be observed in the prevention and management of prescribing errors related to drug-drug interactions in pharmacies. Concerning the assessment phase in The Netherlands, there are two (to some extent different) resources containing information about drug interactions. These resources are translated into drug-interaction signalling software by the five pharmacy information systems that in turn are used by Dutch community pharmacies.[19] The pharmacy information system checks a prescription for drug-drug interactions using stored information about actual drug use of a patient. Actual drug use is derived from previous prescriptions dispensed to that patient for whom a theoretical duration of use is calculated based upon the number of dose units and the prescribed daily dose. In general, the conditions for risk management are advantageous in Dutch pharmacies: electronic prescription entry, computerised medication records and a low degree of fragmented prescription filling due to a high pharmacy compliance of the patient.[20,21]

A limited amount of research has been conducted into the magnitude and nature of drug-drug interaction alerts in community pharmacies as well as the management thereof.[22-24] We were interested in drug-drug interaction alerts occurring in real daily clinical practice, whereas others counted potential drug-drug interactions,[25,26] used large databases[27] or a few general practices,[28] focussed on specific patients,[29] and sometimes included duplicate medications[30] or restricted themselves to potentially hazardous drug combinations.[24,28] We were interested in the frequency of drug-drug interaction alerts

**Table I.** Classification of drug-drug interactions[a]

| Category | Description |
|---|---|
| **Quality of evidence** | |
| 0 | Pharmacodynamic animal studies; *in vitro* studies with limited predictive value for the human *in vivo* situation; data on file |
| 1 | Incomplete, published case reports (no re- or dechallenge, presence of other explaining factors for the adverse reaction) |
| 2 | Well documented, published case reports; retrospective analyses of case series |
| 3 | Controlled, published interaction studies in patients or healthy volunteers, with surrogate end points |
| 4 | Controlled, published interaction studies in patients or healthy volunteers, with clinically relevant end points |
| **Clinical relevance** | |
| A | No inconvenience, insignificant effect |
| B | Short-lived inconvenience |
| C | Inconvenience without residual symptoms; failure of therapy concerning non serious diseases |
| D | Inconvenience with residual symptoms; failure of therapy concerning serious but non-fatal diseases |
| E | Raised risk of dying; failure of life saving therapy; increased risk of pregnancy |
| F | Serious, irrecoverable disablement; potentially lethal cardiac arrhythmia; death; increased risk of pregnancy plus risks concerning mother and/or fetus |

a For further details, please refer to Van Roon et al.[19]

where the number of prescriptions is the denominator, whereas others used the number of patients[31] or the number of drug-related problems.[4,7,32] Along with the prevalence and nature of drug-drug interaction alerts (identification of risk), we were interested in the analysis and management phase in the risk-management process (the management of alerts). The objective of our study was therefore to measure the frequency, nature and management of drug-drug interaction alerts as these occur in the daily practice of Dutch community pharmacies.

## Methods

### Setting and Study Population

A total of 220 Dutch community pharmacies belonging to the pharmacy practice research networks of the SIR Institute for Pharmacy Practice and Policy and of Utrecht University, The Netherlands, were invited to participate in this study. Of these, 63 pharmacies responded positively and were enrolled in the study. These 63 pharmacies serve approximately 600 000 patients.

In the period from July to November 2004, each participating pharmacy was requested to record all drug-drug interaction alerts that occurred over a period of 2 or 3 days. The data had to be collected on one specific day (between Monday and Friday) of the week but pharmacists were free to select which week during the study period they would collect alert data.

### Collection and Classification of Data

On the first form, concerning the documentation of one drug-drug interaction alert, pharmacists collected information related to the alert itself (the medicines involved in the drug-drug interaction, first time or recurrent drug-drug interaction, same or different prescribers), patient data (age, sex) and information about its management by the pharmacy.

