Clinical decision support in community pharmacy

Mette Heringa

Cover design: Martine van der Wal
Lay-out and printing: Gildeprint, Enschede

CIP-gegevens Koninklijke Bibliotheek, Den Haag
Heringa M.
Clinical decision support in community pharmacy
Thesis Utrecht University - with ref. - with summary in Dutch
ISBN: 978-90-393-6846-6

The work presented in this thesis was performed at the Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, and the SIR Institute for Pharmacy Practice and Policy, Leiden. Financial support was provided by the Royal Dutch Pharmacists Association (KNMP), Health Base Foundation, and SIR Institute for Pharmacy Practice and Policy.

For reasons of consistency within this thesis, some terms have been standardized throughout the text. As a consequence the text may differ in this respect from the articles that have been published.

Clinical decision support in community pharmacy

Medicatiebewaking in de openbare apotheek

(met een samenvatting in het Nederlands)

PROEFSCHRIFT

ter verkrijging van de graad van doctor aan de Universiteit Utrecht

op gezag van de rector magnificus, prof.dr. G.J. van der Zwaan, ingevolge het besluit van het college voor promoties in het openbaar te verdedigen op maandag 30 oktober 2017 des middags te 4.15 uur

door

Mette Heringa

geboren op 21 april 1980 te Nijmegen

Promotoren:	Prof.dr. M.L. Bouvy Prof.dr. P.A.G.M. de Smet
Copromotor:	Dr. A. Floor-Schreudering

Contents

1. General introduction

Introduction

Every action or lack of action in health care has a certain risk of harming one's health. This also applies to drug use – which has an important place in today's arsenal of treatment options. In addition to the positive, intended effects of drug use, there is always a risk of unintended, negative effects. Awareness of unintended harm by health care has increased over the last decades. The growing attention for patient safety was instigated by the publication of several influential reports, starting with the United States National Academies Report *'To Err is Human. Building a Safer Health System'* in 1999 [1-3]. Numerous investigations have illustrated the harm caused by medicines [4-6]. In the Netherlands 5.6% of unplanned hospital admissions were considered drug-related. Apart from the high incidence of medication-related harm, it was notable that nearly half of these drug-related hospital admissions were potentially preventable.

In the Netherlands, the recommendations from the 2009 HARM-wrestling report were leading in the efforts to increase patient safety regarding drug use [3, 7]. The attention for safe drug use was also reflected by legislation, which, for example, from 2012 on imposes prescribers to inform pharmacists about patient's renal function in case of renal impairment [8]. In addition, several regulations were introduced, such as mandatory electronic prescribing instead of hand-written prescriptions [9], and registration of medication administration in care homes and home care [10].

Drug therapy related problems

The occurrence of drug-related patient harm is inherent to drug use, as the effect of a pharmacologically active substance in the body is rarely limited to exactly the targeted process or location. For example, in addition to its lipid lowering effects, simvastatin can cause rhabdomyolysis. The risk of patient harm is influenced by the conditions under which the drug is used. When clarithromycin is prescribed to a patient using simvastatin, simvastatin exposure may increase about 10-fold because of the CYP3A4 inhibiting properties of clarithromycin, leading to an increased risk of rhabdomyolysis [11-13]. Because of this known drug-drug interaction, clarithromycin is contra-indicated in patients using simvastatin. Therefore, combining both drugs can be considered as a drug therapy related problem (DTRP).

A DTRP is any undesirable event or risk thereof, experienced by a patient, that involves drug therapy and that actually or potentially interferes with the achievement of an optimal outcome. The range of possible DTRPs is wide, which

is illustrated by DTRP classification systems. The DOCUMENT system consists of seven main categories: problems related to Drug selection (e.g. drug-drug interactions and drug-disease interactions), Overdose or underdose, Compliance, Untreated indication, Monitoring, Education and information, Non clinical, and Toxicity [14, 15]. This list points out that DTRPs can be caused by (omission of) action of either physicians, pharmacists or patients. Prevention of DTRPs can contribute to the reduction of avoidable drug-related patient harm.

Clinical risk management of drug therapy

Clinical risk management (CRM) provides a systematic approach to the development and implementation of risk reducing strategies. It can be applied, to all fields within health care including drug therapy, in order to systematically prevent, detect and solve DTRPs [16-18]. The concept of CRM is based on a cyclic process consisting of four main steps: risk detection, risk assessment, risk management, and evaluation (Figure 1).

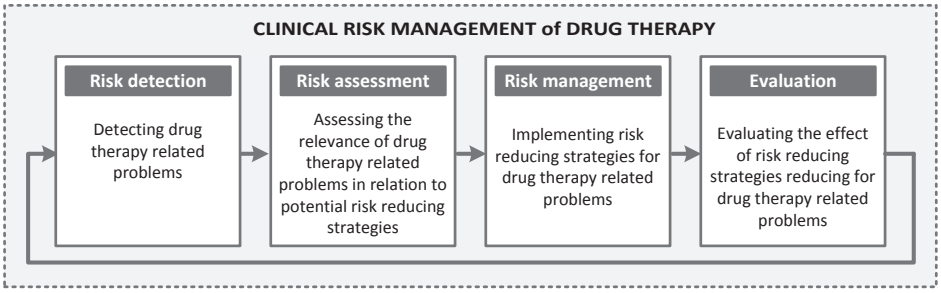


Figure 1: Steps in clinical risk management of drug therapy

CRM of drug therapy should take into account all actors in the drug chain, including drug manufacturers, regulators, guideline and tool developers, prescribers, pharmacists, and patients and their care givers. When all actors ensure correctness or appropriateness of their part of the drug chain, patient harm by drug therapy is minimalized (Figure 2).

The assessment made in CRM of drug therapy is essentially an assessment of the benefit-risk ratio rather than only a risk assessment. For example, the risk of a serious adverse event can be inacceptable for an over-the-counter pain killer, but acceptable for oncologic drugs. Although the risk is the same, the benefit-risk ratio is different. At the population level, this assessment is made by the regulators and guideline developers. For an individual patient, health care professionals

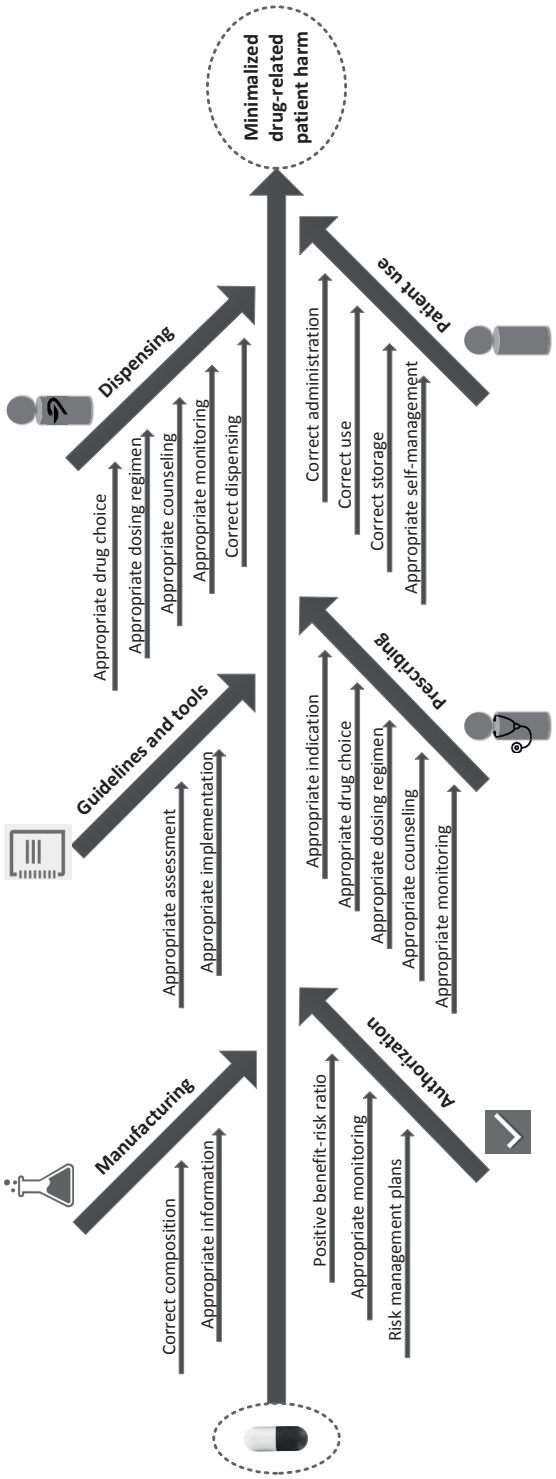


Figure 2. Main steps in realizing minimalized drug-related patient harm

make comparable assessments. In addition, patients eventually make their own benefit-risk assessment for the actual drug use.

Clinical decision support systems

Several risk reducing strategies are applied to increase the benefit-risk ratio of drug use. These strategies range from formularies to guide prescribers in appropriate drug selection to programs to educate patients in correct and timely use of medication. A very common strategy is the use of clinical decision support systems (CDSSs). CDSSs are automated systems which systematically detect DTRPs for an individual patient during either the prescribing or dispensing process. CDSSs are widely used by both prescribers and pharmacists, both in hospitals and primary care. Retrospective studies have shown that a substantial part of current DTRPs could have been detected by CDSSs [19, 20]. A positive effect of CDSSs on outcomes regarding the quality of drug therapy (e.g. guideline adherence or number of DTRPs) has been shown, although the impact on clinical outcomes is less clear [21-32].

CDSSs generate alerts based on algorithms which combine data from the electronic patient record with data from a drug information database. The exact features of the various CDSSs differ highly, varying from basic systems detecting one type of DTRPs (e.g., drug-drug interactions), to advanced systems detecting numerous types of DTRPs [21-32]. In addition to detection of DTRPs, CDSSs often support health care professionals to adhere to guideline-based recommendations.

The guidelines underlying the CDSS alerts, especially for drug-drug interactions and drug-disease interactions, are generally based on the principle of evidence based medicine, which is dominated by risk-benefit assessments [33, 34]. Available evidence on drug-drug interactions or drug-disease interactions, however, is often limited. For example, the advice for drug use in patients with renal impairment is quite often based on a single small pharmacokinetic study (sometimes even unpublished), even for widely used drugs like clarithromycin [35]. For drug-drug interactions it is not exceptional that the exact mechanism is unconfirmed, and that evidence is limited to case-reports. An example is the drug-drug interaction between fusidic acid and statins, with potential risk of rhabdomyolysis observed in case reports, but no clear evidence of a pharmacokinetic or pharmacodynamic mechanism [11, 36]. Drug dosing alerts are generally based on the dosing advices published in the official Summary of Product Characteristics. Other alert types, for example duplicate medication alerts and

alerts on refill non-adherence, are based on theory or practice rather than on scientific evidence.

Drawbacks of clinical decision support systems

Despite their widespread use and positive impact on the quality of drug therapy, CDSSs also have some drawbacks. One of them is the fact that working with the CDSS itself can be a source of errors. For example, default values, like dose suggestions based on most frequently prescribed doses, are easily accepted by health care professionals, although they can be inappropriate for individual patients [37-41].

Another drawback of CDSSs is the high number of generated alerts, and the fact that a substantial part of these alerts is perceived as irrelevant. Most CDSSs have been developed incrementally after their first introduction. Potential newly established risks have continuously been added as an alert. For example, new drug-drug interactions are added when new drugs come to the market, e.g. drugs for the treatment of hepatitis C which have pharmacokinetic interactions with many other drugs [11, 36]. Moreover, new information about drug-drug interactions, sometimes even of already long existing drugs continuously emerges. An example is the risk of hyperkalemia caused by the combination of trimethoprim and renin-angiotensin system inhibitors [11, 36, 42]. In addition to the increase of the number of alerts and per alert type, new types of alerts have been added in CDSSs, e.g. drug-lab alerts and drug-gene alerts [43, 44].

The high number of alerts comes along with a low overall specificity of the alerts [45, 46]. The majority of alerts has been shown to be overridden by health care professionals because they consider the alerts to be irrelevant, with no need to take action [47-52]. An example of low specificity is the drug-drug interaction between diuretics and angiotensin-converting enzyme inhibitors. This drug-drug interaction is only relevant when therapy with an angiotensin-converting enzyme inhibitor is started in a patient already using diuretics because of the risk of severe hypotension. In other situations –either starting the diuretic or chronic use of both drugs - an alert because of concomitant use would be irrelevant [11, 47].

Low alert specificity in combination with a high alert rate is not only troublesome and time-consuming for health care professionals, but also potentially dangerous. It entails the risk of missing important alerts among the high number of irrelevant alerts, which has been reported in many settings [47-52].

In addition to the low specificity of CDSS alerts, sensitivity is not optimal either. It has been shown that complex DTRPs found by health care professionals, were not detected by current CDSSs [53, 54]. For example, multifactorial problems are often not detected, because the risk factors are separately assessed. However, when several factors of low relevance are combined in one patient, the overall relevance could be high. This is illustrated by a case of severe codeine toxicity caused by a moderate dose of 25 mg three times daily [55]. Normally, codeine is partially converted to morphine by CYP2D6 (<10%) and partially metabolized to norcodeine by CYP3A4 (>80%); both metabolites are renally excreted after glucuronidation. Under normal conditions, no clinically relevant drug-drug interaction with CYP3A4 inhibitors has been reported. However, the case report describes a patient who was ultrarapid metabolizer of CYP2D6 (increased formation of morphine), and had an impaired renal function (decreased elimination). Combination with the use of two strong CYP3A4 inhibitors voriconazole and clarithromycin (blocking the other metabolic route) led to severe toxicity with coma. So, conditions which are each in itself not problematic and not 'alert-worthy', together caused a life threatening situation. Alerts based on multifactorial risk estimations could be helpful to detect this kind of situations [56].

Clinical decision making by health care professionals

After a DTRP has been detected by CDSS, the health care professional has to make an assessment. Firstly, the relevance of the alert for the specific patient in the specific situation has to be determined. Secondly, the management options (which can be considered as risk reducing strategies on the individual patient level) have to be assessed, e.g. a dose reduction, a replacement of the drug, or extra monitoring. Often, CDSSs support the assessment and management by providing guideline based management options. However, choosing a management option for an individual patient can be complicated. The evidence for the management options of drug-drug interactions and drug-disease interactions is generally even scarcer than the evidence for the interactions themselves. In addition to clinical considerations based on a patient's health condition, patient preferences should be part of the assessment.

However, up to now, the role of the patient in CRM of drug therapy is limited, despite increased patient involvement in health care in general (for example by the promotion of self-management, the reporting of adverse events, and shared decision making). The current central role of physicians and pharmacists in CRM of drug therapy is consistent with their legal competence on prescribing and dispensing medicines, respectively. Moreover, in the Netherlands they both

have a legal responsibility for the patient's treatment [57]. Pharmacists have, based on their professional expertise, a specific focus on effective and safe drug therapy. Preventing, detecting and solving DTRPs in order to realize patient safety – is considered as one of their core tasks [58].

Objective and outline of the thesis

Establishing the appropriateness and safety of a certain drug in a certain dose for a certain patient is a shared effort of physicians and pharmacists. Therefore, CDSSs are widely used by both physicians and pharmacists. Consequently, these systems have a central role in the detection of DTRPs in clinical practice. However, improvement of both the specificity and the sensitivity of CDSS alerts is necessary. Moreover, clinical decision support could better help health care professionals in the steps following risk detection: the individualized assessment and management of the risk, and the subsequent evaluation. All developments in the field of clinical decision support should contribute to the overall CRM of drug therapy.

Therefore, this thesis aims to provide evidence to guide the development of clinical decision support as a tool for CRM of drug therapy. We investigate the application of CDSSs in daily clinical practice, and we explore several options to improve the detection, assessment and management of DTRPs. We focus on community pharmacy, a setting where it is evident that the patient is a relevant actor in the occurrence and prevention of DTRPs. In this context, eight studies are presented.

The second part of this thesis describes the current practice with respect to the detection and management of DTRPs. In chapter 2.1 the quality of the electronic patient record is explored, as up-to-date medical and pharmaceutical information is a prerequisite for the detection and management of DTRPs. Chapter 2.2 presents an overview of the alerts currently generated by CDSSs in community pharmacy. A detailed investigation of the assessment and management of duplicate medication alerts by community pharmacists is presented in chapter 2.3.

CDSS improvement strategies are needed to increase alert specificity and sensitivity. This is explored in the third part. In chapter 3.1 the large-scale use of advanced CDSSs and point of care testing in community pharmacy is investigated. Chapter 3.2 presents the potential of clustering related drug therapy alerts in order to reduce the alert rate. Chapter 3.3 contains the results of a second potential improvement strategy: better specification of triggers for alert generation.

The fourth part focuses on patients' preferences in the management of a DTRP. In chapter 4.1 a comparison of pharmacists' and patients' preferences regarding drug-drug interaction management is presented. In chapter 4.2 the rationale behind patients' preferences in drug-drug interaction management is explored.

Finally, in the fifth part, the results of the individual investigations are summarized and put into the broader perspective of CRM of drug therapy.

References

1. Audit Commission for Local Authorities and the National Health Services in England and Wales. A spoonful of sugar. 2001, London, United Kingdom.
2. Kohn L, Corrigan J, Donaldson M, eds. To err is human; Building a safer health system. Washington, D.C. United States: National Academy Press 1999.
3. HARM-Wrestling Task Force (Expertgroep Medicatieveiligheid). HARM-WRESTLING. Een voorstel van de Expertgroep Medicatieveiligheid m.b.t. concrete interventies die de extramurale medicatieveiligheid op korte termijn kunnen verbeteren. Ministerie van Volksgezondheid, Welzijn en Sport 2009, The Hague, The Netherlands.
4. Leendertse A, Egberts A, Stoker L, van den Bemt P. Frequency of and Risk Factors for Preventable Medication-Related Hospital Admissions in the Netherlands. *Arch Intern Med* 2008;168:1890-6.
5. Pirmohamed M, James S, Meakin S, Green C, Scott AK, Walley TJ, et al. Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients. *BMJ* 2004;329:15-9.
6. Van der Hooft CS, Dieleman JP, Siemes C, Aarnoudse AJ, Verhamme KM, Stricker BH, et al. Adverse drug reaction-related hospitalisations: a population-based cohort study. *Pharmacoepidemiol Drug Saf* 2008;17:365-71.
7. Warle-van Herwaarden MF, Kramers C, Sturkenboom MC, van den Bemt PM, De Smet PA. Targeting outpatient drug safety: recommendations of the Dutch HARM-Wrestling Task Force. *Drug Saf* 2012;35:245-59.
8. Dutch Ministry of Health, Welfare and Sport (Ministerie van Volksgezondheid, Welzijn en Sport). Regeling van de Minister van Volksgezondheid, Welzijn en Sport van 25 juni 2007, nr. GMT/MVG 2780607, houdende uitvoering van bepalingen van de Geneesmiddelenwet. (Regulations of the Minister of Health attached to the Law on Medicines) 2007 (last update 2016):Artikel 6.10,Artikel 6.11.
9. Royal Dutch Medical Association (Koninklijke Nederlandsche Maatschappij tot bevordering der Geneeskunst, KNMG). Richtlijn elektronisch voorschrijven (Guideline electronic prescribing). 2013, Utrecht, The Netherlands.
10. Task Force Medicatieveiligheid Care. Veilige principes in de medicatieketen. Verpleging - verzorging - thuiszorg. (Safe principles in de drug chain in care homes and home care). ActiZ, KNMP, NVZA, Verenso, BTN, LHV, LOC, NHG, NPCF, V&VN 2012 (update 2016), .
11. Preston CL, ed. Stockley's Drug Interactions (Online). London, United Kingdom: Royal Pharmaceutical Society, The Pharmaceutical Press 2016.
12. Jacobson TA. Comparative pharmacokinetic interaction profiles of pravastatin, simvastatin, and atorvastatin when coadministered with cytochrome P450 inhibitors. *Am J Cardiol* 2004;94:1140-6.
13. Patel AM, Shariff S, Bailey DG, Juurlink DN, Gandhi S, Mamdani M, et al. Statin toxicity from macrolide antibiotic coprescription: a population-based cohort study. *Ann Intern Med* 2013;158:869-76.
14. Williams M, Peterson GM, Tenni PC, Bindoff IK, Stafford AC. DOCUMENT: a system for classifying drug-related problems in community pharmacy. *Int J Clin Pharm* 2012;34:43-52.
15. Kwint HF, Faber A, Gussekloo J, Bouvy ML. Effects of medication review on drug-related problems in patients using automated drug-dispensing systems: a pragmatic randomized controlled study. *Drugs Aging* 2011;28:305-14.
16. Reason J. Human error: models and management. *BMJ* 2000;320:768-70.

17. Misson JC. A review of clinical risk management. *J Qual Clin Pract* 2001;21:131-4.
18. De Smet PA. Clinical risk management of herb-drug interactions. *Br J Clin Pharmacol* 2007;63:258-67.
19. Bobb A, Gleason K, Husch M, Feinglass J, Yarnold PR, Noskin GA. The epidemiology of prescribing errors: the potential impact of computerized prescriber order entry. *Arch Intern Med* 2004;164:785-92.
20. Wright A, Feblowitz J, Phansalkar S, Liu J, Wilcox A, Keohane CA, et al. Preventability of adverse drug events involving multiple drugs using publicly available clinical decision support tools. *Am J Health Syst Pharm* 2012;69:221-7.
21. Garg AX, Adhikari NK, McDonald H, Rosas-Arellano MP, Devereaux PJ, Beyene J, et al. Effects of computerized clinical decision support systems on practitioner performance and patient outcomes: a systematic review. *JAMA* 2005;293:1223-38.
22. Bright TJ, Wong A, Dhurjati R, Bristow E, Bastian L, Coeytaux RR, et al. Effect of Clinical Decision-Support Systems: A Systematic Review. *Ann Intern Med* 2012;157:29-43.
23. Kuperman GJ, Bobb A, Payne TH, Avery AJ, Gandhi TK, Burns G, et al. Medication-related clinical decision support in computerized provider order entry systems: a review. *J Am Med Inform Assoc* 2007;14:29-40.
24. Tamblyn R, Huang A, Taylor L, Kawasumi Y, Bartlett G, Grad R, et al. A randomized trial of the effectiveness of on-demand versus computer-triggered drug decision support in primary care. *J Am Med Inform Assoc* 2008;15:430-8.
25. Curtain C, Peterson GM. Review of computerized clinical decision support in community pharmacy. *J Clin Pharm Ther* 2014;39:343-8.
26. Ojeleye O, Avery A, Gupta V, Boyd M. The evidence for the effectiveness of safety alerts in electronic patient medication record systems at the point of pharmacy order entry: a systematic review. *BMC Med Inform Decis Mak* 2013;13:69.
27. Motulsky A, Lamothe L, Sicotte C. Impacts of second-generation electronic prescriptions on the medication management process in primary care: a systematic review. *Int J Med Inform* 2013;82:473-91.
28. Robertson J, Walkom E, Pearson SA, Hains I, Williamsone M, Newby D. The impact of pharmacy computerised clinical decision support on prescribing, clinical and patient outcomes: a systematic review of the literature. *Int J Pharm Pract* 2010;18:69-87.
29. Calabretto J, Warren J, Bird L. Pharmacy decision support: where is it? A systematic literature review. *Int J Pharm Pract* 2005;13:157-63.
30. Metzger J, Welebob E, Bates DW, Lipsitz S, Classen DC. Mixed results in the safety performance of computerized physician order entry. *Health Aff (Millwood)* 2010;29:655-63.
31. Kaushal R, Shojania KG, Bates DW. Effects of computerized physician order entry and clinical decision support systems on medication safety: a systematic review. *Arch Intern Med* 2003;163:1409-16.
32. Spina JR, Glassman PA, Belperio P, Cader R, Asch S, Primary Care Investigative Group of the VA Los Angeles Healthcare System. Clinical relevance of automated drug alerts from the perspective of medical providers. *Am J Med Qual* 2005;20:7-14.
33. Floor-Schreudering A, Geerts AF, Aronson JK, Bouvy ML, Ferner RE, De Smet PA. Checklist for standardized reporting of drug-drug interaction management guidelines. *Eur J Clin Pharmacol* 2014;70:313-8.

34. Payne TH, Hines LE, Chan RC, Hartman S, Kapusnik-Uner J, Russ AL, et al. Recommendations to Improve the Usability of Drug-Drug Interaction Clinical Decision Support Alerts. *J Am Med Inform Assoc* 2015;22:1243-50.
35. Royal Dutch Pharmacists Association (KNMP). Zakboek Verminderde Nierfunctie (Dutch guidelines for drug-dosing in chronic kidney disease). The Hague, The Netherlands 2012.
36. Borgsteede SD, ed. Commentaren Medicatiebewaking 2015-2016 (Commentaries medication surveillance). Houten, The Netherlands: Health Base Foundation 2015.
37. Koppel R, Metlay JP, Cohen A, Abaluck B, Localio AR, Kimmel SE, et al. Role of computerized physician order entry systems in facilitating medication errors. *JAMA* 2005;293:1197-203.
38. Eslami S, Abu-Hanna A, de Keizer NF, de Jonge E. Errors associated with applying decision support by suggesting default doses for aminoglycosides. *Drug Saf* 2006;29:803-9.
39. Wetterneck TB, Walker JM, Blosky MA, Cartmill RS, Hoonakker P, Johnson MA, et al. Factors contributing to an increase in duplicate medication order errors after CPOE implementation. *J Am Med Inform Assoc* 2011;18:774-82.
40. Brown CL, Mulcaster HL, Triffitt KL, Sittig DF, Ash JS, Reygate K, et al. A systematic review of the types and causes of prescribing errors generated from using computerized provider order entry systems in primary and secondary care. *J Am Med Inform Assoc* 2017;24:432-40.
41. Cheung KC, van der Veen W, Bouvy ML, Wensing M, van den Bemt PM, de Smet PA. Classification of medication incidents associated with information technology. *J Am Med Inform Assoc* 2014;21:e63-70.
42. Antoniou T, Gomes T, Juurlink DN, Loutfy MR, Glazier RH, Mamdani MM. Trimethoprim-sulfamethoxazole-induced hyperkalemia in patients receiving inhibitors of the renin-angiotensin system: a population-based study. *Arch Intern Med* 2010;170:1045-9.
43. Dawes M, Aloise MN, Ang JS, Cullis P, Dawes D, Fraser R, et al. Introducing pharmacogenetic testing with clinical decision support into primary care: a feasibility study. *CMAJ Open* 2016;4:E528-34.
44. Bayoumi I, Al Balas M, Handler SM, Dolovich L, Hutchison B, Holbrook A. The effectiveness of computerized drug-lab alerts: a systematic review and meta-analysis. *Int J Med Inform* 2014;83:406-15.
45. Eppenga WL, Derijks HJ, Conemans JM, Hermens WA, Wensing M, de Smet PAGM. Comparison of a basic and an advanced pharmacotherapy-related clinical decision support system in a hospital care setting in the Netherlands. *J Am Med Inform Assoc* 2012;19:66-71.
46. Handler SM, Altman RL, Perera S, Hanlon JT, Studenski SA, Bost JE, et al. A systematic review of the performance characteristics of clinical event monitor signals used to detect adverse drug events in the hospital setting. *J Am Med Inform Assoc* 2007;14:451-8.
47. Van der Sijs H, Aarts J, Vulto A, Berg M. Overriding of drug safety alerts in computerized physician order entry. *J Am Med Inform Assoc* 2006;13:138-47.
48. Van der Sijs H, Mulder A, van Gelder T, Aarts J, Berg M, Vulto A. Drug safety alert generation and overriding in a large Dutch university medical centre. *Pharmacoepidemiol Drug Saf* 2009;18:941-7.
49. Buurma H, De Smet PAGM, Egberts AC. Clinical risk management in Dutch community pharmacies: the case of drug-drug interactions. *Drug Saf* 2006;29:723-32.
50. Isaac T, Weissman JS, Davis RB, Massagli M, Cyrulik A, Sands DZ, et al. Overrides of medication alerts in ambulatory care. *Arch Intern Med* 2009;169:305-11.
51. Nanji KC, Slight SP, Seger DL, Cho I, Fiskio JM, Redden LM, et al. Overrides of medication-related clinical decision support alerts in outpatients. *J Am Med Inform Assoc* 2014;21:487-91.

52. Weingart SN, Toth M, Sands DZ, Aronson MD, Davis RB, Phillips RS. Physicians' decisions to override computerized drug alerts in primary care. *Arch Intern Med* 2003;163:2625-31.
53. Van Doormaal JE, Rommers MK, Kosterink JG, Teepe-Twiss IM, Haaijer-Ruskamp FM, Mol PG. Comparison of methods for identifying patients at risk of medication-related harm. *Qual Saf Health Care* 2010;19:e26.
54. De Wit HA, Hurkens KP, Mestres Gonzalvo C, Smid M, Sipers W, Winkens B, et al. The support of medication reviews in hospitalised patients using a clinical decision support system. *Springerplus* 2016;5:871.
55. Gasche Y, Daali Y, Fathi M, Chiappe A, Cottini S, Dayer P, et al. Codeine intoxication associated with ultrarapid CYP2D6 metabolism. *N Engl J Med* 2004;351:2827-31.
56. De Smet PAGM. Nieuwe generatie medicatiebewaking. *Pharmaceutisch Weekblad* 2005;14:483-485.
57. Dutch Ministry of Health, Welfare and Sport (Ministerie van Volksgezondheid, Welzijn en Sport). Wet op de geneeskundige behandelingsovereenkomst: Burgerlijk Wetboek, Boek 7 Bijzondere overeenkomsten, Afdeling 5. De overeenkomst inzake geneeskundige behandeling (Medical treatment contracts act), update 2007.
58. Royal Dutch Pharmacists Association (KNMP). Nederlandse Apotheeknorm (Dutch Pharmacy Standard). 2006, The Hague, The Netherlands.

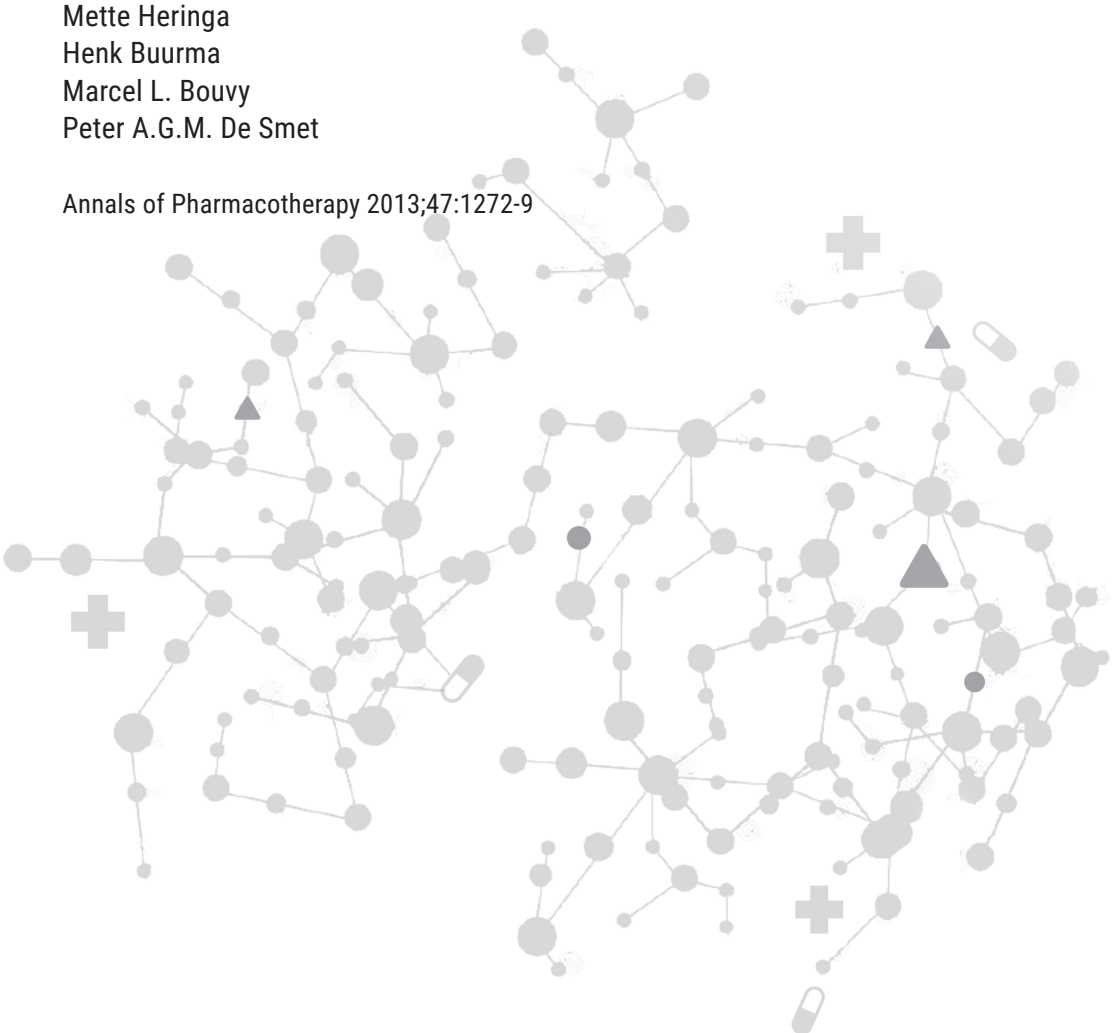
2. Clinical decision support: current practice

Chapter 2.1

Missed drug therapy alerts as a consequence of incomplete electronic patient records in Dutch community pharmacies

Annemieke Floor-Schreudering
Mette Heringa
Henk Buurma
Marcel L. Bouvy
Peter A.G.M. De Smet

Annals of Pharmacotherapy 2013;47:1272-9



Abstract

Objective

Complete and up-to-date medical and pharmaceutical information in the electronic patient record (EPR) is a prerequisite for comprehensive risk management in community pharmacy. We aimed to analyze which information is missing in the EPR and which drug therapy alerts, therefore, fail to appear.

Methods

Pharmacy students selected patients who were dispensed a prescription drug and enlisted for more than three months in the participating pharmacies. Patients received a questionnaire in which they were asked to verify their medication history, and to provide additional patient information. For each enrolled patient, the students collected all relevant information from the EPR. Self-reported data from the patient were compared with data retrieved from the EPR. Missed information in the EPR was evaluated based on national professional guidelines.

Results

Questionnaires were received from 67% of the selected patients (442/ 660). Prescription drugs were missing in the EPR of 14% of the 442 patients, non-prescription drugs in 44%, diseases in 83% and intolerabilities in 16%. In 38% of the patients (166/442), drug therapy alerts failed to appear because of missing information: drug-disease interactions in 34% of the patients, duplicate medications in 4%, drug-drug interactions (DDIs) in 4%, and drug intolerabilities in 2%. Among the (non)prescription drugs missing, NSAIDs were most frequently responsible for the missed alerts. Diseases most frequently associated with missed alerts were gastroesophageal reflux disease, renal insufficiency, asthma/chronic obstructive pulmonary disease, and heart failure.

Discussion and Conclusion

Relevant patient information was frequently missing in the EPRs. The nonappearance of drug therapy alerts may have had clinical consequences for patients.

Introduction

Incomplete or outdated medical and pharmaceutical information in electronic patient records (EPRs) represents a risk of overlooking of drug-related problems and missing drug therapy alerts [1-3]. Improving the quality of this information in the EPR may, therefore, contribute to more effective comprehensive risk management. For this reason, community pharmacists have initiated medication reconciliation, in which patients' medication orders are compared with the medications they are actually taking. Studies have shown that medication reconciliation can identify a large number of potentially harmful discrepancies [4, 5] .

Along with prescription drugs, non-prescription drugs, and complementary drugs, pharmacists should document other relevant patient information in the EPR for both therapeutic risk management and patient counselling purposes, for example, diseases, intolerabilities, personal experiences and habits, and practical drug use problems [6]. A previous study showed discrepancies between the relevant patient information in the EPR and the information given by the patient directly after the patient's first visit to a community pharmacy [5]. To our knowledge, it has not been assessed before whether this medical and pharmaceutical information gap persists for patients enlisted for at least three months in a community pharmacy and what potential implications the missing information may have for patient harm. Therefore, our aim was to analyze what information was missing in the EPRs and what drug therapy alerts will fail to appear as a consequence.

Methods

Setting

A total of 78 Dutch community pharmacies, belonging to the Utrecht University Pharmacy Practice Research Network (UPPER; which comprises about 50% of all 1,948 Dutch pharmacies), were invited to participate in this survey during the first half of 2008. Pharmacy master's students, who were practically training in these pharmacies, selected patients, distributed patient questionnaires, and collected pharmacy data. The students received written and verbal instructions from the researcher, and a help desk was available throughout the research period. The work was conducted in compliance with the requirements of the UPPER institutional review board.

