LEADING ARTICLE

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Potential Determinants of Drug-Drug Interaction Associated Dispensing in Community Pharmacies

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Abstract

Although the number of clinically relevant drug-drug interactions (DDIs) is probably low, DDIs may be responsible for a substantial number of hospital admissions. In some countries, the pharmacist is responsible for preventing the use of unsafe or non-effective drug regimens. Specifically they should avoid the dispensing of combinations of drugs that may cause serious DDIs. In order to assess the determinants related to community pharmacies and associated with these dispensings, a systematic literature review was conducted. Medline and International Pharmaceutical Abstracts were searched for articles published in English between 1993 and 2003. Additional relevant articles were identified by screening the reference lists of relevant articles.

Seven papers were located. The determinants described in the literature were divided into three groups. The first group focussed on the relationship between the pharmacist and the prescriber. The number of prescribers is of importance as well as the number of dispensing pharmacies. Both a high number of primary care physicians and multiple dispensing pharmacies increased the risk of DDIs. The availability, quality and sensitivity of the medication surveillance software appeared to be a second important determinant. Both too many and too few signals increased the risk of dispensing interacting drugs. The third group of determinants was related to the pharmacist and pharmacy organisation. Signals from the surveillance program are usually judged first by technicians and subsequently managed by the pharmacist. Consequently, knowledge, instructions and supervision are important determinants. A fourth group of determinants was identified in literature assessing interventions by pharmacists, including interventions for DDIs. A higher workload was associated with lower intervention rates, which indicated a higher risk of dispensing interacting drugs.

The determinants identified in this review can be used to develop strategies to minimise patient harm resulting from DDIs. Further assessment of the relation

between these determinants and the dispensing of DDIs and of the relation between DDI-associated dispensing and patient harm is recommended.

One of the consequences of multiple drug use is the risk of one drug influencing the effect of a second drug. This so-called drug-drug interaction (DDI) is defined as a pharmacokinetic or pharmacodynamic influence of drugs on each other, which can result, besides desired effects, in reduced effectiveness or increased toxicity.[1] The seriousness and clinical relevance of DDIs vary considerably. Although DDIs are probably common, only 10–12% of the prescriptions involving a DDI have serious clinical consequences.[2-4] The seriousness of the DDI should be weighed against the benefit of both drug therapies and the availability of alternatives.

Previously, the tasks of the pharmacist focussed on the production and dispensing of a limited number of drugs. With the growing number of available drugs and the increasing complexity of drug therapy, such as in the treatment of HIV-related diseases, the role of the pharmacist is changing rapidly from product-centred to patient-centred. In some countries, including The Netherlands, one of the present responsibilities of the pharmacist is to prevent the use of unsafe or non-effective drug regimens. In The Netherlands, every pharmacist is obliged to use a medication surveillance program for this task. One of their responsibilities is to prevent the dispensing of interacting drugs, which carries too much risk for patient harm. Studies assessing interventions by pharmacists show that the percentage of prescriptions that are intercepted ranges from 0.75% to 1.9%.[5-10] This variation may partly be attributable to variations in the definition of intervention. The percentage of intercepted prescriptions that prevent adverse clinical consequences ranges from 0.27% to 0.95%.[5-8] Only between 0.011% and 0.078% of the prescriptions are intercepted because of a DDI.[5,6,8] Although this low percentage suggests that DDIs are of no clinical significance, the adverse consequences may be substantial.[6] Different studies suggest that the number of hospital admissions due to DDIs is up to 3% of all admissions.[11-14] This could be an underestimation because of the inability of practitioners and pharmacists to identify a DDI as the cause of an adverse outcome. It is possible that a drug-related problem is ascribed to the last prescribed drug and not to a interaction of this drug with another one.