Information about management was divided into 'external action' (communication with the patient or relative, communication with the prescriber and prescription modification) and internal procedures that required 'no external action' (e.g. interaction already evaluated in the past, incorrect alert, acceptable interaction or other reason not to intervene). 'Communication with prescriber' included contacts with anticoagulation clinics concerning drug-drug interactions, especially for patients using oral anticoagulants.

The second form concerned the basic characteristics of each research day, such as the total number of alerts and the number of prescriptions. The third form concerned the basic characteristics of the pharmacy, including the general performance as to the management of drug-drug interaction alerts. A study protocol advised participating pharmacists to con-

tact the helpdesk in case of any uncertainty regarding any of the three forms.

Afterwards, all drug-drug interactions were classified by the research team into categories of clinical relevance (A–F) as well as categories of available evidence (0–4), according to the classification system developed and maintained by a working group of the Scientific Institute of Dutch Pharmacists.[19] This classification system is described in brief in table I. The classification system means that, for example, subtype 4F is indicating an interaction with a substantial greater risk than that classified as 1A. It is related to the classification system used in Sweden, which has been described for research purposes elsewhere.[25]

### Data Analysis

After inspection, data from the registration forms were entered into a database (Microsoft Access 2000) and analysed using standard descriptive data analysis (SPSS version 12.0). Logistic regression analysis was used to measure the strength of the association between alert characteristics and external action by the pharmacists.

## Results

The 63 participating pharmacies comprised almost 4% of all Dutch pharmacies (about 1750 in total). There was a large variation between pharmacies with respect to the daily number of prescriptions (average 282; range 95–750), which reflects that both small and large pharmacies participated in the study. Thirty pharmacies (47.6%) collected data for 3 days, another 30 (47.6%) collected for 2 days and three (4.8%) collected for 1 day. This was an average of 2.4 research days per pharmacy.

A total of 43 129 prescription-only medicines were dispensed during the study period of 153 research days. The pharmacies collected data on 2572 drug-drug interaction alerts during this time, meaning that 16.8 alerts per day per pharmacy (range 2–53) were reported. About 6% of all presented prescriptions generated a drug-drug interaction alert (on average, one drug-drug interaction alert per 16.8

**Table II.** Frequency and nature of the 20 most frequently encountered drug-drug interaction alerts

| Description of interaction | Number | Frequency (%) | Evidence-relevance[a] |
|---|---|---|---|
| Renin-angiotensin system inhibitors – diuretics | 348 | 13.53 | 3D |
| β-Adrenoceptor antagonists (β-blockers) – NSAIDs | 278 | 10.81 | 3C |
| NSAIDs – renin-angiotensin system inhibitors | 266 | 10.34 | 3D |
| Diuretics – NSAIDs | 154 | 5.99 | 3D |
| Bisphosphonates – complex forming divalent metallic ions | 111 | 4.32 | 0A |
| Renin-angiotensin system inhibitors – potassium-sparing diuretics/ potassium supplements | 100 | 3.89 | 2F |
| Oral contraceptives – antibacterials | 94 | 3.65 | Not classified |
| NSAIDs (excluding selective COX-2 inhibitors) – SSRIs | 78 | 3.03 | 4C |
| Corticosteroids – NSAIDs | 66 | 2.57 | 3C |
| Coumarin anticoagulants – antibacterials | 61 | 2.37 | Not classified |
| Digoxin – diuretics | 57 | 2.22 | 3A |
| β-Blockers/calcium channel antagonists – α-adrenoceptor antagonists | 51 | 1.98 | 3B |
| Coumarin anticoagulants – NSAIDs | 47 | 1.83 | Not classified |
| Calcium channel antagonists – β-blockers | 42 | 1.63 | 3E |
| Methotrexate – NSAIDs/salicylates | 39 | 1.52 | 3E |
| Levothyroxine – iron | 39 | 1.52 | 3C |
| Simvastatin/atorvastatin – diltiazem/verapamil | 38 | 1.48 | 3E |
| Non-selective β-blockers – β-adrenoreceptor agonists | 33 | 1.28 | 3C |
| Oral hypoglycaemic drugs – selective β-blockers | 32 | 1.24 | 3B |
| Insulin – selective β-blockers | 26 | 1.01 | 3B |

a See table I.