Study population

We calculated that a sample size of 400 patients would be needed. On a fixed day, the students in each participating pharmacy selected a maximum of 12 patients who were dispensed a prescription drug. The selected patient had to be enlisted in the participating pharmacy for a period longer than three months. The students informed the selected patients about the purpose of the study and provided them with a print of their medication history from the EPR (dispensed medication data concerning the past 12 months as well as contraindications and intolerabilities) and a patient questionnaire that included written instructions (reading level: independent user). In this questionnaire, the patients were asked to verify their printed medication history and to provide additional, relevant patient information. They had to return the questionnaire within two weeks to their pharmacy in a prepaid return envelope.

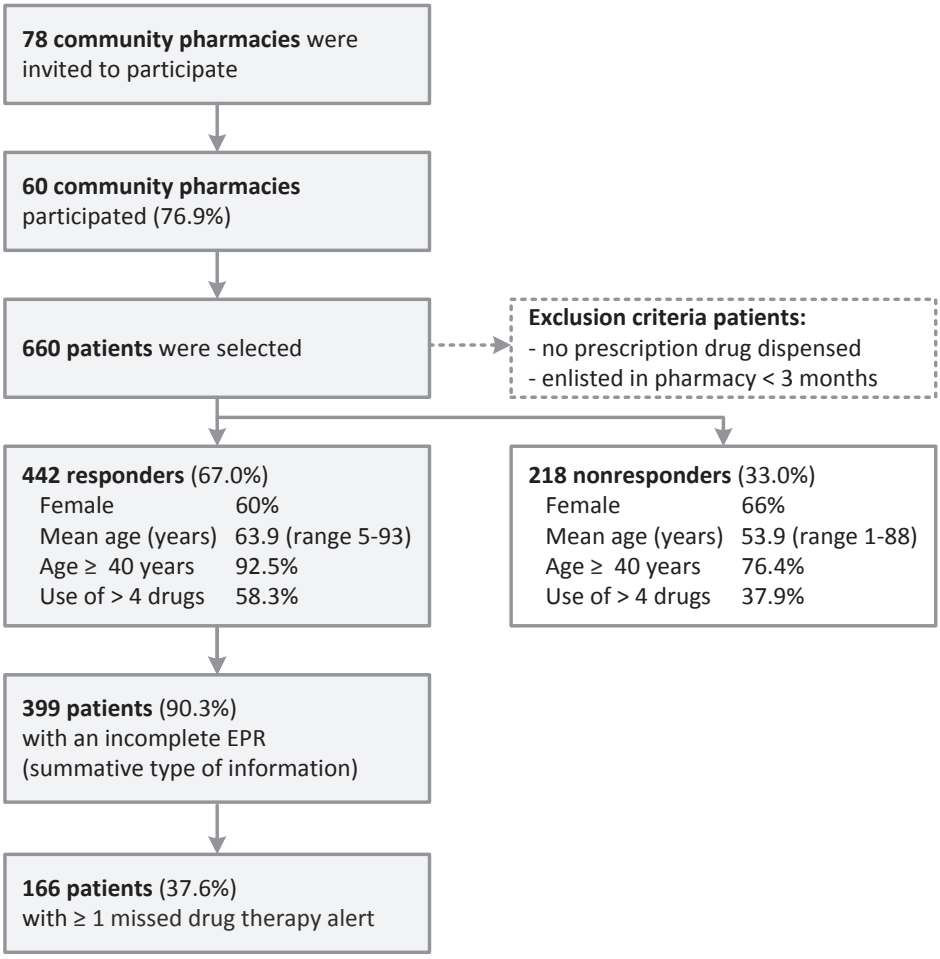
The students collected all relevant patient information from the EPR of each selected patient (the EPR may also contain non-coded patient information in its free-text fields). Only patients for whom both the patient questionnaire and the data from the EPR were available were included in the analysis (Figure 1). For patients younger than 16 years, the parents or legal guardians were contacted.

Data collection

The questionnaire was adapted from our previous study [5] and pretested in five community pharmacies. We collected two types of relevant patient information [5, 7]:

1. The *summative* type, which concerns data that should be recorded according to the professional Dutch Pharmacy Standard (NAN 2006) [8] in order to generate drug therapy alerts by the pharmacy information system: date of birth, sex, (non)prescription drugs, diseases (including renal insufficiency), pregnancy/ lactation/desire for motherhood, and intolerabilities (intolerance/ allergy).
2. The *formative* type, concerning data for which information collection is not obligatory according to the NAN 2006 but which may nevertheless be important for the provision of pharmaceutical care: swallowing problems; walking difficulties; poor vision; poor hearing; hemoglobin A1c (HbA1c); blood pressure, and renal function values; smoking; periods of fasting (Ramadan); and difficulties opening packaging and difficulties administering medication (e.g. inhalers for asthma) [6].

In addition, basic characteristics of the participating pharmacies were collected.



EPR = electronic patient record

Figure 1: Response flow chart

Data analysis

Data were entered into a Microsoft Access database. Univariate logistic analysis (SPSS version 19.0; SPSS Inc, Chicago, IL) was used to compare responding and nonresponding patients. Descriptive analysis was used to compare the data from the patient's EPR with the self-reported data from the patient.

Two pharmacists from the research group (AFS and MH) independently evaluated all missing summative types of information in the EPR- that is, whether or not drug therapy alerts, such as a drug-drug interaction (DDI), drug-disease interaction, drug intolerability (allergy/intolerance) or duplicate medication

(concurrent use of two drugs from the same therapeutic class), could have failed to appear, based on current national professional guidelines [9]. When no consensus was reached, a third pharmacist from the research group (MLB or PAGMDS) was consulted.

Results

In all, 60 pharmacies participated in the study (77% of the 78 invited community pharmacies and 3% of all 1,948 Dutch pharmacies). Compared with the average Dutch pharmacy, the pharmacies participating in our study had more pharmacists (2.23 vs. 1.49 full-time equivalents; p = 0.021) and were more often equipped with a certified Quality System (66% vs. 57%; p = 0.182) [10, 11]. The most frequent reason for not participating was the workload in the pharmacy. Of the 660 selected patients, 442 (67%) returned the patient questionnaire (Figure 1). The students collected patient information from the EPR of 587 patients (442 responders and 145 non-responders). For 73 patients, no information was collected at all. Therefore, basic characteristics were available for 145 of the 218 non-responders. These were different from the characteristics of the 442 responding patients. Older patients (aged ≥ 40 years) and patients with more than four medications had a significantly higher probability of responding (OR 3.8; 95% CI 2.3-6.5 and OR 4.3; 95% CI 1.2-15.5, respectively).

Summative types of information

Summative types of information were missing in the EPR of 399 of the 442 patients (90.3%). One or more prescription drugs were missing in the EPR of 13.6% (60/442) of patients (Table 1). In total, 82 of 2,435 prescription drugs that were self-reported by the patients had not been recorded in the EPR. Prescription drugs that were most frequently missing in the EPR were analgesics (n=10), anxiolytics and hypnotics (n=6), dermatological corticosteroids (n=6), cardiac drugs (n=5), and drugs for obstructive airway diseases (n=5).

Whereas 47.5% (210/442) of patients self-reported the use of non-prescription drugs and herbal and dietary supplements, only 8.6% (38/442) of the patients had their use of non-prescription drugs and supplements registered in their EPR (in total, 25 non-prescription drugs). Products most frequently missing were vitamins (n=146), acetaminophen (n=59), homeopathic and herbal medicines (n=47), glucosamine (n=26) and omega-3 fatty acids (n=32).

Table 1: Number of patients with information in the EPR, and information reported by the patient and information missed in the EPR (n=442 patients)

	EPR n (%)	Patient n (%)	Missed in EPR n (%)
Drug use			
One or more prescription drugs [a]	438 (99.1)	435 (98.4)	60 (13.6)
One or more non-prescription drugs [a]	38 (8.6)	210 (47.5)	196 (44.3)
Diseases			
One or more diseases [a]	268 (60.6)	405 (91.6)	365 (82.6)
Intolerabilities			
One or more intolerabilities (intolerances/allergies)[a]	74 (16.7)	97 (21.9)	72 (16.3)
Specific conditions			
Pregnancy [a], lactation [a] (female participants 16-42)	1 (3.4)	2 (0.5)	2 (0.5)
Walking difficulties [b]	4 (0.9)	101 (22.9)	97 (21.9)
Swallowing problems [b]	1 (0.2)	24 (5.4)	23 (5.2)
Poor vision [b]	1 (0.2)	65 (14.7)	64 (14.5)
Poor hearing [b]	1 (0.2)	84 (19.0)	83 (18.8)
Fasting (e.g. Ramadan) [b]	1 (0.2)	11 (2.5)	10 (2.3)
Diagnostic and monitoring data			
Blood pressure [b]	5 (1.1)	178 (40.3)	176 (39.8) [c]
HbA1c [b]	3 (0.7)	33 (7.5)	32 (7.3) [d]
Renal function [b]	8 (1.8)	10 (2.3)	8 (1.8) [e]
Personal experiences/habits			
Smoking (age >12 years) [b]	3 (0.7)	86 (19.5)	84 (19.0)
Drug use problems			
Difficulties opening medical packaging [b]	6 (1.4)	72 (16.3)	68 (15.4)
Difficulties administering medication [b]	3 (0.7)	31 (7.0)	31 (7.0)

EPR = electronic patient record; HbA1c = hemoglobin A_{1c}

[a] Summative type of patient data; [b] Formative type of patient data ; [c] Systolic blood pressure ≥140 mmHg reported by 88 patients; [d] HbA1c ≥7.0% reported by 16 patients; [e] Renal function ≤ 60% of the normal renal function reported by 3 patients

In the EPR, at least one disease had been recorded for 60.6% (268/442) of the patients; 91.6% (405/442) of the patients reported that they had at least one disease. A large number (1,111 of 1,482) of diseases self-reported by the patient had not been documented in the EPR, of which cardiovascular disease (n=124), osteoarthritis (n=98), hypertension (n=86), gastroesophageal reflux disease (n=72) and elevated cholesterol levels (n=58) were most frequently missing.

In the EPR of 16.3% (72/442) of the patients, a total of 97 of 144 self-reported intolerabilities were missing; those concerning antibiotics (n=28), acetylsalicylic

acid/ nonsteroidal anti-inflammatory drugs (NSAIDs; n=11), statins (n=4), iodine (n=4) and opioids (n=4) were most frequently missing.

Formative types of information

Formative types of information were missing in the EPR of 76.2% (337/442) of the patients. Table 1 shows that almost no data were recorded in the EPR concerning specific conditions, diagnostic and monitoring data, personal experiences and habits, and drug use problems, whereas patients often self-reported such data (including HbA1c values, renal function values and blood pressure values).

Missed drug therapy alerts

The absence of medical and/or pharmaceutical data of the summative type contributed to the missing of 434 drug therapy alerts in 166 of 442 patients (37.6%), an average of 2.6 missed alerts per patient (range 1-11). Table 2 presents the number of patients with at least one missed alert.

For one-third of all patients (150/442), at least one drug-disease interaction alert had not been generated. In total, 375 drug-disease interaction alerts had been missed. The top 10 of these alerts are presented in Table 3. Gastroesophageal reflux disease-NSAIDs and asthma/chronic obstructive pulmonary disease (COPD)-NSAIDs (excluding COX-2 [cyclooxygenase-2] inhibitors) were the most frequently missed. The management of each of these 375 drug-disease interactions required one or more actions. In more than half (224/375) of these cases, the patient should have been consulted and instructed (e.g. contact physician when symptoms aggravate). In 45.1% (169/375) of the interactions, the pharmacist should have checked whether the dosage regimen or dosage form needed adjustment (e.g. in case of renal insufficiency, the dosage of triamterene should be adjusted to the estimated creatinine clearance of the patient); in 35.7%

Table 2: Number of patients with at least one missed drug therapy alert as a result of missing summative types of information in the EPR (n=442 patients)

Drug therapy alert	Number of patients n (%)
Drug-disease interaction	150 (33.9)
Duplicate medication	18 (4.0)
Drug-drug interaction	16 (3.6)
Drug intolerability	10 (2.2)
Drug-pregnancy interaction	1 (0.2)
Total	**166 (37.6)**

EPR = electronic patient record

(134/375), whether the drug choice needed adaptation (e.g. replace high-dose amitriptyline with a non-tricyclic antidepressant drug in patients with angina pectoris); in 14.9% (56/375), whether the patient was adequately monitored (e.g. monitoring of blood pressure in hypertensive patients using prednisolone); in 6.9% (26/375), whether a prophylactic drug needed to be added (e.g. add proton pump inhibitor to NSAID in high-risk patients); and in 6.7% (25/375), whether a drug should have been withheld (e.g. benzodiazepines in patients with sleep apnea).

At least one DDI alert was missed in 3.6% (16/442) of the patients. In total, 27 DDI alerts were missed, which are presented in Table 3. Interactions with NSAIDs were the most frequently missed DDI alerts. According to prevailing DDI guidelines, the management of each of the 27 DDIs required one or more actions. The pharmacist should have examined in 17 of the missed DDI alerts whether the patient was monitored (e.g. monitoring of renal function in heart failure patients using a RAS-inhibitor and an NSAID, after the decision had been made that NSAID use was inevitable). In 14 DDIs, the pharmacist should have consulted and instructed the patient (e.g. take thyroid hormone at least two hours before calcium carbonate). In 12 DDIs, the pharmacist should have checked whether the drug needed to be changed (e.g. replace nonselective beta-blocker with selective beta-blocker when using an oral antidiabetic drug); in four DDIs, whether another drug needed to be added (e.g. add gastric protection to NSAID in elderly patients using paroxetine, after the decision had been made that NSAID use was inevitable); in two DDIs, whether the drug should have been withheld (e.g. vitamin K in users of vitamin K antagonists); and in one DDI, whether the dosage regimen needed adjustment (e.g. lower start doses of RAS-inhibitor in patients using loop diuretics).

At least one duplicate medication alert was missed in 4.0% (18/442) of the patients. In total, 20 duplicate medication alerts were missed (Table 3). Of these duplicate medications, 15 were considered non-plausible according to the guidelines (e.g. two topical corticosteroids); five of these duplicate medications were plausible (e.g. oxazepam and temazepam). Duplicate medications with NSAIDs and with acetaminophen were most frequently missed.

At least one drug intolerability alert was missed in 2.2% (10/442) of the patients. NSAIDs (n=3) were the most frequently encountered drug intolerabilities (Table 3).

One pregnancy was missing in the EPRs. This pregnant patient was using ibuprofen according to her EPR. The pharmacist should have counselled the

Table 3: Missed drug therapy alerts as a result of missing summative types of information in the EPR

Drug therapy alert	n (%)
Drug-disease interactions (n=375): top 10	
GERD - NSAIDs	44 (11.7)
Asthma/COPD - NSAIDs (excl. COX -2 inhibitors)	25 (6.7)
Heart failure - Beta-agonist bronchodilators	14 (3.7)
Asthma/COPD - Opioids	12 (3.2)
Hypertension - Antithrombotics	12 (3.2)
GERD - Nitrates	11 (2.9)
GERD - Calcium channel blockers	10 (2.7)
Sleep apnea - Benzodiazepines	10 (2.7)
Diabetes Mellitus - RAS-inhibitors	8 (2.1)
Renal insufficiency - RAS-inhibitors	8 (2.1)
Other	221 (58.9)
Drug-drug interactions (n=27)	
NSAIDs - Beta-blockers	5 (18.5)
NSAIDs - Diuretics	5 (18.5)
NSAIDs - RAS-inhibitors	5 (18.5)
Vitamin K antagonists - Vitamin K substances	2 (7.4)
NSAIDs - Corticosteroids	2 (7.4)
NSAIDs - Serotonin reuptake inhibitors	2 (7.4)
Thyroid hormones - Calcium carbonate	2 (7.4)
Bisphosphonates - Calcium carbonate	1 (3.7)
Beta-blockers - Hypoglycemic agents	1 (3.7)
QT-prolonging drugs - QT-prolonging drugs	1 (3.7)
RAS-inhibitors - Diuretics	1 (3.7)
Duplicate medications (n=20)	
NSAIDs	4 (20.0)
Acetaminophen	4 (20.0)
Benzodiazepines	3 (15.0)
Corticosteroids	3 (15.0)
Nitrates	2 (10.0)
Opioids	1 (5.0)
RAS-inhibitors	1 (5.0)
Insulin	1 (5.0)
Beta-agonist bronchodilators	1 (5.0)
Drug intolerabilities (n=11)	
NSAIDs	3 (27.3)
Proton pump inhibitors	2 (18.2)
Acetaminophen	2 (18.2)
Atorvastatin	1 (9.1)
Sotalol	1 (9.1)
Oxazepam	1 (9.1)
Nifedipine	1 (9.1)
Drug-pregnancy interaction (n=1)	
NSAIDs	1 (100)

EPR = electronic patient record; COX = cyclooxygenase; COPD = chronic obstructive pulmonary disease; GERD = gastroesophageal reflux disease; NSAIDs = non-steroidal anti-inflammatory drugs; RAS = renin–angiotensin system

patient about the potentially negative effects during pregnancy and should have advised her to preferably use another analgesic.

Table 4 shows the missed diseases, (non-)prescription drugs, and intolerabilities as a function of the drug therapy alerts that failed to appear. Among the prescription drugs missing in the EPR, NSAIDs (n=16), opioids (n=6), and RAS-inhibitors (n=6) were most frequently responsible for missed alerts. The non-prescription drugs most frequently responsible were NSAIDs (n=26), acetaminophen (n=6), benzodiazepines (apparently obtained without a doctor's prescription; n=4), and calcium carbonate (n=4). The diseases most frequently associated with missed alerts were gastroesophageal reflux disease (n=67), renal insufficiency (n=45), asthma/COPD (n=39), heart failure (n=34), and hypertension (n=29). (See also Appendix 1)

Table 4: Number of summative types of information in the EPR missing, resulting in missed drug therapy alerts

Drug therapy alert	Alerts (n)	Information missing				
		Prescription drug	Non-prescription drug	Disease	Intolerability	Other
Drug-disease interaction	375	24	18	354	-	-
Drug-drug interaction	27	11	16	-	-	-
Duplicate medication	20	13	11	-	-	-
Drug intolerability	11	3	1	-	9	-
Drug-pregnancy interaction	1	-	-	-	-	1
Total	**434**	**51**	**46**	**354**	**9**	**1**

Discussion

Our study shows that relevant medical and/or pharmaceutical information was frequently missing in the EPRs. This may lead to potentially hazardous situations in more than one-third of the patients because pharmacy information systems will fail to generate drug therapy alerts, such as DDIs, duplicate medications, drug-disease interactions, drug intolerabilities and drug-pregnancy/lactation interactions.

In our study, gastroesophageal reflux disease, renal insufficiency, asthma/COPD, heart failure, and hypertension accounted for almost 50% of all missed alerts. Another important finding was that NSAIDs were responsible for almost 10% of all the missing alerts and were involved in 57% of all missed alerts involving non-prescription drugs. Calcium carbonate was frequently involved in

missed DDI alerts involving non-prescription drugs. This confirms a finding by Olesen et al [12]. We also found that some drugs frequently involved in our missed alerts (NSAIDs, opioids, nitrates, and benzodiazepines) are described in a systematic review on medication history errors [2].

Although we found almost three times as many patients with self-reported intolerabilities [13], the number of self-reported antibiotic allergies was comparable with that in another study [14]. In our study, we did not investigate whether patients may erroneously have misclassified pharmacological side effects as allergies (e.g. diarrhea caused by antibiotics classified as penicillin allergy). For each of the missed drug intolerability alerts, the pharmacist should have assessed the precise nature of the intolerability because another study has shown that unconfirmed allergies occur frequently [15]. Accepting these misdiagnoses as real allergies may cause harm to patients because they can lead to inappropriate switching to a less-effective or more harmful drug without a clinical need for this.

The potential clinical consequences of the 375 missed drug-disease interaction alerts in our study population encompassed an increased risk of disease/symptom aggravation (76.0%), bleeding (8.3%), cardiac arrhythmias (5.3%), hypotension (2.1%), myocardial infarction (1.3%), hyperkalemia (0.5%), lactic acidosis (0.5%), thrombosis (0.5%), bowel dysfunction (0.5%), hemolysis (0.3%) and several other side effects of the drug (8.5%). In 2.9% of the missed drug-disease interactions, this may have resulted in decreased effectiveness of the drug. The potential clinical consequences of the 27 missed DDI alerts in our study population were decreased effectiveness of one of the involved drugs (20 DDIs) and increased risk of side effects/toxicity (17 DDIs). These risks potentially encompassed nephrotoxicity (10 DDIs), bleeding (4 DDIs), cardiac arrhythmias (1 DDI), hypotension (1 DDI) and masking of hypoglycemia (1 DDI).

Our results included a limited number of missed alerts that might have had serious clinical consequences [16]. For example, two male patients of 83 years and 76 years of age, were at risk for gastrointestinal bleeding because they self-reported a history of peptic ulcer while using low-dose acetylsalicylic acid on prescription without gastric protection [17]. A female patient of 64 years had both a bleeding risk and a risk of aggravation of heart failure because she self-reported use of ibuprofen tablet (600 mg) in addition to the use of ibuprofen sachet (600mg) on prescription while having heart failure and diabetes mellitus [18].

Relevant formative types of information (e.g. swallowing problems; walking difficulties; poor vision; HbA1c, blood pressure and renal function values; smoking;

drug use problems) were missing in the majority of the EPRs of the patients in our study. Our results show, for example, that half of the missing diagnostic and monitoring information in the EPRs might be clinically relevant because patients reported blood pressure and HbA1C values outside the normal range. One out of five patients in our study population self-reported smoking, which may cause drug interactions, but it should also have led to counseling on smoking cessation [19]. Walking difficulties were self-reported in one-fifth of our patients. Because these may be associated with falls in older patients, the use of fall-risk increasing drugs (FRIDs) by these patients should have been reviewed [20].

The patients also self-reported several practical problems related to drug taking: difficulties with the opening of medical packaging, difficulties administering medication (e.g. eye drops), swallowing problems, and poor vision. These problems could have been overcome by switching to an alternative medication, dosage form, or package or by additional counselling by the pharmacist [21].

It is becoming more apparent that medication taking is prone to high error rates, which can decrease the effectiveness of drug therapy [22]. Therefore, pharmacists should be aware of the practical drug use problems that patients encounter and of the ability of the patient to administer the medication. This suggests that formative types of information should also become summative, that is, it should become obligatory to collect and document these in the EPRs. At the same time an overload of drug therapy alerts with questionable clinical relevance should be avoided [23]. Current drug therapy alerts evolve towards clinical decision rules in which patient characteristics (e.g. age and disease) and relevant diagnostic and monitoring data are also taken into account [24]. Further research is needed to fine-tune the content of these clinical decision rules.

Our study shows that pharmacists should ensure that EPRs are complete and up-to-date [24-26]. This not only requires efforts from the pharmacists but also from patients and prescribers. It is apparent that relevant medical and pharmaceutical information about the patient should be collected not only at a patient's first visit to the pharmacy, but at consecutive contacts as well, especially in potentially hazardous situations (e.g. after discharge from hospital).

This study has several limitations. First, it is conceivable that the pharmacies participating in our study had a more positive attitude toward providing high-quality pharmaceutical care than the average Dutch pharmacy because they had more full-time equivalent pharmacists and, more often, a certified quality system, and all of them were active in facilitating student internships. Therefore,

our study may have underestimated the degree of incompleteness of EPRs in pharmacies and the number of missed drug therapy alerts.

Second, our responding patients were older and used more drugs compared with the non-responders. This is not surprising because these patients might have more time and interest in their drug use. Although our study population might not represent the average community pharmacy population, we believe the high number of incomplete EPRs and missed drug therapy alerts shows the importance of our research.

Finally, we considered the data provided by the patient as our point of reference, but patients may have forgotten to report information or may have misinterpreted diseases, contraindications, and intolerances. However, we believe that this risk was reduced by using a self-administered structured questionnaire, as a result of which patients were able to complete the questionnaire at a time and place that was convenient for them, and by providing the patients with their medication history and written instructions. Moreover, several studies have shown that the accuracy of self-reported information can be substantial [27, 28].

Conclusion

This study shows that in about one-third of patients enlisted in community pharmacy, drug therapy alerts failed to appear in the pharmacy information system because medical and/or pharmaceutical data of the summative type were not complete in the EPR. The nonappearance of alerts may have had clinical consequences for patients. The missed diagnostic and monitoring data, practical drug use problems, and specific conditions in the EPR may have further compromised the effectiveness and safety of their drug therapies. To protect patients from potential risk by drug-related problems pharmacists should make every effort to complete and update EPRs.

Acknowledgements

We thank all pharmacy master students and the 60 community pharmacies who participated in this study. Special thanks to W. Göttgens, L. Hulst, J. Manni and A. Prins who helped in the design of the study. Special thanks to L. Blom, who helped in the design of the study and the written and verbal instructions for the students.

References

1. Fitzgerald RJ. Medication errors: the importance of an accurate drug history. *Br J Clin Pharmacol* 2009;67:671-5.
2. Tam VC, Knowles SR, Cornish PL, Fine N, Marchesano R, Etchells EE. Frequency, type and clinical importance of medication history errors at admission to hospital: a systematic review. *CMAJ* 2005;173:510-5.
3. Buurma H, De Smet PAGM, Kruijtbosch M, Egberts AC. Disease and intolerability documentation in electronic patient records. *Ann Pharmacother* 2005;39:1640-6.
4. Johnson CM, Marcy TR, Harrison DL, Young RE, Stevens EL, Shadid J. Medication reconciliation in a community pharmacy setting. *J Am Pharm Assoc (2003)* 2010;50:523-6.
5. Floor-Schreudering A, de Smet PAGM, Buurma H, Egberts AC, Bouvy ML. Documentation quality in community pharmacy: completeness of electronic patient records after patients' first visits. *Ann Pharmacother* 2009;43:1787-94.
6. De Smet PA, Denneboom W, Kramers C, Grol R. A composite screening tool for medication reviews of outpatients: general issues with specific examples. *Drugs Aging* 2007;24:733-60.
7. Rhydderch M, Edwards A, Elwyn G, Marshall M, Engels Y, Van den Hombergh P, et al. Organizational assessment in general practice: a systematic review and implications for quality improvement. *J Eval Clin Pract* 2005;11:366-78.
8. Royal Dutch Pharmacists Association (KNMP). Nederlandse Apotheeknorm (Dutch Pharmacy Standard). 2006, The Hague, The Netherlands.
9. Royal Dutch Pharmacists Association (KNMP). The G-Standaard: structure, safety assessment and decision support. 2011, The Hague, The Netherlands.
10. Griens AMGF, Lukaart JS, Vaart van der RJ. Facts and Figures 2010. utch Foundation for Pharmaceutical Statistics (Stichting Farmaceutische Kengetallen, SFK) 2010, The Hague, The Netherlands.
11. HKZ, expertise centre on quality review in healthcare and welfare. Harmonisation of quality review in health care and welfare; 2008, Utrecht, The Netherlands.
12. Olesen C, Harbig P, Barat I, Damsgaard EM. Absence of 'over-the-counter' medicinal products in on-line prescription records: a risk factor of overlooking interactions in the elderly. *Pharmacoepidemiol Drug Saf* 2013;22:145-50.
13. Gomes E, Cardoso MF, Praca F, Gomes L, Marino E, Demoly P. Self-reported drug allergy in a general adult Portuguese population. *Clin Exp Allergy* 2004;34:1597-601.
14. Macy E, Poon K-Y T. Self-reported antibiotic allergy incidence and prevalence: age and sex effects. *Am J Med* 2009;122:778.e1,778.e7.
15. Messaad D, Sahla H, Benahmed S, Godard P, Bousquet J, Demoly P. Drug provocation tests in patients with a history suggesting an immediate drug hypersensitivity reaction. *Ann Intern Med* 2004;140:1001-6.
16. Warle-van Herwaarden MF, Kramers C, Sturkenboom MC, van den Bemt PM, De Smet PA. Targeting outpatient drug safety: recommendations of the Dutch HARM-Wrestling Task Force. *Drug Saf* 2012;35:245-59.
17. Earnshaw SR, Scheiman J, Fendrick AM, McDade C, Pignone M. Cost-utility of aspirin and proton pump inhibitors for primary prevention. *Arch Intern Med* 2011;171:218-25.
18. Bleumink GS, Feenstra J, Sturkenboom MC, Stricker BH. Nonsteroidal anti-inflammatory drugs and heart failure. *Drugs* 2003;63:525-34.
19. Kroon LA. Drug interactions with smoking. *Am J Health Syst Pharm* 2007;64:1917-21.

20. Huang AR, Mallet L, Rochefort CM, Eguale T, Buckeridge DL, Tamblyn R. Medication-related falls in the elderly: causative factors and preventive strategies. *Drugs Aging* 2012;29:359-76.
21. Mehuys E, Dupond L, Petrovic M, Christiaens T, Van Bortel L, Adriaens E, et al. Medication management among home-dwelling older patients with chronic diseases: possible roles for community pharmacists. *J Nutr Health Aging* 2012;16:721-6.
22. Garfield S, Barber N, Walley P, Willson A, Eliasson L. Quality of medication use in primary care--mapping the problem, working to a solution: a systematic review of the literature. *BMC Med* 2009;7:50,7015-7-50.
23. Van der Sijs H, Aarts J, van Gelder T, Berg M, Vulto A. Turning off frequently overridden drug alerts: limited opportunities for doing it safely. *J Am Med Inform Assoc* 2008;15:439-48.
24. Rommers MK, Teepe-Twiss IM, Guchelaar HJ. A computerized adverse drug event alerting system using clinical rules: a retrospective and prospective comparison with conventional medication surveillance in the Netherlands. *Drug Saf* 2011;34:233-42.
25. Eppenga WL, Derijks HJ, Conemans JM, Hermens WA, Wensing M, de Smet PAGM. Comparison of a basic and an advanced pharmacotherapy-related clinical decision support system in a hospital care setting in the Netherlands. *J Am Med Inform Assoc* 2012;19:66-71.
26. Kuperman GJ, Bobb A, Payne TH, Avery AJ, Gandhi TK, Burns G, et al. Medication-related clinical decision support in computerized provider order entry systems: a review. *J Am Med Inform Assoc* 2007;14:29-40.
27. Klungel OH, de Boer A, Paes AH, Herings RM, Seidell JC, Bakker A. Influence of question structure on the recall of self-reported drug use. *J Clin Epidemiol* 2000;53:273-7.
28. Kriegsman DM, Penninx BW, van Eijk JT, Boeke AJ, Deeg DJ. Self-reports and general practitioner information on the presence of chronic diseases in community dwelling elderly. A study on the accuracy of patients' self-reports and on determinants of inaccuracy. *J Clin Epidemiol* 1996;49:1407-17.

Appendix 1: Number of missed drug therapy alerts as a result of missing summative types of information in the EPR

	Drug therapy alerts					
Missing Information	**Drug-drug interaction**	**Drug-disease interaction**	**Drug-intolerability interaction**	**Duplicate medication**	**Drug-pregnancy interaction**	**TOTAL**
Prescription drugs - total	**11**	**24**	**3**	**13**		**51**
NSAIDs	7	8		1		16
RAS-inhibitors	2	3		1		6
Opioids		5		1		6
Corticosteroids (local)		1		3		4
Benzodiazepines				3		3
Diuretics		2				2
Nitrates				2		2
Acetaminophen			1	1		2
Triptans		2				2
Hypoglycemic agents	1	1				2
Other	1	2	2	1		6
Non-prescription drugs – total	**16**	**18**	**1**	**11**		**46**
NSAIDs	11	12		3		26
Acetaminophen		1	1	4		6
Calcium carbonate	3	1				4
Benzodiazepines		2		2		4
Vitamin K substances	2					2
Other		2		2		4
Disease - total		**354**				**354**
GERD		67				67
Renal insufficiency		45				45

Appendix 1: Number of missed drug therapy alerts as a result of missing summative types of information in the EPR (*continued*)

	Drug therapy alerts					
Missing Information	**Drug-drug interaction**	**Drug-disease interaction**	**Drug-intolerability interaction**	**Duplicate medication**	**Drug-pregnancy interaction**	**TOTAL**
Asthma/COPD		39				39
Heart failure		34				34
Hypertension		29				29
Peptic ulcer		19				19
Psoriasis		18				18
Diabetes Mellitus		16				16
Sleep apnea		14				14
Angina Pectoris		13				13
Prostatic hyperplasia		11				11
Other		49				49
Intolerability - total			**9**			**9**
NSAIDs			3			3
Acetaminophen			1			1
Nifedipine			1			1
Proton pump inhibitor			1			1
Atorvastatin			1			1
Oxazepam			1			1
Sotalol			1			1
Other					**1**	**1**
Pregnancy					1	1
Total	**27**	**375**	**11**	**20**	**1**	**434**

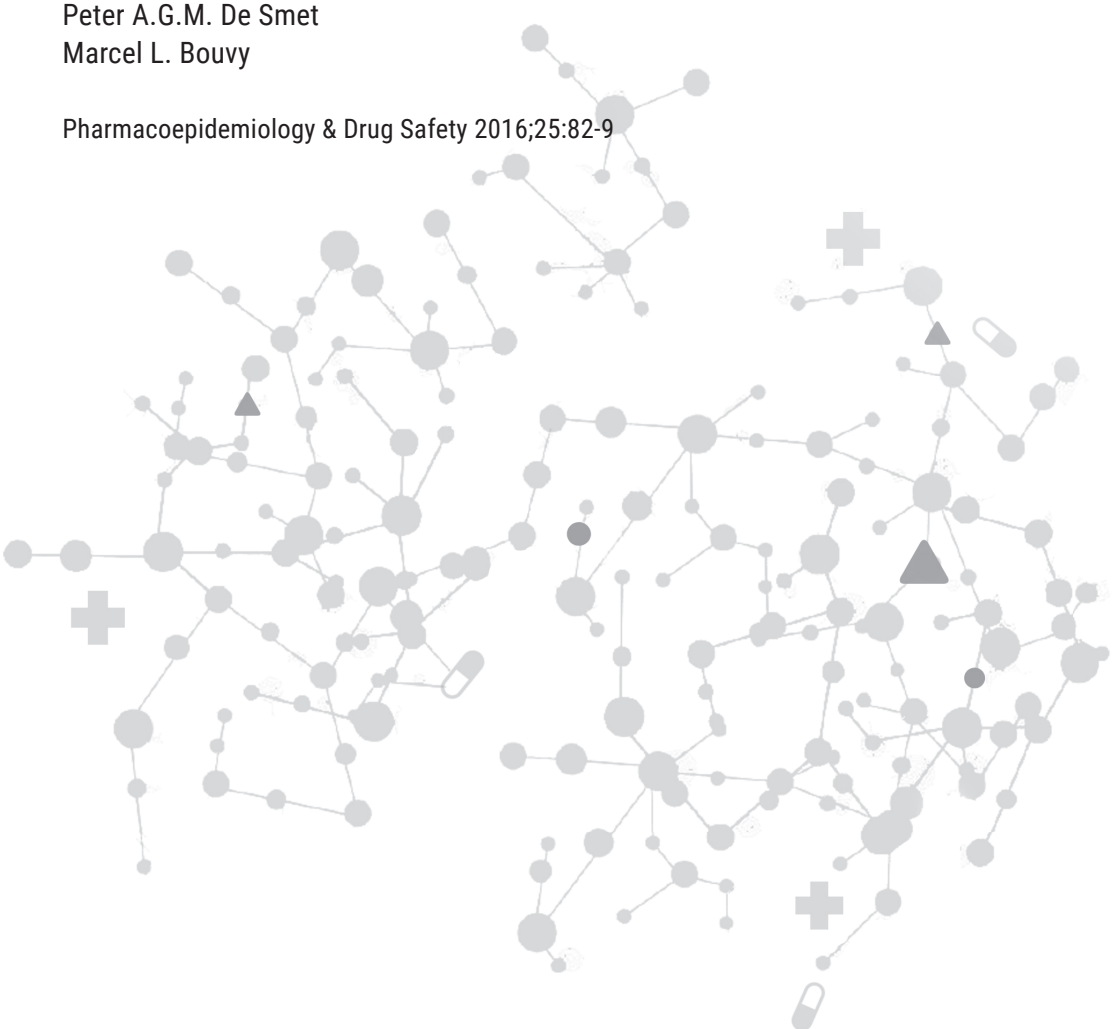
EPR = electronic patient record; COPD = chronic obstructive pulmonary disease; GERD = gastroesophageal reflux disease; NSAIDs = non-steroidal anti-inflammatory drugs; RAS = renin–angiotensin system

Chapter 2.2

Nature and frequency of drug therapy alerts generated by clinical decision support in community pharmacy

Mette Heringa
Annemieke Floor-Schreudering
P. Chris Tromp
Peter A.G.M. De Smet
Marcel L. Bouvy

Pharmacoepidemiology & Drug Safety 2016;25:82-9



Abstract

Objective

The aim of this study is to investigate the nature, frequency and determinants of drug therapy alerts generated by a clinical decision support system (CDSS) in community pharmacy in order to propose CDSS improvement strategies.