In this review we searched for process and structure characteristics that have a relationship with the dispensing of interacting drugs. Process and structure characteristics determine the outcome of care, which can be understood in terms of death, disease, disability, discomfort and dissatisfaction.[15] The dispensing of drugs involving a DDI is assessed as a proxy for the outcome of healthcare. There are three reasons for focussing on the determinants for DDI-associated dispensing. First, DDIs are a clearly defined type of error and they have a relation with the present tasks of the pharmacists. Second, DDIs are considered to be an important cause of adverse events. Third, the dispensing of drugs that are part of a DDI can be traced in databases. In locations where the patient's medication history is filed, it is relatively easy to trace DDIs during observational assessment in the future.

The objective of the review was to investigate which determinants within community pharmacies are associated with a high frequency of DDI-associated dispensing.

1. Literature Search Methodology

Determinants in this literature review were identified by searching Medline and International Pharmaceutical Abstracts (IPA) for articles published between January 1993 and December 2003. This timeframe was chosen because the tasks of the pharmacist have changed considerably in the last decade. Therefore, we assumed that literature written before 1993 would not apply to current daily practice.

In the Medline search the results of two strategies were combined. The first one used the medical subject heading (MeSH) descriptors 'drug-interac-

tions', 'drug-antagonism', 'drug-synergism' and 'medication-errors'. The second one used the MeSH descriptor 'community pharmacy services' or the keyword 'dispens*' for all fields. To exclude studies concerning dispensing in hospital pharmacies, papers with the keywords 'hospital pharmacy services' were omitted.

In the IPA search the results of a similar strategy were used. The first search used the terms 'drug interactions', 'medication errors', 'medication error?' and 'dispensing error?'. The latter two were searched for the title only. The second search used the terms 'community pharmacy services' and 'dispens?'. Studies with the terms 'hospital pharmacy services' or 'institutional hospital pharmacy' were excluded.

Papers from both searches were included if they were written in English, were applicable to community pharmacy services and to DDI-associated dispensing and described determinants involved in the dispensing of DDIs. Articles that matched the inclusion criteria were selected and additional relevant articles were identified by screening the reference lists of these articles. Papers looking at prescriber or patient characteristics as determinants were outside the scope of this review.

The Medline search yielded 134 articles and the IPA search yielded 357 articles. Reference tracking and verification as to whether the articles met the inclusion criteria resulted in the selection of seven articles on determinants of dispensing interacting drugs.[1,16-21] None of the articles discussed the entire range of determinants involved in DDI-associated dispensing.

2. DDI-Associated Determinants

The determinants for the dispensing of interacting drugs could be divided into three groups (table I). The first group describes the 'relationship with the prescriber' and the other groups ('medication surveillance program' and 'pharmacy organisation') described determinants within the pharmacy.

Table I. Determinants for drug-drug interaction (DDI)-associated dispensing

Study	Independent variable	Effect	Dependent variable	Size of effect
Relationship with prescriber				
Tamblyn et al.[21]	Single primary care physician	Lower	Receiving DDI	Cardiovascular drugs OR = 0.70; 99% CI 0.6, 0.8 Psychotropic drugs OR = 0.79; CI not given NSAID OR = 0.94; CI not given
Medication surveillance program				
Tamblyn et al.[21]	Single dispensing pharmacy	Lower	Receiving DDI	Cardiovascular OR = 0.68; 99% CI 0.6, 0.8 Psychotropic drugs OR = 0.79; CI not given NSAID OR = 0.75; CI not given
Halkin et al.[17]	Introduction of medication surveillance program	Lower	Dispensing severe DDIs	OR = 0.28; 95% CI 0.26, 0.30
Tamblyn et al.[20]	Introduction of medication surveillance program	Higher	Discontinuation rate of prescriptions for DDIs	OR = 1.33; 95% CI 0.90, 1.95
Hazlet et. al.[18]	Software does not recognise interaction	Higher	Risk of DDI	NA
Schalekamp[1]	Software gives too many signals	Higher	Risk of DDI	NA
Bates & Leape[16]	Software does not sufficiently alert	Higher	Risk of DDI	NA
Pharmacy organisation				
Schalekamp[1] Heijboer-Vinks[19]	Management of medication surveillance signals	NA	NA	NA

NA = not available; **OR** = odds ratio.