**COX** = cyclo-oxygenase; **SSRIs** = selective serotonin reuptake inhibitors.

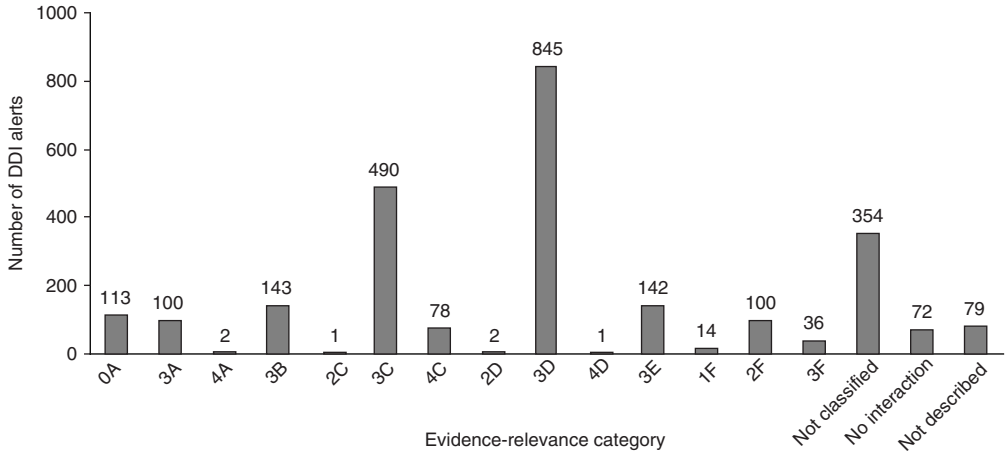


**Fig. 1.** Number of drug-drug interaction (DDI) alerts reported during the study, classified by evidence-relevance category.

prescriptions). The interaction alerts occurred in 1891 patients, an average of 1.4 interaction alerts per patient (range 1–12).

Of all alerts, about two-thirds (n = 1613) concerned women and almost 80% concerned people >50 years of age (30.9% concerned people >75 years of age). Of all alerts, 31.1% (n = 800) occurred for the first time and in 21% of the alerts (n = 539) two different prescribers were involved.

The 20 most frequently occurring drug-drug interaction alerts are presented in table II.[1] These account for about 76% of all alerts (n = 1960). The top ten most frequently reported drug-drug interactions accounted for 60% (n = 1556) and the top five for 45% (n = 1157) of all alerts. Cardiovascular drugs were predominantly involved, such as ACE inhibitors, diuretics, β-adrenoceptor antagonists (β-blockers), potassium-sparing diuretics, coumarin anticoagulants and digoxin. NSAIDS, oral contraceptives and antibacterials were also frequently encountered.

Figure 1 shows the number of alerts per evidence-relevance category. Most drug-drug interactions that occur are generally evidence-based (category 3) and have a risk of moderate-to-serious inconveniences (categories C and D). Drug-drug interactions that might have serious clinical consequences (categories E and F) were found less frequently: 292 (0.7%) of all prescriptions (n = 43 129).

In figure 2, we report on the process of the management of alerts in the selected pharmacies. A total number of 702 alerts (27.3%) led to external action of the pharmacy, meaning either a modification of one of the concerned prescriptions (n = 65; 9.3%), communication with the prescriber or anticoagulation clinic (n = 90; 12.8%) or communication with the patient or relative (n = 547; 77.9%). Modifications of a prescription concerned the last prescribed drug (n = 25), the first prescribed drug (n = 25), a dosage alteration (n = 6), a temporary discontinuation of use of the first medicine (n = 4) and an addition of an extra drug, particularly proton pump inhibitors (n = 4). Communication with the prescriber could take place before or after dispensing and concerned mostly communication with the anticoagulation clinic (70%). This communication was largely carried out by fax: an average of once every 4–5 days per pharmacy.