Methods

This is a retrospective analysis of dispensed drugs and drug therapy alerts generated by a CDSS in community pharmacies.

Results

Data were extracted from the CDSS of 123 community pharmacies. After taking a 10% random sample of patients with a prescription in the period August 2013 – July 2014, 1,672,169 dispensed prescriptions from 81,742 patients were included in the analysis. Of all processed prescriptions, 43% led to one or more drug safety alerts, most frequently drug-drug interaction alerts (15% of all prescriptions), drug-disease interaction alerts (14%), duplicate medication alerts (13%), and dosing alerts (7%). The majority of prescriptions with alerts (80%) were clustered in a minority of patients (16%). The therapeutic drug group of the prescribed drug was the most important determinant of alert generation. Prescriptions for antithrombotic agents accounted for 9.4% of all prescriptions with an alert, beta-blocking agents for 7.5% and angiotensin-converting enzyme inhibitors for 6.1%.

Discussion and Conclusion

The investigated CDSS in Dutch community pharmacy generated one or more drug therapy alerts in nearly half of the processed prescriptions. The majority of alerts were concentrated in a minority of therapeutic drug groups and patients. To decrease the alert burden, CDSS improvements should be directed at the prioritization and integration of drug therapy alerts for these therapeutic groups within patients.

Introduction

Clinical decision support systems (CDSS) are widely used by prescribers and pharmacists to detect drug therapy related problems. These systems have been developed and extended gradually over time. The current systems generate a multitude of drug therapy alerts, but only a minority of these alerts leads to an intervention. This creates a risk of overriding important drug therapy alerts because of 'alert fatigue' [1-4]. Therefore, improvement strategies for CDSSs are necessary.

The problem of the overload of alerts has mainly been studied among prescribers and in hospitals [1-6]. Other investigations focused on a defined subset of alerts, for example, drug-drug interactions [7-9]. Little is known about the overall situation in community pharmacy [9-11].

The situation in secondary care differs from the primary care setting in several ways. Firstly, the population of patients is very different, as is the drug use. Secondly, patients in primary care are routinely followed for long periods during which additional information on co-morbidities is added to the electronic patient record (EPR). This enables more extensive monitoring on drug-disease interactions. Thirdly, outpatients are not monitored on a daily basis as in hospitals. Without daily check-ups by health care professionals and frequent lab measurements, other precautions are necessary in case of a potentially unstable health condition. As a consequence, in primary care drug therapy alerts are often managed by instructing patients on warning signs and self-management. Finally, early or late refills of repeat prescriptions and other logistical issues can affect the generation of drug therapy alerts, for example, alerts on therapy adherence. Because of these differences, the type and frequency of drug therapy alerts in community pharmacies are probably different from the alerts generated at prescribing and in hospitals.

To be able to propose CDSS improvement strategies for community pharmacy, a clear understanding of the current situation is necessary. Therefore, we aim to investigate the frequency, nature and determinants of drug therapy alerts generated by a CDSS in community pharmacy.

Methods

Setting

Dutch community pharmacies use CDSSs from a limited number of software suppliers. The pharmacy information system Pharmacom® (by TSS PharmaPartners®) is used by approximately 55% of Dutch community pharmacies. The EPR in Pharmacom includes data on dispensed medication and coded chronic diseases. Depending on the local situation, these data can be linked to the corresponding data in the information system of the general practitioner (GP).

Pharmacom includes clinical decision support with drug therapy alerts in seven categories (Table 1) [12]. Every alert is shown in a pop-up window. For drug-drug interaction alerts and drug-disease interaction alerts, it is obligatory to enter information on the management of the alert (by either choosing standardized management options or free text). For the other alert types, recording of the alert management is not obligatory, but actively clicking a button is required to leave the pop-up window and continue the process. Furthermore, administrative alerts are generated, e.g. alerts on change of manufacturer. These alerts are not in scope of this investigation.

Data collection

Two-hundred fifty randomly chosen pharmacies of the 1080 community pharmacies using the Pharmacom system were invited by letter to participate in this study (with a reminder after three weeks). To participate, invited pharmacists had to fill in a short questionnaire concerning pharmacy characteristics and CDSS settings. Moreover the pharmacists had to authorize the supplier of the information system to extract anonymized patient data.

For participating pharmacies the following patient data were extracted over the period August 2012 – July 2014: basic patient characteristics (gender, date of birth and coded diseases) [12], dispensed medication (including dose, prescriber, start and end date) and all generated drug therapy alerts.

Data analysis

The extracted data and the data from the pharmacy questionnaire were recorded in a Microsoft Access database. Per pharmacy, 10% of patients to whom at least one drug was dispensed in the period August 2013 – July 2014 were randomly selected and included in the analysis.

The data were analyzed using SPSS (version 20.0; SPSS Inc. Chicago, IL, USA) and MLwIN (MLwIN version 2.31, Centre for Multilevel Modelling, University of Bristol, UK).

The characteristics of the pharmacies in our sample were compared to national data over 2012 with a one-sample *t*-test [13]. Multilevel logistic regression analysis was used to estimate the association between the generation of an alert and pharmacy characteristics (full time equivalent pharmacist employed, shared patient record with GP for > 50% of patients, agreement with GP about recording of diseases in the EPR), patient characteristics (gender, age, number of diseases recorded in the EPR, number of medicines in use according to the EPR) and prescription characteristics (GP versus other prescriber, first dispensing, use of a multi dose drug dispensing system, therapeutic drug group of prescription [17 most used drug groups]). For all analyses, a second order penalized quasi-likelihood estimation procedure was used, with a random intercept at the pharmacy level, at the visit level (all processed prescriptions for a certain patient on a certain date) and at the patient level. A p-value < 0.05 was considered statistically significant.

Ethics and confidentiality

As this was a retrospective database analysis, the study was exempt from ethical review. To protect the privacy of the patients and pharmacists, all data that could be related to an individual patient or individual pharmacy were anonymized.

Results

Almost 50% (n=123) of the 250 invited pharmacies agreed to participate in the study. The number of full time equivalent (FTE) employed pharmacists per pharmacy in our sample did not differ from the average Dutch pharmacy (1.39 vs 1.41 FTE, p = 0.68) [13]. The pharmacies in our sample did employ more pharmacy technicians than the average Dutch pharmacy (6.31 vs 5.56 FTE, p = 0.008).

The random sample of 10% of the patients included data of 81,742 patients who had 667,172 pharmacy visits and received 1,672,169 prescriptions (Figure 1). The CDSS generated at least one drug therapy alert in 42.9% of all dispensed prescriptions (range over pharmacies 31.5% – 55.4%). In more than half of the visits at least one drug therapy alert was generated. Over one year, one or more alerts were generated for two third of the patients (Figure 1). The three therapeutic drug groups most frequently leading to an alert were antithrombotic

agents (9.4% of all prescriptions with an alert), beta-blocking agents (7.5%) and angiotensin-converting enzyme (ACE) inhibitors (6.1%).

The most common alerts concerned drug-drug interactions (15.5% of all prescriptions) and drug-disease interactions (13.9%), followed by duplicate medication alerts and dosing alerts. Hypersensitivity alerts were generated in only 0.1% of the dispensed prescriptions (Table 1).

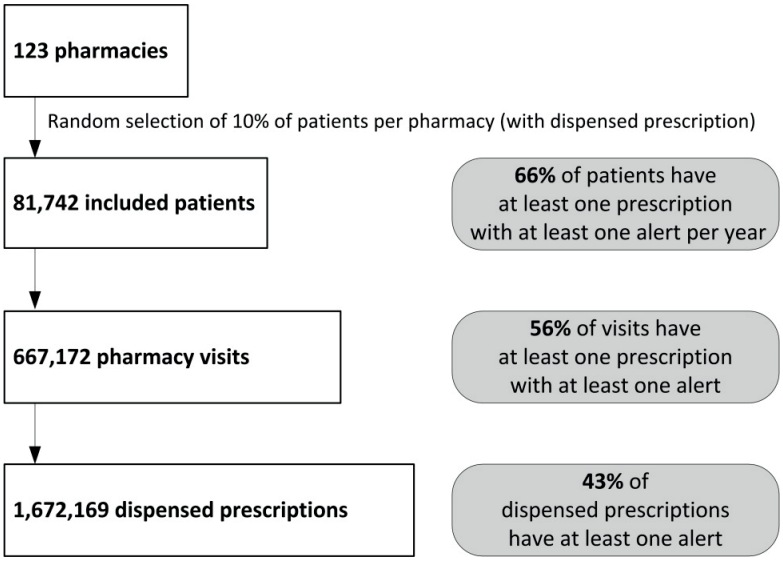


Figure 1: Percentage of patients, pharmacy visits and prescriptions with at least one drug therapy alert

Drug-drug interactions

Drugs most frequently leading to a drug-drug interaction were antithrombotic agents (12.8% of all prescriptions leading to a drug-drug interaction), ACE-inhibitors (11.8%) and beta-blocking agents (8.8%) (Table 2). The interaction between ACE-inhibitors / angiotensin II antagonists and diuretics was the most frequent drug-drug interaction alert (14.8%), followed by the interaction between antidiabetics and beta-blocking agents (9.1%) and the interaction between non-steroidal anti-inflammatory drugs (NSAIDs) and ACE-inhibitors / angiotensin II antagonists (4.8%).

Table 1: Alert type and management, and % of all prescriptions (n=1,672,169) with at least one alert

Alert type	Details and management	% of prescriptions with at least one alert (range over pharmacies)
Drug-drug interaction	Concurrent use of drugs potentially influencing the effect of at least one of them; need for therapy adjustment, monitoring or patient instruction. Specific management guidelines per drug-drug interaction.	15.5 (7.5 – 22.1)
Drug-disease interaction	Patient with a concomitant condition (recorded in the EPR) in which the prescribed drug is contraindicated or which necessitates precautions, e.g. monitoring or patient instruction. Including specific dosing advices on impaired renal function. Specific management guidelines per drug-disease interaction.	13.9 (3.9 – 24.6)
Duplicate medication	Possibility of concurrent use of two drugs with the same or comparable (same therapeutic group) active ingredients, with an assumed overlap in the period of use as recorded in the EPR. Check on unintentional combined use or overuse.	13.1 (6.4 – 27.7)
Dosing alert	Dose is either outside the normal range for the age, weight, height (when relevant) and indication for this patient, or the dose cannot be checked by the CDSS because of lack of a dosing regimen. Check whether the dose is correct.	6.9 (3.5 - 12.5)
Specific checks at first dispensing	Check at first dispensing on specific relevant items according to the alert, for example, cytostatic dosing scheme, drugs impairing driving abilities, teratogenic drugs with a pregnancy prevention program.	3.5 (1.1 – 10.3)
Refill non-adherence	Based on the daily use registered in the EPR, the patient visits the pharmacy later than expected for a refill. Check for non-adherence or dose change.	3.2 (0.0 - 11.5)
Hypersensitivity	Recorded allergy (immunological) for the drug or therapeutic class prescribed. Also used for recorded intolerances (non-immunological). Reconsider prescription.	0.1 (0.0 – 1.0)
All alerts		42.9 (31.5 – 55.4)

CDSS: clinical decision support system; EPR: electronic patient record

Drug-disease interactions

For about half of the patients (47.7%), at least one disease was recorded in the EPR. The most frequently recorded diseases in the EPR were hypertension (19.6% of the patients), obstructive pulmonary disease (16.6%), diabetes mellitus (9.4%), depression (8.1%) and angina pectoris (4.2%).

Drugs most frequently leading to a drug-disease interaction alert were beta-blocking agents (12.8% of prescriptions with a drug-disease interaction), ACE-inhibitors (10.4%) and high-ceiling diuretics (6.7%) (Table 2). The most frequently generated drug-disease interaction alerts referred to the use of ACE-inhibitors in diabetes mellitus (9.2% of alerts), followed by the use of beta-blocking agents in obstructive pulmonary disease (8.5%) and the use of diuretics in renal impairment (7.9%).

Duplicate medication alerts

Duplicate medication alerts were most frequently generated for antithrombotic agents (13.8% of the prescriptions with a duplicate medication alert), antidepressants (5.9%) and beta-blocking agents (5.2%) (Table 2). The top three of drugs most frequently leading to duplicate medication alerts consisted of dipyridamole (5.2%), levothyroxine (4.2%), and low-dose acetylsalicylic acid (3.8%). For dipyridamole and low-dose acetylsalicylic acid, most alerts concerned the combined use of two different platelet aggregation inhibitors. For levothyroxine, combination of several strengths was the main reason for the alert generation.

Dosing alerts

Dosing alerts were most frequently generated for hypnotics and sedatives (7.7%) – mainly benzodiazepines. Of these alerts, 79% were generated in patients over 65 years, for whom a lower dose of benzodiazepines is recommended. A further 5.2% of prescriptions with dosing alerts concerned antithrombotic agents. Half of them were caused by prescriptions for acenocoumarol – mostly because no (estimated or mean) daily use was recorded in the EPR. The alerts on other analgesics and antipyretics (4.4% of the prescriptions with a dosing alert) were for over 90% caused by prescriptions for paracetamol, mainly in a dose of 4 gram daily for adults, because of the upper limit for long term use of 3 g daily.

Other alert types

Refill non-adherence alerts were most frequently generated for lipid-modifying agents (12.2%), beta-blocking agents (9.0%) and antidepressants (9.0%) (Table 2). Alerts regarding specific checks at first dispensing were generated for a very

heterogeneous group of medicines (e.g. warnings to check the dosing scheme of antineoplastic agents, or notification of drugs that influence driving ability). Hypersensitivity alerts were most frequently generated for antithrombotic agents, mainly salicylates.

Table 2: Top 5 of involved therapeutic drug groups (ATC-class) for prescriptions within each alert type

Drug-drug interaction
B01A: antithrombotic agents (12.8%)
C09A: ACE-inhibitors, plain (11.8%)
C07A: beta-blocking agents (8.8%)
C09C: angiotensin II antagonists, plain (7.0%)
N06A: antidepressants (5.7%)
Drug-disease interaction
C07A: beta-blocking agents (12.8%)
C09A: ACE-inhibitors, plain (10.4%)
C03C: high-ceiling diuretics (6.7%)
N02A: opioids (6.5%)
B01A: antithrombotic agents (5.9%)
Duplicate medication
B01A: antithrombotic agents (13.8%)
N06A: antidepressants (5.9%)
C07A: beta-blocking agents (5.2%)
A02B: drugs for peptic ulcer and GERD (5.2%)
N05A: antipsychotics (4.7%)
Dosing alert
N05C: hypnotics and sedatives (7.7%)
B01A: antithrombotic agents (5.2%)
N02A: opioids (4.6%)
R03B: other drugs for obstructive airway disease (e.g., glucocorticoids and anticholinergics) (4.5%)
N02B: other analgesics and antipyretics (e.g. paracetamol) (4.4%)
Refill non-adherence
C10A: lipid-modifying agents, plain (12.2%)
C07A: beta-blocking agents (9.0%)
N06A: antidepressants (9.0%)
R03A: adrenergics, inhalants (8.3%)
B01A: antithrombotic agents (7.5%)

ACE = angiotensin-converting enzyme; ATC = anatomical therapeutic chemical classification; GERD = gastro-esophageal reflux disease.

Multilevel analysis

The multilevel logistic regression analysis showed that the association between pharmacy characteristics and the generation of drug therapy alerts was of little importance compared to the other determinants (Table 3). Of patient characteristics, the number of diseases recorded in the patients' EPR had the strongest positive association with alert generation. The association with increasing age and increasing number of medicines was less pronounced. Of prescription characteristics, the therapeutic drug group of the prescription was strongly associated with an increased percentage of prescriptions with an alert. The strongest positive association was found for ACE-inhibitors / angiotensin II antagonists, thyroid drugs and selective serotonin reuptake inhibitors; the strongest negative association was found for proton pump inhibitors, statins and dihydropyridine calcium-channel blockers. A negative association was found between alert generation and prescriptions of the GP compared with other prescribers.

Clustering of alerts

Eighty percent of all prescriptions with an alert concerned 16% of the patients (Figure 2). The clustering of alerts differs per alert type. Prescriptions with drug-drug interaction alerts and with drug-disease interaction alerts were most strongly clustered within certain patients: 80% of these prescriptions was dispensed to respectively 5.3% and 4.1% of the patients. Eighty percent of all prescriptions with dosing alerts were dispensed to 11.8% of the patients; for duplicate medication alerts, this percentage was 12.3%, and for refill non-adherence alerts 13.0%.

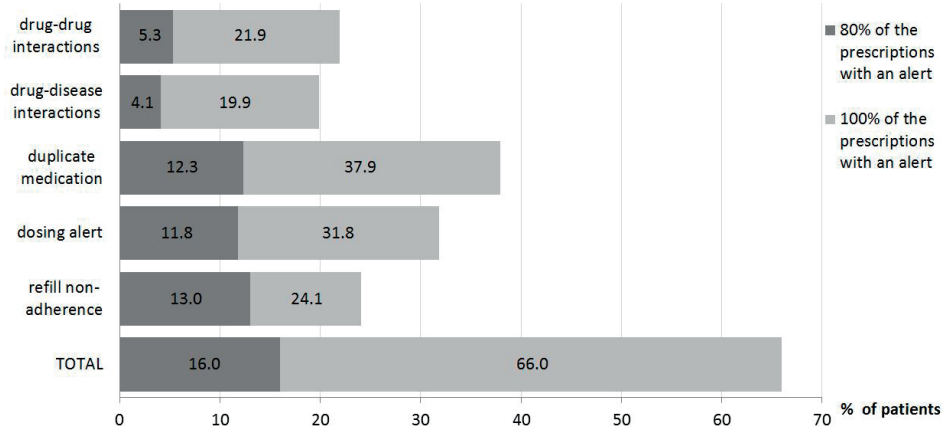


Figure 2: Clustering of prescriptions with alerts within patients

Table 3: Determinants of drug therapy alert generation by CDSS (n=1,647,595 prescriptions)[a]

			prescriptions (%)		OR[b] (95% CI)	p-value	OR adjusted[c] (95% CI)	p-value
			no alert n=939,718	alert(s) n=707,877				
PHARMACY	FTE pharmacist	≥1	791,758 (84.3)	588,604 (83.2)	1.1 (1.0-1.2)	0.19	1.0 (0.9-1.1)	0.94
	Shared patient record with GP for > 50% of patients		680,863 (72.5)	521,327 (73.6)	1.0 (0.9-1.1)	0.58	0.9 (0.8-1.1)	0.27
	Agreement with GP about recording of diseases in the EPR	informal (oral)	384,215 (40.9)	288,704 (40.8)	0.9 (0.8-1.0)	0.13	0.9 (0.8-1.0)	0.02
		formal (written)	134,983 (14.4)	104,646 (14.8)	0.9 (0.8-1.1)	0.38	0.9 (0.8-1.1)	0.33
		no	420,520 (44.7)	314,527 (44.4)	1 (reference)		1 (reference)	
PATIENT	Gender	female	569,219 (60.6)	426,621 (60.3)	0.9 (0.9-0.9)	<0.001	0.9 (0.9-0.9)	<0.001
	Age	0-18	41,094 (4.4)	15,919 (2.2)	1 (reference)		1 (reference)	
		19-64	358,925 (38.2)	249,627 (35.3)	1.8 (1.7-1.9)	<0.001	1.2 (1.2-1.2)	<0.001
		65+	539,699 (57.4)	442,331 (62.5)	2.8 (2.7-2.9)	<0.001	1.4 (1.3-1.5)	<0.001
	Number of diseases recorded in the EPR	0	222,265 (23.7)	102,589 (14.5)	1 (reference)		1 (reference)	
		1-2	331,605 (35.3)	218,745 (30.9)	2.2 (2.1-2.3)	<0.001	2.0 (2.0-2.1)	<0.001
		3-5	286,452 (30.5)	255,560 (36.1)	3.6 (3.5-3.8)	<0.001	3.3 (3.2-3.5)	<0.001
		6+	99,396 (10.6)	130,983 (18.5)	5.9 (5.6-6.2)	<0.001	5.6 (5.2-6.0)	<0.001
	Number of medicines in use	0	132,578 (14.1)	64,212 (9.1)	1 (reference)		1 (reference)	
		1-3	246,079 (26.2)	159,290 (22.5)	1.3 (1.3-1.3)	<0.001	1.3 (1.3-1.3)	<0.001
		4-7	229,827 (24.5)	173,940 (24.6)	1.6 (1.5-1.6)	<0.001	1.4 (1.4-1.5)	<0.001
		8+	331,234 (35.2)	310,435 (43.9)	1.7 (1.6-1.7)	<0.001	1.5 (1.5-1.5)	<0.001

Table 3: Determinants of drug therapy alert generation by CDSS (n=1,647,595 prescriptions)[a] *(continued)*

		prescriptions (%)		OR[b] (95% CI)	p-value	OR adjusted[c] (95% CI)	p-value
		no alert n=939,718	alert(s) n=707,877				
PRESCRIPTION	Prescriber GP (versus other)	791,758 (84.3)	588,604 (83.2)	0.8 (0.8-0.8)	<0.001	0.9 (0.9-0.9)	<0.001
	First dispensing	140,194 (14.9)	107,039 (15.1)	1.3 (1.3-1.3)	<0.001	1.5 (1.5-1.5)	<0.001
	Multi-dose drug dispensing system	414,802 (44.1)	308,958 (43.6)	0.8 (0.8-0.8)	<0.001	0.8 (0.8-0.8)	<0.001
	Therapeutic group of prescription (ATC)						
	Beta-blocking agents (selective) (C07AB)	34,819 (3.7)	45,261 (6.4)	1 (reference)		1 (reference)	
	Proton pump inhibitors (A02BC)	97,099 (10.3)	22,193 (3.1)	0.1 (0.1-0.1)	<0.001	0.1 (0.1-0.1)	<0.001
	Biguanides (metformin) (A10BA)	23,164 (2.5)	15,991 (2.3)	0.4 (0.4-0.4)	<0.001	0.4 (0.4-0.4)	<0.001
	Salicylates antithrombotic (B01AC06/08)	32,757 (3.5)	38,290 (5.4)	1.1 (1.0-1.1)	<0.001	1.1 (1.1-1.1)	<0.001
	Low-ceiling diuretics (C03A/B)	19,061 (2.0)	12,422 (1.8)	0.5 (0.5-0.5)	<0.001	0.5 (0.5-0.5)	<0.001
	High-ceiling diuretics (C03C)	15,220 (1.6)	24,504 (3.5)	0.9 (0.8-0.9)	<0.001	0.9 (0.8-0.9)	<0.001
	Dihydropyridines (C08CA)	27,900 (3.0)	11,220 (1.6)	0.2 (0.2-0.2)	<0.001	0.2 (0.2-0.2)	<0.001
	ACE-inhibitors / angiotensin II antagonists (C09A/C)	22,196 (2.4)	64,529 (9.1)	3.0 (2.9-3.1)	<0.001	3.0 (2.9-3.1)	<0.001
	Statins (C10AA)	74,364 (7.9)	21,215 (3.0)	0.2 (0.1-0.2)	<0.001	0.2 (0.1-0.2)	<0.001
	Thyreomimetics (H03AA)	7,807 (0.8)	20,245 (2.9)	2.6 (2.5-2.8)	<0.001	2.7 (2.6-2.8)	<0.001
	Antibiotics (systemic) (J01)	23,172 (2.5)	15,504 (2.2)	0.5 (0.5-0.5)	<0.001	0.5 (0.5-0.5)	<0.001
	NSAIDs (M01A)	13,643 (1.5)	20,480 (2.9)	1.6 (1.6-1.7)	<0.001	1.6 (1.5-1.6)	<0.001
	Opioids (N02A)	8,566 (0.9)	17,508 (2.5)	1.5 (1.5-1.6)	<0.001	1.4 (1.4-1.5)	<0.001
	Antipsychotics (N05A)	14,009 (1.5)	18,653 (2.6)	1.4 (1.3-1.4)	<0.001	1.3 (1.3-1.4)	<0.001
	SSRIs (N06AB)	12,834 (1.4)	19,427 (2.7)	1.7 (1.6-1.7)	<0.001	1.7 (1.7-1.8)	<0.001
	Sympathicomimetics (inhalation) (R03AC)	5,448 (0.6)	7,796 (1.1)	1.1 (1.1-1.2)	<0.001	1.1 (1.1-1.2)	<0.001
	Other	507,659 (54.0)	332,639 (47.0)	0.4 (0.4-0.5)	<0.001	0.4 (0.4-0.4)	<0.001

ATC = anatomical therapeutic chemical; CDSS = clinical decision support system; EPR = electronic patient record; FTE = fulltime equivalent; GP = general practitioner; NSAID = non-steroidal anti-inflammatory drug; OR = odds ratio; RAS = renin-angiotensin system; SSRI = selective serotonin reuptake inhibitor; 95% CI = 95% confidence interval;

[a] excluding all prescriptions with one or more missing determinants; [b] multilevel analysis with random intercept at patient level, visit level and pharmacy level; [c] multilevel analysis with random intercept at patient level, visit level and pharmacy level; OR adjusted for all other determinants in table.

Discussion

This study showed that 43% of all prescriptions processed in Dutch community pharmacies generated at least one drug therapy alert. The most frequent alerts were drug-drug interactions (15% of all prescriptions), drug-disease interactions (14%), and duplicate medication alerts (13%). The incidence of drug therapy alerts in this study is higher than in most previous investigations into drug therapy alerts, although reported numbers vary highly [2-5]. In an investigation into alert overriding by prescribers in ambulatory care, it has been reported that 6.6% of the prescriptions caused an alert [3]. In a hospital setting a percentage of 34% has been reported [2].

There are several factors that may contribute to the high percentage of prescriptions with an alert in our investigation compared with previous research. Firstly, CDSSs have already been in use in the Netherlands for decades. It has been extended gradually, both with respect to the number of alert types (extension of modules in the CDSS) and with respect to the number of alerts for every alert type (extension of drug database). The extension of the number of alerts can be illustrated by the number of drug-drug interactions. In an investigation in Dutch community pharmacies in 2004, 6% of all prescriptions led to a drug-drug interaction alert, compared to 15.5% in our study [7]. The main reason can be found in the extension of the drug-drug interaction database incorporated in the CDSS. A comparable increase of the incidence of alerts over time within a certain setting has also been found by other investigators [4]. Secondly, because of the ageing of society, multimorbidity, and as a consequence polypharmacy have increased steadily over the last decades. Thirdly, in the Netherlands, most patients visit one community pharmacy for (nearly) all their medication [14]. Therefore, the EPR is quite complete with respect to prescribed medications, and a considerable number of diseases are recorded in the EPR [15-17]. This situation enables CDSS checks on drug-disease interactions and on potential non-adherence or overuse. In our results, both the number of medicines in use and the number of diseases recorded in the EPR were associated with the percentage of prescriptions leading to an alert. In our study, for 47.7% of the patients, at least one chronic disease was recorded in the EPR. From a previous study, we know that in about one-thirds of the patients, drug-disease interactions are missed because of incomplete disease registrations in the pharmacy [16]. In case of more complete EPRs, even higher alert rates can be expected.

In the results of the multilevel analysis it was shown that fewer alerts were generated for prescriptions of the GP compared with other prescribers. This could

partly result from the fact the more complex patients are more often treated by other prescribers. Moreover, the CDSS of Dutch GPs is similar to the pharmacists' CDSS and shared EPRs are quite common, whereas for other prescribers the availability of information can be different.

To improve the performance of the CDSS, several strategies have been proposed, mainly for hospitals and for drug-drug interactions [5, 18-24]. Overall, the results are moderate and often specific for the investigated setting. In our results, many different alert types contributed substantially to the total number of alerts. CDSS improvement strategies focused on one alert type would have a limited effect on the total alert burden. Although pharmacy characteristics were associated with alert volume, these characteristic were insignificant compared to patient and drug characteristics. We showed that the majority of prescriptions with an alert concerned a minority of therapeutic drug groups and a minority of patients. Therefore, we propose to focus on these two areas as principal targets for general CDSS improvement strategies.

The first focus area is the therapeutic drug group of a prescription, which is clearly associated with the number of prescriptions with an alert. The highest percentage of prescriptions with an alert was seen for ACE-inhibitors and angiotensin II antagonists, thyroid drugs and selective serotonin reuptake inhibitors. This is inherent to the pharmacological properties of these drug groups. In absolute numbers, prescriptions of ACE-inhibitors, beta-blocking agents and low dose salicylates accounted together for 23% of all prescriptions with an alert. This can be explained by the numerous known interactions and the frequent use of these drugs. The overrepresentation of certain drug therapy groups in the alert generation and the increase of alerts over time do raise questions about the best criteria for the addition and prioritization of alerts in a CDSS. Overall, there is a tendency to add an alert for every new identified potential risk. Alerts are added even if the proposed risk-reducing strategy has not yet been evaluated and even if the risk is of minor relevance compared with other alerted risks of the same drug. To keep the alert burden manageable, it is important to pay careful attention to the risk-benefit balance of the proposed management options. For example, the most frequent drug-disease interactions in our investigation (ACE-inhibitors in diabetes mellitus and beta-blocking agents in obstructive pulmonary disease) concern therapies that are generally evidence based, but may require some additional monitoring. Although potentially harmful effects may occur, the clinical relevance of the warning at the population level could be questioned. At the same time, there is a considerable overlap between the therapeutic drug groups leading to alerts and the therapeutic drug groups lead-

ing to medication errors and hospital admissions, e.g. beta-blocking agents, non-steroidal anti-inflammatory drugs, ACE-inhibitors, opioids and acetylsalicylic acid [25-27]. Thus, it is extremely important to detect possible risks concerning these drugs – and to give priority to the most relevant ones. For drug-drug interactions, several guidelines and considerations for appraisal of their relevance exists [28-30]. For other alert types, less guidance is available [31, 32]. It is advisable to develop drug therapy alerts based on integrated guidelines for all alert types with a focus on their relative prioritization and their risk-benefit ratio.

The subset of patients whose prescriptions led to the majority of alerts is another target area for CDSS improvement. In our investigation, 80% of the prescriptions with alerts were dispensed to 16% of the patients. Improving the alerts and workflow for these patients potentially has a large impact on the total number of alerts. Moreover, the risk of overseeing important alerts because of alert fatigue is presumably the highest for patients with many alerts. Current CDSSs generate alerts during prescription processing for logistical reasons. Instead, we suggest a patient centered approach, in which alerts are triggered by changes in the EPR (concerning therapy, diseases, lab values etc.) rather than by prescriptions. For example, the generation of the two most generated drug-drug interactions (ACE-inhibitors / angiotensin II antagonists – diuretics, and antidiabetics - beta-blocking agents) could be limited to the moment of therapy start or adjustment. And for a patient with diabetes mellitus using multiple cardiovascular medications, a well-timed integrated alert on monitoring of blood pressure, renal function and electrolytes could replace several prescription-based alerts on drug-drug interactions and drug-disease interactions. An up-to-date and complete EPR is required for the implementation of this kind of CDSS improvement strategies. Therefore, sharing information between health care professionals – in compliance with the patient's privacy - is essential.

Our study has several limitations. Our data are based on dispensed prescriptions. Alerts that prohibited dispensing are not registered and therefore not included in our dataset. However, from other investigations it is known that the percentage of prescriptions, which are not dispensed because of drug therapy alerts is relatively low because of the low specificity of the alerts [7, 33]. This does not mean that these alerts are all unnecessary, but it emphasizes the need for increased specificity and prioritization of alerts. Moreover, our study has been performed in one CDSS. In other settings, the specific alerts may differ because of differences in the individual algorithms for alert generation, but a comparable overall pattern is expected. Furthermore, in our investigation, we have focused on the appearance of alerts, not on their relevance. However, it is likely that

starting improvement from situations with a high absolute number of alerts is an efficient way to decrease the absolute alert burden, as other investigations have shown that the majority of drug therapy alerts are judged as irrelevant and therefore overridden [3, 4, 7, 33].

Conclusion

In conclusion, in community pharmacy, 43% of all prescriptions led to the generation of one or more drug therapy alerts. The majority of alerts were generated based on a minority of therapeutic drug groups and in a minority of patients. To decrease the alert burden, CDSS improvements should be directed at the prioritization and integration of drug therapy alerts for these therapeutic groups within patients.

Acknowledgements

We thank all community pharmacists who participated in this study. Thanks to Patrick Souverein and Svetlana Belitser for their advice on the data analysis.

References

1. Van der Sijs H, Aarts J, Vulto A, Berg M. Overriding of drug safety alerts in computerized physician order entry. *J Am Med Inform Assoc* 2006;13:138-47.
2. Van der Sijs H, Mulder A, van Gelder T, Aarts J, Berg M, Vulto A. Drug safety alert generation and overriding in a large Dutch university medical centre. *Pharmacoepidemiol Drug Saf* 2009;18:941-7.
3. Isaac T, Weissman JS, Davis RB, Massagli M, Cyrulik A, Sands DZ, et al. Overrides of medication alerts in ambulatory care. *Arch Intern Med* 2009;169:305-11.
4. Nanji KC, Slight SP, Seger DL, Cho I, Fiskio JM, Redden LM, et al. Overrides of medication-related clinical decision support alerts in outpatients. *J Am Med Inform Assoc* 2014;21:487-91.
5. Eppenga WL, Derijks HJ, Conemans JM, Hermens WA, Wensing M, de Smet PAGM. Comparison of a basic and an advanced pharmacotherapy-related clinical decision support system in a hospital care setting in the Netherlands. *J Am Med Inform Assoc* 2012;19:66-71.
6. Bryant AD, Fletcher GS, Payne TH. Drug interaction alert override rates in the meaningful use era: no evidence of progress. *Appl Clin Inform* 2014;5:802-13.
7. Buurma H, De Smet PAGM, Egberts AC. Clinical risk management in Dutch community pharmacies: the case of drug-drug interactions. *Drug Saf* 2006;29:723-32.
8. Murphy JE, Forrey RA, Desiraju U. Community pharmacists' responses to drug-drug interaction alerts. *Am J Health Syst Pharm* 2004;61:1484-7.
9. Indermitte J, Erba L, Beutler M, Bruppacher R, Haefeli WE, Hersberger KE. Management of potential drug interactions in community pharmacies: a questionnaire-based survey in Switzerland. *Eur J Clin Pharmacol* 2007;63:297-305.
10. Curtain C, Peterson GM. Review of computerized clinical decision support in community pharmacy. *J Clin Pharm Ther* 2014;39:343-8.
11. Ojeleye O, Avery A, Gupta V, Boyd M. The evidence for the effectiveness of safety alerts in electronic patient medication record systems at the point of pharmacy order entry: a systematic review. *BMC Med Inform Decis Mak* 2013;13:69.
12. Borgsteede SD, ed. Commentaren Medicatiebewaking 2015-2016 (Commentaries medication surveillance). Houten, The Netherlands: Health Base Foundation 2015.
13. Dutch Foundation for Pharmaceutical Statistics (Stichting Farmaceutische Kengetallen, SFK). Facts and Figures 2013 (Data en Feiten 2013). 2013, The Hague, The Netherlands.
14. Buurma H, Bouvy ML, De Smet PAGM, Floor-Schreudering A, Leufkens HG, Egberts AC. Prevalence and determinants of pharmacy shopping behaviour. *J Clin Pharm Ther* 2008;33:17-23.
15. Floor-Schreudering A, de Smet PAGM, Buurma H, Egberts AC, Bouvy ML. Documentation quality in community pharmacy: completeness of electronic patient records after patients' first visits. *Ann Pharmacother* 2009;43:1787-94.
16. Floor-Schreudering A, Heringa M, Buurma H, Bouvy ML, De Smet PA. Missed drug therapy alerts as a consequence of incomplete electronic patient records in Dutch community pharmacies. *Ann Pharmacother* 2013;47:1272-9.
17. Buurma H, De Smet PAGM, Kruijtbosch M, Egberts AC. Disease and intolerability documentation in electronic patient records. *Ann Pharmacother* 2005;39:1640-6.
18. Seidling HM, Phansalkar S, Seger DL, Paterno MD, Shaykevich S, Haefeli WE, et al. Factors influencing alert acceptance: a novel approach for predicting the success of clinical decision support. *J Am Med Inform Assoc* 2011;18:479-84.