2.1 Relationship With Prescriber

Tamblyn et al.[21] assessed whether the risk of a DDI increased with the number of prescribers. Patients who had a single primary-care physician or a single dispensing pharmacy were less likely to be prescribed concomitant medications causing a DDI.

2.2 Medication Surveillance Program

In the study by Halkin et al.,[17] the introduction of medication surveillance software for DDIs in the majority of community pharmacies and physician offices reduced the dispensing of prescriptions with severe interactions by 67.5 %. Tamblyn et al.[20] also found that, although it was not significant, the introduction of medication surveillance programs by primary care physicians increased the discontinuation rate of prescriptions involving interacting drugs. On the other hand, discussion exists as to whether medication surveillance programs can prevent the dispensing of all relevant DDIs. In letters to the editor, both Cavuto et al.[22] and Kraft and Dore[23] reported that some of the pharmacists using a computer program were unable to prevent well documented DDIs. In their reply, Bates and Leape[16] discussed the reasons why pharmacists failed to intervene in spite of the use of a medication surveillance program. First, the software may not be able to correctly identify clinically important DDIs because the software is not up-to-date or well documented DDIs are otherwise absent from the database.[18] Second, because of an overload of interaction signals, pharmacists may have grown accustomed to skipping through them rapidly. Too many warnings complicate medication surveillance because the identification of relevant signals becomes more difficult. They are most often caused by repeated warnings for the same patient, managed in an earlier dispensing.[1] The third reason why pharmacists may be unable to intervene in spite of the use of medication surveillance programs is that the program does recognise certain drug combinations, but does not sufficiently alert the pharmacist or technician that a DDI is present and that the dispensing should be prevented.[16]

2.3 Pharmacy Organisation

The management of the signals generated by the medication surveillance program is important.[1,19] In the first place, the sensitivity of the software is an issue. Both ignoring signals that need to be managed and an overload of signals should be avoided. A signal must be judged on relevance and, if relevant, it must be followed by an appropriate action. In community pharmacies most signals will be noticed first by technicians. They should be instructed and supervised on how to judge and, if possible, how to manage these signals. The last issue is the knowledge of the pharmacist in managing DDIs and the ability of the pharmacist to judge the risk of DDIs.

3. Discussion

The purpose of this literature review was to identify determinants of DDI-associated dispensing in community pharmacies. Determinants concerning the prescriber or the patient, for example interactions with over-the-counter drugs, were outside the scope of this review. Although the number of interventions related to DDIs is small, DDIs may be a major risk for hospital admission. Studies were identified that assessed the interventions by pharmacists and the number of hospital admissions caused by DDIs, but no studies were found that assessed the relationship between these interventions and hospital admissions. In some countries, pharmacists have a task to prevent serious DDIs. Focus on the determinants in the pharmacy may reduce the dispensing of drugs involving a DDI and improve patient outcome. The determinants of interest for surveillance of DDI-associated dispensing could be divided into three groups. These groups are ‘relationship with the prescriber’, ‘medication surveillance program’ and ‘pharmacist and pharmacy organisation’. Proper attention paid to these determinants can contribute to the prevention of the dispensing of interacting drugs.

In the first group, Tamblyn et al.[21] found that an increasing number of prescribers or pharmacists involved in the dispensing of drugs increases the risk of dispensing DDIs. The influence of the number and kind of prescribers was also described by stud-

ies assessing interventions by pharmacists, including interventions for DDIs (table II). A high number of interventions suggests a high risk for DDI-associated dispensing as the risk of a DDI remaining unnoticed might increase. Although interventions for DDIs were only a small part of the total number of interventions, these studies give insight into what may go wrong during the process of drug dispensing. Pharmacists more often modified prescriptions from specialists than prescriptions from the patient's own general practitioner (GP) and prescriptions from GPs other than the patient's own GP.[5] Westein et al.[9] also found that prescriptions from specialists had higher intervention rates than prescriptions from the patient's own GP, although this result was not significant. The higher intervention rates for specialist prescriptions and for prescriptions from GPs other than the patient's own GP, show the importance of a central point for the drug therapy to be coordinated. A higher, but not significant, intervention rate was also found for drugs taken as part of a complex drug therapy.[9]

A direct prescription order communication between the prescriber and the pharmacist gave rise to less interventions than a prescription order communicated by the patient or a representative.[8] Intervention rates were higher for handwritten prescriptions and for when the GP had no online access to the actual patient's medication record in the pharmacy computer.[5] Handwritten prescriptions require extra attention by the pharmacy because they can imply that no medication surveillance by computer took place during the prescribing process. In addition, misreading the prescription can lead to the wrong drug being dispensed.