Communication with the patient mostly concerned advice to separate the timing of intake of the two medications (interval of ≥2 hours; 19%), advice to check blood pressure regularly (16%), advice to use extra contraceptive measures (10%), warning concerning the potential deterioration of heart failure/oedema (6%), advice to contact their doctor about the influence on potassium level (3%), warn-

**1** All drug-drug interaction alerts found in this study are presented on our website http://www.stevenshof.nl.

ing concerning potential stomach problems (3%) and warning as to probable disturbance of the menstrual cycle (3%). In addition, pharmacies provided specific written information concerning the drug-drug interaction (16%) or advised the patient to inform the anticoagulation clinic about the drug-drug interaction with respect to coumarin anticoagulant use (9%).

In the other instances, there was no external intervention (n = 1860; 72.3%) [figure 2]. Slightly >76% (1425 of 1860) concerned internal procedures, concluding that evaluation of the drug-drug interaction alert had already taken place in the past. In 5.5% (103 of 1860), the evaluation led to the conclusion that the alert appeared to be incorrect, mainly because one of the interacting drugs prescribed in the past had already been stopped by the patient. In 6.1% (113 of 1860), the pharmacist decided that the drug-drug interaction was acceptable since the latest prescribed drug, mostly NSAIDs, was only prescribed for a short period of time. In 4.2% (n = 78), the pharmacist assessed the outcome of the interaction not to be relevant. There were several other reasons (n = 141; 7.6%) presented by the pharmacists not to intervene, such as discharge from hospital, drug prescribed by a specialist, stomach protection already in use, blood pressure control is well known or first-prescribed drug already stopped by prescriber.

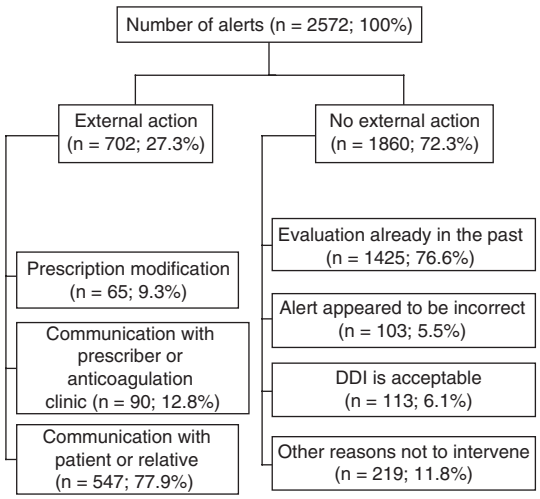


**Fig. 2.** Drug-drug interaction (DDI) alert management in Dutch community pharmacies. Total does not add up to 100% because of missing values, where the action taken was unknown.

Adjusted for several variables, we found that drug-drug interaction alerts occurring for the first time had a considerably higher probability (odds ratio [OR] 7.48, 95% CI 6.06, 9.24) for external action by pharmacists (table III). Other determinants for external action were female sex (OR 1.35, 95% CI 1.09, 1.68) and youngest-age category (<50 years) [OR 1.43, 95% CI 1.08, 1.89]. A higher relevance category (D–F) unexpectedly signified a lower probability for external action (OR 0.77, 95% CI 0.60, 0.99). Stratifying for first alerts, however, we found no significant (95% CI) differences between sex, age and prescriber categories as well as between relevance and evidence categories.

Comparing coumarin drug-drug interactions, which are not classified by the assessment committee (see table I), with other drug-drug interactions and stratifying for first alerts, we found a considerably higher probability for external action by pharmacies (OR 5.8, 95% CI 3.3, 10.2; adjusted for age, sex and prescriber) [data not shown].

## Discussion

We found a high frequency of drug-drug interaction alerts of which most appeared to be recurrently occurring. These kinds of alerts turned out to be the main reason for pharmacies not to act externally. In a minority of alerts, the pharmacy acted externally, especially directed at the patient. A first alert was the main determinant for acting externally.