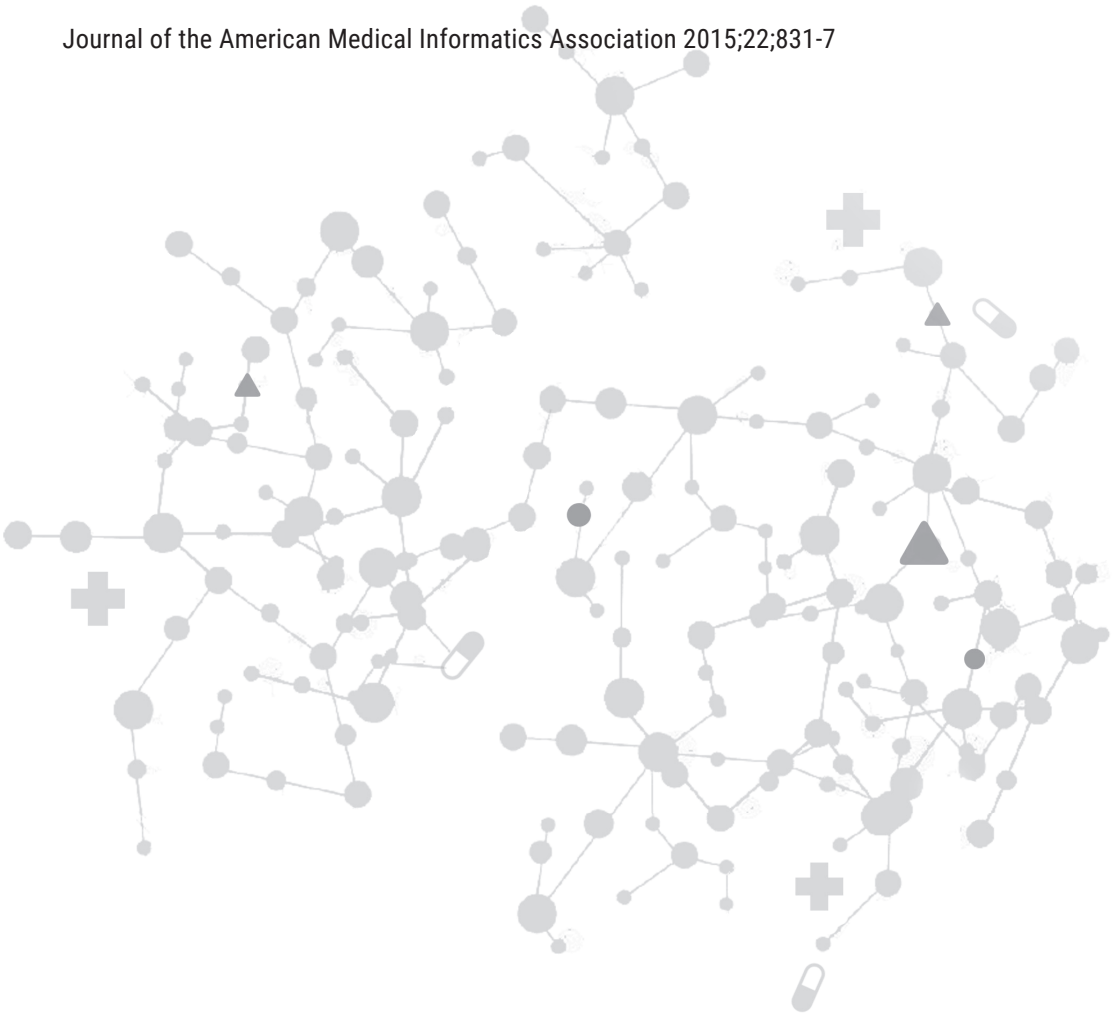
19. Seidling HM, Klein U, Schaier M, Czock D, Theile D, Pruszydlo MG, et al. What, if all alerts were specific - Estimating the potential impact on drug interaction alert burden. *Int J Med Inform* 2014;83:285-91.
20. Phansalkar S, van der Sijs H, Tucker AD, Desai AA, Bell DS, Teich JM, et al. Drug-drug interactions that should be non-interruptive in order to reduce alert fatigue in electronic health records. *J Am Med Inform Assoc* 2013;20:489-93.
21. Rommers MK, Teepe-Twiss IM, Guchelaar HJ. A computerized adverse drug event alerting system using clinical rules: a retrospective and prospective comparison with conventional medication surveillance in the Netherlands. *Drug Saf* 2011;34:233-42.
22. McCoy AB, Thomas EJ, Krousel-Wood M, Sittig DF. Clinical decision support alert appropriateness: a review and proposal for improvement. *Ochsner J* 2014;14:195-202.
23. Parke C, Santiago E, Zussy B, Klipa D. Reduction of clinical support warnings through recategorization of severity levels. *Am J Health Syst Pharm* 2015;72:144-8.
24. Payne TH, Hines LE, Chan RC, Hartman S, Kapusnik-Uner J, Russ AL, et al. Recommendations to Improve the Usability of Drug-Drug Interaction Clinical Decision Support Alerts. *J Am Med Inform Assoc* 2015;22:1243-50.
25. Leendertse A, Egberts A, Stoker L, van den Bemt P. Frequency of and Risk Factors for Preventable Medication-Related Hospital Admissions in the Netherlands. *Arch Intern Med* 2008;168:1890-6.
26. Saedder EA, Brock B, Nielsen LP, Bonnerup DK, Lisby M. Identifying high-risk medication: a systematic literature review. *Eur J Clin Pharmacol* 2014;70:637-45.
27. Pirmohamed M, James S, Meakin S, Green C, Scott AK, Walley TJ, et al. Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients. *BMJ* 2004;329:15-9.
28. Floor-Schreudering A, Geerts AF, Aronson JK, Bouvy ML, Ferner RE, De Smet PA. Checklist for standardized reporting of drug-drug interaction management guidelines. *Eur J Clin Pharmacol* 2014;70:313-8.
29. Scheife RT, Hines LE, Boyce RD, Chung SP, Momper JD, Sommer CD, et al. Consensus Recommendations for Systematic Evaluation of Drug-Drug Interaction Evidence for Clinical Decision Support. *Drug Saf* 2015;38:197-206.
30. Van Roon EN, Flikweert S, le Comte M, Langendijk PN, Kwee-Zuiderwijk WJ, Smits P, et al. Clinical relevance of drug-drug interactions : a structured assessment procedure. *Drug Saf* 2005;28:1131-9.
31. Ferner RE, Coleman JJ. An algorithm for integrating contraindications into electronic prescribing decision support. *Drug Saf* 2010;33:1089-96.
32. Van der Sijs H, Baboe I, Phansalkar S. Human factors considerations for contraindication alerts. *Stud Health Technol Inform* 2013;192:132-6.
33. Heringa M, Floor A, Meijer WM, De Smet PA, Bouvy ML. Nature and management of duplicate medication alerts. *J Am Med Inform Assoc* 2015;22:831-7.

Chapter 2.3

Nature and management of duplicate medication alerts

Mette Heringa
Annemieke Floor-Schreudering
Willemijn M. Meijer
Peter A.G.M. De Smet
Marcel L. Bouvy

Journal of the American Medical Informatics Association 2015;22;831-7



Abstract

Objective

To investigate the nature of duplicate medication (DM) alerts, their management by community pharmacists and potential characteristics of DM alerts that lead to interventions by pharmacists.

Methods

Observational study in 53 community pharmacies. Each pharmacist registered the nature and management of 24 DM alerts on a structured form.

Results

On average, the clinical decision support systems generated 20.4 DM alerts per 100 dispensed drugs. In half of the 1272 registered alerts, the pharmacists judged that there was no risk for concurrent use of both prescriptions. In 32% of the alerts, the DM alert was generated for an intentional combination. In 17% of the alerts, there was a risk for unintentional concurrent use.

In 32% of the alerts the pharmacists decided that one or more actions were needed: the electronic patient record was updated in 15% of the alerts and in 19% of the alerts the pharmacists performed an external action – for example, informing the patient or modifying the prescription (including five therapeutic prescription modifications and 22 logistic prescription modifications). Alerts concerning first dispensing were more likely to be followed by an external action than alerts concerning refills (40% vs 14%, $p < 0.001$).

Discussion and Conclusion

In community pharmacy, prescription modifications based on DM alerts are rare, but DM alerts lead with some regularity to other actions, - for example patient instruction and update of the electronic patient record. As the current DM alerts are diverse and nonspecific in detecting situations where external action is considered relevant, other ways of alerting should therefore be considered.

Introduction

Clinical decision support systems (CDSS) generate a continuous flow of drug therapy alerts. In some cases these alerts lead to clinical interventions. In the majority of cases, however, the alert is judged irrelevant for a particular patient [1-6]. When too many alerts are not followed by a clinical intervention and are overridden (apart from the question whether this is appropriate), this contributes to 'alert fatigue'. A potential consequence is that relevant drug therapy alerts may be overridden mistakenly [1-3, 5, 7]. Drug-drug interaction alerts have been investigated extensively in this respect [2, 4, 8-10]. Little is known about most other types of drug therapy alerts [7]. Yet, duplicate medication (DM) alerts contribute substantially to the total number of alerts, so their specificity is of similar relevance as that of drug-drug interaction alerts [11, 12].

DM alerts are intended to detect inappropriate duplication of therapeutic groups or active ingredients (e.g. the unintentional combination of two different NSAIDs (non-steroidal anti-inflammatory drugs), or the concurrent use of a branded drug and a generic version containing the same active ingredient) [13, 14].

Studies in several settings have estimated the proportion of relevant DM alerts from a few percent [15] to up to 70% [12, 16]. In a Dutch hospital setting, 80% of DM alerts were overridden [1], and only 4.1% of the DM alerts were rated as clinically relevant [11]. Research on DM alerts in community pharmacy is lacking. In community pharmacies there might be even more alerts on duplicate medication than in hospitals, because there is increased likeliness that outpatients receive prescriptions from different prescribers, because community pharmacists are not always informed about changes in therapy, and because of the logistic process, for example early refill of prescriptions because of holidays.

Our objective was to investigate the nature of DM alerts and their management by community pharmacists. Moreover, we aimed to identify characteristics of DM alerts that lead to interventions by pharmacists.

Methods

Data collection

DM alerts were collected by community pharmacists who were participating in a postmaster training program between March 2013 and March 2014. Each

pharmacist was assigned to register a total of 24 DM alerts in daily practice. During four allocated timeslots of two hours each, spread over the week, the pharmacists analyzed the first six DM alerts that occurred during the dispensing process.

For each alert, details were registered on a structured, pretested form (Appendix 1). These included data of the patient (date of birth, sex) and of the alert itself: drugs involved, type of prescriber (general practitioner, specialist or other); handwritten or electronic prescription, first dispensing or refill.

The pharmacists also registered information on the situation underlying the alert generation and its management (retrieval of additional information and performed actions). They had to classify the alerts on three items (Appendix 1):

- Situation underlying the DM alert: in which situation had the alert been generated: no (risk for) concurrent use; intentional concurrent use; (risk for) unintentional concurrent use.
- Retrieval of additional data collection, in which way had the pharmacist retrieved the information needed to decide on whether action should be taken: by consulting the electronic patient record (EPR); contacting the prescriber; contacting the patient; or by a written clarification of the prescriber on the prescription.
- Performed action, which action had been taken by the pharmacist to manage the alert: modification of the prescription; instructing the patient; updating the EPR; or no action at all. All actions except updating the EPR were defined as external actions.

A list with all prescriptions dispensed to the patient in the previous year was printed. Information about the pharmacies and the settings of the CDSS was collected by the pharmacists on a separate form. On this form, the pharmacists also provided information on the number of DM alerts and the total number of processed prescriptions on one day of the DM alert collection.

Typology of DM alert

A DM alert is generated when two prescriptions with the same or comparable active substances are filled with an overlap in the assumed period of use. Its aim is to prevent harm caused by inappropriate DM. All Dutch community pharmacies use CDSSs which generate DM alerts. We used the following DM alert categories based on the drugs involved:

- type 1: overlapping prescriptions of the same active ingredient in the same strength per dose unit and in the same dosage form.

- type 2: overlapping prescriptions of the same active ingredient, but in different strength per dose unit and/or in a different dosage form and/or in a combined preparation with another active ingredient.
- type 3: overlapping prescriptions of two different active ingredients belonging to the same pharmacological or therapeutic class.

Data analysis

All data were entered into a Microsoft Access database. The forms were checked on consistency by the primary researcher (M.H.). When there was inconsistency, a third pharmacist (M.B. or A.F.) was consulted. The data were analyzed and descriptive statistics were performed (SPSS version 20.0; SPSS Inc, Chicago, IL, USA). Logistic regression analyses were performed to analyze determinants of external action (age of the patient, sex of the patient, first dispensing, type of prescriber, handwritten or electronic prescription). A p-value <0.05 was considered statistically significant.

Ethics and confidentiality

In order to protect the patient's privacy, all medical data were anonymized by the community pharmacist. The work was conducted in compliance with the requirements of the institutional review board of the Utrecht University Pharmacy Practice Research Network.

Results

Fifty-three Dutch community pharmacists participated in the study. The mean number of generated DM alerts per 100 dispensed drugs was 20.4 (range 4.4 - 36.7).

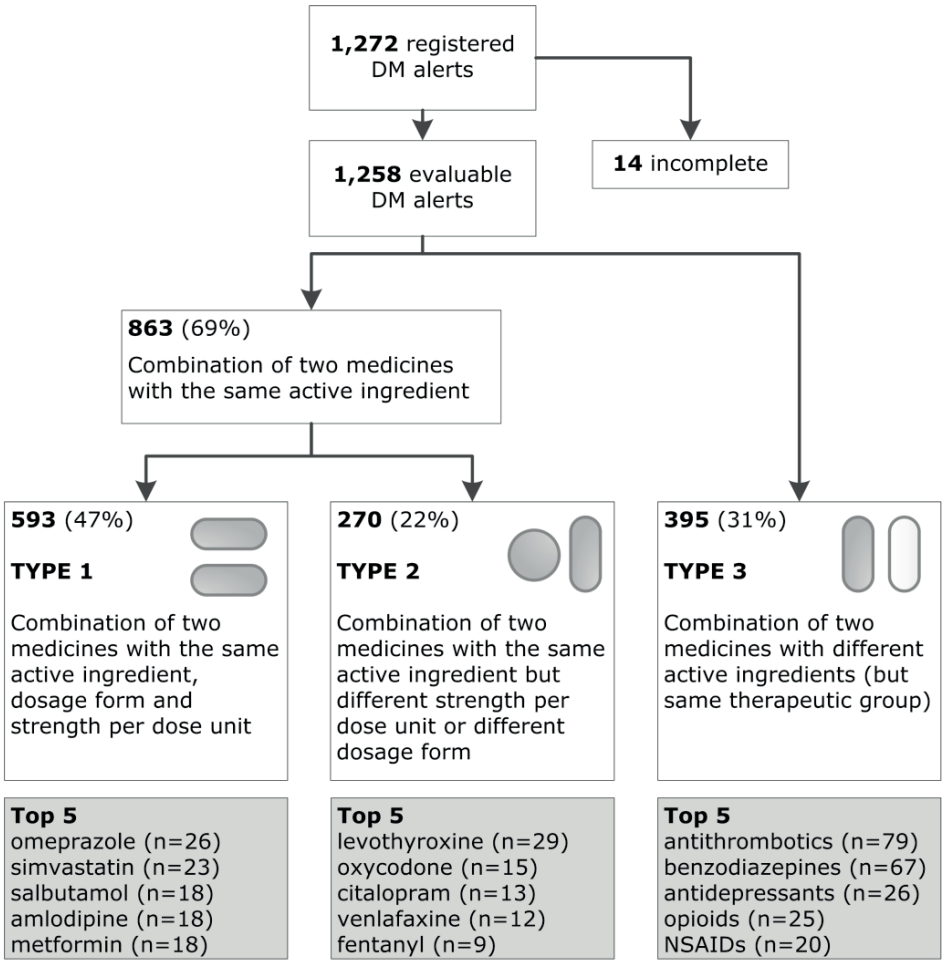
Each pharmacist returned 24 DM alert forms. This resulted in a total of 1272 registered alerts. Fourteen alerts were excluded, because of incomplete information on the drugs involved.

The 1258 remaining alerts were categorized based on the type of DM alert (Figure 1). Of the alerts 47% (n=593) were a type 1 alert. These alerts most frequently concerned chronic medications for the cardiovascular system (ATC group C; n=162), the nervous system (ATC group N; n=121), or the alimentary tract (ATC group A; n=103).

Twenty-two percent of the alerts (n=270) were type 2 alerts. Most of these alerts resulted from combinations of medications for the nervous system (ATC group

N; n=104), the alimentary tract (ATC group A; n=39) and systemic hormonal preparations (ATC group H; n=38).
Thirty-one percent of the alerts (n=395) were DM alert type 3. Most of these alerts were generated for prescriptions of medicines for the nervous system (ATC group N; n=138) and the blood (ATC group B; n=82).

In half of the alerts (51%; n=631) the pharmacists judged that there was no (risk for) concurrent use of both prescriptions (Table 1). The main reasons for these alerts were an early refill and/or a switch to a pharmaceutically identical product from another manufacturer. In 32% of the alerts (n=397), the pharmacist concluded that the DM alert was generated because of an intentional combination. In 17% of the alerts (n=210), the pharmacist was of the opinion that there was a risk for unintentional concurrent use. Generally these alerts related to a therapy switch between drugs from the same therapeutic group or between different strengths of the same drug (n=171). In 92% of these alerts (n=158) the pharmacist reported that the patient was already aware of the fact that both drugs should not be used concurrently.



DM = duplicate medication; NSAIDs = non-steroidal anti-inflammatory drugs

Figure 1: Nature of duplicate medication alerts

Table 1: Situations underlying the DM alerts (n=1,238)[a]

Situation	Details	Number of alerts (%)	Example
No (risk for) concurrent use	Early refill	336 (27.1%)	Early refill of metformin because of holidays.
	EPR: assumed period of use incorrect	107 (8.6%)	Assumed period of use of acenocoumarol in EPR is incorrect because of variable use.
	EPR: dose increased by prescriber	33 (2.7%)	Dose of metformin was increased by the prescriber from two to three tablets daily.
	Overuse, intended	16 (1.3%)	Patient used more salbutamol than prescribed because of insufficient asthma control.
	Other	139 (11.2 %)	Logistic reasons, mainly because of changes of trademark of the same product.
(Risk for) unintentional concurrent use	Switch, patient had already been informed	158 (12.8%)	A switch from metoprolol 25 mg sustained release to metoprolol 50 mg sustained release, or a switch from nitrofurantoin to amoxicillin + clavulanic acid. Patients were aware of these therapy changes.
	Switch, patient had not been informed yet	13 (1.1%)	A switch from pantoprazole to esomeprazole. Patient did not know he should not take pantoprazole any more.
	Unintentional duplicate prescription	14 (1.1%)	A first prescription for morphine while codeine was in use, or two identical prescriptions on the same day (logistic error).
	Other	25 (2.0%)	Dispensing two drugs for subsequent use, e.g. amoxicillin/ clarithromycin/pantoprazole and pantoprazole.
Intentional concurrent use	Intentional concurrent use	397 (32.1%)	Aspirin + clopidogrel (in the first year after an ischemic coronary event) or levothyroxine 100 mcg + 25 mcg

DM = duplicate medication; EPR = electronic patient record; [a] Twenty alerts missing because of insufficient or inconsistent data

In 62% of the alerts (n=779) the EPR contained sufficient information for the pharmacist to decide whether action was needed. In 9% of the alerts (n=111) the prescriber had provided a written clarification of the DM alert on the prescription itself. In one third of the DM alerts the pharmacists needed to retrieve additional information and contacted the patient or prescriber, respectively 25% (n=317) and 6% (n=70). Contact with the prescriber was more frequent for type 3 alerts (11%) than for type 2 alerts (5%; $p = 0.017$) or type 1 alerts (2%; $p < 0.001$). Besides, there were situations where, according to the pharmacist, no additional information was needed at all and situations where the pharmacist contacted other related parties, e.g. homecare.

Overall, in one third of the alerts (n=393) a total of 427 actions were taken by the pharmacists (Table 2). The EPR was updated in 15% of the alerts and the pharmacists performed an external action in 19% of the alerts. The most frequent external action was instructing the patient (14% of the alerts). In 2.2% of the alerts, the prescription was modified or cancelled for therapeutic reasons (0.4%) or for non-therapeutic reasons (1.8%) – the last ones being mainly logistic.

In the multiple logistic regression analysis first dispensing was the only determinant that was associated with an external action by the pharmacist: at first dispensing, 40% of the alerts led to an external action, compared to 14% for refill ($p < 0.001$) (Table 3). The other investigated determinants (age, sex, ATC-group-code of the prescription, type of prescriber and handwritten prescription) were not associated with performing an external action.

In a stratified multiple logistic regression analysis on alert type (data not shown) none of the investigated determinants were associated with performing an external action for DM alerts type 1. For type 2 and type 3 alerts, first dispensing remained the major determinant associated with an external action by the pharmacists compared to refill (type 2: 44% vs 14%, $p < 0.001$; type 3: 36% vs 7% ($p < 0.001$). Moreover, for type 3 alerts, handwritten prescriptions were more likely to be followed by external action than electronic prescriptions (35% vs 16 %, $p = 0.011$).

Table 2: Performed actions by the pharmacists to manage the DM alert (n=1,282) based on 1,248[a] DM alerts

Action		n[b] (% of alerts)	Example
No (external) action	No action	855 (68.5%)	-
	Updating the electronic patient record	192 (15.4%)	Correct dosing instructions and daily use in the electronic patient record: e.g. three tablets metformin 500 mg daily instead of two. Assumed period of use was updated accordingly.
External action	Instructing the patient	175 (14.0%)	Instruct the patient not to use the new and the old prescription concurrently, e.g., diclofenac and meloxicam.
	Other action, e.g. informing other health care professionals	33 (2.6%)	Ask home care to check the stock at the patient's home, e.g., inhalation medication.
	Modifying the prescription / therapy	5 (0.4%)	Contact the prescriber resulting in a therapy change, e.g. stopping codeine because of starting morphine.
	Modifying the prescription, not therapy-related (mainly logistic).	22 (1.8%)	Dispense less than prescribed to prevent stocking at patient's houses. For example, when a patient hoards medicines because of reimbursement issues.

DM = duplicate medication

[a] Ten alerts missing because of insufficient or inconsistent data; [b] more than one action per alert was possible.

Table 3: Determinants of external actions based on DM alerts (n=1,105 alerts[a])

		Number of alerts (%)		OR external action crude (95% CI)	OR external action adjusted[b] (95% CI)
		External action 213	No (external) action 892		
Age	Per year	Mean (SD) 58.7 (21.5) years	Mean (SD) 60.1 (20.7) years	1.0 (1.0-1.0)	1.0 (1.0-1.0)
Sex	Female	128 (60.1%)	502 (56.3%)	1.2 (0.9-1.6)	1.1 (0.8-1.5)
First dispensing		85 (39.9%)	130 (14.6%)	3.9 (2.8-5.4)	3.9 (2.7-5.5)
Handwritten prescription		21 (9.9%)	61 (6.8%)	1.5 (0.9-2.5)	1.7 (0.9-3.3)
Prescriber	General practitioner	163 (76.5%)	663 (74.3%)	1 (reference)	1 (reference)
	Specialist	43 (20.2%)	206 (23.1%)	0.8 (0.6-1.2)	0.7 (0.4-1.1)
	Other	7 (3.3%)	23 (2.6%)	1.2 (0.5-2.9)	1.5 (0.6-3.6)
ATC new prescription[c]	A (alimentary)	37 (17.4%)	108 (12.1%)	1.2 (0.7-1.9)	1.6 (0.9-2.7)
	B (blood)	12 (5.6%)	90 (10.1%)	0.4 (0.2-0.9)	0.7 (0.4-1.5)
	C (cardiovascular)	48 (22.5%)	170 (19.1%)	0.9 (0.6-1.5)	1.4 (0.8-2.2)
	N (nervous system)	51 (23.9%)	270 (30.3%)	0.6 (0.4-1.0)	0.9 (0.5-1.4)
	R (respiratory)	18 (8.5%)	96 (10.8%)	0.6 (0.3-1.1)	0.8 (0.4-1.4)
	Other	47 (22.1%)	158 (17.7 %)	1 (reference)	1 (reference)

ATC = anatomical therapeutic chemical classification; DM = duplicate medication; OR = odds ratio; SD = standard deviation; 95% CI = 95% confidence interval

[a] analysis based on 1,105 alerts (excluding all alerts with at least one missing variable); [b] OR adjusted for all other determinants in table; [c] only ATC-groups with more than 100 alerts shown separately

Discussion

This study shows that CDSS in Dutch community pharmacies generate many DM alerts. In one fifth of these alerts the pharmacists performed an external action, for example, instructing the patient or informing other health care professionals. Prescription modifications were rare (2.2%).

The majority of DM alerts were either generated because refill prescriptions were filled too early, or because patients used intended combinations such as different strengths of levothyroxine or opioids, or because patients concurrently and intentionally used drugs with comparable active substances such as two antithrombotics or psychoactive substances. For medications causing DM alerts type 2 (same active ingredient, different strength or dosage form) and type 3 (different but comparable active ingredients), both intentional combinations and therapy switches are common, so verification by the pharmacist is important. This is consistent with our finding that the DM alerts of type 2 and 3 were more

likely to be followed by external action at first dispensing compared to refill, because first dispensing is the primary moment for verification.

For type 3 alerts, external action was more likely for handwritten prescriptions compared to electronic prescriptions. This could be related to the fact that electronic prescriptions mainly originate from computerized physician order entry including clinical decision support (with type 3 DM alerting), while for handwritten prescriptions the prescriber possibly was not aware of the potential duplicate medication.

Although the proportion of actual prescription modifications was low, our study showed that DM alerts did contribute to safe drug use in other ways. DM alerts stimulated the pharmacists to have a complete and up to date EPR, which is essential for safe drug use [17]. Moreover, DM alerts led to detection of overuse / misuse and overdose. For instance, an early refill of a benzodiazepine can be a way to detect overuse. In case of type 2 alerts, the combined doses of the active ingredient must be checked to prevent overdosing (e.g. the total daily dose of paracetamol in case of combined use of paracetamol and a preparation containing both tramadol and paracetamol).

The majority of DM alerts in our study did not lead to an external action. This indicates that the relevance of most of the alerts was judged as low by the pharmacists. This is consistent with the results of investigations on DM in several other settings [7, 11, 15]. Although the relevance of the majority of the individual DM alerts is considered low, an earlier study showed that 4.5% of prescription modifications in community pharmacies in the Netherlands were a response to DMs [18]. Moreover, Wright et al showed that in hospitals, a majority of the potential Adverse Drug Events (ADEs) and a substantial part of the actually occurring ADEs were caused by DM [19]. This suggests that preventing inappropriate duplicate medication may prevent patient harm.

CDSSs can help to detect situations of potentially inappropriate duplicate medication. But when alerts are nonspecific in detecting situations which pharmacists assess as relevant to perform external action, this contributes to the risk of 'alert fatigue'. Therefore, strategies to improve the specificity of DM alerts should be considered [20].

Based on our data, we suggest six strategies (Table 4). Currently, for DM alerts type 1, most CDSSs generate a DM alert when the overlap between two prescriptions exceeds 14 days. However, the additional explanations reported by the pharmacists in our study suggest that for chronic medications, action is

often limited to cases with an overlap of > 30 days. Enabling different overlap criteria per therapeutic class could reduce the number of irrelevant alerts (e.g. maintaining a short overlap criterion for drugs with a risk of misuse, such as benzodiazepines, and prolong the overlap for chronic medications without a substantial risk of overuse).

As we found that first dispensing was a major determinant of external action, enabling suppression of repeat DM alerts is a second strategy. When a pharmacist judges a certain combination as intentional at first dispensing, manual suppression of these alerts for this patient in the future could be a useful tool to reduce the total number of alerts. To do this safely, the suppression should automatically end in case of relevant changes in the health situation of the patient, e.g. change in systemic drug therapy, new contra-indications and deviating lab values. Moreover, the pharmacist should be able to enter an end date for the alert suppression in case of combinations which are appropriate during a specific period of time, for example, the combination of two different antithrombotics in the first year after an ischemic coronary event (responsible for 6% of the DM alerts in our study). For some combinations (e.g., immunosuppressive drugs after transplantation) lifelong alert suppression may be indicated.

For type 2 alerts, it could even be considered to restrict alert generation to first dispensing instead of offering the possibility of active manual alert suppression. A precondition for this option is the availability of an advanced check on the cumulative daily dose of an active ingredient by the CDSS, rather than checking the daily dose of every prescription separately.

Suppression of repeat alerts for intentional combinations is preceded by an evaluation by the pharmacist at first dispensing. In our study, in 9% of the alerts, the pharmacist contacted the prescriber to retrieve additional information. The judgment process by the pharmacist could be facilitated by sharing the prescriber's reason for overriding an alert electronically with the pharmacist. Although the fact that two prescriptions are from the same prescriber is suggestive for an intentional combination, this single fact is too implicit to consider it sufficient to suppress DM alerts automatically.

Although our study did not specifically focus on alerts for therapeutic classes with a high risk of adverse drug reactions, restricting DM alerts to such drugs should be considered [7].

In addition, for therapeutic groups where combinations are commonly intentional but also carry a high clinical risk, the use of advanced clinical decision

support should be considered [11, 21, 22]. When indications, risk factors, lab monitoring results, age, etc. can be incorporated in the decision algorithm for alert generation, increased specificity can be expected. In case of an intentional combination of antithrombotics, more specific alerting is possible when the decision algorithm is using data like indication, start date, exact combination of drugs and the advised period of concurrent use. To realize this kind of clinical decision rules, DM alerts of drugs that are frequently intentionally combined should be investigated in more detail to elucidate specific factors (such as lab values, indications, and duration of use) determining their relevance. Such factors, which were not included in our study (although they were reported in the additional explanations), will probably differ highly among the different therapeutic groups.

Changing CDSS criteria for alert generation should be done with caution, as experiences with refining drug-drug interaction alerting has shown that improved specificity without loss of sensitivity is difficult to realize and may even have unexpected results, e.g. more alert overriding instead of less [22-24]. The use of advanced CDSSs tends to be promising, but both theoretical estimations and practical experiences are mainly limited to refining alert generation by integrating lab values in the decision algorithms in hospitals [11, 25-27]. About the impact of other suggested strategies for refinement of DM alerts, little is known. Historically there is a tendency of alerting every possible risk and this tendency has been reinforced by the –legitimate- focus on patient safety and drug related problems [28-30]. However, reducing patient harm by clinical risk management does not only include identifying potential risks, but also assessing and prioritizing them. Risk reducing strategies, like the implementation of changes in (advanced) CDSSs, should result from such an assessment rather than from the fear of missing alerts.

Table 4: Improvement strategies for DM alerting

Strategy	Most applicable for
Adaption of overlap criteria for alert generation (per therapeutic class)	DM alert type 1
Manual suppression of repeat DM alerts	DM alert type 3
Automatic suppression of repeat DM alerts	DM alert type 2
Sharing override reasons between prescriber and pharmacist	DM alert type 1, 2 and 3
Restriction of alerts to high risk drugs	DM alert type 1, 2 and 3
Advanced clinical decision support, generating alerts based on all patient characteristics in the EPR	DM alert type 3

DM = duplicate medication; EPR = electronic patient record

Our study has several limitations. It reflects how pharmacists perceived and managed DM alerts in daily practice. Their judgment (e.g., not to perform any action) was not checked independently by a second pharmacist and it is possible that it was incorrect in a few cases. For a few combinations of medicines, the judgment of the pharmacist that it was an intentional and appropriate combination raised a question, because it was not clearly supported by the explanation provided. In one of these rare cases, the combination of chlorthalidone and hydrochlorothiazide was judged as intentional by the managing pharmacist, without proper explanation.

The fact that the pharmacists had to document the alerts may sometimes have influenced their management. If this was the case, it would probably have led to an overestimation of the number of external actions. Nevertheless, the overall number of therapy changes and external actions we found still was quite low.

Conclusion

In community pharmacy DM alerts are generated frequently (20 alerts per 100 dispensed drugs). One-fifth of the alerts trigger pharmacists to perform an external action. Most frequently the patient is instructed and seldom prescriptions are modified for drug therapy related reasons. The current DM alerts are nonspecific in detecting situations where external action is considered relevant. Because of the diversity of the DM alerts, different CDSS improvement strategies should be considered for different types of DM alerts.

Acknowledgements

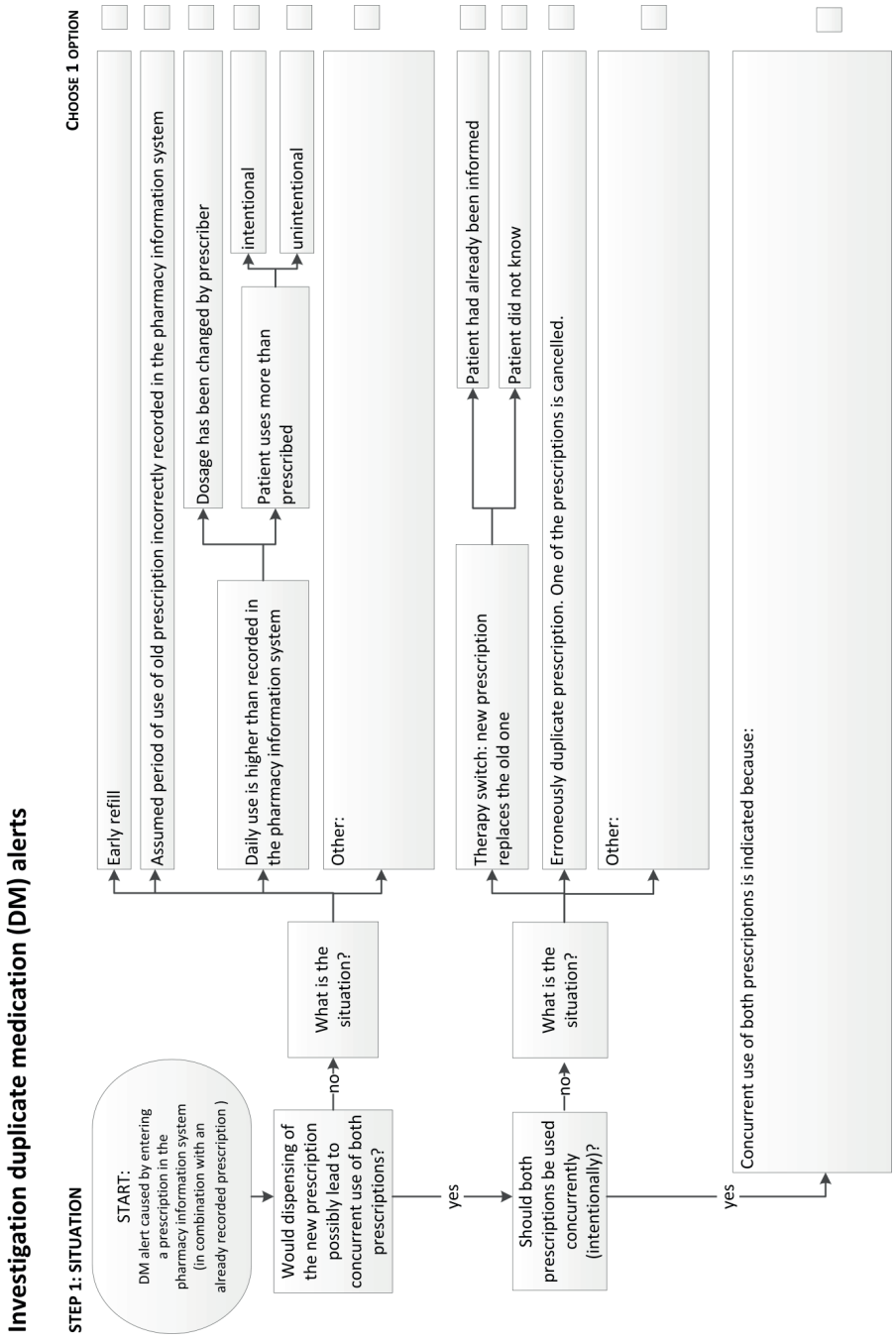
We thank all community pharmacists who participated in this study. Special thanks to Caroline van de Steeg-van Gompel, PhD, who coordinated the participation of the pharmacists.