The second group found that the medication surveillance program and its sensitivity is important. Differences exist between the degree of computerisation and the availability of medication histories in community pharmacies, which are largely influenced by the environment. In The Netherlands all pharmacists are obliged to keep records of the drugs that are dispensed. In the first place, the availability of medication surveillance programs is of interest for reducing the dispensing of DDIs; in the second place, the way these programs are used is important. Hazlet et al.[18] assessed the differences between software programs in detecting a non-representative, but well documented, group of interactions. Although they assessed differences between software programs only, they also found differences between users of the same software program, which emphasises the importance of fine-tuning the sensitivity of the program. Different studies suggest that only some of the signals produced lead to interventions.[9,25,26] Westein et al.[9] did not find any association between the number of signals and the number of interventions. Therefore, it is important that the number of irrelevant signals is low, but that all relevant DDIs are detected and managed correctly. It is recommended that attention is paid to both the quality and the sensitivity of the software.

The third group described the influence of the pharmacist and pharmacy organisation. These determinants may play an important role in avoiding DDI-associated dispensing. This group is influenced to a large extent by the environment, for example the contribution of technicians in the community pharmacy and the use of medication surveillance programs. Studies assessing interventions by pharmacists, including interventions for DDIs, reported that pharmaceutical care training[24] and higher work satisfaction[10] were associated with higher intervention rates. No difference in intervention rates was found between chain pharmacies and independently owned pharmacies.[8]

This literature review has some limitations. The ultimate purpose of the review was to associate determinants of the dispensing of interacting drugs with the outcome of healthcare. In this review, these dispensings were assessed as a proxy for outcome. The relationship between the dispensing of interacting drugs and outcome can be assumed based on studies indicating that DDI-associated interventions prevent patient harm[6] and that DDIs are a cause of hospital admissions.[11-14] The literature search was limited to the Medline and IPA databases and possibly caused publication bias and the exclusion of data that is published in journals not selected in Medline or IPA. Only a limited number of studies were found

Table II. Determinants for interventions including interventions for drug-drug interactions (DDIs)

Study	Independent variable	Effect	Dependent variable	Size of effect
Relationship with prescriber				
Buurma et al.[5]	Prescriptions from specialists	Higher	Prescription interventions	OR = 1.82; 95% CI 1.57, 2.11 27.5% in intervention sample versus 17.6% in control sample
Westein et al.[9]				OR = 1.21; 95% CI 0.69, 1.72
Buurma et al.[5]	GP not being patient's own GP	Higher	Prescription interventions	OR = 1.49; 95% CI 1.02, 2.17 3.1% in intervention sample versus 2.4% in control sample
Westein et al.[9]	Drugs part of complex drug therapy	Higher	Prescription interventions	
	>3 prescribers			OR = 1.75; 95% CI 0.51, 2.99
	>15 prescriptions in 3 months			OR = 1.60; 95% CI 0.80, 2.40
	>3 different medications			OR = 1.48; 95% CI 0.98, 1.99
Rupp et al.[8]	Direct prescription order transmission between GP and pharmacist	Lower	Prescription interventions	7.2% in intervention sample versus 18.9% in control sample
Buurma et al.[5]	Handwritten prescriptions	Higher	Modification	OR = 3.30; 95% CI 2.90, 3.75
	Physician has online access to actual patients medication record	Lower	Modification	OR = 1.61; 95% CI 1.33, 1.94
Medication surveillance program				
Westein et al.[9]	Number of signals	No relationship	Interventions	
Pharmacist and pharmacy organisation				
Currie et al.[24]	Pharmaceutical care training	Higher	Interventions	OR = 8.1; 95% CI 4.7, 14.2
Westerlund et al.[10]	Work satisfaction	Higher	Drug-related problem detection rate	R_c = 0.020; 95% CI −0.157, 0.197
Rupp et al.[8]	Chain and independent pharmacies	No difference	Interventions	