The frequency of drug-drug interaction alerts, about 6% of all prescriptions, was almost 2-fold higher than was found in another Dutch study by van Mil et al.[22] (3.3%). A limitation of the latter study was its dependence on the active registering of all drug-related problem alerts by participating pharmacies over a long period of time.

The drug-drug interaction alerts particularly involved cardiovascular drug classes and NSAIDs, in accordance with other studies.[26] Due to differences regarding setting, study population or definition of drug-drug interactions, some authors have found other drugs or drug classes to be (more frequently) involved in interaction alerts.[27,30] The frequency of alerts for drug-drug interactions that can have seri-

**Table III.** Determinants for external action of pharmacies after having a drug-drug interaction alert[a]

| Characteristic | External action (n = 702) | | | No external action [n = 1860 (%)] | OR (95% CI) crude | OR (95% CI) adjusted[b] |
|---|---|---|---|---|---|---|
| | modification prescription [n = 65 (%)] | communication with prescriber [n = 90 (%)] | communication with patient [n = 547 (%)] | | | |
| **Patient-related** | | | | | | |
| Sex | | | | | | |
| male | 30 (46.2) | 42 (46.7) | 145 (26.5) | 732 (39.4) | 1 [ref] | 1 [referent] |
| female | 35 (53.8) | 48 (53.3) | 401 (73.3) | 1124 (60.4) | 1.45 (1.21, 1.75) | 1.35 (1.09, 1.68) |
| Age | | | | | | |
| 0–50 years | 20 (30.8) | 12 (13.3) | 191 (34.9) | 308 (16.6) | 2.19 (1.73, 2.77) | 1.43 (1.08, 1.89) |
| 51–65 years | 22 (33.8) | 20 (22.2) | 113 (20.7) | 511 (27.5) | 0.92 (0.72, 1.17) | 0.91 (0.69, 1.20) |
| 66–75 years | 10 (15.4) | 16 (17.8) | 101 (18.5) | 445 (23.9) | 0.86 (0.67, 1.11) | 0.80 (0.60, 1.07) |
| >75 years | 13 (20.0) | 42 (46.7) | 142 (26.0) | 596 (32.0) | 1 [ref] | 1 [referent] |
| **Prescriber-related** | | | | | | |
| Same prescriber | 37 (56.9) | 58 (64.4) | 409 (74.8) | 1509 (81.1) | 1 [ref] | 1 [referent] |
| Different prescriber | 24 (36.9) | 32 (35.6) | 138 (25.2) | 343 (18.4) | 1.69 (1.38, 2.07) | 1.13 (0.89, 1.44) |
| **Drug-drug interaction related** | | | | | | |
| Recurrent alert | 7 (10.8) | 25 (27.8) | 214 (39.1) | 1481 (79.6) | 1 [ref] | 1 [referent] |
| First alert | 56 (86.2) | 65 (72.2) | 324 (59.2) | 352 (18.9) | 7.61 (6.27, 9.24) | 7.48 (6.06, 9.24) |
| **Relevance categories**[c] | | | | | | |
| A–C | 22 (33.8) | 19 (21.1) | 204 (37.3) | 681 (36.6) | 1 [ref] | 1 [referent] |
| D–F | 27 (41.5) | 25 (27.8) | 154 (28.2) | 928 (49.9) | 0.62 (0.50, 0.76) | 0.77 (0.60, 0.99) |
| **Evidence categories**[c] | | | | | | |
| 1–2 | 4 ( 6.2) | 3 ( 3.3) | 12 ( 2.2) | 96 ( 5.2) | 1 [ref] | 1 [referent] |
| 3–4 | 45 (69.2) | 41 (45.6) | 295 (53.9) | 1451 (78.0) | 1.33 (0.80, 2.20) | 1.02 (0.58, 1.78) |

a Not all values add up to 100% because of missing values where the action taken was unknown.