References

1. Van der Sijs H, Mulder A, van Gelder T, Aarts J, Berg M, Vulto A. Drug safety alert generation and overriding in a large Dutch university medical centre. *Pharmacoepidemiol Drug Saf* 2009;18:941-7.
2. Van der Sijs H, Aarts J, Vulto A, Berg M. Overriding of drug safety alerts in computerized physician order entry. *J Am Med Inform Assoc* 2006;13:138-47.
3. Van der Sijs H, van Gelder T, Vulto A, Berg M, Aarts J. Understanding handling of drug safety alerts: a simulation study. *Int J Med Inform* 2010;79:361-9.
4. Buurma H, De Smet PAGM, Egberts AC. Clinical risk management in Dutch community pharmacies: the case of drug-drug interactions. *Drug Saf* 2006;29:723-32.
5. Isaac T, Weissman JS, Davis RB, Massagli M, Cyrulik A, Sands DZ, et al. Overrides of medication alerts in ambulatory care. *Arch Intern Med* 2009;169:305-11.
6. Tamblyn R, Huang A, Taylor L, Kawasumi Y, Bartlett G, Grad R, et al. A randomized trial of the effectiveness of on-demand versus computer-triggered drug decision support in primary care. *J Am Med Inform Assoc* 2008;15:430-8.
7. Kuperman GJ, Bobb A, Payne TH, Avery AJ, Gandhi TK, Burns G, et al. Medication-related clinical decision support in computerized provider order entry systems: a review. *J Am Med Inform Assoc* 2007;14:29-40.
8. Buurma H, Schalekamp T, Egberts AC, de Smet PAGM. Compliance with national guidelines for the management of drug-drug interactions in Dutch community pharmacies. *Ann Pharmacother* 2007;41:2024-31.
9. Bjerrum L, Andersen M, Petersen G, Kragstrup J. Exposure to potential drug interactions in primary health care. *Scand J Prim Health Care* 2003;21:153-8.
10. Reis AM, Cassiani SH. Evaluation of three brands of drug interaction software for use in intensive care units. *Pharm World Sci* 2010;32:822-8.
11. Eppenga WL, Derijks HJ, Conemans JM, Hermens WA, Wensing M, de Smet PAGM. Comparison of a basic and an advanced pharmacotherapy-related clinical decision support system in a hospital care setting in the Netherlands. *J Am Med Inform Assoc* 2012;19:66-71.
12. Nanji KC, Slight SP, Seger DL, Cho I, Fiskio JM, Redden LM, et al. Overrides of medication-related clinical decision support alerts in outpatients. *J Am Med Inform Assoc* 2014;21:487-91.
13. Pharmaceutical Care Network Europe Foundation. Classification for Drug-Related Problems V6.2 (revised 14-01-2010). 2010, .
14. Kwint HF, Faber A, Gussekloo J, Bouvy ML. Effects of medication review on drug-related problems in patients using automated drug-dispensing systems: a pragmatic randomized controlled study. *Drugs Aging* 2011;28:305-14.
15. Spina JR, Glassman PA, Belperio P, Cader R, Asch S, Primary Care Investigative Group of the VA Los Angeles Healthcare System. Clinical relevance of automated drug alerts from the perspective of medical providers. *Am J Med Qual* 2005;20:7-14.
16. Shah NR, Seger AC, Seger DL, Fiskio JM, Kuperman GJ, Blumenfeld B, et al. Improving acceptance of computerized prescribing alerts in ambulatory care. *J Am Med Inform Assoc* 2006;13:5-11.
17. Floor-Schreudering A, Heringa M, Buurma H, Bouvy ML, De Smet PA. Missed drug therapy alerts as a consequence of incomplete electronic patient records in Dutch community pharmacies. *Ann Pharmacother* 2013;47:1272-9.

18. Buurma H, de Smet PAGM, van den Hoff OP, Egberts AC. Nature, frequency and determinants of prescription modifications in Dutch community pharmacies. *Br J Clin Pharmacol* 2001;52:85-91.
19. Wright A, Feblowitz J, Phansalkar S, Liu J, Wilcox A, Keohane CA, et al. Preventability of adverse drug events involving multiple drugs using publicly available clinical decision support tools. *Am J Health Syst Pharm* 2012;69:221-7.
20. Coleman JJ, van der Sijs H, Haefeli WE, Slight SP, McDowell SE, Seidling HM, et al. On the alert: future priorities for alerts in clinical decision support for computerized physician order entry identified from a European workshop. *BMC Med Inform Decis Mak* 2013;13:111.
21. Seidling HM, Klein U, Schaier M, Czock D, Theile D, Pruszydlo MG, et al. What, if all alerts were specific - Estimating the potential impact on drug interaction alert burden. *Int J Med Inform* 2014;83:285-91.
22. Duke JD, Li X, Dexter P. Adherence to drug-drug interaction alerts in high-risk patients: a trial of context-enhanced alerting. *J Am Med Inform Assoc* 2013;20:494-8.
23. Van der Sijs H, Aarts J, van Gelder T, Berg M, Vulto A. Turning off frequently overridden drug alerts: limited opportunities for doing it safely. *J Am Med Inform Assoc* 2008;15:439-48.
24. Bryant AD, Fletcher GS, Payne TH. Drug interaction alert override rates in the meaningful use era: no evidence of progress. *Appl Clin Inform* 2014;5:802-13.
25. Rommers MK, Teepe-Twiss IM, Guchelaar HJ. A computerized adverse drug event alerting system using clinical rules: a retrospective and prospective comparison with conventional medication surveillance in the Netherlands. *Drug Saf* 2011;34:233-42.
26. Van Doormaal JE, Rommers MK, Kosterink JG, Teepe-Twiss IM, Haaijer-Ruskamp FM, Mol PG. Comparison of methods for identifying patients at risk of medication-related harm. *Qual Saf Health Care* 2010;19:e26.
27. Seidling HM, Phansalkar S, Seger DL, Paterno MD, Shaykevich S, Haefeli WE, et al. Factors influencing alert acceptance: a novel approach for predicting the success of clinical decision support. *J Am Med Inform Assoc* 2011;18:479-84.
28. Audit Commission for Local Authorities and the National Health Services in England and Wales. A spoonful of sugar. 2001, London, United Kingdom.
29. Kohn L, Corrigan J, Donaldson M, eds. To err is human; Building a safer health system. Washington, D.C. United States: National Academy Press 1999.
30. Leendertse A, Egberts A, Stoker L, van den Bemt P. Frequency of and Risk Factors for Preventable Medication-Related Hospital Admissions in the Netherlands. *Arch Intern Med* 2008;168:1890-6.

Appendix 1: Structured form for DM alert registration (translated to English)



STEP 2 PATIENT + DATE

Sex: 0 Male 0 Female **Date of birth:**

Date of alert generation:

STEP 3 MEDICATION

New prescription: name + strength per dose unit:

Dosage:

New prescription: first dispensing?	0 yes	0 no	
Prescriber new prescription?	0 general practitioner	0 specialist	0 other
Type of new prescription?:	0 electronic	0 handwritten	
Both presciptions from same prescriber?	0 yes	0 no	

STEP 4 ALERT

Code and type of alert (e.g.: PD 729, or DM)

Additional information shown in the pharmacy information system (see protocol: mean daily use, overlap, etc)

STEP 5 ACTION

Way of retrieval of additional information (choose one or more)

0 contacting prescriber 0 consulting EPR 0 contacting patient 0 explicit clarification on prescription 0 other ....

Was the alert followed by action? (choose one or more)

0 update EPR 0 modification/cancellation prescription 0 instructing patient 0 no action 0 other....

STEP 6 PRINT LIST

A. Print standardized list of dispensed medication (see protocol!)
B. Anonymize the list by cutting off the personal data (see protocol);
C. Attach the list to this form

3. Improvement strategies for clinical decision support

Chapter 3.1

Clinical decision support and optional point of care testing of renal function for safe use of antibiotics in elderly patients: a retrospective study in community pharmacy practice

Mette Heringa
Annemieke Floor-Schreudering
Peter A.G.M. De Smet
Marcel L. Bouvy

Submitted

Abstract

Objective

To investigate the management of drug therapy alerts on safe use of antibiotics in elderly patients with (potential) renal impairment and the contribution of optional creatinine point of care testing (PoCT) in community pharmacy practice.

Methods

Community pharmacists used a clinical decision support system (CDSS) for seven antibiotics. Alerts were generated during prescription processing in case of previously registered renal impairment, and when no information on renal function was available for patients aged 70 and over. Pharmacists could perform PoCT when renal function could not be retrieved from other health care professionals. Actions were registered in the CDSS. A retrospective descriptive analysis of alert management and medication dispensing histories was performed. Logistic regression was performed on PoCT cases to analyze determinants of identifying patients with renal impairment.

Results

351 pharmacists registered the management of 88,391 alerts for 64,763 patients. For 68,721 alerts (77.7%) the pharmacist retrieved a renal function above the threshold for intervention. 1.8% of the alerts (n=1,532) led to a prescription modification because of renal impairment; in 3.0% of the alerts (n=2,631) the patient had renal impairment, but the pharmacist judged that no intervention was needed. Pharmacists performed 1,988 PoCTs (2.2%); determinants for finding renal impairment were age and number of medicines in use.

Discussion and Conclusion

Implementation of a CDSS in community pharmacies contributed to prevention of potential inappropriate (dosing of) antibiotics in elderly patients with renal impairment. Creatinine PoCT was of added value in a limited number of cases, especially in the very elderly.

Introduction

Renal impairment is common, with chronic kidney disease affecting up to 10% of the population, and over 25% of the elderly [1-3]. An impaired renal function has been shown to be an important risk factor for medication related hospital admissions [4, 5]. Drug elimination can be reduced in case of renal impairment, which can result in drug accumulation and toxicity. Moreover, reduced renal elimination may decrease the effectiveness of drugs acting in the urine (for example nitrofurantoin) [6]. Therefore, some drugs should be avoided in renal impairment, and for other drugs the dosage should be adjusted according to the patient's renal function.

Clinical decision support systems (CDSSs) can help to prevent several types of drug therapy related problems [7, 8]. Health care professionals have successfully used CDSSs to detect potentially inappropriate drug use in patients with a known impaired renal function [9-12]. Moreover, CDSSs can be used to detect situations in which information on patients' renal function is lacking while this information is needed for safe drug use.

Pharmacists can contribute to safe drug use in patients with renal impairment by checking whether the prescribed dose has been adequately adjusted to the renal function. It has been shown that CDSS based interventions by community pharmacists can reduce the number of drug therapy related problems with regard to renal impairment [13-15]. Therefore, it is important that information on patients' renal function is available in community pharmacy. Investigations in the Netherlands showed that this information is often incomplete [16-18]. When information on the renal function cannot be obtained (from, for example, the physician), but is urgently needed, a Point of Care Test (PoCT) may be an alternative to estimate the renal function. It has been shown on a small scale that PoCT of creatinine is applicable in community pharmacies [19].

An urgent need for information on renal function could inter alia be expected in case of prescriptions for antibiotics, as an immediate start of the drug is generally needed. Several commonly used antibiotics are renally excreted and need dose adjustment in case of renal impairment. Although PoCT in community pharmacy has been investigated, as well as several kinds of CDSSs, the combination has not yet been implemented on a large scale.

We aimed to investigate the management of drug therapy alerts on safe use of antibiotics in elderly patients with (potential) renal impairment and the contribution of optional PoCT of renal function in daily community pharmacy practice.

Methods

Setting

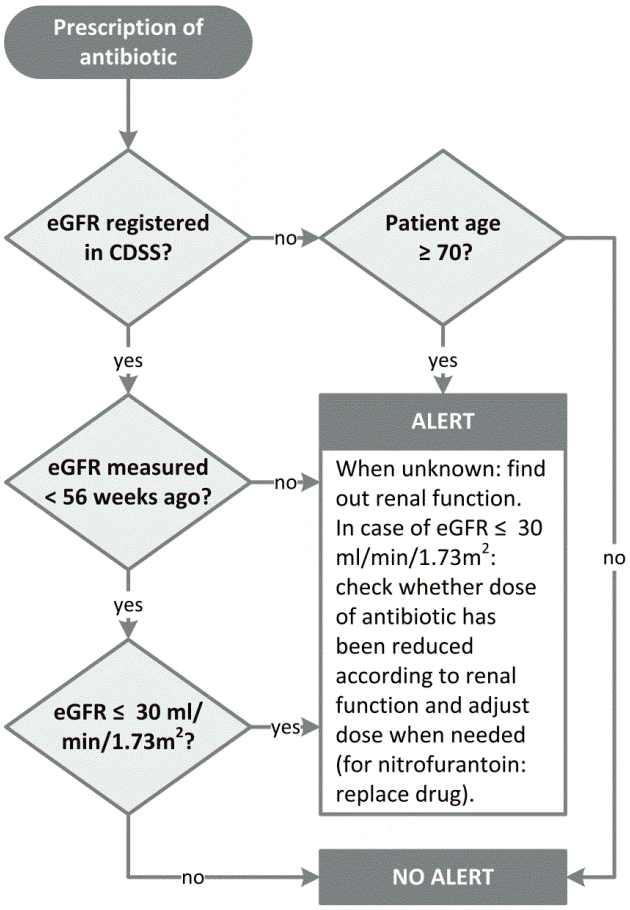
Clinical decision support rules on antibiotic use in renal impairment and PoCT for creatinine were implemented in 351 community pharmacies between June 2015 – August 2016. The participating pharmacies were franchisees of 'Service Apotheek' and were distributed over the Netherlands in both rural and urban areas. These pharmacists routinely used a web-based clinical decision support system (CDSS) in addition to their pharmacy information system. Patients' medication dispensing history, age and gender were automatically available in the CDSS. Renal function had to be registered manually. The CDSS could generate pop-up alerts during the prescription processing in the pharmacy information system. All pharmacists were trained in performing PoCT, interpretation of renal function measures, and registration in the CDSS by attending three half-day meetings (before start, after three months and after six months) and by e-learning.

Clinical decision support rules

Seven clinical decision support rules were implemented, for amoxicillin + clavulanic acid, ciprofloxacin, clarithromycin, co-trimoxazole, nitrofurantoin, norfloxacin, and trimethoprim. Alerts were triggered by the CDSS for patients with a documented estimated glomerular filtration rate (eGFR) ≤ 30 ml/min/1.73m^2, for patients with an outdated eGFR (measured > 56 weeks ago), and for patients aged 70 years and older for whom no eGFR had been registered in the CDSS. For the algorithm of the clinical decision rule, see Figure 1. When an alert was triggered, a drug-specific advice for dose adjustment in case of an eGFR ≤ 30 ml/min/1.73m^2 was displayed (except for nitrofurantoin, where replacement of the drug was advised). Based on the advice, pharmacists had to check the dose manually and adjust it when needed, after consultation with the prescriber. The displayed advices were in accordance with the Dutch national guidelines on drug dosing in renal impairment [20]; differences with international guidelines exist – comparable to the differences between international guidelines [21]. The Dutch national guidelines are widely accepted by physicians and pharmacists.

PoCT for creatinine

Pharmacists had the possibility to use the Menarini Statsensor Creatinine Xpress-meter for PoCT with capillary puncture. With this meter, blood creatinine level can be measured within one minute with sufficient accuracy to detect renal impairment in adults [22]. In the study, PoCT was intended for situations



CDSS = clinical decision support system;
eGFR = estimated glomerular filtration rate

Figure 1: Algorithm of clinical decision support rule antibiotics and renal function

where information on the renal function was urgently needed and not available from other sources (e.g. the general practitioner). Pharmacists were trained on estimating the GFR based on the creatinine measurement (using basically the MDRD [Modification of Diet in Renal Disease] formula [23], and using the Cockcroft & Gault equation for creatinine clearance [24] where appropriate). Calculations of eGFR were performed similarly as performed by laboratories in both primary and secondary care in the Netherlands. On a local level, pharmacists made arrangements with general practitioners about the exchange of information on renal function, the use of PoCT and the follow up after a PoCT measurement. Protocols and leaflets to inform both GP's and patients about PoCT were provided to the participating pharmacists.

Data collection and analysis

The pharmacists registered the alert management in the CDSS according to predefined options regarding the situation and intervention; additional free text could be entered. Data from the CDSS were registered in a central database. Anonymized data were extracted from this database for all alerts, including alert management, medication dispensing history for the four months preceding the alert (including dosing regimen and anatomical therapeutic chemical classification [ATC, [25]]), and registered data on renal function.

The data were analyzed using Microsoft Access and SPSS (version 20.0; SPSS Inc. Chicago, IL, USA). The data were checked for completeness and consistency with regard to the combination of the registered alert management, dispensed medicine, and renal function. Data registration was considered incomplete when information in one of the data fields was lacking while the other data fields suggested that the pharmacist had the information available. Data registration was considered inconsistent when the information in the different data fields was not matching. For examples of the data check, see Appendix 1.

In this study, an eGFR ≤ 50 ml/min/1.73m^2 was considered as impaired renal function and ≤ 30 ml/min/1.73m^2 as severely impaired renal function. These thresholds were derived from categories used in the Dutch guidelines on drug dosing in renal impairment [20], which are based on the 2004 European Medicines Agency Guideline [26]. Descriptive statistics were performed. Logistic regression analyses were performed to analyze determinants of finding an impaired renal function (≤ 50 ml/min/1.73m^2) when performing PoCT (age, gender, number of medicines in use, and alert triggering medicine). Although the threshold for dose adjustment for the antibiotics in the investigated clinical decision support rules was 30 ml/min/1.73m^2, a higher threshold was used to determine for which patient groups PoCT in community pharmacy could be most relevant (which is important to know because PoCT is not common practice yet). Consistent with the dosing advices, the threshold of 50 is in the Netherlands often used for informing pharmacists on impaired renal function; it indicates a need for closer monitoring of renal function and of current and future drug use. A p-value < 0.05 was considered statistically significant.

Ethics and confidentiality

As this was a retrospective anonymized database analysis, the study was exempt from ethical review. To protect patients' and pharmacists' privacy, only anonymous data were extracted from the CDSS. Data could not be used to identify individual patients or pharmacies.

Results

The 351 participating pharmacies dispensed 749,659 prescriptions of the seven investigated antibiotics and they registered the management of 88,391 alerts. Incomplete data recording (see Appendix 1) was found in 15.4% of the records; it was almost entirely caused by lacking registration of the eGFR. The data consistency check showed inconsistent registration in 4.1% of the records.

The 88,391 alerts were generated for 64,763 patients. Most alerts were generated for prescriptions of nitrofurantoin (43,417 alerts, 49.1%), followed by amoxicillin + clavulanic acid (16,994 alerts, 19.2%) and ciprofloxacin (11,519 alerts, 13.0%), see Table 1. The majority of the alerts were generated for patients aged 70-79 (42,126 alerts, 47.7%) and patients aged 80-89 (35,168 alerts, 39.8%). The very elderly - aged 90 years and over – accounted for 11.7% of the alerts (n = 10,306); only 0.9% of the alerts were generated for patients under 70 years of age (n = 791).

For 93.3% of the 88,391 alerts, the data recording showed that they were generated because information on renal function was lacking or outdated. In 15.5% of the alerts, the pharmacist decided to dispense the prescribed drug without recent information on the renal function of the patient (Table 1). In 2.0% of the alerts, the pharmacist had patient information indicating a special situation, for example that it concerned a patient on dialysis. For the other alerts (82.5%), the pharmacist obtained or already had information on the patient's renal function. This information led to unchanged dispensing in the majority of cases, most often because the eGFR was above the threshold of 30 ml/min/1.73m^2 (77.7% of the alerts). In addition, in 3.0% of the cases (n=2,631), the pharmacist judged that no intervention was needed although the eGFR was below 30 ml/min/1.73m^2, e.g. because the prescribed dose was appropriate for this renal function. In 1.4% of the alerts, the prescribed dose was adjusted after intervention by the pharmacist, and in 0.4% of the alerts the drug was replaced. So, the management of alerts led overall to 1,532 prescription modifications (1.8%) because of renal impairment. Within the patient group with renal impairment (eGFR ≤ 30 ml/min/1.73m^2) (n=4163), the intervention rate was 36.8% (1,532 cases with intervention). Patients aged 90 and over accounted for 24.7% of the prescription modifications (n=378).

In 1,988 cases (2.2% of the alerts), the pharmacist performed a PoCT to obtain information on the renal function before dispensing the antibiotic. In 1,852 of the PoCTs, the eGFR was documented in the CDSS. In 170 of these cases (9.2%), the eGFR obtained by PoCT was ≤ 50 ml/min/1.73m^2, of which 18 cases (1.0%) ≤ 30 ml/min/1.73m^2. The PoCT measurements resulted in 15 prescription modifica-

Table 1: Frequency and management of alerts on antibiotics and renal function

	Nitrofurantoin	Amoxicillin + clavulanic acid	Ciprofloxacin	Trimethoprim	Co-trimoxazole	Clarithromycin	Norfloxacin	Total
Total number of prescriptions	343,848	178,990	91,697	53,816	38,640	31,073	11,595	**749,659**
% of prescriptions with alert	12.6	9.5	12.6	13.4	9.7	10.5	19.3	11.8
Total number of alerts	43,417	16,994	11,519	7,229	3,744	3,251	2,237	**88,391**
Alert management (% of alerts)								
Dose adjustment	6 (0.0)	493 (2.9)	303 (2.6)	214 (3.0)	80 (2.1)	57 (1.8)	48 (2.1)	**1,201 (1.4)**
Replacement of drug	295 (0.7)	6 (0.0)	8 (0.1)	9 (0.1)	5 (0.1)	8 (0.2)	0 (0.0)	**331 (0.4)**
eGFR > 30 ml/min/1.73m^2, no dose adjustment needed	35,113 (80.9)	12,783 (75.2)	8,714 (75.6)	5,230 (72.3)	2,741 (73.2)	2,485 (76.4)	1,655 (74.0)	**68,721 (77.7)**
eGFR ≤ 30 ml/min/1.73m^2, prescribed dose is appropriate	0 (0.0)	840 (4.9)	720 (6.3)	546 (7.6)	287 (7.7)	125 (3.8)	113 (5.1)	**2,631 (3.0)**
Dispensed, renal function unknown	7,090 (16.3)	2,552 (15.0)	1,555 (13.5)	1,103 (15.3)	539 (14.4)	510 (15.7)	394 (17.6)	**13,743 (15.5)**
Other situations, e.g. dialysis with monitoring in hospital, terminally ill patient	913 (2.1)	320 (1.9)	219 (1.9)	127 (1.8)	92 (2.5)	66 (2.0)	27 (1.2)	**1,764 (2.0)**

eGFR = estimated glomerular filtration rate

tions (0.8% of the PoCT). In three cases, nitrofurantoin was replaced by another antibiotic. In 12 cases, the dose of the antibiotic was reduced.

The logistic regression analysis (Table 2) showed that age and number of medicines in use were significantly associated with identifying a patient with an impaired renal function (eGFR ≤ 50 ml/min/1.73m^2) by PoCT. The percentage of PoCT with an eGFR ≤ 50 ml/min/1.73m^2 was 6.1% for patients under 80 years of age, 11.6% for patients of 80-89 years old, and 29.2% for patients 90 years of age and older ($p < 0.01$). The percentage of PoCT with an eGFR ≤ 50 ml/min/1.73m^2 increased with the number of medicines in use, from 5.8% for patients not using any medication, to 15.8% for patients using eight or more medicines ($p < 0.01$).

At the end of the study period, 49,178 of the 64,763 patients (75.9%) had a renal function registered in the CDSS. For 13,252 (26.9%) of the patients with a documented renal function, at least one eGFR ≤ 50 ml/min/1.73m^2 had been registered. For 2,144 patients (4.4%) at least one eGFR ≤ 30 ml/min/1.73m^2 had been registered.

Table 2: Determinants of impaired renal function identification by PoCT

		Number of PoCT[a] (%)		OR renal impairment crude (95% CI)	OR renal impairment adjusted[b] (95% CI)
		eGFR ≤ 50 ml/min/1.73m² n=170	eGFR > 50 ml/min/1.73m² n=1,682		
Age	70-79[c]	70 (41.2%)	1,083 (64.4%)	1 (reference)	1 (reference)
	80-89	69 (40.6%)	524 (31.2%)	2.0 (1.4-2.9) *	1.9 (1.3-2.7)*
	90 +	31 (18.2%)	75 (4.5%)	6.4 (3.9-10.4) *	5.4 (3.3-8.8)*
Gender	Female	124 (72.9%)	1,151 (68.4%)	1.2 (0.9-1.8)	1.2 (0.8-1.8)
Number of medicines in use	0	25 (14.7%)	408 (24.3%)	1 (reference)	1 (reference)
	1-3	47 (27.6%)	650 (38.6%)	1.2 (0.7-1.9)	1.1 (0.6-1.8)
	4-7	69 (40.6%)	469 (27.9%)	2.4 (1.5-3.9) *	2.0 (1.2-3.2)*
	8+	29 (17.1%)	155 (9.2%)	3.1 (1.7-5.4) *	2.2 (1.2-4.0)*
Alert triggering antibiotic	Nitrofurantoin	85 (50.0%)	825 (49.0%)	1.2 (0.8-1.7)	1.0 (0.6-1.6)
	Amoxicillin + clavulanic acid	35 (20.6%)	392 (23.3%)	1 (reference)	1 (reference)
	Ciprofloxacin	20 (11.8%)	218 (13.0%)	1.0 (0.6-1.8)	1.1 (0.6-2.0)
	Trimethoprim	12 (7.1%)	109 (6.5%)	1.2 (0.6-2.5)	1.1 (0.5-2.3)
	Co-trimoxazole	7 (4.1%)	59 (3.5%)	1.3 (0.6-3.1)	1.2 (0.5-2.9)
	Clarithromycin	6 (3.5%)	49 (2.9%)	1.4 (0.5-3.4)	1.3 (0.5-3.4)
	Norfloxacin	5 (2.9%)	30 (1.8%)	1.9 (0.7-5.1)	1.2 (0.4-3.5)

eGFR = estimated glomerular filtration rate; OR = odds ratio; PoCT = point of care testing for creatinine; 95% CI = 95% confidence interval

[a] analysis based on 1,852 PoCT with registered eGFR; [b] OR adjusted for all other determinants in table; [c] including 4 patients < 70

* $p < 0.01$

Discussion

The 351 participating pharmacists managed nearly 90,000 alerts on antibiotics and impaired renal function in 15 months. This led to over 1,500 prescription modifications and nearly 2,000 PoCTs. The percentage of prescription modifications (1.8% of the alerts) was quite low. However, for patients with an impaired renal function (eGFR ≤ 30 ml/min/1.73m^2), we observed a much higher intervention rate of 36.8%. Low intervention rates (< 10%) are not uncommon in routinely used CDSSs [27-30]. The low overall intervention rate in our study was specifically caused by triggering of alerts by missing information on renal function (over 90% of the alerts).

Better exchange and registration of the available information on renal function would have reduced the number of unnecessary CDSS alerts in our study, thereby

increasing the percentage of relevant alerts. This is caused by the fact that in 78% of the alerts in our investigation, the information on renal function retrieved by the pharmacists showed an eGFR > 30 ml/min/1.73m^2. If the renal function had been available in the CDSS beforehand, no alert would have appeared. So, the main reason for alert generation in our study was the high number of missing or outdated eGFR values in the CDSS.

Furthermore, in 3% of the alerts, the renal function was impaired, but the dose of the antibiotic had already been adjusted. Probably, the prescriber was aware of the impaired renal function and wrote the prescription according to the dosing guidelines. These alerts would not appear in an improved, more specific CDSS with automatic consideration of the actual dose in relation to the reference dose (taking into account the indication), a function that was missing in the investigated CDSS. So, combining better registration of renal function in the CDSS and extended CDSS functionality would have reduced the number of alerts by 81%.

The total number of 1,988 performed PoCTs was relatively low, which indicates that in most cases pharmacists were well able to retrieve information on renal function from other sources, for example the prescriber (or that the pharmacist judged that dispensing without information on renal function was acceptable). In 0.8% of the PoCTs, the prescription was modified – which was less than the overall result of 1.8% prescription modifications. This can be explained by the fact that for patients with risk factors for renal impairment (for example diabetes), it is more likely that information on renal function was already available. In 9% of the PoCTs an impaired renal function was found. This implicates that the 'number needed to test' to identify one patient with an eGFR ≤ 50 ml/min/1.73m^2 was 11. We showed that from the characteristics generally available in community pharmacy, higher age and higher number of medicines in use were in multiple regression analysis associated with PoCT identification of patients with an impaired renal function. In patients aged 90 years and over, the 'number needed to test' to identify one patient with an eGFR ≤ 50 ml/min/1.73m^2 was only 3. Based on this results, performing PoCT is probably the most worthwhile in the patient groups with the highest age; further research is needed to better specify in which patient groups PoCT should be used for the optimal balance between efficiency and safety.

More in general, PoCT is useful when information on renal function is urgently needed, when the intended drug needs dose adjustment or replacement even in case of mild or moderate impaired renal function, and when the prescribed drug has a narrow therapeutic window. The antibiotics included in this investigation

needed dose adjustment in case of a severely impaired renal function (eGFR ≤ 30ml/min/1.73m^2). This explains the limited number of prescription modifications after PoCT. Although at the time of the POCT no intervention may have been needed, the retrieved (impaired) renal function can be useful for assessment of other prescriptions in the near future. The identification of patients with a severely impaired renal function can especially be relevant when the patient has not been diagnosed with renal impairment before. Although PoCT for creatinine is not completely equivalent to laboratory measurement, it has been shown to be sufficiently accurate for detecting relevantly impaired renal function [22].

By the end of the study period, a renal function was registered for about 75% of the patients. This percentage is in the upper range of results from some recent surveys about the availability of information on renal function in community pharmacy [16, 17]. This suggests that the routine use of the CDSS can contribute to better documentation of renal function. In about 15% of the alerts, the antibiotic was dispensed while the pharmacist had no information on the patient's renal function. The reasons can be several: for example, no information on renal function was available over the last year, but 18 months ago the renal function was normal. When the patient has a stable health condition, the pharmacist probably judged it very unlikely that the current eGFR was under 30 ml/min/1.73m^2 (the threshold for intervention for the antibiotics in this investigation).

The CDSS generated alerts based on the most recent registered renal function. A measurement of up to 13 months ago (56 weeks) was considered recent – consistent with yearly monitoring. Renal function can however fluctuate over time, especially in patients with an unstable condition (for example, after hospital admission) [31]. Single point measurements therefore have limited validity and after finding a potentially impaired renal function, repeated measurements are needed. Moreover, the estimated GFR can be an underestimation or overestimation of the actual value. Formulas for estimating GFR should be applied carefully, and the patients' individual characteristics should be taken into account [32, 33]. Future CDSSs could be improved by incorporating historical trends in patients' renal function and patient characteristics affecting GFR estimates in the algorithms. But even then clinical decision support is only a tool to detect a potential problem. The management of an alert needs an individualized assessment by a competent health care professional.

This retrospective observational study has strengths and limitations. A major strength is the large sample size: the management of nearly 90,000 alerts was investigated and the CDSS and PoCT were used in over 350 pharmacies. There-

fore, our study gives an overview of routine alert management by community pharmacists. Moreover, it shows that a CDSS can be successfully implemented on a large scale in daily community pharmacy practice, as our study included one sixth of all community pharmacies in the Netherlands.

A first limitation is that the appropriateness of the alert management and the renal function estimation by the pharmacists for the concerning patients was not assessed by the researchers (e.g., whether dispensing without knowing the renal function was acceptable). The estimation and interpretation of the renal function and the relevance of the intervention are dependent on individual patient characteristics. Future research could elucidate the appropriateness of pharmacists' assessment of CDSS alerts regarding renal function.

Secondly, because of the routine registration in daily practice and the large number of participating pharmacists, incorrect registrations might have occurred. To reduce variation, all pharmacists were trained on correct registration of alert management. We checked data consistency and rated it as acceptable for a large scale observational study in daily practice, with less than 5% of inconsistent registrations. Data completeness was good, except for registration of the value of eGFR, which was missing in about 15% of the records. However, because information on eGFR category (≤ or > 30 ml/min/1.73m^2) was available for the records concerned, it is unlikely that study results were relevantly affected.

Insight in the current management of drug therapy alerts on renal impairment can contribute to better CDSSs and to better alert management by the health care professional. In future research, a focus on the interpretation of renal function measures on the level of the individual patient supported by CDSSs could complement the current knowledge in this field.

Conclusion

Implementation of a CDSS in community pharmacies contributed to prevention of potential inappropriate (dosing of) antibiotics in elderly patients with renal impairment. Pharmacists retrieved most data on renal functions from other health care professionals. Nevertheless, the availability of PoCT of renal function was of added value in a limited number of cases, especially in the very elderly.

Acknowledgements

We thank P. Hoogland from Service Apotheek, a Dutch community pharmacy franchise organization, and M. Spies from NControl, the associated data warehouse, for provision of the data. We thank B. Rostai (Utrecht University) for his valuable comments.

References

1. Mills KT, Xu Y, Zhang W, Bundy JD, Chen CS, Kelly TN, et al. A systematic analysis of worldwide population-based data on the global burden of chronic kidney disease in 2010. *Kidney Int* 2015;88:950-7.
2. Zhang QL, Rothenbacher D. Prevalence of chronic kidney disease in population-based studies: systematic review. *BMC Public Health* 2008;8:117,2458-8-117.
3. De Nicola L, Zoccali C. Chronic kidney disease prevalence in the general population: heterogeneity and concerns. *Nephrol Dial Transplant* 2016;31:331-5.
4. Leendertse AJ, Van Dijk AE, De Smet PAGM, Egberts ACG, Van Den Bemt PMLA. Contribution of Renal Impairment to Potentially Preventable Medication-Related Hospital Admissions. *Ann Pharmacother* 2012;46:625-33.
5. Leendertse A, Egberts A, Stoker L, van den Bemt P. Frequency of and Risk Factors for Preventable Medication-Related Hospital Admissions in the Netherlands. *Arch Intern Med* 2008;168:1890-6.
6. Oplinger M, Andrews CO. Nitrofurantoin contraindication in patients with a creatinine clearance below 60 mL/min: looking for the evidence. *Ann Pharmacother* 2013;47:106-11.
7. Curtain C, Peterson GM. Review of computerized clinical decision support in community pharmacy. *J Clin Pharm Ther* 2014;39:343-8.
8. Bright TJ, Wong A, Dhurjati R, Bristow E, Bastian L, Coeytaux RR, et al. Effect of Clinical Decision-Support Systems: A Systematic Review. *Ann Intern Med* 2012;157:29-43.
9. Bayoumi I, Al Balas M, Handler SM, Dolovich L, Hutchison B, Holbrook A. The effectiveness of computerized drug-lab alerts: a systematic review and meta-analysis. *Int J Med Inform* 2014;83:406-15.
10. Seidling HM, Schmitt SP, Bruckner T, Kaltschmidt J, Pruszydlo MG, Senger C, et al. Patient-specific electronic decision support reduces prescription of excessive doses. *Qual Saf Health Care* 2010;19:e15.
11. Awdishu L, Coates CR, Lyddane A, Tran K, Daniels CE, Lee J, et al. The impact of real-time alerting on appropriate prescribing in kidney disease: a cluster randomized controlled trial. *J Am Med Inform Assoc* 2016;23:609-16.
12. Nanji KC, Slight SP, Seger DL, Cho I, Fiskio JM, Redden LM, et al. Overrides of medication-related clinical decision support alerts in outpatients. *J Am Med Inform Assoc* 2014;21:487-91.
13. Via-Sosa MA, Lopes N, March M. Effectiveness of a drug dosing service provided by community pharmacists in polymedicated elderly patients with renal impairment--a comparative study. *BMC Fam Pract* 2013;14:96.
14. Joosten H, Drion I, Boogerd KJ, van der Pijl EV, Slingerland RJ, Slaets JP, et al. Optimising drug prescribing and dispensing in subjects at risk for drug errors due to renal impairment: improving drug safety in primary healthcare by low eGFR alerts. *BMJ Open* 2013;3:e002068.
15. Pourrat X, Sipert AS, Gatault P, Sautenet B, Hay N, Guinard F, et al. Community pharmacist intervention in patients with renal impairment. *Int J Clin Pharm* 2015;37:1172-9.
16. Smits E, Houben E, de Smet PAGM, Szerencsi K, vanHerk-Sukel MPP, Herings RMC, et al. The Availability of Information on Impaired Renal Function in the Community Pharmacy, A Descriptive Pilot Study. *HSOA Journal of Nephrology and Renal Therapy* 2016;2:003.
17. Koster ES, Philbert D, Noordam M, Winters NA, Blom L, Bouvy ML. Availability of information on renal function in Dutch community pharmacies. *Int J Clin Pharm* 2016;38:797-801.