GP = general practitioner; **OR** = odds ratio; $\mathbf{R_c}$ = slope.

to have exclusively assessed the dispensing of concomitant medications that do interact. A number of studies assessed the interventions by pharmacists, including the interventions for DDIs. It can reasonably be expected that determinants described in these studies are also applicable to the dispensing of DDIs. An additional determinant found was workload, with three of the four studies finding that an elevated number of dispensed prescriptions was significantly associated with a lower intervention rate and probably indicated a higher patient risk (table III).[6-8,10]

Most of the studies covered in this article were sensitive to bias, such as selection bias and bias because participants were aware that they were being observed. Most likely participating pharmacists were not afraid to show their shortcomings and probably had an increased level of attention during the observation period. Consequently, the number of actions taken by pharmacists may be overestimated and, thus, patient risk may be underestimated. Finally, none of the studies in the literature assessed the whole range of determinants for DDI-associated dispensing. Therefore, it cannot be guaranteed that no determinants were missed. Also, the definition of DDI used in the studies varied to a large extent. Because there is a wide range in the seriousness of DDIs, a drug combination could be considered as a DDI in one study, but not in another. Finally, the determinants identified in the studies for the dispensing of DDIs were influenced by the environment, for example legislation, the division of tasks between pharmacists and other personnel, and the healthcare system. Because most studies were performed in different countries, results may not be comparable to one another.

Table III. Influence of workload on community pharmacy services

Study	Country, year	Method	Study population	Independent variable	Dependent variable	Correlation
Caleo et al.[6]	Australia, 1996	Case series	580 pharmacy days	Prescriptions per pharmacy	Intervention rate	No
Hawksworth et al.[7]	UK, 1999	Case series	840 pharmacy days	Prescriptions per pharmacy	Intervention rate	Yes Correlation coefficient: −0.65
Rupp et al.[8]	US, 1992	Case-control	445 pharmacy days	Prescriptions per pharmacist per hour	Intervention rate	Yes Regression coefficient: −0.40
Westerlund et al.[10]	Sweden, 1999	Case series	144 pharmacy professionals[a]	Weighted transactions	Drug-related problem detection rate	Yes Regression coefficient: 5×10^{-6}

a 34 pharmacists, 71 prescriptionists and 39 pharmacy technicians.

4. Conclusion

In conclusion, there are three groups of determinants for the dispensing of DDIs in community pharmacy services. These groups are ‘relationship with the prescriber’, ‘medication surveillance program’ and ‘pharmacy organisation’. In studies assessing interventions by pharmacists, including the interception of prescriptions involving DDIs, deter-

minants such as workload were found. It can reasonably be expected that these determinants have a relationship with the dispensing of DDIs. To validate these results, further assessment of the relationship between DDI-associated dispensing and patient harm is necessary. The results of this review are used in an observational study on the association between the determinants and the dispensing of DDIs in community pharmacies.