b Adjusted for all other characteristics.

c Only categories with assessment of certain degree of relevance or evidence are presented (see table I).

ous clinical consequences (categories E and F in the Dutch classification system) was half as high in our study as was found by Merlo et al.[25] (0.7% of all prescriptions versus 1.4%, respectively). However, in the study conducted by Merlo et al.,[25] an irrelevant dosage form (non-nebulised forms of asthma drugs) accounted for 52.2% for this high-relevance category (category D in Swedish system). On the other hand, in our study, such a problem may not be excluded as well, and moreover, an important group of drug-drug interactions concerning coumarin was part of the 'not classified' category.

A large part of all drug-drug interaction alerts concerned renewals of drug combinations. Too many alerts, of which most are not relevant anymore, may be a main reason to override the alerts.[33] Moreover, drug-drug interaction alerts are only one of many alerts presented on pharmacy computer screens, such as those concerning duplicate medications, dose-related problems, drug-disease interactions and intolerabilities.[4,7,22,32] Most pharmacy computer systems offer ample opportunity to actively suppress alerts for a certain period of time, a system flexibility that is advocated elsewhere.[33] About one-third of the participating pharmacies in this study used this function; however, as far as we could verify, not systematically. The opportunity to actively suppress alerts for a certain period of time, but also to produce (certain) alerts only in case of prescriptions for new medicines or in the case of dosage changes, should be studied in more detail. Algorithms may also be applied by the system so that in certain instances no alert will show up (e.g. NSAIDs prescribed for a short period of time). This

problem is amplified by the fact that some drug-drug interaction alerts (we counted 12 different combinations of drugs leading to a drug-drug interaction) occur that have been classified as having no relevance (n = 72; 2.8% of all alerts). In addition, it is necessary to alert in some instances when certain drugs are discontinued.

In this study, we found that 1.63% of all dispensed prescriptions resulted in external action being taken in response to an interaction alert. In his study, van Mil et al.[22] is less specific: 0.46% of all prescriptions led to an advice or change of dose. One may estimate it as positive that pharmacies acted significantly more externally in case a drug combination occurred for the first time. In addition, following stratification for first alerts, other determinants for external action, such as female sex and youngest age category, were no longer found to be significantly different between pharmacies. However, there are some data indicating that improvements are possible.

We found a high incidence of pharmacy actions directed at the patient, approximately 78% of all external actions. In a study about prescription modifications, we found a high frequency of patient contacts to solve prescription-related problems.[4] Contrary to this, Knapp et al.[23] found that in his study about drug-related problems, US pharmacies contacted the prescriber in 56.1% of cases, reviewed the patient profile in 21% and interviewed the patient or his representative in 18.9%. The question is whether all patients can deal with all types of information reported in this study. In particular, the information about serum potassium level measurements may cause problems. Contacting the anticoagulation clinic may be problematic for some patients as well, such as older people. In these cases, pharmacists should reconsider this type of action, of which we think the doctor (or anticoagulation clinic) is the best target.

Reversibly, we revealed a high frequency of internal pharmacy proceedings (72.3%) not leading to communication with doctors or patients. Recurrent alerts were a main reason for this (n = 1481; 79.6%). Nevertheless, in 14.2% of the recurrent alerts, such an alert was followed by external action, mostly communication with the patient (see table III). This may be understandable in cases where the information was given months or even years after the previous alert. Information about a possible deterioration of oral contraceptive effectiveness (because of antibacterial use, see table II) is probably a good example of a repeated intervention. In this example, 15 recurrent alerts led to 13 communication actions towards patients. On the other hand, of all first alerts, only 55.8% were followed by external action.