18. Floor-Schreudering A, Heringa M, Buurma H, Bouvy ML, De Smet PA. Missed drug therapy alerts as a consequence of incomplete electronic patient records in Dutch community pharmacies. *Ann Pharmacother* 2013;47:1272-9.
19. Geerts AF, De Koning FH, De Vooght KM, Egberts AC, De Smet PA, van Solinge WW. Feasibility of point-of-care creatinine testing in community pharmacy to monitor drug therapy in ambulatory elderly patients. *J Clin Pharm Ther* 2013;38:416-22.
20. Royal Dutch Pharmacists Association (KNMP). Zakboek Verminderde Nierfunctie (Dutch guidelines for drug-dosing in chronic kidney disease). The Hague, The Netherlands 2012.
21. Vidal L, Shavit M, Fraser A, Paul M, Leibovici L. Systematic comparison of four sources of drug information regarding adjustment of dose for renal function. *BMJ* 2005;331:263.
22. Kosack CS, de Kieviet W, Bayrak K, Milovic A, Page AL. Evaluation of the Nova StatSensor(R) Xpress(TM) Creatinine point-of-care handheld analyzer. *PLoS One* 2015;10:e0122433.
23. Levey AS, Greene T, Kusek JW, Beck GJ. A simplified equation to predict glomerular filtration rate from serum creatinine. *J Am Soc Nephrol* 2000;11:155a.
24. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron* 1976;16:31-41.
25. WHO Collaborating Centre for Drug Statistics Methodology. ATC/DDD Index 2016. Accessed August 2016. Available at: www.whocc.no/atc_ddd_index.
26. Committee for Medicinal Products for Human Use (CHMP). Note for guidance on the evaluation of the pharmacokinetics of medicinal products in patients with impaired renal function. European Medicines Agency 2004, London, United Kingdom.
27. Bryant AD, Fletcher GS, Payne TH. Drug interaction alert override rates in the meaningful use era: no evidence of progress. *Appl Clin Inform* 2014;5:802-13.
28. Eppenga WL, Derijks HJ, Conemans JM, Hermens WA, Wensing M, de Smet PAGM. Comparison of a basic and an advanced pharmacotherapy-related clinical decision support system in a hospital care setting in the Netherlands. *J Am Med Inform Assoc* 2012;19:66-71.
29. Buurma H, De Smet PAGM, Egberts AC. Clinical risk management in Dutch community pharmacies: the case of drug-drug interactions. *Drug Saf* 2006;29:723-32.
30. Van der Sijs H, Aarts J, Vulto A, Berg M. Overriding of drug safety alerts in computerized physician order entry. *J Am Med Inform Assoc* 2006;13:138-47.
31. Eppenga WL, Wester WN, Derijks HJ, Hoedemakers RM, Wensing M, De Smet PA, et al. Fluctuation of the renal function after discharge from hospital and its effects on drug dosing in elderly patients--study protocol. *BMC Nephrol* 2015;16:95.
32. Eppenga WL, Kramers C, Derijks HJ, Wensing M, Wetzels JF, De Smet PA. Drug therapy management in patients with renal impairment: how to use creatinine-based formulas in clinical practice. *Eur J Clin Pharmacol* 2016;72:1433-9.
33. Eppenga WL, Kramers C, Derijks HJ, Wensing M, Wetzels JF, De Smet PA. Individualizing pharmacotherapy in patients with renal impairment: the validity of the Modification of Diet in Renal Disease formula in specific patient populations with a glomerular filtration rate below 60 ml/min. A systematic review. *PLoS One* 2015;10:e0116403.

Appendix 1: Check of consistency and completeness of data registration

Examples of check on consistency and completeness of data registration	Registered alert management		[III] Registered renal function	[IV] Corresponding record in medication dispensing history (based on ATC of the medication for which the alert had been generated)
	[I] Situation	[II] Intervention		
Example 1: consistent and complete	Renal function is below threshold and dose is too high	Dose adjustment	eGFR ≤ 30 ml/min/1.73m^2 (≤ 56 weeks ago)	Medication record with reduced dose (appropriate for renal impairment)
Example 2: consistent and complete	Renal function unknown; dispensed	No intervention	No registered renal function	Medication record with normal dose
Example 3: inconsistent (on item IV)	Renal function is below threshold and dose is too high	Dose adjustment	eGFR ≤ 30 ml/min/1.73m^2 (≤ 56 weeks ago)	Medication record with normal dose
Example 4: inconsistent (on item III)	Renal function is above threshold	No intervention	eGFR ≤ 30 ml/min/1.73m^2 (> 56 weeks ago)	Medication record with normal dose
Example 5: incomplete (on item III)	Renal function is below threshold and dose is too high	Dose adjustment	No registered renal function	Medication record with reduced dose (appropriate for renal impairment)

ATC = anatomical therapeutic chemical classification [25]; eGFR = estimated glomerular filtration rate

Chapter 3.2

Lower alert rates by clustering of related drug interaction alerts

Mette Heringa
Hidde Siderius
Annemieke Floor-Schreudering
Peter A.G.M. De Smet
Marcel L. Bouvy

Journal of the American Medical Informatics Association 2017;24:54-59

Abstract

Objective

We aimed to investigate to what extent clustering of related drug interaction alerts (drug-drug and drug-disease interaction alerts) would decrease the alert rate in clinical decision support systems (CDSSs).

Methods

We conducted a retrospective analysis of drug interaction alerts generated by CDSSs in community pharmacies. Frequently generated combinations of alerts were analyzed for associations in a 5% random data sample (dataset 1). Alert combinations with similar management recommendations were defined as clusters. The alert rate was assessed by simulating a CDSS generating one alert per cluster per patient instead of separate alerts. The simulation was performed in dataset 1 and replicated in another 5% data sample (dataset 2).

Results

Data were extracted from the CDSSs of 123 community pharmacies. Dataset 1 consisted of 841,572 dispensed prescriptions and 298,261 drug interaction alerts. Dataset 2 was comparable. Twenty-two frequently occurring alert combinations were identified. Analysis of these associated alert combinations for similar management recommendations resulted in three clusters (related to renal function, electrolytes, diabetes and cardiovascular diseases). Using the clusters in alert generation reduced the alert rate within these clusters by 53%-70%. The overall number of drug interaction alerts was reduced by 11% in dataset 1 and by 12% in dataset 2. This corresponds to a decrease of 21 alerts per pharmacy per day.

Discussion and Conclusion

Using clusters of drug interaction alerts with similar management recommendations in CDSSs can substantially decrease the overall alert rate. Further research is needed to establish the applicability of this concept in daily practice.

Introduction

Clinical decision support systems (CDSSs) are a useful tool in detecting drug therapy related problems [1-3]. However, in daily practice, physicians and pharmacists override up to 95% of the alerts [4-7]. When only a minority of alerts lead to action, this can lead to 'alert fatigue', with the risk of missing important alerts. Several strategies to reduce alert fatigue have been investigated, both in simulations and in daily practice [7-20]. These strategies involve changes in the usability design of CDSSs (e.g., changing the presentation of alerts from interruptive to noninterruptive) [17-22], reassessment of the clinical relevance of alerts in order to turn off irrelevant alerts [8-11] and incorporation of more clinical characteristics in the algorithms generating the alerts (e.g. lab measurements, duration of use, prophylactic medication in use) [7, 12-16]. In general, the majority of these strategies were targeted at increasing the specificity of individual alerts, often in small subsets of alerts. These investigations led to varying results, but override rates tended to stay considerably high [23]. Therefore, there is a need for exploration of additional strategies.

In community pharmacy, the majority of drug-drug interaction alerts and drug-disease interaction alerts (hereafter referred to as drug interaction alerts) are generated for a minority of patients, namely patients with multimorbidity and polypharmacy [24]. When many alerts are generated for the same patient at the same moment, overlooking one of them is conceivable. Moreover, a few therapeutic drug groups are responsible for the majority of the alerts [24]. Besides, it is known that a small number of drug-drug interactions account for the majority of the generated drug-drug interaction alerts [5, 25, 26]. Based on these findings, it is likely that the majority of drug interaction alerts concern a limited subset of potential problems. This can lead to the generation of several alerts for the same patient at the same moment related to the same risk (e.g. several drug-drug and drug-disease interactions pointing out the risk of increased potassium levels). One integrated alert could potentially replace individual alerts, which would reduce the alert rate without changing the content of the recommendations presented to health care professionals.

In this study, we aim to investigate whether there are associations between the drug-drug interaction alerts and drug-disease interaction alerts that occur for a patient, and to what extent clustering of related drug interaction alerts that are concurrently generated would decrease the alert rate in CDSSs.

Methods

Setting

Dutch community pharmacies use CDSSs from a limited number of software suppliers. The pharmacy information system Pharmacom® (by TSS PharmaPartners®) is used by approximately 55% of Dutch community pharmacies. The electronic patient record in the system includes data on dispensed medications and coded chronic diseases. Prescriptions can be sent electronically from physician to pharmacy (for most general practitioners), or printed prescriptions can be used (for most other prescribers). Clinical decision support with drug therapy alerts, including drug-drug interactions and drug-disease interactions, is an integral part of the pharmacy information system. Alerts are generated during the processing of the prescription in the community pharmacy, before dispensing takes place. Identical drug interaction alerts are generated for first-time and repeat prescriptions. Every alert is displayed in a separate popup window with specific management recommendations. Background information on the alert and management recommendations is available on a website and in a reference book [27].

Pharmacists regularly contact prescribers about the management of drug interactions. The CDSS of Dutch general practitioners is similar to the pharmacists' CDSS and shared electronic patient records are quite common. For other prescribers, the availability of information is mostly different.

Data collection

Invitations to participate in this study were mailed to 250 randomly chosen pharmacies from the 1080 community pharmacies using the Pharmacom system (with a reminder after three weeks). Pharmacists had to authorize TSS PharmaPartners to extract anonymous patient data. For participating pharmacies, the following patient data were extracted over the period August 2012 to July 2014: basic patient characteristics (including coded chronic diseases), dispensed medications (including dispensing date, dose, dosing regimen), and all generated drug therapy alerts.

Data analysis

The data were analyzed using Microsoft Access and SPSS (version 20.0; SPSS Inc. Chicago, IL, USA). Two random samples of 5% of patients per pharmacy to whom at least one drug was dispensed in the period August 2013 to July 2014 were selected (dataset 1 and dataset 2). Dataset 1 was used to identify clusters of drug interaction alerts and to simulate generation of drug interaction alerts based on these clusters. The simulation of clustered generation of drug interaction alerts was replicated in dataset 2 to test for consistency of the results.

Cluster identification

Clusters were identified in five steps (Figure 1):

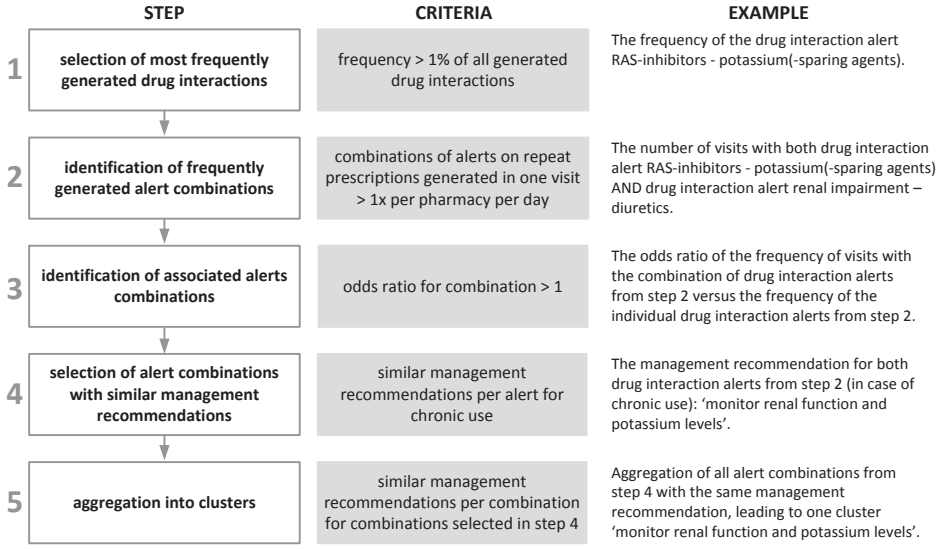


Figure 1: Steps of cluster identification

1. The most frequently generated drug interaction alerts were selected. A cutoff of 1% of the total number of generated drug interaction alerts was used.
2. For the alerts selected in step one, the most frequently generated combinations of alerts within a pharmacy visit were determined (i.e., combinations of alerts generated for prescriptions dispensed to the same patient on the same day in the same pharmacy). From this step on, first-time prescriptions were excluded from the analysis. The management recommendation texts for drug interactions differentiate between first-time prescriptions and repeat prescriptions. For example, when adding an angiotensin converting enzyme (ACE) inhibitor to a therapy with diuretics, the recommendation is to start with half the normal starting dose for three days, and to take the first dose just before bed time. But when both drugs are chronically used, the recommendation is to monitor renal function and potassium levels. Because of the very specific management recommendations on therapy start, the potential for clustering of alerts on first-time prescriptions is limited.
   All combinations of alerts on repeat prescriptions with an average frequency of at least once per day per pharmacy were selected.
3. Overrepresentation of the combinations of two alerts relative to the frequency of the individual alerts was determined, analogous to the reporting odds

ratios used in the analysis of spontaneous report databases [28]. Alert combinations with an odds ratio significantly above 1 were considered associated alert combinations (p-value < 0.05 was considered statistically significant). Steps 2 and 3 were repeated to identify whether the selected combinations of two alerts were associated with a third alert, etc.

4. For the associated alert combinations from step 3, the management recommendations were assessed for similarities. Combinations where all included alerts had similar management recommendations in case of chronic use were selected. For example, the drug-drug interaction renin-angiotensin system (RAS) inhibitors – potassium-sparing agents / potassium, and the drug-disease interaction renal impairment – diuretics are accompanied by a similar recommendation: monitor renal function and potassium levels.
5. All drug interaction alert combinations with similar management recommendations were combined into clusters. For example, when there were three combinations of drug interactions, all relating to potassium monitoring, all drug interaction alerts belonging to these combinations were aggregated into one cluster.

Simulation of clustered alert generation

Alert generation based on the identified clusters was simulated in both dataset 1 and 2. The frequency of the occurrence of alerts within a cluster was assessed by determining the frequency of alerts in any of the potential underlying alert combinations (e.g. in a cluster of four alerts, there are six possible combinations of two alerts, four combinations of three alerts and one combination of four alerts: all these combinations were part of the cluster). As in the identification of the clusters, first-time prescriptions were disregarded. The number of simulated clustered alerts was subtracted from the originally generated number of alerts to calculate the potential reduction of alerts. For example, in our original database there was a visit with three alerts: 1) RAS-inhibitors – diuretics; 2) renal impairment – diuretics; and 3) renal impairment – ACE-inhibitors. All alerts were part of the same cluster. In the simulation (the clustered alert generation), we counted one alert for this situation, compared to three alerts in the original situation.

Ethics and confidentiality

As this was a retrospective database analysis, the study was exempt from ethical review. To protect the privacy of patients and pharmacists, only anonymous data were extracted from the CDSS to prevent the identification of individual patients or pharmacies.

Results

Of the 250 invited pharmacies, 123 (49%) agreed to participate in the study. The two random samples of 5% included data of over 80,000 patients who received over 1.6 million prescriptions (Figure 2). The prescriptions generated nearly 0.6 million drug interaction alerts, corresponding to an average of 185 drug interaction alerts per pharmacy per day. Eight percent of these alerts were generated on first-time prescriptions. The top 10 dispensed drugs in our sample included the same drugs as the nationwide top 10 dispensed drugs in community pharmacies [29].

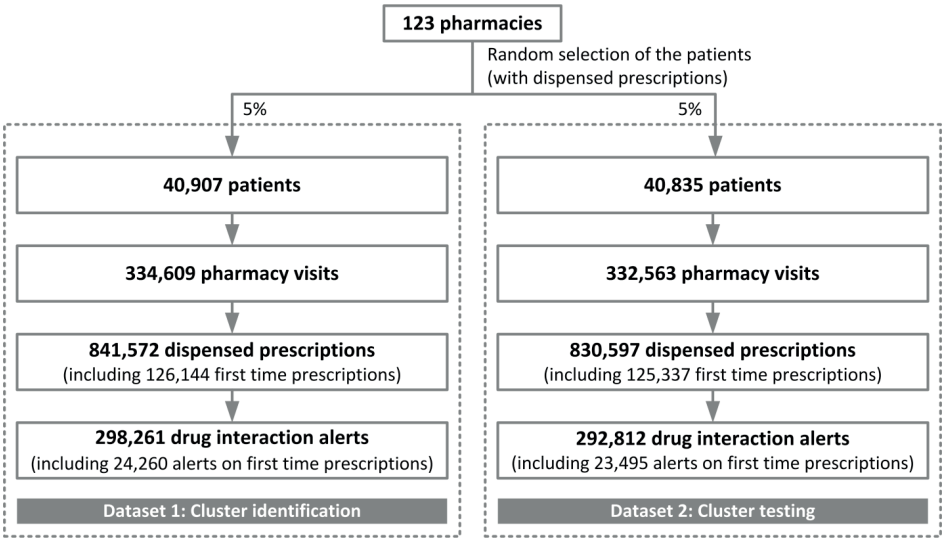


Figure 2: Dataset characteristics

Identified clusters

Dataset 1 contained 298,261 generated drug interaction alerts. Twenty-eight drug interactions had a frequency over 1% of all generated drug interaction alerts. This selection consisted of 16 drug-drug interactions and 12 drug-disease interactions (Table 1). These 28 drug interactions accounted for 59.5% of all generated drug interaction alerts.

Twenty-two combinations of alerts (20 combinations of two alerts and two combinations of three alerts) occurred at least once per pharmacy per day. All combinations were significantly associated: the combination of alerts was overrepresented relative to the frequency of the individual alerts (Appendix 1). Fourteen of these associated combinations had similar management recommendations (Appendix 1). Based on these management recommendations, three clusters of alerts were identified: monitoring of potassium levels and renal

function; monitoring of potassium levels and renal function plus monitoring of diabetes, and monitoring of blood pressure and/or heart failure (Table 2).

Table 1: Drug interaction alerts with a frequency >1% of all drug interaction alerts (n=298,261)[a]

drug interaction	type	% of drug interaction alerts
RAS-inhibitors - diuretics	drug-drug	7.6%
antidiabetics - beta-blocking agents	drug-drug	4.6%
diabetes - ACE-inhibitors	drug-disease	4.5%
obstructive pulmonary disease - beta-blocking agents	drug-disease	4.2%
renal impairment - diuretics	drug-disease	3.9%
NSAIDs - RAS-inhibitors	drug-drug	2.3%
RAS-inhibitors - potassium-sparing agents / potassium	drug-drug	2.3%
bisphosphonates - polyvalent cations	drug-drug	2.2%
vitamin K antagonists - (es)omeprazole	drug-drug	2.1%
renal impairment - ACE-inhibitors	drug-disease	2.1%
heart failure - beta-blocking agents	drug-disease	2.0%
beta-blocking agents - NSAIDs	drug-drug	1.9%
thyroid drugs - polyvalent cations	drug-drug	1.7%
salicylates (antithrombotic) - SRIs	drug-drug	1.6%
renal impairment - antidiabetics	drug-disease	1.5%
diabetes - thyroid drugs	drug-disease	1.5%
vitamin K antagonists - metformin	drug-drug	1.4%
digoxin - diuretics	drug-drug	1.4%
salicylates (antithrombotic) - NSAIDs	drug-drug	1.3%
SRIs - diuretics	drug-drug	1.3%
diabetes - SRIs	drug-disease	1.2%
P2Y12-inhibitors - salicylates (antithrombotic)	drug-drug	1.2%
corticosteroids - salicylates (antithrombotic)	drug-drug	1.1%
renal impairment - minerals	drug-disease	1.1%
diabetes - antipsychotics	drug-disease	1.1%
gout - diuretics	drug-disease	1.1%
ulcus pepticum - antithrombotic agents	drug-disease	1.0%
NSAIDs - SRIs	drug-drug	1.0%

ACE = angiotensin converting enzyme; NSAID = non-steroidal anti-inflammatory drug; RAS = renin-angiotensin system; SRI = serotonin reuptake inhibitor

[a] based on dataset 1

Table 2: Comparison of number of alerts for clustered generation of drug interaction alerts and the original CDSS.[a]

Cluster	Management recommendation (for repeat prescriptions)	Alerts in cluster		Number of alerts		Change in alert rate
				original CDSS	clustered alert generation	
Cluster A	Monitor renal function + potassium	RAS-inhibitors - diuretics RAS-inhibitors - potassium(-sparing diuretics) Renal impairment - diuretics Renal impairment - ACE-inhibitors	Dataset 1	13,694	4,920	**-64%**
			Dataset 2	14,014	5,151	**-63%**
Cluster B	Monitor renal function + potassium + diabetes	RAS-inhibitors - diuretics Renal impairment - diuretics Renal impairment - ACE-inhibitors Renal impairment - antidiabetics Diabetes - ACE-inhibitors Antidiabetics - beta-blocking agents	Dataset 1	30,999	9,369	**-70%**
			Dataset 2	31,918	9,484	**-70%**
Cluster C	Monitor blood pressure / heart failure[b]	NSAIDs - RAS-inhibitors Beta-blocking agents - NSAIDs	Dataset 1	4,077	1,866	**-54%**
			Dataset 2	5,226	2,463	**-53%**

ACE = angiotensin converting enzyme; CDSS = clinical decision support system; NSAID = non-steroidal anti-inflammatory drug; RAS = renin-angiotensin system

[a] first-time prescriptions excluded

[b] depending on the indication of the RAS-inhibitor and the beta-blocking agent.

Alert rates

The alert simulation using clusters resulted in reductions of 64%, 70%, and 54% respectively, for the alerts included in the three clusters compared to the original situation in dataset 1 (Table 2). Replication in dataset 2 showed comparable reductions. Clustered alert generation for these three clusters reduced the overall number of drug interaction alerts from 298,261 to 265,464 (-11%) in dataset 1 and from 292,812 to 258,752 in dataset 2 (-12%). This corresponds to a decrease of 21 drug interaction alerts per pharmacy per day.

Discussion

In this investigation, we identified three frequently occurring clusters of drug interaction alerts, consisting of eight drug interaction alerts. The use of these clusters in a CDSS simulation led to a decrease of over 50% for the alerts in the clusters. The overall drug interaction alert rate decreased by more than 10%, corresponding to a decrease of 21 alerts per pharmacy per day. The clusters were related to renal function, electrolytes, diabetes and cardiovascular diseases: common chronic conditions with extensive chronic drug use.

Several strategies to reduce alert fatigue have been investigated, most of them targeted at increased alert specificity [7-16]. The results of these strategies are diverse, ranging from limited success, to decreases in the alert rate ranging from 50% to 90% within specific subsets of alerts [7, 12, 15, 16]. All of those previous attempts to reduce the alert burden were different from our approach, as we focused on an overview of all alerts with the same management recommendations within one patient. In contrast to other strategies, our method does not focus on individual alerts or subsets, and therefore can be extended to all alerts without adaption or reassessment of individual alerts.

Our study shows that the concept of clustering of alerts has potential. Even when using only three clusters together consisting of only eight alerts, a reduction of more than 10% of the total drug interaction alert rate was realized. We see potential for extension of this strategy in four directions. First, more drug-drug interactions and drug-disease interactions could be incorporated in these three clusters. For example many other less frequently generated alerts advise to monitor renal function and potassium levels.

Second, new clusters can be created for other management recommendations. For example clusters on monitoring sodium levels or monitoring the international normalized ratio (INR).

Third, other alert types could also be included in the alert clustering. Lab-drug alerts, age-drug alerts, duplicate medication alerts and dosing alerts all are eligible candidates for clustered alerting.

Fourth, for alerts with similar management recommendations for first-time and repeat prescriptions, first-time prescriptions could be included in the clusters. For the purpose of consistency, this would be useful. The effect on alert rate would be limited, because alerts on first-time prescriptions concerned only 8% of the alerts.

More generally, this study suggests two new areas for CDSS improvement. The first one concerns a further extension of the concept of clustering. In our investigation, we started with selection of frequently generated drug interaction alerts (with one or more management recommendations each), and looked for the potential of combining the alerts of several drug interactions. For the health care professional, the recommendation is more important than the interaction itself. Therefore, we propose a reverse approach, realizing recommendation-based alerting: for every recommendation, rather than for every drug interaction, an alert is generated. This alert can be based on one or more drug interactions. This approach supports a patient-centered way to do clinical risk management instead of the current drug interaction-centered way. The need for an integrated approach is underlined by the fact that comorbidity clusters can be defined, and multimorbidity reduces the applicability of monodisciplinary guidelines [30-33].

The second area for improvement relates to the moment of alerting. In our study, it was noticed that alert timing was a recurrent aspect in the assessment of similarity of management recommendations. For example, the manage-ment recommendations of the clusters we identified, all advised (half-)yearly reassessment or monitoring. There is no need to generate these alerts for every repeat prescription, unless there is a change in the patient's health condition. In addition, some drug interactions are mainly relevant at the start of the therapy. Examples in our clusters are the drug-drug interaction between RAS-inhibitors and diuretics, and the drug-disease interaction between ACE-inhibitors and diabetes (recommending intensified blood glucose monitoring at the start) [27]. Generation of these alerts could be limited to first-time prescriptions. Therefore, the combination of specific alert timing and alert clustering could further reduce the alert rate.

This study simulated a clustered generation of drug interaction alerts and demonstrated the potential of clustered alert generation in one CDSS. The study has

several limitations. In our investigation we focused on all generated alerts, without assessing their clinical relevance. Obviously, it is also important to increase the specificity of alerts to reduce the number of irrelevant alerts. Therefore, alert clustering is a complementary strategy.

A second limitation is that our study is based on data from only one CDSS. In other settings other CDSSs will be used, leading to differences in the specific alerts that will be generated. However, a comparable pattern of overlapping management recommendations can be expected. We therefore believe our strategy can be applied to most CDSSs.

Lastly, the decrease in alert rate by clustered alert generation in clinical practice can be different from our simulation. We have not investigated how a clustered alert should be displayed, or how health care professionals would perceive clustered alerts. Therefore, the applicability of this concept still has to be proven. In future investigations, the design and the management of the alert are of major importance. It has been shown that the design of alerts affects their efficiency and results [21, 22]. A clustered alert is an alert with one recommendation, shown in one window, but based on more than one drug interaction. All drugs, diseases, and other risk factors related to the concerning recommendation should be concisely shown to enable the health care professional to make a proper judgement. Because of the combination of information in one window, paying special attention to the alert design is advised in order to prevent a data overload. Moreover, the actual management of clustered alerts should be investigated. With fewer alerts, there is less risk of confusion about several comparable alerts and overseeing one of them. However, there is a clear need to manage the single new alert correctly, and to judge its relevance properly. The effect of clustered alert generation on interventions by health care professionals must be established to rule out any unexpected results and to optimize the concept before implementing it in daily practice.

Conclusion

The use of three clusters of drug interactions with similar management recommendations in alert generation decreased the alert rate of the alerts in clusters by more than 50%. The overall alert rate for drug interactions was reduced by more than 10% (corresponding to a decrease of 21 drug interaction alerts per pharmacy per day). Extension of drug alert clustering can potentially further reduce the alert rate.

Acknowledgements

We thank all community pharmacists who participated in this study.

References

1. Kuperman GJ, Bobb A, Payne TH, Avery AJ, Gandhi TK, Burns G, et al. Medication-related clinical decision support in computerized provider order entry systems: a review. *J Am Med Inform Assoc* 2007;14:29-40.
2. Curtain C, Peterson GM. Review of computerized clinical decision support in community pharmacy. *J Clin Pharm Ther* 2014;39:343-8.
3. Ojeleye O, Avery A, Gupta V, Boyd M. The evidence for the effectiveness of safety alerts in electronic patient medication record systems at the point of pharmacy order entry: a systematic review. *BMC Med Inform Decis Mak* 2013;13:69.
4. Nanji KC, Slight SP, Seger DL, Cho I, Fiskio JM, Redden LM, et al. Overrides of medication-related clinical decision support alerts in outpatients. *J Am Med Inform Assoc* 2014;21:487-91.
5. Van der Sijs H, Mulder A, van Gelder T, Aarts J, Berg M, Vulto A. Drug safety alert generation and overriding in a large Dutch university medical centre. *Pharmacoepidemiol Drug Saf* 2009;18:941-7.
6. Isaac T, Weissman JS, Davis RB, Massagli M, Cyrulik A, Sands DZ, et al. Overrides of medication alerts in ambulatory care. *Arch Intern Med* 2009;169:305-11.
7. Eppenga WL, Derijks HJ, Conemans JM, Hermens WA, Wensing M, de Smet PAGM. Comparison of a basic and an advanced pharmacotherapy-related clinical decision support system in a hospital care setting in the Netherlands. *J Am Med Inform Assoc* 2012;19:66-71.
8. Phansalkar S, van der Sijs H, Tucker AD, Desai AA, Bell DS, Teich JM, et al. Drug-drug interactions that should be non-interruptive in order to reduce alert fatigue in electronic health records. *J Am Med Inform Assoc* 2013;20:489-93.
9. Kawazoe Y, Miyo K, Kurahashi I, Sakurai R, Ohe K. Prediction-based threshold for medication alert. *Stud Health Technol Inform* 2013;192:229-33.
10. Parke C, Santiago E, Zussy B, Klipa D. Reduction of clinical support warnings through recategorization of severity levels. *Am J Health Syst Pharm* 2015;72:144-8.
11. Van der Sijs H, Aarts J, van Gelder T, Berg M, Vulto A. Turning off frequently overridden drug alerts: limited opportunities for doing it safely. *J Am Med Inform Assoc* 2008;15:439-48.
12. Rommers MK, Teepe-Twiss IM, Guchelaar HJ. A computerized adverse drug event alerting system using clinical rules: a retrospective and prospective comparison with conventional medication surveillance in the Netherlands. *Drug Saf* 2011;34:233-42.
13. Duke JD, Li X, Dexter P. Adherence to drug-drug interaction alerts in high-risk patients: a trial of context-enhanced alerting. *J Am Med Inform Assoc* 2013;20:494-8.
14. Seidling HM, Klein U, Schaier M, Czock D, Theile D, Pruszydlo MG, et al. What, if all alerts were specific - Estimating the potential impact on drug interaction alert burden. *Int J Med Inform* 2014;83:285-91.
15. Czock D, Konias M, Seidling HM, Kaltschmidt J, Schwenger V, Zeier M, et al. Tailoring of alerts substantially reduces the alert burden in computerized clinical decision support for drugs that should be avoided in patients with renal disease. *J Am Med Inform Assoc* 2015;22:881-7.
16. Helmons PJ, Suijkerbuijk BO, Nannan Panday PV, Kosterink JG. Drug-drug interaction checking assisted by clinical decision support: a return on investment analysis. *J Am Med Inform Assoc* 2015;22:764-72.
17. Payne TH, Hines LE, Chan RC, Hartman S, Kapusnik-Uner J, Russ AL, et al. Recommendations to Improve the Usability of Drug-Drug Interaction Clinical Decision Support Alerts. *J Am Med Inform Assoc* 2015;22:1243-50.

18. Phansalkar S, Edworthy J, Hellier E, Seger DL, Schedlbauer A, Avery AJ, et al. A review of human factors principles for the design and implementation of medication safety alerts in clinical information systems. *J Am Med Inform Assoc* 2010;17:493-501.
19. Zachariah M, Phansalkar S, Seidling HM, Neri PM, Cresswell KM, Duke J, et al. Development and preliminary evidence for the validity of an instrument assessing implementation of human-factors principles in medication-related decision-support systems--I-MeDeSA. *J Am Med Inform Assoc* 2011;18 Suppl 1:i62-72.
20. Tamblyn R, Huang A, Taylor L, Kawasumi Y, Bartlett G, Grad R, et al. A randomized trial of the effectiveness of on-demand versus computer-triggered drug decision support in primary care. *J Am Med Inform Assoc* 2008;15:430-8.
21. Russ AL, Chen S, Melton BL, Johnson EG, Spina JR, Weiner M, et al. A Novel Design for Drug-Drug Interaction Alerts Improves Prescribing Efficiency. *Jt Comm J Qual Patient Saf* 2015;41:396-405.
22. Melton BL, Zillich AJ, Russell SA, Weiner M, McManus MS, Spina JR, et al. Reducing prescribing errors through creatinine clearance alert redesign. *Am J Med* 2015;128:1117-25.
23. Bryant AD, Fletcher GS, Payne TH. Drug interaction alert override rates in the meaningful use era: no evidence of progress. *Appl Clin Inform* 2014;5:802-13.
24. Heringa M, Floor-Schreudering A, Tromp PC, De Smet PA, Bouvy ML. Nature and frequency of drug therapy alerts generated by clinical decision support in community pharmacy. *Pharmacoepidemiol Drug Saf* 2016;25:82-9.
25. Buurma H, De Smet PAGM, Egberts AC. Clinical risk management in Dutch community pharmacies: the case of drug-drug interactions. *Drug Saf* 2006;29:723-32.
26. Zwart-van Rijkom JE, Uijtendaal EV, ten Berg MJ, van Solinge WW, Egberts AC. Frequency and nature of drug-drug interactions in a Dutch university hospital. *Br J Clin Pharmacol* 2009;68:187-93.
27. Borgsteede SD, ed. Commentaren Medicatiebewaking 2015-2016 (Commentaries medication surveillance). Houten, The Netherlands: Health Base Foundation 2015.
28. Van Puijenbroek E, Diemont W, van Grootheest K. Application of quantitative signal detection in the Dutch spontaneous reporting system for adverse drug reactions. *Drug Saf* 2003;26:293-301.
29. Dutch Foundation for Pharmaceutical Statistics (Stichting Farmaceutische Kengetallen, SFK). Facts and Figures 2013 (Data en Feiten 2013). 2013, The Hague, The Netherlands.
30. Vanfleteren LE, Spruit MA, Groenen M, Gaffron S, van Empel VP, Bruijnzeel PL, et al. Clusters of comorbidities based on validated objective measurements and systemic inflammation in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2013;187:728-35.
31. Tinetti ME, McAvay G, Trentalange M, Cohen AB, Allore HG. Association between guideline recommended drugs and death in older adults with multiple chronic conditions: population based cohort study. *BMJ* 2015;351:h4984.
32. Dumbreck S, Flynn A, Nairn M, Wilson M, Treweek S, Mercer SW, et al. Drug-disease and drug-drug interactions: systematic examination of recommendations in 12 UK national clinical guidelines. *BMJ* 2015;350:h949.
33. Hughes LD, McMurdo ME, Guthrie B. Guidelines for people not for diseases: the challenges of applying UK clinical guidelines to people with multimorbidity. *Age Ageing* 2013;42:62-9.