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References

1. Schalekamp T. Omgaan met geneesmiddeleninteracties. Geneesmiddelenbulletin 1997; 31 (8): 87-94
2. Bergendal L, Friberg A, Schaffrath A. Potential drug-drug interactions in 5,125 mostly elderly out-patients in Gothenburg, Sweden. Pharm World Sci 1995; 17 (5): 152-7
3. Linnarsson R. Drug interactions in primary health care: a retrospective database study and its implications for the design of a computerized decision support system. Scand J Prim Health Care 1993; 11 (3): 181-6
4. Merlo J, Liedholm H, Lindblad U, et al. Prescriptions with potential drug interactions dispensed at Swedish pharmacies in January 1999: cross sectional study. BMJ 2001; 323 (7310): 427-8
5. Buurma H, de Smet PA, van den Hoff OP, et al. Nature, frequency and determinants of prescription modifications in Dutch community pharmacies. Br J Clin Pharmacol 2001; 52 (1): 85-91
6. Caleo S, Benrimoj S, Collins D, et al. Clinical evaluation of community pharmacists' interventions. Int J Pharm Pract 1996; (4): 221-7
7. Hawksworth GM, Corlett AJ, Wright DJ, et al. Clinical pharmacy interventions by community pharmacists during the dispensing process. Br J Clin Pharmacol 1999; 47 (6): 695-700
8. Rupp MT, DeYoung M, Schondelmeyer SW. Prescribing problems and pharmacist interventions in community practice. Med Care 1992; 30 (10): 926-40
9. Westein MP, Herings RM, Leufkens HG. Determinants of pharmacists' interventions linked to prescription processing. Pharm World Sci 2001; 23 (3): 98-101
10. Westerlund T, Almarsdottir AB, Melander A. Factors influencing the detection rate of drug-related problems in community pharmacy. Pharm World Sci 1999; 21 (6): 245-50
11. Huic M, Mucolic V, Vrhovac B, et al. Adverse drug reactions resulting in hospital admission. Int J Clin Pharmacol Ther 1994; 32 (12): 675-82
12. Jankel CA, Fitterman LK. Epidemiology of drug-drug interactions as a cause of hospital admissions. Drug Saf 1993; 9 (1): 51-9
13. McDonnell PJ, Jacobs MR. Hospital admissions resulting from preventable adverse drug reactions. Ann Pharmacother 2002; 36 (9): 1331-6
14. Peyriere H, Cassan S, Floutard E, et al. Adverse drug events associated with hospital admission. Ann Pharmacother 2003; 37 (1): 5-11
15. Donabedian A. The seven pillars of quality. Arch Pathol Lab Med 1990; 114 (11): 1115-8
16. Bates DW, Leape LL. Pharmacies and prevention of potentially fatal drug interactions. JAMA 1996; 275 (14): 1086-7
17. Halkin H, Katzir I, Kurman I, et al. Preventing drug interactions by online prescription screening in community pharmacies and medical practices. Clin Pharmacol Ther 2001; 69 (4): 260-5
18. Hazlet TK, Lee TA, Hansten PD, et al. Performance of community pharmacy drug interaction software. J Am Pharm Assoc 2001; 41 (2): 200-4
19. Heijboer-Vinks IC. Kwaliteitszorg in de medicatiebewaking. Den Haag: KNMP/WINAp, 1998
20. Tamblyn RM, Huang A, Perreault R, Jacques A, Roy D, Hanley J, et al. The medical office of the 21st century (MOXXI): effectiveness of computerized decision-making support in reducing inappropriate prescribing in primary care. CMAJ 3 A.D. 2003; 169 (6): 549-556
21. Tamblyn RM, McLeod PJ, Abrahamowicz M, et al. Do too many cooks spoil the broth?: multiple physician involvement in medical management of elderly patients and potentially inappropriate drug combinations. CMAJ 1996; 154 (8): 1177-84
22. Cavuto NJ, Woosley RL, Sale M. Pharmacies and prevention of potentially fatal drug interactions. JAMA 1996; 275 (14): 1086-7
23. Kraft KE, Dore FH. Computerized drug interactions programs: how reliable? [letter]. JAMA 1996; 275 (14): 1087
24. Currie JD, Chrischilles EA, Kuehl AK, et al. Effect of a training program on community pharmacists' detection of and intervention in drug-related problems. J Am Pharm Assoc 1997; NS37 (2): 182-91
25. Armstrong EP, Denemark CR. How pharmacists respond to online, real-time DUR alerts. J Am Pharm Assoc 1998; 38 (2): 149-54
26. van Mil JWF, Dudok van Heel MC, Boersma M, et al. Interventions and documentation for drug-related problems in Dutch community pharmacies. Am J Health Syst Pharm 2001; 58 (15): 1428-31

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