Let us look at one important drug-drug interaction, i.e. a renin-angiotensin system inhibitor administered with a diuretic (see table II), to find some explanations. There were 60 first alerts of this drug-drug interaction, for which there is only a need for action in case of a first prescription of a renin-angiotensin system inhibitor. Excluding missing values and incorrect classifications, we found 38 such cases, for 22 of which the pharmacy undertook no action. Indeed, the actual clinical significance of an alert and therefore the management of the pharmacy will also depend on other information, such as the patient's history, co-morbidities, preferences for treatment and specialisation of the prescriber.[27] Based upon the descriptions of actions that the pharmacies gave, we may conclude that for 15 cases, the management was accurate (e.g. discharge from hospital); however, for seven cases, no action or an incorrect management was described.

We found that for some alerts that were followed by internal-only procedures, the pharmacist registered a reason not to intervene such as discharging the patient from the hospital or that the drug was prescribed by a specialist. We were unable to study whether these reasons were appropriate or not. The adherence to guidelines concerning the management of drug-drug interactions as well as the reasons (not) to adhere to these, is a worthwhile subject for further study. This also applies to our unexpected finding that drug-drug interactions with a high grading of clinical relevance led less often to external action than those with a lower grading.

### Limitations

This study has some limitations. The participating pharmacies constituted a voluntary sample, which may have led to a positive-selection bias concerning the performance of pharmacies. Secondly, it may be possible that some drug-drug interaction alerts were not registered because the register-

ing pharmacist or technician overlooked them or because of omissions of the software systems, meaning that not all alerts were shown on the daily reports that contain all alerts of drug-related problems from the day before.

The degree of under-reporting may be even higher when we realise that over-the-counter drugs, such as NSAIDs or herbal medicines such as St John's Wort, are seldom registered in The Netherlands. These examples are assessed in literature as important drug-drug interactions.[18,34] In his study about drug-related problems concerning non-prescription drugs, Westerlund et al.[7] found several drug-drug interactions, about 3% of all registered problems. There is a low risk of under-reporting because of a low degree of fragmented prescription filling in The Netherlands.[20,21]

The absolute and relative frequency of drug-drug interaction alerts depends on the type of surveillance programme. Basically, there are two drug-interaction knowledge systems used in Dutch community pharmacies. There are several differences with respect to the surveillance of drug-drug interactions between these two systems. Some drug-drug interactions, covered by one system (we found 79 cases in our study), will not be covered by the other one (we found 115 cases in our study), meaning a lower frequency of the respective drug-drug interactions in this study. Moreover, the level of relevance of drug-drug interactions is sometimes differently assessed in both systems, which has consequences as to the management of the pharmacist. Divergent assessments of drug-drug interactions, made by the two working groups maintaining and developing the two knowledge systems, account for the observed differences. Similar differences as to the judgement of drug-drug interactions have been described concerning important drug-interaction compendia.[35]

## Conclusion

A high frequency of drug-drug interaction alerts in daily pharmacy practice was found. Most concerned recurrent alerts, which were also the main reason not to act externally. An abundance of apparently non-relevant alerts implies the risk of overriding these. Drug-drug interactions with no or low evidence/relevance should be reconsidered as part of computerised drug-interaction surveillance systems. The opportunity to actively suppress alerts for a certain period of time or to produce (certain) alerts only in case of prescriptions for new medicines or in the case of dosage changes should be studied in more detail.

There are indicators that management by pharmacies can be improved concerning patient-oriented advices and a consistent way of managing recurrent alerts, first alerts and alerts concerning important but avoidable drug-drug interactions. Since the pharmacy organisation is a potential determinant of drug-drug interaction-associated dispensing, pharmacists should focus on knowledge, instructions and supervision to ameliorate their part of the risk-management process of medicines.[36]

## Acknowledgements

We would very much like to thank all 63 pharmacists who participated in this study. Special thanks to Mrs Martine Kruijtbosch, MSc and Mr Willem Rump, PhD, for their support in collecting the data and developing the technical infrastructure, and Mr Tom Schalekamp, PharmD, for his critical comments on drafts of the manuscript.

No sources of funding were used to assist in the preparation of this study. The authors have no conflicts of interest that are directly relevant to the content of this study.

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