Appendix 1: Frequently generated alert combinations[a]

Alert 1	Alert 2	Alert 3	Frequency[b]	OR (95% CI)	Management recommendation: monitor:			
					renal function + potassium	renal function + potassium + diabetes	blood pressure / heart failure	no similarity
RAS-inhibitors – diuretics	diabetes – ACE-inhibitors	-	5121	18.9 (18.2 - 19.7)		X		
RAS-inhibitors – diuretics	renal impairment – diuretics	-	5083	23.7 (22.6 - 24.7)	X			
RAS-inhibitors – diuretics	RAS-inhibitors – potassium (-sparing agents)	-	3924	44.4 (41.8 - 47.2)	X			
RAS-inhibitors – diuretics	renal impairment – ACE-inhibitors	-	3483	25.3 (23.9 - 26.7)	X			
renal impairment – diuretics	renal impairment – ACE-inhibitors	-	3337	72.1 (68.1 - 76.4)	X			
RAS-inhibitors – diuretics	obstructive pulmonary disease – beta-blocking agents	-	3033	9.1 (8.7 - 9.6)				X
RAS-inhibitors – diuretics	antidiabetics – beta-blocking agents	-	2751	7.5 (7.2 - 7.9)		X		
antidiabetics – beta-blocking agents	diabetes – ACE-inhibitors	-	2716	18.7 (17.8 - 19.7)		X		
RAS-inhibitors – diuretics	heart failure – beta-blocking agents	-	2671	15.5 (14.7 - 16.4)				X
diabetes – ACE-inhibitors	renal impairment – ACE-inhibitors	-	2327	26.3 (24.9 - 27.9)		X		
renal impairment – diuretics	heart failure – beta-blocking agents	-	2291	32.9 (31.0 - 34.8)				X
renal impairment – diuretics	renal impairment – minerals	-	2049	81.2 (75.3 - 87.7)				X

Appendix 1: Frequently generated alert combinations[a] (*continued*)

Alert 1	Alert 2	Alert 3	Frequency[b]	OR (95% CI)	Management recommendation: monitor:			
					renal function + potassium	renal function + potassium + diabetes	blood pressure / heart failure	no similarity
obstructive pulmonary disease – beta-blocking agents	heart failure – beta-blocking agents	-	2009	27.6 (26.0 - 29.3)				X
RAS-inhibitors – diuretics	digoxin – diuretics	-	1992	18.8 (17.6 - 20.1)				X
RAS-inhibitors – diuretics	vitamin K antagonists – (es) omeprazole	-	1873	7.6 (7.2 - 8.1)				X
NSAIDs – RAS-inhibitors	beta-blocking agents – NSAIDs	-	1866	72.5 (67.7 - 77.7)			X	
renal impairment – diuretics	renal impairment – antidiabetics	-	1857	44.6 (41.7 - 47.8)		X		
RAS-inhibitors – potassium (-sparing agents)	renal impairment – diuretics	-	1667	18.5 (17.4 - 19.7)	X			
RAS-inhibitors – diuretics	gout – diuretics	-	1650	21.0 (19.5 - 22.6)				X
diabetes – ACE-inhibitors	renal impairment – diuretics	-	1619	7.8 (7.4 - 8.3)		X		
RAS-inhibitors – diuretics	renal impairment – diuretics	renal impairment – ACE-inhibitors	3192	204.3 (190.8 - 218.8)	X			
RAS-inhibitors – diuretics	diabetes – ACE-inhibitors	renal impairment – ACE-inhibitors	1686	38.0 (35.5 - 40.5)		X		

ACE = angiotensin converting enzyme; NSAID = non-steroidal anti-inflammatory drug; OR = odds ratio; RAS = renin-angiotensin system; SRI = serotonin reuptake inhibitor; 95% CI = 95% confidence interval;

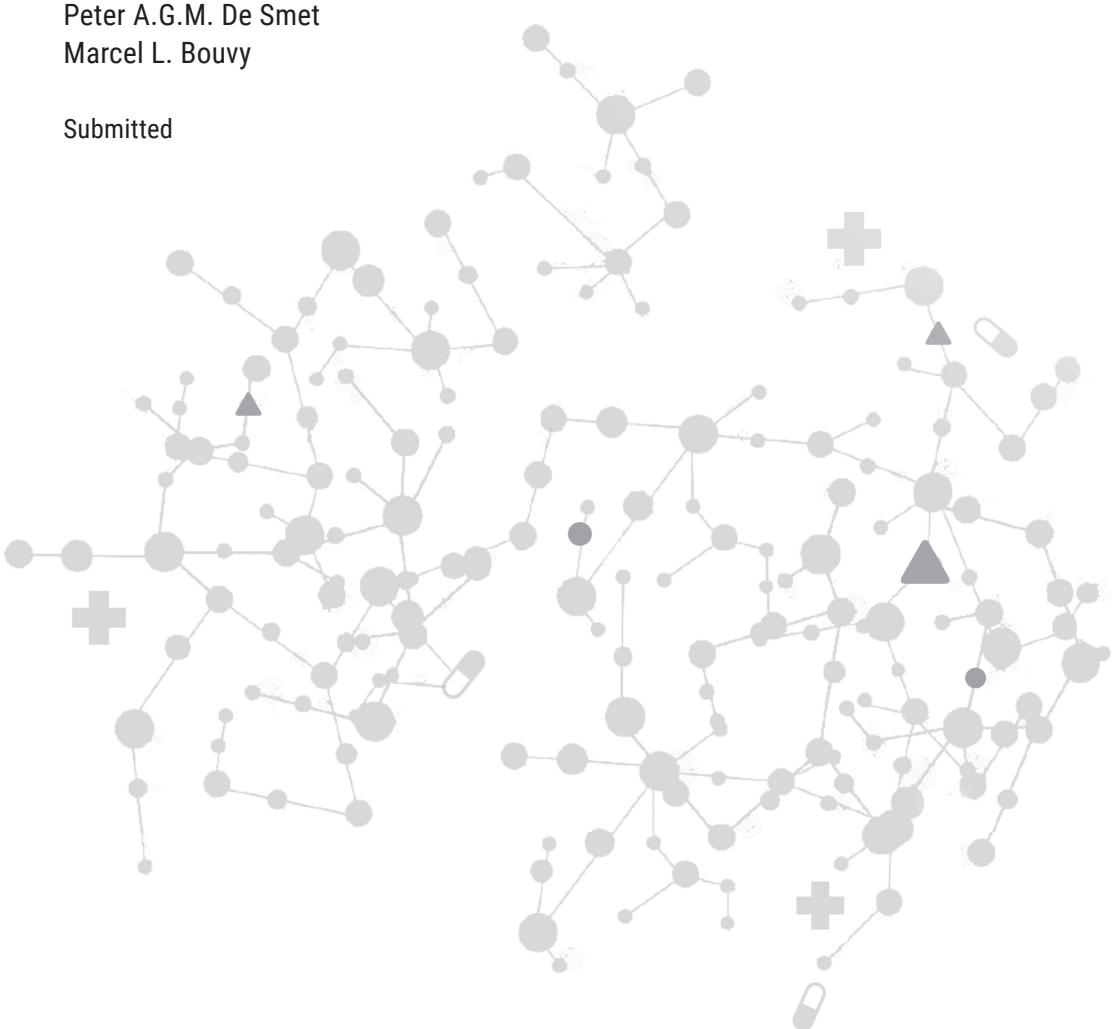
[a] Based on dataset 1; [b] An alert frequency of over 1600 alerts in this 5% data sample corresponds to an average frequency of at least once per day per pharmacy

Chapter 3.3

Better specification of triggers to reduce the number of drug interaction alerts in primary care

Mette Heringa
Annet van der Heide
Annemieke Floor-Schreudering
Peter A.G.M. De Smet
Marcel L. Bouvy

Submitted



Abstract

Objective

Drug interaction alerts (drug-drug and drug-disease interaction alerts) for chronic medications substantially contribute to alert fatigue in primary care. The aim of this study was to determine which events require (re)assessment of a drug interaction and whether using these events as triggers in clinical decision support systems (CDSSs) would affect the alert rate.

Methods

Two random 5% data samples from the CDSSs of 123 community pharmacies were used: dataset 1 and 2. The top 10 of most frequent drug interaction alerts not involving laboratory values were selected. To reach consensus on events that should trigger alerts (e.g. first time dispensing, dose modification) for these drug interactions, a two-step consensus process was used. An expert panel of community pharmacists participated in an online survey and a subsequent consensus meeting. A CDSS with alerts based on the consensus was simulated in both datasets.

Results

Dataset 1 and 2 together contained 1,672,169 prescriptions which led to 591,073 alerts. Consensus on events requiring alerts was reached for the ten selected drug interactions. The simulation showed a reduction of the alert rate of 93.0% for the ten selected drug interactions (comparable for dataset 1 and 2), corresponding with a 28.3% decrease of the overall drug interaction alert rate.

Discussion and Conclusion

By consensus-based better specification of the events that trigger drug interaction alerts in primary care, the alert rate for these drug interactions was reduced by over 90%. This promising approach deserves further investigation to assess its consequences and applicability in daily practice.

Introduction

The detection and management of drug therapy related problems is important to prevent medication errors. Clinical decision support systems (CDSSs) are widely used to detect drug-drug interactions and drug-disease interactions (hereafter referred to as drug interactions) [1-3]. However, in daily clinical practice most alerts generated by CDSSs do not lead to an intervention: the specificity of alerts is low [4-7].

Up to now, one of the main strategies to improve the specificity of alerts has been the use of advanced clinical decision rules: the incorporation of more clinical characteristics (like renal function and potassium levels) in the algorithms generating alerts or not [7-12]. The results from these advanced clinical decision rules range from limited effect to a 90% decrease in the alert rate for a specific subset of alerts [7, 9, 11, 12].

Most research into advanced clinical decision support has been performed in hospitals, where – unlike in the community – recent clinical values are generally readily available [7, 11-15]. Differences between hospitals and primary care can have an important effect on the potential of CDSS improvement strategies. In primary care, the majority of the prescriptions concern chronic medications [16, 17]. First time prescriptions and repeat prescriptions often trigger the same alerts. However, many drug interactions are mainly relevant at or immediately after the start of therapy [18-20]. In one study, first drug-drug interaction alerts were eight times more likely to be followed by an action compared with recurrent alerts [21]. Moreover, recurrent alerts have been shown to contribute substantially to alert fatigue in primary care [22]. So, for chronic medications, the need for an alert may be different between first time prescriptions and repeat prescriptions. Another difference with hospitals is that in primary care patients are not continuously monitored, and they are responsible for drug administration themselves. Therefore, health care professionals need to instruct the patients on correct drug use and monitoring. To evaluate whether the patient has understood the advice on a drug interaction and acts accordingly, follow up is needed, which can be supported by CDSS alerts.

It can be suboptimal when every repeat prescription without distinction triggers alerts. Alerts should only be triggered in situations requiring (re)assessment of the drug interaction by a health care professional. When it is possible to better specify events indicating this situation (e.g. a change of daily dose) per drug interaction, these events could serve as triggers for alert generation in CDSSs.

The objective of this study was to determine which events require (re)assessment of a drug interaction and whether using these events as triggers in CDSSs would affect the drug interaction alert rate.

Methods

Setting

In the Netherlands, over 50% of the community pharmacies use the same pharmacy information system (Pharmacom® by TSS PharmaPartners®) that includes clinical decision support. The system's electronic patient record contains a dispensing history and coded chronic diseases. During processing of prescriptions, the system generates drug therapy alerts, including drug-drug interaction alerts and drug-disease interaction alerts. First time prescriptions and repeat (renewal) prescriptions trigger identical alerts. Drug interaction alerts are based on the drug information database of the Health Base Foundation [18]; specific manage-ment recommendations and background information are available in the system. Identical alerts are generated for regular dispensing (for chronic medications: renewal of prescription every three months) and for multi-dose drug dispensing (generally repeated on a weekly basis) [23]. Pharmacists can suppress an alert manually for a specific patient for a specified period; suppression is lifted in case of changes in the registered patient information, e.g. change of dose, or refill non-adherence.

Dataset

250 randomly chosen pharmacies from 1,080 community pharmacies using the Pharmacom system were asked to provide anonymized patient data over the period August 2012 to July 2014 [16, 17]. Extracted data included patient characteristics (age, gender, coded chronic diseases), dispensed medications (including dispensing date, dose, dosing regimen, multi-dose drug dispensing), and all generated drug therapy alerts. The data were analyzed using Microsoft Access 2010 and SPSS (version 23.0; SPSS Inc. Chicago, IL). Two random non-overlapping samples of 5% of patients per pharmacy to whom at least one drug was dispensed in the period August 2013 to July 2014 were selected (dataset 1 and dataset 2). The dispensing history over the period August 2012 to July 2013 was used to determine first time dispensing and second time dispensing, first time dispensing being defined as the dispensing of a drug which has not been

dispensed to the patient in the preceding 12 months, and second time dispensing as the first dispensing thereafter.

Study design

The investigation consisted of three main steps (Figure 1):

1. Selection of drug interactions

1a) In dataset 1, drug interaction alerts were listed by frequency. For this listing only, alerts generated for first time prescriptions were excluded to select drug interactions with repeat alerts.

1b) Starting from the most frequently generated alerts, drug interactions were excluded when the management guidelines advised monitoring of laboratory values or blood pressure (Appendix 1) [18, 19]. For these drug interactions, laboratory values should be incorporated in alert generation in addition to the triggers included in this investigation, but availability of laboratory values is not yet commonplace in every community pharmacy [14, 15]. The top 10 of remaining alerts were selected.

2. Two-step consensus process on events requiring an alert

2a) For the selected drug interactions, the management recommendations including background information were examined for information on situations which require (re)assessment of a drug interaction [18-20]. Based on this information, a proposal on events which should serve as alert triggers was drafted. Potential triggers considered for all drug interactions were first dispensing leading to alert, the second dispensing leading to alert, further dispensing of repeat prescriptions, change of daily dose, change of dosing frequency, discontinuation, refill non-adherence (generating an alert when the patient visits the pharmacy later than expected for a refill, based on the registered daily use - a proxy for non-compliance or intermittent use), and the first dispensing one year after the first alert. Additional triggers were considered depending on the nature of the drug interaction (e.g. new co-medication or new co-morbidity).

2b) An expert panel was set up for conducting a two-step consensus development process consisting of an online survey and a subsequent meeting [24, 25]. The aim was to reach consensus on events which require drug interaction (re) assessment, and which therefore should serve as triggers for alert generation, without compromising patient safety.

The ten expert panel members were recruited from the advisory committees from the Health Base Foundation, which consist of practicing community pharmacists who regularly advise on the content of the drug safety alerts and patient counseling information.

2c) The online survey was designed using NETQ (Survalyzer, Utrecht, The Netherlands). For all ten selected alerts, the proposal on triggers from step 2a was presented. The expert panel members were asked to agree or disagree; in the latter case they could suggest alternative events. In addition they were asked to suggest special situations that may need different alert triggers.

2d) A two hour consensus meeting was held with the expert panel and attended by the researchers (AH, MH and MB). The results of the survey were used as input for the discussion, aiming to reach consensus on events that should trigger alerts. Agreement by two third of the panel members was set as threshold for consensus. When for an event no consensus was reached, the event was included as a trigger, to be on the safe side. After the consensus meeting, a report with the results was sent to the expert panel members for information purposes only.

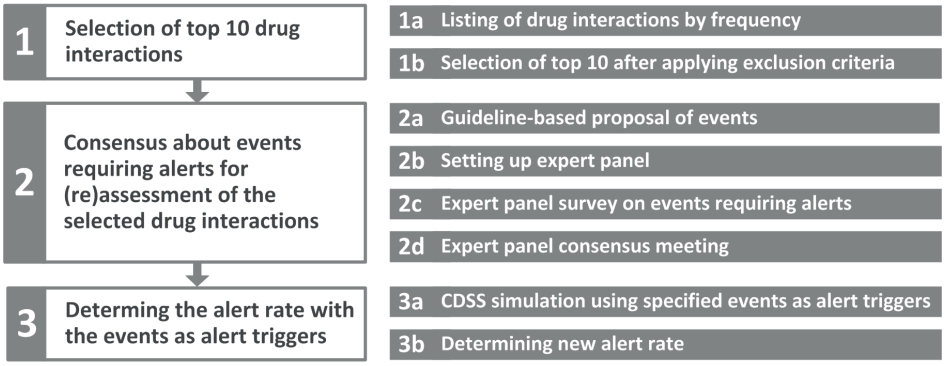
3. Determining the alert rate with the events as triggers

3a) To identify the impact of the consensus on the alert rate, a CDSS using the specified events as alert triggers was simulated. It was assessed which of the original alerts in the current CDSS did match one of the events defined in the consensus meeting (e.g. second time dispensing, change of daily dose). The simulation was performed in dataset 1 and replicated in dataset 2 to check for consistency. The simulation was performed separately on multi-dose drug dispensing and regular dispensing.

3b) The number of alerts generated by the simulation was subtracted from the original number of alerts to calculate the potential reduction of alerts, both in dataset 1 and 2. For the simulated situation, the contribution of each individual trigger (e.g. first time dispensing, change of daily dose) to the total number of alerts was determined.

Ethics and confidentiality

As this was a retrospective database analysis, the study was exempt of ethical review. To protect the privacy of patients and pharmacists, the data extracted from the pharmacy information system were anonymous. Data could not be used to trace individual patients or pharmacies.



CDSS = clinical decision support system

Figure 1: Research steps

Results

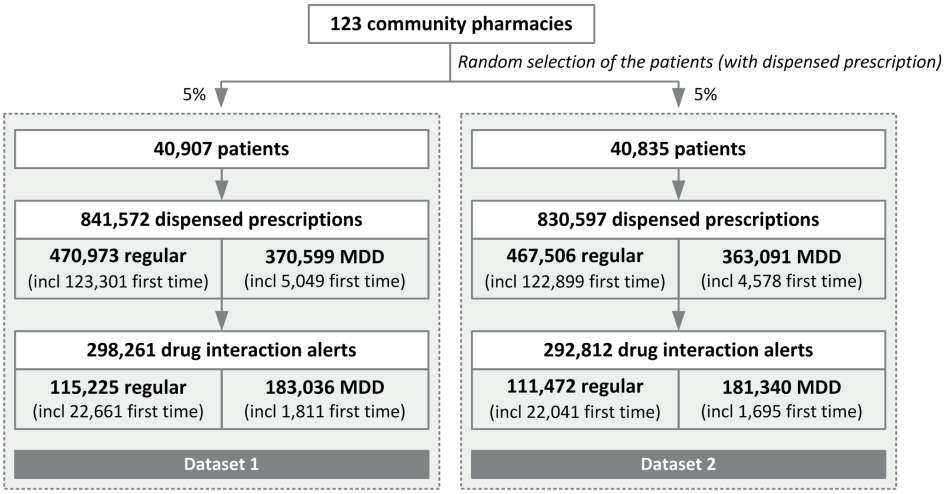
Data were extracted from the CDSS of 123 community pharmacies. Dataset 1 and 2 together contained 1,672,169 prescriptions leading to 591,073 drug interactions alerts (Figure 2), corresponding to an average of 185 drug interaction alerts per pharmacy per day.

Multi-dose drug dispensing accounted for 43.9% of the prescriptions and for 61.6% of the drug interaction alerts. First time prescriptions accounted for 15.3% of the prescriptions and for 8.2% of the alerts. The top 10 of selected alerts - after application of exclusion criteria - accounted for 31.9% of the drug interaction alerts for repeat prescriptions (Table 1).

In the survey, consensus was reached on the majority of proposed triggers; however, additional suggestions were made. Seven pharmacists attended the consensus meeting. In the meeting, consensus was reached for all triggers but one (Table 2). For 'Obstructive pulmonary disease – beta-blocking agents' no consensus was reached on the need for a reassessment alert at second time dispensing.

The reduction in alert rate for the ten selected drug interactions when comparing the simulation with the original CDSS was 93.0% in dataset 1 and 93.1% in dataset 2. Because of the high consistency of results in dataset 1 and dataset 2 (Appendix 2), combined results are presented in Table 3. For regular dispensing, the reduction in alert rate was 81.5%, ranging from 67.5% to 96.4% for the individual drug interactions. The alert rate reduction for multi-dose drug dispensing was 98.4% (range 96.7% to 99.3%). By changing the alert generation for ten selected drug

interactions, the overall alert rate for all drug-drug and drug-disease interactions was decreased by 28.3%.



MDD = multi-dose drug dispensing

Figure 2: Dataset characteristics

In the simulated situation, 'refill non-adherence' was the most common trigger for alerts (31.5% of the alerts). First and second time dispensing accounted for respectively 27.8% and 14.8% of the alerts, and the alert one year after first dispensing contributed for 16.2%. The other triggers – together accounting for 9.6% of the alerts - were of minor importance.

Table 1: Characteristics of selected drug interactions

Drug interaction	% of alerts[a]	Management recommendation [18]
RAS-inhibitors – diuretics[b]	8.0	When starting RAS-inhibitor: start low, go slow. Instruct patient to take RAS-inhibitor at bed time, sitting on the bed.
Diabetes – ACE-inhibitors	4.7	Instruct patient to monitor and report symptoms of hypoglycemia and (for patients with blood glucose meter) to monitor blood glucose more frequently during first days of use.
Obstructive pulmonary disease – beta-blocking agents	4.4	Instruct patient to monitor symptoms of obstructive pulmonary disease.
Antidiabetics – beta-blocking agents	4.2	Inform patient that symptoms of hypoglycemia may be less prominent.
Bisphosphonates – polyvalent cations	2.3	Instruct patient to take separately.
Heart failure – beta-blocking agents	2.1	Start low; instruct patient to monitor symptoms of edema.
Thyroid drugs – polyvalent cations	1.7	Instruct patient to take separately.
Salicylates (antithrombotic) – SRIs	1.7	Consider gastro-intestinal protection (unless patient is under 60 years or between 60-70 without peptic ulcer in anamnesis), and instruct patient on its use.
Diabetes – thyroid drugs	1.6	Instruct patient to monitor and report symptoms of hypo-/ hyperglycemia and (for patients with blood glucose meter) to monitor blood glucose more frequently during first days of use.
Diabetes – SRIs	1.3	Instruct patient to monitor and report symptoms of hypoglycemia and (for patients with blood glucose meter) to monitor blood glucose more frequently during first days of use.

ACE = angiotensin converting enzyme; RAS = renin-angiotensin system; SRI = serotonin reuptake inhibitor
[a]Percentage of the total number of drug interaction alerts in dataset 1; first time dispensing excluded; [b]Alert only generated for dispensing of RAS-inhibitor

Table 2: Consensus on events requiring alerts for drug interaction (re)assessment

Drug interaction	Event							Additional events	Each dispensing
	First dispensing leading to alert	Second dispensing leading to alert	One year after first alert	Change of daily dose	Change of dosing frequency	Discontinuation	Refill non-adherence		
RAS-inhibitors – diuretics	+[a]	-	-	-	-	-	+[a]	-	-
Diabetes – ACE-inhibitors	+	+	-	+	-	+	+	-	-
Obstructive pulmonary disease – beta-blocking agents	+	#	+	+	-	-	-	-	-
Antidiabetics – beta-blocking agents	+	+	+	+[d,e]	-	-	+	-	-
Bisphosphonates – polyvalent cations	+	+	-	+[c]	+[c]	-	-	-	-
Heart failure – beta-blocking agents	+	+	-	+[d]	-	-	+	Dose modification loop diuretic[b]	-
Thyroid drugs – polyvalent cations	+	+	-	+[c]	+[c]	-	-	-	-
Salicylates (antithrombotic) – SRIs	According to guideline [18]: no alert for patients under 60 years and for patients between 60-70 without peptic ulcer in anamnesis; no alert when gastric protection is already in use (based on dispensing history). In all other cases: alert with each dispensing. Moreover, alert in case of refill non-adherence of the proton pump inhibitor								+
Diabetes – thyroid drugs	+	+	-	+	-	+	+	-	-
Diabetes – SRIs	+	+	-	+	-	+	+	-	-

ACE = angiotensin converting enzyme; RAS = renin-angiotensin system; SRI = serotonin reuptake inhibitor

[a] for RAS-inhibitor only; [b] proxy for instable heart failure; [c] for polyvalent cation only; [d] dose increase only; [e] for beta-blocking agent only

no consensus reached

Table 3: Number of alerts for the consensus-based simulation compared with the original CDSS

Drug interaction	Regular dispensing			Multi-dose drug dispensing			Overall		
	Number of alerts		Change in alert rate	Number of alerts		Change in alert rate	Number of alerts		Change in alert rate
	Original CDSS	Simulation		Original CDSS	Simulation		Original CDSS	Simulation	
RAS-inhibitors – diuretics	14,379	2,345	- 83.7%	30,420	210	- 99.3%	44,799	2,555	- 94.3%
Diabetes – ACE-inhibitors	8,480	1,706	- 79.9%	17,998	249	- 98.6%	26,478	1,955	- 92.6%
Obstructive pulmonary disease – beta-blocking agents	7,783	2,011	- 74.2%	16,607	373	- 97.8%	24,390	2,384	- 90.2%
Antidiabetics – beta-blocking agents	8,787	1,631	- 81.4%	14,481	322	- 97.8%	23,268	1,953	- 91.6%
Bisphosphonates – polyvalent cations	5,030	693	- 86.2%	9,251	112	- 98.8%	14,281	805	- 94.4%
Heart failure – beta-blocking agents	1,838	598	- 67.5%	9,125	297	- 96.7%	10,963	895	- 91.8%
Thyroid drugs – polyvalent cations	3,368	466	- 86.2%	5,973	39	- 99.3%	9,341	505	- 94.6%
Salicylates (antithrombotic) – SRIs	2,956	106	- 96.4%	7,586	158	- 97.9%	10,542	264	- 97.5%
Diabetes – thyroid drugs	2,584	587	- 77.3%	6,041	85	- 98.6%	8,625	672	- 92.2%
Diabetes – SRIs	1,969	455	- 76.9%	4,844	71	- 98.5%	6,813	526	- 92.3%
TOTAL	**57,174**	**10,598**	**- 81.5%**	**122,326**	**1,916**	**- 98.4%**	**179,500**	**12,514**	**- 93.0%**

ACE = angiotensin converting enzyme; CDSS = clinical decision support system; RAS = renin-angiotensin system; SRI = serotonin reuptake inhibitor

Discussion

This study showed broad consensus of pharmacists on the events that should trigger alerts for ten common drug interactions. The simulation in a CDSS based on this consensus resulted in a 93% lower alert rate compared with the original CDSS for the ten concerning drug interactions. By reducing the alert rate for this selection only, the overall alert rate for drug interactions was decreased by nearly 30%, corresponding to a reduction of 52 drug interaction alerts per pharmacy per day.

The reduction was most pronounced for multi-dose drug dispensing (98.4%), which can be explained by the high – weekly - dispensing frequency, leading to recurrent alerts in an otherwise unchanged situation. Although the result for multi-dose drug dispensing contributed to the huge overall effect, the data showed also a high reduction of the alert rate for regular (mostly three monthly) dispensing (81.5%). The effect seen in our investigation can be understood from the chronic nature of the therapies involved in the drug interactions that were investigated. For example, when a patient has been instructed on the drug-drug interaction between renin-angiotensin system (RAS) inhibitors and diuretics (precautions during first days of use of the RAS-inhibitor, see Table 1), the patient can continue combined use without the need for further instructions.

The study showed that triggering alerts by very specific events rather than by every repeat prescription was an effective approach to reduce the alert rate. The decrease in alert rate was in the upper range compared with other CDSS improvement strategies [7, 8, 11, 12]. An advantage of our approach is the potential for extension to other drug interaction alerts. Based on existing recommendations on drug interaction management, the expert panel relatively easily reached consensus on events that should or should not trigger alerts. Moreover, the consensus suggests that the events can almost completely be derived from the general characteristics of the drug interaction, like the nature, moment of onset and duration of the drug interaction effect. For example: the reached consensus for the drug-drug interaction ‘bisphosphonates - polyvalent cations’ is applicable to all drug interactions involving complex formation that should be managed by separation of dosing moments. This potential generalizability can facilitate extension to other drug interactions.

For the implementation of the investigated strategy in CDSSs in daily practice, some prerequisites can be defined. Firstly, for optimal support of the health care professional, the CDSS should provide specific management recommendations for every event that triggers an alert. For example: the management recom-

mendation at first dispensing should guide the instruction on monitoring, while the recommendation for the same drug interaction at second time dispensing should guide evaluation of the interaction effect. However, better specification of management recommendations should not result in a one-size-fits-all protocol without taking into account the situation and preferences of an individual patient. Secondly, even in case of better specification of alert triggers, a CDSS should still offer the possibility to manually overrule the settings. Depending on the individual patient, the need for an alert can be different. For example, when it turns out at second dispensing that a patient has not understood the instructions given at first dispensing, a follow-up at third dispensing can be needed. CDSS alerts are a tool to detect drug therapy related problems, but cannot replace an individualized assessment by the health care professional. Thirdly, when a CDSS uses narrowed down events as alert triggers, these events must be registered on a structural basis. A complete and up-to-date electronic patient record including medication use and chronic conditions is needed [26]. Fourthly, implementation of these triggers should not hamper the performance of the CDSS. In current Dutch CDSSs this technical prerequisite is met.

By combining our findings with investigations on advanced clinical decision support in hospitals [7, 11, 27], a general strategy for CDSS improvement emerges. Alerts are only needed when there is a change in the patient's situation, which requires (re)assessment of the drug interaction by a health care professional. Events related to dispensing, for example first time dispensing, can be important triggers indicating a change in the patient's situation. The same holds for events like the registration of a new laboratory value or condition (e.g. to evaluate a patients' medication in case of pregnancy). It is unlikely that repeat prescriptions in an unchanged situation are useful triggers. Not all situations which require an alert for (re)assessment of the drug interaction are directly related to an event like registration of diseases, laboratory values or medications. Actually, sometimes the need for reassessment of a drug interaction is driven by the absence of an event – e.g. when a patient does not show up for a medication refill or for laboratory testing. Or by a change in external circumstances (e.g., a heat wave). Moreover, alerts in primary care should support counseling and follow-up on drug interaction alerts, because patients are not continuously monitored, and patients are responsible for correct drug administration themselves. Research has shown that the most frequent external action performed by community pharmacists in case of a drug-drug interaction alert is communication with the patient (78% of all external actions) [21]. In our investigation, second time dispensing and the evaluation alert after one year accounted for one-third of

the alerts. The expert panel incorporated these moments because of the need to evaluate whether the patient has experienced any interaction effect, and whether the patient needs further counseling on the drug interaction. Using standardized, consensus-based events like second time dispensing as trigger to evaluate a drug interaction alert is a first step. Further tailoring these alerts based on patients' (information) needs is an interesting future perspective.

Our study has several limitations. Firstly, we used an expert panel to determine the events requiring an alert. Another group of experts could have reached different conclusions. However, the expert panel consisted of practicing community pharmacists who were experienced in advising on CDSSs and patient counseling. Secondly, in the original CDSS where our data came from, pharmacists had the possibility to manually suppress alerts for a specific patient and period. Suppressed alerts, however, were included in the database. Pharmacists who already actively used the possibility of suppression will experience less reduction in alert rate by using better specified triggers, but they still have the advantage of a reduced need for time-consuming and error-prone manual suppression of alerts. For every pharmacy and every CDSS the exact reduction of the alert rate will be different. However, the principle of specific triggering alerts can be favorable for nearly every setting, with the highest impact in case of a high dispensing frequency. Thirdly, our study was a simulation, and real world effects can be different. Further research is needed to assure that no relevant alerts are missed when alerts are only triggered by the specified events. There is a risk that a few of the alerts which are no longer generated, would have led to intervention in current practice. This risk should be weighed against the current risk of overseeing alerts because of alert fatigue. It should also be taken into account that it is possible that recurrent alerts in current daily practice sometimes serve as a safety net for issues which are insufficiently covered otherwise. Therefore, a thorough investigation in daily practice is needed to rule out any unexpected consequences affecting patient safety. Fourthly, we investigated only a subset of 10 frequent drug interactions, which included mainly drugs that can be combined but only with appropriate counseling or monitoring. This type of advice is especially relevant in primary care, where patients are not subject of continuous monitoring such as in hospital. Because of the nature of the investigated drug interactions, most – but not all - of the consensus-based triggers were related to dispensing. With other drug interactions, other triggers can be expected to be relevant. However, by focusing on the most frequent drug interactions, we were able to show the potential of the proposed approach in primary care.

Conclusion

Events that should trigger drug interaction alerts in primary care can be more specific. A simulation of consensus-based specific triggers reduced the alert rate for the concerning drug interactions by over 90%. This promising approach to reduce the alert load deserves further investigation to assess its consequences and applicability in daily practice.

Ackowledgements

We thank the expert panel and all community pharmacists who participated in this study.

References

1. Kuperman GJ, Bobb A, Payne TH, Avery AJ, Gandhi TK, Burns G, et al. Medication-related clinical decision support in computerized provider order entry systems: a review. *J Am Med Inform Assoc* 2007;14:29-40.
2. Curtain C, Peterson GM. Review of computerized clinical decision support in community pharmacy. *J Clin Pharm Ther* 2014;39:343-8.
3. Ojeleye O, Avery A, Gupta V, Boyd M. The evidence for the effectiveness of safety alerts in electronic patient medication record systems at the point of pharmacy order entry: a systematic review. *BMC Med Inform Decis Mak* 2013;13:69.
4. Nanji KC, Slight SP, Seger DL, Cho I, Fiskio JM, Redden LM, et al. Overrides of medication-related clinical decision support alerts in outpatients. *J Am Med Inform Assoc* 2014;21:487-91.
5. Van der Sijs H, Mulder A, van Gelder T, Aarts J, Berg M, Vulto A. Drug safety alert generation and overriding in a large Dutch university medical centre. *Pharmacoepidemiol Drug Saf* 2009;18:941-7.
6. Isaac T, Weissman JS, Davis RB, Massagli M, Cyrulik A, Sands DZ, et al. Overrides of medication alerts in ambulatory care. *Arch Intern Med* 2009;169:305-11.
7. Eppenga WL, Derijks HJ, Conemans JM, Hermens WA, Wensing M, de Smet PAGM. Comparison of a basic and an advanced pharmacotherapy-related clinical decision support system in a hospital care setting in the Netherlands. *J Am Med Inform Assoc* 2012;19:66-71.
8. Seidling HM, Klein U, Schaier M, Czock D, Theile D, Pruszydlo MG, et al. What, if all alerts were specific - Estimating the potential impact on drug interaction alert burden. *Int J Med Inform* 2014;83:285-91.
9. Czock D, Konias M, Seidling HM, Kaltschmidt J, Schwenger V, Zeier M, et al. Tailoring of alerts substantially reduces the alert burden in computerized clinical decision support for drugs that should be avoided in patients with renal disease. *J Am Med Inform Assoc* 2015;22:881-7.
10. Duke JD, Li X, Dexter P. Adherence to drug-drug interaction alerts in high-risk patients: a trial of context-enhanced alerting. *J Am Med Inform Assoc* 2013;20:494-8.
11. Rommers MK, Teepe-Twiss IM, Guchelaar HJ. A computerized adverse drug event alerting system using clinical rules: a retrospective and prospective comparison with conventional medication surveillance in the Netherlands. *Drug Saf* 2011;34:233-42.
12. Helmons PJ, Suijkerbuijk BO, Nannan Panday PV, Kosterink JG. Drug-drug interaction checking assisted by clinical decision support: a return on investment analysis. *J Am Med Inform Assoc* 2015;22:764-72.
13. Cornu P, Steurbaut S, Gentens K, Van de Velde R, Dupont AG. Pilot evaluation of an optimized context-specific drug-drug interaction alerting system: A controlled pre-post study. *Int J Med Inform* 2015;84:617-29.
14. Koster ES, Philbert D, Noordam M, Winters NA, Blom L, Bouvy ML. Availability of information on renal function in Dutch community pharmacies. *Int J Clin Pharm* 2016;38:797-801.
15. Smits E, Houben E, de Smet PAGM, Szerencsi K, vanHerk-Sukel MPP, Herings RMC, et al. The Availability of Information on Impaired Renal Function in the Community Pharmacy, A Descriptive Pilot Study. *HSOA Journal of Nephrology and Renal Therapy* 2016;2:003.
16. Heringa M, Floor-Schreudering A, Tromp PC, De Smet PA, Bouvy ML. Nature and frequency of drug therapy alerts generated by clinical decision support in community pharmacy. *Pharmacoepidemiol Drug Saf* 2016;25:82-9.

17. Heringa M, Siderius H, Floor-Schreudering A, de Smet PA, Bouvy ML. Lower alert rates by clustering of related drug interaction alerts. *J Am Med Inform Assoc* 2017;24:54-9.
18. Borgsteede SD, ed. Commentaren Medicatiebewaking 2015-2016 (Commentaries medication surveillance). Houten, The Netherlands: Health Base Foundation 2015.
19. Preston CL, ed. Stockley's Drug Interactions (Online). London, United Kingdom: Royal Pharmaceutical Society, The Pharmaceutical Press 2016.
20. Van Roon EN, Flikweert S, le Comte M, Langendijk PN, Kwee-Zuiderwijk WJ, Smits P, et al. Clinical relevance of drug-drug interactions : a structured assessment procedure. *Drug Saf* 2005;28:1131-9.
21. Buurma H, De Smet PAGM, Egberts AC. Clinical risk management in Dutch community pharmacies: the case of drug-drug interactions. *Drug Saf* 2006;29:723-32.
22. Ancker JS, Edwards A, Nosal S, Hauser D, Mauer E, Kaushal R, et al. Effects of workload, work complexity, and repeated alerts on alert fatigue in a clinical decision support system. *BMC Med Inform Decis Mak* 2017;17:36,017-0430-8.
23. Wekre LJ, Spigset O, Sletvold O, Sund JK, Grimsmo A. Multidose drug dispensing and discrepancies between medication records. *Qual Saf Health Care* 2010;19:e42.
24. Nair R, Aggarwal R, Khanna D. Methods of formal consensus in classification/diagnostic criteria and guideline development. *Semin Arthritis Rheum* 2011;41:95-105.
25. Kea B, Sun BC. Consensus development for healthcare professionals. *Intern Emerg Med* 2015;10:373-83.
26. Floor-Schreudering A, Heringa M, Buurma H, Bouvy ML, De Smet PA. Missed drug therapy alerts as a consequence of incomplete electronic patient records in Dutch community pharmacies. *Ann Pharmacother* 2013;47:1272-9.
27. De Wit HA, Hurkens KP, Mestres Gonzalvo C, Smid M, Sipers W, Winkens B, et al. The support of medication reviews in hospitalised patients using a clinical decision support system. *Springerplus* 2016;5:871.

Appendix 1: Application of exclusion criteria on most frequent drug interaction alerts

Drug interaction	Type	% of alerts[a]	Exclusion	Management recommendation [18] which is reason for exclusion
RAS-inhibitors – diuretics	Drug-drug	8.0	No	
Diabetes – ACE-inhibitors	Drug-disease	4.7	No	
Obstructive pulmonary disease – beta-blocking agents	Drug-disease	4.4	No	
Antidiabetics – beta-blocking agents	Drug-drug	4.2	No	
Renal impairment – diuretics	Drug-disease	4.1	Yes	Monitor renal function
RAS-inhibitors – potassium-sparing agents/potassium	Drug-drug	2.3	Yes	Monitor potassium
Bisphosphonates – polyvalent cations	Drug-drug	2.3	No	
Vitamin K antagonists – (es)omeprazole	Drug-drug	2.2	Yes	Monitor INR
Renal impairment – ACE-inhibitors	Drug-disease	2.2	Yes	Monitor potassium and renal function
Heart failure – beta-blocking agents	Drug-disease	2.1	No	
NSAIDs – RAS-inhibitors	Drug-drug	2.1	Yes	Monitor blood pressure (and renal function and potassium in case of heart failure)
Thyroid drugs – polyvalent cations	Drug-drug	1.7	No	
Beta-blocking agents – NSAIDs	Drug-drug	1.7	Yes	Monitor blood pressure
Salicylates (antithrombotic) – SRIs	Drug-drug	1.7	No	
Renal impairment – antidiabetics	Drug-disease	1.7	Yes	Monitor renal function
Diabetes – thyroid drugs	Drug-disease	1.6	No	
Vitamin K antagonists – metformin	Drug-drug	1.5	Yes	Monitor INR
Digoxin – diuretics	Drug-drug	1.5	Yes	Monitor potassium
SRIs – diuretics	Drug-drug	1.3	Yes	Monitor sodium
Diabetes – SRIs	Drug-disease	1.3	No	

ACE = angiotensin converting enzyme; INR = international normalized ratio prothrombin time; NSAID = nonsteroidal anti-inflammatory drug; RAS = renin-angiotensin system; SRI = serotonin reuptake inhibitor; [a]Percentage of the total number of drug interaction alerts in dataset 1; first time dispensing excluded

Appendix 2: Alert rates for dataset 1 versus dataset 2

Drug interaction	Dataset 1			Dataset 2		
	Number of alerts		Change in alert rate	Number of alerts		Change in alert rate
	Original CDSS	Simulation		Original CDSS	Simulation	
RAS-inhibitors – diuretics	22,646	1,295	- 94.3%	22,153	1,260	- 94.3%
Diabetes – ACE-inhibitors	13,331	1,003	- 92.5%	13,147	952	- 92.8%
Obstructive pulmonary disease – beta-blocking agents	12,447	1,161	- 90.7%	11,943	1,223	- 89.8%
Antidiabetics – beta-blocking agents	12,073	1,002	- 91.7%	11,195	951	- 91.5%
Bisphosphonates – polyvalent cations	6,619	396	- 94.0%	7,662	409	- 94.7%
Heart failure – beta-blocking agents	5,861	478	- 91.8%	5,102	417	- 91.8%
Thyroid drugs – polyvalent cations	5,011	291	- 94.2%	4,330	214	- 95.1%
Salicylates (antithrombotic) – SRIs	4,731	125	- 97.4%	5,811	139	- 97.6%
Diabetes – thyroid drugs	4,426	350	- 92.1%	4,199	322	- 92.3%
Diabetes – SRIs	3,649	292	- 92.0%	3,164	234	- 92.6%
TOTAL	**90,794**	**6,393**	**- 93.0%**	**88,706**	**6,121**	**- 93.1%**

ACE = angiotensin converting enzyme; RAS = renin-angiotensin system; SRI = serotonin reuptake inhibitor

4. Including the patient perspective in clinical decision support

Chapter 4.1

Preferences of patients and pharmacists with regard to the management of drug-drug interactions: a choice-based conjoint analysis

Mette Heringa
Annemieke Floor-Schreudering
Hans Wouters
Peter A.G.M. De Smet
Marcel L. Bouvy

Accepted for publication in Drug Safety

Abstract

Objective

Management of drug-drug interactions (DDI) is a complex process, in which risk-benefit assessments should be combined with the patient's perspective. The aim of this study was to determine patients' and pharmacists' preferences with regard to DDI management.

Methods

We assessed preferences on DDI management by an online choice-based conjoint survey (discrete choice experiment) about a fictitious DDI, concerning combination of a chronically used cardiovascular drug and an antibiotic for pneumonia. Participating patients and pharmacists had to choose twelve times between two management options. The options were described by five attributes, including risk, benefit and practical consequences. Each attribute could have two different levels, which were varied over the twelve choice tasks. Latent class analysis was used to identify potential classes of patients and pharmacists with distinct patterns of similar preferences.

Results

298 patients using cardiovascular medication and 178 pharmacists completed the questionnaire. The latent class model for both patients and pharmacists resulted in three classes. For patients, in one class most importance was attached to avoiding switch of medication (class probability 20%), in a second class to a lower risk of adverse events (41%), and in a third class to blood sampling (39%). For pharmacists, again one class attached highest importance to avoiding switch of medication (31%). The other classes gave priority to curing pneumonia (31%) and avoiding blood sampling (38%).

Discussion and Conclusion

The results showed diverging preferences regarding DDI management both among patients and pharmacists. Different groups attached different value to risk and benefit versus practical considerations. Awareness of existing variability of preferences and possible incongruence between pharmacists and patients is a step forward towards shared decision making in DDI management.

Introduction

Clinical risk management of drug-drug interactions (DDIs) is complex. The management recommendations for DDIs often provide health care professionals with several options (e.g. additional monitoring, switch to an alternative drug, dose adjustment). These recommendations are generally based on the principle of evidence-based medicine and are dominated by risk-benefit assessments [1, 2]. In DDI management, these assessments are difficult because at least two drug therapies are involved and because the evidence for the different management options is generally limited. Moreover, recognizing the importance of shared decision making, the patient's perspective should be included [3-5]. In shared decision making, patients and health care professionals make health care decisions together, taking into account both scientific evidence and the patient's values and preferences [6].

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach offers an Evidence-to-Decision framework for clinical decisions [7, 8]. Because of the similarity of aspects involved in DDI decision making and clinical decision making in general, the GRADE approach has also been proposed for the assessment of drug-drug interaction management [1, 9]. In the GRADE model, variability in how patients value the main outcome is included. The acceptability and the feasibility of a recommendation for patients and health care professionals are also part of the model. Thus, it is recognized that patients' values and preferences and their variability are relevant in the development of DDI management recommendations.

In addition to the role of patients' preferences in the development of recommendations, the patients' perspective should be taken into account in the application of recommendations in daily practice [5, 10]. Currently, DDI management by pharmacists and physicians does usually not explicitly involve the patient's perspective. Little is known about patients' preferences in the field of DDI management and about potential incongruence with the professionals' preferences. Based on investigations on patient preferences in other drug-related issues, variability among patients could be expected [11-13]. Both patients' and health care professionals' perspectives may influence the choice for a specific DDI management option. Insight in these perspectives is useful for shared decision making in this field. Therefore we aimed to investigate patients' and pharmacists' preferences with regard to DDI management.

Methods

Study design

A structured online questionnaire was administered to patients and community pharmacists. The core task was a choice-based conjoint (CBC) task on a fictitious DDI regarding a patient using cardiovascular medication who was in need of an antibiotic because of suspected pneumonia. In the CBC, respondents had to choose between hypothetical options to determine to which characteristics of an option they attached value (see below). The CBC task was essentially the same for pharmacists and patients. Patients were asked to choose for themselves; pharmacist for a patient in general. The pharmacist questionnaire consisted of three parts: sociodemographic characteristics, the CBC task, and an open question on situations or patients groups in which the preferences of the pharmacist would be different from the choices made in the CBC. The patient questionnaire additionally contained general questions on sociodemographic characteristics and drug use, and two validated questionnaires on numeracy and health literacy.

Participants and protocol

Pharmacists were recruited from the Utrecht Pharmacy Practice Network for Education and Research (UPPER), which includes two third of the 1,900 Dutch community pharmacies [14]. The usual response rate in this network is 10-15%. E-mail invitations with the URL of the online questionnaire were sent with a reminder after 1-2 weeks.

Patients were recruited by a convenience sample of five community pharmacies from different regions in the Netherlands. Patients who were using cardiovascular drugs were selected to ensure that the presented fictitious DDI would be plausible. A random selection of 200 patients per pharmacy was made out of patients who met the following inclusion criteria: 1) Over 40 years of age. 2) Use of cardiovascular medication based on dispensing data. We considered the following cardiovascular medication (ATC [anatomical therapeutic chemical] class [15]): lipid modifying agents (C10), platelet aggregation inhibitors (B01AC), and antihypertensive drugs (C03 diuretics, C07 beta-blocking agents, C08 calcium channel blockers, or C09 renin angiotensin system inhibitors). 3) registered indication for cardiovascular risk management: hypertension, heart failure, coronary disease, diabetes mellitus or stroke. 4) e-mail address being available. 5) no known terminal illness or impaired cognition. Patients were invited by e-mail by their own pharmacist, with a reminder after 1-2 weeks.

Choice based conjoint task

Conjoint analyses and discrete choice experiments, such as CBC, are increasingly used in health care to elicit and quantify respondents' preferences [16, 17]. In CBC, respondents choose between hypothetical options which vary systematically in the value (level) of selected attributes, which reflects issues relevant for the decision. A CBC task was developed in accordance with guidelines [18-20], using Sawtooth Software (Lighthouse Studio version 9.2.0, Orem, Utah, United States of America). The CBC was based on a fictive case illustrative of DDIs (Figure 1), and plausible for a broad group of respondents: cardiovascular medications are among the most frequently used drugs and they often cause DDIs [21]. Realistic attributes and levels were chosen (Table 1), representing four common management options of DDIs which could be applied after consultation between prescriber, pharmacist and patient: 1) no action, use both drugs concurrently; 2) replacement of the medicine the patient is already using; 3) replacement of the newly prescribed medicine; 4) additional monitoring such as blood testing[1]. The case, attributes and levels were selected based on considerations relevant in the development of drug interaction management guidelines [1, 8, 9], and the content of DDI management guidelines itself [22, 23]. The preselection of attributes was verified in five focus group meetings with patients using cardiovascular drugs, which are part of parallel running investigation (manuscript in preparation). Based on the focus groups no new attributes were added, but the cost component was excluded. In the Netherlands, this attribute is rarely relevant for individual patients because of the insurance coverage.

The respondents had to respond to 12 choice sets with two DDI management options. Because of the complexity of the subject, the number of options was limited to two per choice set; no opt-out option was available, consistent with reality. The options to choose from were characterized by a full profile of five attributes. The attributes were presented in the same order for any given patient, but the order was randomized between patients. A balanced overlap design (with level balance and near-orthogonality) was used to create the choice sets [18, 24]. Twenty different combinations of 12 choice sets were generated, which were randomly assigned to the respondents. The CBC was preceded by an explanation of the case and the choice task; a pop-up with additional information on the attributes and levels was available during the CBC.

The questionnaire was pre-tested by patients and pharmacists for understanding, feasibility and wording. A number of 12 choice sets was chosen to limit the time needed to complete the questionnaire to 10 minutes for pharmacists and to 15 minutes for patients. The questionnaire was adapted according to the feed-

back in a cyclic process (two respondents per group per cycle), until after three cycles no new issues were identified and good understanding was reached. For a translated example of a choice set, see Figure 1.

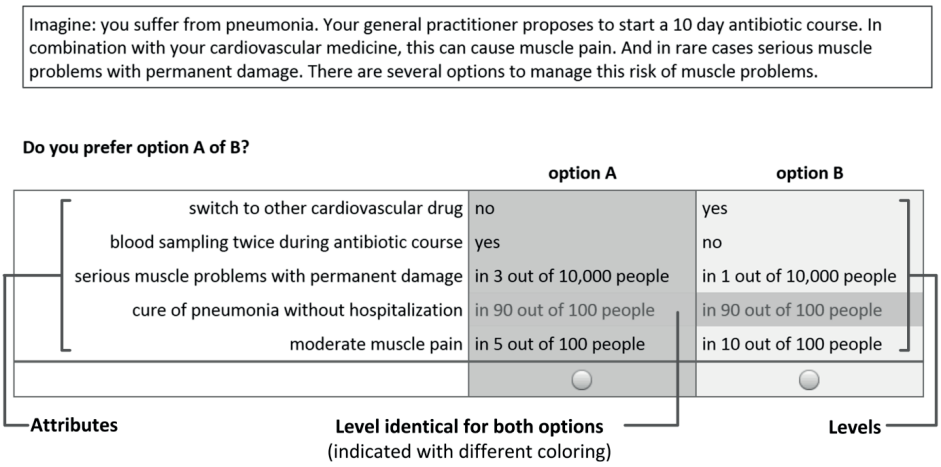


Figure 1: Annotated example of choice set for patients

Health literacy and numeracy measurement

Measures of health literacy and numeracy were included to detect potential associations with preferences, as literacy and numeracy can influence decision making [25-29]. The validated Functional Communicative and Critical Health Literacy Scales (FCCHL) and the Subjective Numeracy Scale (SNS) were used. The FCCHL consists of three subscales: functional (five items), communicative (five items) and critical (four items) [30, 31]. Each item is rated on a four-point scale, ranging from 1 (never / easy) to 4 (often / hard). After reversion of all scores, the scores on the items in a (sub)scale are summed and divided by the number of items in the scale to calculate a scale score (theoretical range 1–4, a higher score indicating higher health literacy). The SNS consists of eight items which are rated on a six-point scale, ranging from 1 (not at all good / never) to 6 (extremely good / very often) [27, 28, 32]. After reversion of item 7, the total score is calculated by summing the item scores and dividing them by eight. The theoretical range is 1-6, a higher score indicating higher numeracy.

Table 1: Attributes and levels

Attribute	Explanation	Levels	Corresponding DDI management option[a]
Serious muscle problems with permanent damage	The risk of serious muscle problems with permanent damage	In 1 out of 10,000 people	MO2, MO3, MO4
		In 3 out of 10,000 people	MO1
Blood sampling twice during antibiotic course	Whether or not blood sampling twice during the antibiotic course. By blood testing, muscle problems can be diagnosed at an early stage, before they become serious	no	MO1, MO2, MO3
		yes	MO4
Curing pneumonia without hospitalization	The chance of recovering from pneumonia without hospitalization	In 95 out of 100 people	MO1, MO2, MO4
		In 90 out of 100 people	MO3
Moderate muscle pain	The risk of moderate muscle pain. With moderate muscle pain you are limited in your daily activities (work, hobby)	In 5 out of 100 people	MO2, MO3
		In 10 out of 100 people	MO1, MO4
Switch to other cardiovascular drug	Whether or not switching to another cardiovascular medicine, instead of the one you are using at the moment	no	MO1, MO3, MO4
		yes	MO2

MO = management option

[a] MO1) no action, use both drugs concurrently, MO2) replacement of the medicine the patient is already using, MO3) replacement of the newly prescribed medicine of choice, or MO4) extra monitoring by blood testing.

Sample size

Because of the exploratory nature of this study and the potential variability, an a priori estimation of effect size was not available. Taking into account general guidelines for CBC, the targeted sample size was 200 respondents per group [18, 19]. The aim of our study was to get a general overview of preferences and potential variability in DDI management based on a fictitious case, rather than getting an exact estimate of choice behavior in DDI management.

Data analysis

For descriptive statistics of basic characteristics Microsoft Excel 2010 and SPSS (version 20.0, SPSS Inc., Chicago, IL, USA) were used. For non-responders analysis for patients, differences between groups were analyzed using the T-test for normally distributed continuous variables and the Pearson chi square test for categorical variables. A p-value < 0.05 was considered statistically significant. Only completed questionnaires were included in further analysis.

The CBC data were analyzed by Sawtooth Software. CBC-analysis results in utilities, which are similar to a regression coefficient and represents the relative attractiveness (preference) of an attribute-level and therefore its relative influence on the respondents' choice. Positive utilities reflect the preferred level; higher values reflect higher attractiveness. The importance of an attribute, i.e. how much it contributes to the respondents' choice, is calculated by dividing the absolute value of the utility by the sum of the absolute value of all utilities.

We analyzed the CBC data by a latent class analysis [33] to examine the presence of classes (subgroups) of respondents with different preferences. In latent class analysis, the classes are derived from distinct patterns of similar preferences in the data. Latent class analysis for one to five classes was performed. For identified classes, the probability a respondent belonged to this class was calculated. The most likely number of classes was evaluated by assessing goodness of fit indices for the model, including the LogLikelihood, McFadden's pseudo rho^2 (value between 0.2 and 0.4 indicates good fit), AIC (Akaike information criterion; lower values indicate better fit) and BIC (Bayesian information criterion; lower values indicate better fit) [20, 33]. Moreover mean class probabilities were taken into account to maintain reasonable class sizes and the pattern of utilities for every solution was assessed. It was tested whether every attribute significantly contributed to the model by a Chi Square test on the -2LogLikelihood (difference between model with and without every single attribute).

For the final solution, every respondent was assigned to the class for which he had highest probability and a comparison was made with respect to basic characteristics in SPSS. ANOVA (analysis of variance) was used for normally distributed continuous variables and the Pearson chi square test for categorical variables. A p-value < 0.05 was considered statistically significant.

Ethics and confidentiality

The Institutional Review Board of the Division of Pharmacoepidemiology and Clinical Pharmacology of Utrecht University approved the investigation and the work was conducted in compliance with its requirements. Only anonymous data were collected. Respondents did not sign informed consent, as an anonymous survey among volunteers did not fall within the scope of the Dutch Act on Medical Research Involving Human Subjects.

Results

Respondents

An invitation was sent to 1,312 pharmacists between September and December 2016. The questionnaire was accessed by 236 pharmacists (18.0%) and completed by 178 pharmacists (13.5%). For basic characteristics, see Table 2. Five pharmacists selected 200 eligible patients each; e-mail invitations were sent to 1000 patients between September and December 2016. The online questionnaire was accessed by 393 patients (39.3%), and 298 patients (29.8%) completed the questionnaire. Between patients who completed the questionnaire and patients who did not complete the questionnaire but did fill out the basic characteristics, there were differences with respect to age (mean age 64.4 vs 67.9, $p = 0.01$) and educational level (low 26.9% vs 48.0%, medium 39.1% vs 33.3%, high 34.0% vs 18.7%; $p < 0.01$). No differences were seen with respect to gender, duration of use of cardiovascular drugs and number of medicines in use.

Latent class analysis

The latent class analysis for both patients and pharmacists resulted in a three class model. McFadden's pseudo rho^2 was 0.24 for patients and 0.37 for pharmacists. Fit statistics indicated improvement in model fit with each additional class (Appendix 1), but with decreasing gain in model fit. With more than three classes small classes and unclear differentiation arose compared to the number of respondents and attributes. The three-class-models were stable and had an average maximum class membership probability of 89.0% and 89.8% for patients and pharmacists, respectively. All attributes significantly contributed to the model for both pharmacists and patients.

Table 2: Descriptive characteristics of respondents

Patients		**n=298**
Age	mean (sd)	64.4 (9.6)
Gender	Male	186 (62.4%)
Educational level[a]	Low	79 (26.9%)
	Medium	115 (39.1%)
	High	100 (34.0%)
Number of medicines in use	mean (sd)	4.7 (2.7)
Duration of use of cardiovascular medicines	≤ 5 years	27.9%
	> 5 years	72.1%
SNS	mean (sd)	4.2 (0.8)
FCCHL total	mean (sd)	2.9 (0.5)
FCCHL functional	mean (sd)	3.0 (0.5)
FCCHL communicative	mean (sd)	3.2 (0.6)
FCCHL critical	mean (sd)	2.6 (0.7)

Pharmacists		**n=178**
Age	mean (sd)	43.2 (11.2)
Gender	Male	77 (43.3%)
Years of practice in community pharmacy	0-5	36 (20.2%)
	6-15	57 (32.0%)
	>15	85 (47.8%)
Location of pharmacy	Village (up to 20,000 inhabitants)	71 (39.9%)
	Town (20,00-150,000 inhabitants)	61 (34.3%)
	City (over 150,000 inhabitants)	46 (25.8%)
Type of community pharmacy	Community health center	92 (51.7%)
	Other	86 (48.3%)

FCCHL = Functional Communicative and Critical Health Literacy Scales; sd = standard deviation; SNS = subjective numeracy scale

[a] educational level was categorized as low (primary education or lower secondary), medium (intermediate/higher secondary or intermediate vocational), or high (higher vocational/university); 4 respondents missing.

For patients, level utility and attribute importance are shown per class in Table 3. In all classes, lower risks of serious muscle problems and moderate muscle pain were preferred over a higher risk, and higher chance of cure of pneumonia was preferred over a lower chance. For blood sampling and switch of cardiovascular drug, preferences were less consistent. In the first class, most importance was attached to avoiding a switch of the cardiovascular drug in use, followed by minimizing the risk of serious muscle problems. This class was labelled 'stability focused'. In the second class, most value was attached to minimizing the risk of serious muscle problems and maximizing the chance of curing pneumonia without hospitalization. This second class was labelled 'risk focused'. In the third patient class, labelled 'certainty focused', options with blood sampling were preferred over options without blood sampling. The patients' descriptive characteristics shown in Table 2 were not significantly associated with class assignment (Appendix 2a).

The pharmacists' results are shown in Table 4. In all classes, lower risks of harm were preferred over higher risks, higher chances of cure were preferred over lower chances, and avoidance of blood sampling and of switch of current medication was preferred. In the first class, the highest importance was attached to the risk of serious muscle problems and the chance of curing pneumonia without hospitalization. This first pharmacist class was labelled 'risk focused'. In the second class, maintaining the current cardiovascular medication was valued most; this class was labelled 'stability focused'. In the third class, priority was given to avoidance of blood sampling, followed by avoidance of the switch of current cardiovascular medication and a low risk of serious muscle problems. This pharmacist class was labelled 'practicality focused'. Age, gender and years of practice of pharmacists were in a univariate analysis all associated with class assignment (respectively $p = 0.01$, $p = 0.00$; $p = 0.02$), see Appendix 2b. The 'risk focused' pharmacists were the oldest, with the most years of practice and more often male. The 'stability focused' pharmacists were the youngest, with the least years of practice and most often female.

Table 3: Results latent class analysis patients

Attribute	Level	Class 1: 'stability focused' (20.3%)[a]		Class 2: 'risk focused' (41.0%)[a]		Class 3: 'certainty focused' (38.7%)[a]	
		Utility (SE)	RI	Utility (SE)	RI	Utility (SE)	RI
Muscle damage	1 out of 10,000	0.62 (0.09)[b]	21.9%	1.39 (0.07)[b]	49.7%	0.21 (0.04)[b]	25.6%
	3 out of 10,000	-0.62 (0.09)[b]		-1.39 (0.07)[b]		-0.21(0.04)[b]	
Blood sampling twice	No	-0.28 (0.08)[b]	9.7%	0.005 (0.05)	0.2%	-0.25 (0.03)[b]	30.5%
	Yes	0.28 (0.08)[b]		-0.005 (0.05)		0.25 (0.03)[b]	
Curing pneumonia without hospitalization	95 out of 100	0.14 (0.08)	4.9%	0.68 (0.06)[b]	24.3%	0.04 (0.04)	5.1%
	90 out of 100	-0.14 (0.08)		-0.68 (0.06)[b]		-0.04 (0.04)	
Moderate muscle pain	5 out of 100	0.13 (0.07)	4.6%	0.52 (0.05)[b]	18.7%	0.18 (0.04)[b]	22.1%
	10 out of 100	-0.13 (0.07)		-0.52 (0.05)[b]		-0.18 (0.04)[b]	
Switch of cardiovascular drug	No	1.68 (0.12)[b]	58.9%	0.20 (0.05)[b]	7.0%	-0.13 (0.04)[b]	16.8%
	Yes	-1.68 (0.12)[b]		-0.20 (0.05)[b]		0.13 (0.04)[b]	

RI = relative importance; SE = standard error

[a] average class probability; [b] $p < 0.05$

Table 4: Results latent class analysis pharmacists

Attribute	Level	Class 1: 'risk focused' (31.3%)[a]		Class 2: 'stability focused' (31.1%)[a]		Class 3: 'practicality focused' (37.6%)[a]	
		Utility (SE)	RI	Utility (SE)	RI	Utility (SE)	RI
Muscle damage	1 out of 10,000	0.60 (0.06)[b]	40.6%	0.44 (0.10)[b]	11.7%	0.72 (0.08)[b]	20.0%
	3 out of 10,000	-0.60 (0.06)[b]		-0.44 (0.10)[b]		-0.72 (0.08)[b]	
Blood sampling twice	No	-0.06 (0.06)	3.8%	0.45 (0.09)[b]	11.9%	1.39 (0.10)[b]	38.8%
	Yes	0.06 (0.06)		-0.45 (0.09)[b]		-1.39 (0.10)[b]	
Curing pneumonia without hospitalization	95 out of 100	0.61 (0.06)[b]	41.4%	0.43 (0.09)[b]	11.3%	0.32 (0.07)[b]	8.8%
	90 out of 100	-0.61 (0.06)[b]		-0.43 (0.09)[b]		-0.32 (0.07)[b]	
Moderate muscle pain	5 out of 100	0.17 (0.06)[b]	11.6%	0.14 (0.09)	3.8%	0.26 (0.07)[b]	7.1%
	10 out of 100	-0.17 (0.06)[b]		-0.14 (0.09)		-0.26 (0.07)[b]	
Switch of cardiovascular drug	No	0.04 (0.06)	2.5%	2.31 (0.20)[b]	61.2%	0.90 (0.09)[b]	25.2%
	Yes	-0.04 (0.06)		-2.31 (0.20)[b]		-0.90 (0.09)[b]	

RI = relative importance; SE = standard error

[a] average class probability; [b] $p < 0.05$

Pharmacists' additional considerations

Eighty six pharmacists (48%) reported one or more situations in which their preferences would be different than expressed in the CBC task. Clinical, risk-related situations (e.g. muscle problems in anamnesis, very serious cardiovascular disease) were reported by 64 pharmacists, issues with respect to the practicality and feasibility of the management options (e.g. switch of medication is undesirable for mentally retarded patients; blood testing is undesirable for immobile patients) by 16, patient preferences (unwilling to switch medication, fear of adverse events, fear of needles) by 14, and prescriber preferences by 5.

Discussion

Both for patients and pharmacists, divergent preferences with regard to DDI management were observed. Among both patients and pharmacists, in one class highest importance was attached to risks and benefits (avoidance of serious muscle problems, cure of pneumonia). This pattern of preferences can be characterized as 'risk focused' (31.3% and 41.0%). Similarly among both pharmacists and patients, in a second class (31.1% and 20.3%) highest importance was attached to avoiding changes in the current therapy ('stability focused'). For pharmacists, the third class was 'practicality focused' (37.6%): highest importance was attached to avoidance of blood sampling and to a lesser extent, like the previous class, to the avoidance of changes in the current therapy. In contrast, in the patients' third class (38.7%) blood sampling was unexpectedly preferred over no blood sampling in otherwise identical situations ('certainty focused').

Pharmacists in the 'risk focused' class were older and more often male, while pharmacists in the 'stability focused' class were younger and more often female. This difference has parallels with the transition of pharmacy practice in the last decades, towards a more patient-oriented perspective. However, the number of pharmacists spontaneously reporting patient preferences as a reason for other DDI management considerations, was limited (n=14; 7.9%).

For patients, we found no clear association between preference class and descriptive statistics, although an association with educational level cannot be excluded. No relationship with health literacy was observed. About one quarter of patients who started the questionnaire, did not finish it; this included relatively more patients with lower education. Due to the complexity of assessment of DDI management options, patients with low health literacy or low numeracy may have been underrepresented in our study. The mean SNS-score on numeracy

and the mean overall FCCHL-score on health literacy in this study were in the same range as in the validation studies [27, 31].

Decision making about DDIs is complex, as it includes several aspects: a) a new or changing condition in which treatment is assumed necessary, b) a risk of the combination of both drugs, of which the exact height is often unknown and c) the potential management options of the DDI, which may affect both the risk and benefit of a) and b), and which may also introduce new risks. We combined the characteristics of these aspects in one conjoint task, which enabled respondents to integrate the consequences of the management options. The fact that the task description focused primarily on managing the DDI may have highlighted the risk originating from the DDI (serious muscle problems). The presentation of data may have influenced the respondents in several ways. Firstly, serious events with low risk were included as attribute. We used descriptions with absolute risks and fixed denominators for optimal understanding [34-37]. Nevertheless, understanding (rare) risks and incorporate them in health care decisions is difficult, especially for people with lower health literacy and lower numeracy [25, 38, 39]. Secondly, risk perception is strongly influenced by contextual factors, e.g. whether it is presented and perceived as a dangerous problem or not [40-42]. Thirdly, people are sensitive to the framing of risks in terms of loss or gain. People tend to respond stronger on options described as losses (e.g. a new serious adverse event) rather than as gains (more effective cure of pneumonia) [34]. However, this is also likely to happen in daily clinical practice.

In this context, it is interesting that the analysis showed that all patients attached importance to the risk of serious muscle problems, despite the low risk. Better chances to cure pneumonia – a serious condition - were valued less. For pharmacists, who are used to risk interpretation, this was not the case. When it comes to differences between pharmacists and patients, the expressed preferences for the blood sampling attribute is notable. Pharmacists - as expected - preferred a management option solution without blood sampling, as there is no benefit in the act of blood sampling itself as long as the levels of the other attribute are identical. For one of the pharmacist classes ('practicality focused'), prevention of blood sampling was even the most important factor. In contrast, in the 'certainty focused' patient class, blood testing was preferred over no blood testing. It is conceivable that these patients expected better control with blood tests, even in case all other shown attribute levels were identical. A comparable effect has been observed with price, where more expensive goods were incorrectly assumed to be of better quality [43, 44]. Although the real value of the expressed preference of blood sampling over no sampling can be questioned, the results do suggest

that most patients in this study, who chronically use cardiovascular drugs, do not experience blood sampling as very burdensome.

This study is not without limitations. Firstly, we investigated a fictitious DDI. Therefore we cannot draw conclusions about preferences in any specific situation. Patients may choose differently when they are confronted with a DDI in daily practice and pharmacists may choose differently for specific patients. However, it is likely that preferences will also vary in daily clinical practice. Secondly, invi-tations were sent by e-mail. Although internet access is high in the Netherlands (in 2016: 94% of the general population; 78% in the population over 65 years [45]), the oldest and frailest patients may well have been underrepresented. Moreover, patients chronically using cardiovascular drugs are often subject to DDIs, but they need not to be representative for all patients facing DDIs. Thirdly, the subject of our CBC was complex. Respondents not completely understand-ing the task may have given irrational or random answers and identifying irra-tional answers is difficult [43, 44]. Some respondents may have used simplifying heuristics, ranking attributes in importance rather than making a trade-off [46]. However, it is plausible that some attributes were deliberately valued extremely high or low by respondents. Irrational answers may have influenced the exact estimates, but are unlikely to have influenced the overall pattern. The preferred levels for all classes were consistent with prior expectations for both risk and benefit attributes (preference for lower risk and higher benefit). Fourthly, physi-cians were not included in the investigation. Although pharmacists are the health care professionals mostly involved in DDI management, consultation with the prescriber is an important part of the process. Therefore, further investigations into DDI decision making should preferably include all three main stakeholders: patients, pharmacists and physicians.

The observed variability in DDI management preferences can lead to incongruence between patients' and pharmacists' assessments. Awareness of their own preference and patients' preferences can help health care professionals in shared decision making. This can be stimulated by incorporating the divergence of pref-erences in DDI management recommendations [47]. Further research is needed to get insight into the DDI decision making process and to investigate the value and implementation of shared decision making about DDI in daily practice.

Conclusion

Our results show that there is considerable variability in DDI management preferences, both among patients and pharmacists. Some of them attach highest importance to clinical risks and benefits, while others highly value practical implications (like the acceptation or rejection of blood testing). Awareness of existing variability enables its incorporation in the development and application of DDI management recommendations: a step forward towards shared decision making in this field.

Acknowledgements

We thank all patients and all pharmacists who participated in this study.

References

1. Floor-Schreudering A, Geerts AF, Aronson JK, Bouvy ML, Ferner RE, De Smet PA. Checklist for standardized reporting of drug-drug interaction management guidelines. *Eur J Clin Pharmacol* 2014;70:313-8.
2. Payne TH, Hines LE, Chan RC, Hartman S, Kapusnik-Uner J, Russ AL, et al. Recommendations to Improve the Usability of Drug-Drug Interaction Clinical Decision Support Alerts. *J Am Med Inform Assoc* 2015;22:1243-50.
3. Schoemaker CG, van der Weijden T. Patient preferences versus evidence-based medicine: did the pioneers of evidence-based medicine take the patient's preferences into account?. *Ned Tijdschr Geneeskd* 2016;160:D24.
4. Greenhalgh T, Howick J, Maskrey N, Evidence Based Medicine Renaissance Group. Evidence based medicine: a movement in crisis?. *BMJ* 2014;348:g3725.
5. Neumann I, Santesso N, Akl EA, Rind DM, Vandvik PO, Alonso-Coello P, et al. A guide for health professionals to interpret and use recommendations in guidelines developed with the GRADE approach. *J Clin Epidemiol* 2016;72:45-55.
6. Stiggelbout AM, Van der Weijden T, De Wit MP, Frosch D, Legare F, Montori VM, et al. Shared decision making: really putting patients at the centre of healthcare. *BMJ* 2012;344:e256.
7. Guyatt GH, Oxman AD, Kunz R, Falck-Ytter Y, Vist GE, Liberati A, et al. Going from evidence to recommendations. *BMJ* 2008;336:1049-51.
8. Alonso-Coello P, Oxman AD, Moberg J, Brignardello-Petersen R, Akl EA, Davoli M, et al. GRADE Evidence to Decision (EtD) frameworks: a systematic and transparent approach to making well informed healthcare choices. 2: Clinical practice guidelines. *BMJ* 2016;353:i2089.
9. Scheife RT, Hines LE, Boyce RD, Chung SP, Momper JD, Sommer CD, et al. Consensus Recommendations for Systematic Evaluation of Drug-Drug Interaction Evidence for Clinical Decision Support. *Drug Saf* 2015;38:197-206.
10. Pollard S, Bansback N, Bryan S. Physician attitudes toward shared decision making: A systematic review. *Patient Educ Couns* 2015;98:1046-57.
11. Britten N, Denford S, Harris-Golesworthy F, Jibson S, Pyart N, Stein K. Patient involvement in drug licensing: a case study. *Soc Sci Med* 2015;131:289-96.
12. Postmus D, Mavris M, Hillege H, Salmonson T, Ryll B, Plate A, et al. Incorporating patient preferences into drug development and regulatory decision making: Results from a quantitative pilot study with cancer patients, carers, and regulators. *Clin Pharmacol Ther* 2015.
13. Hazlewood GS, Bombardier C, Tomlinson G, Thorne C, Bykerk VP, Thompson A, et al. Treatment preferences of patients with early rheumatoid arthritis: a discrete-choice experiment. *Rheumatology (Oxford)* 2016;55:1959-68.
14. Koster ES, Blom L, Philbert D, Rump W, Bouvy ML. The Utrecht Pharmacy Practice network for Education and Research: a network of community and hospital pharmacies in the Netherlands. *Int J Clin Pharm* 2014;36:669-74.
15. ATC/DDD Index 2016. Accessed August 2016. Available at: www.whocc.no/atc_ddd_index.
16. Vass C, Gray E, Payne K. Discrete choice experiments of pharmacy services: a systematic review. *Int J Clin Pharm* 2015.
17. Vass C, Rigby D, Payne K. The Role of Qualitative Research Methods in Discrete Choice Experiments. *Med Decis Making* 2017;37:298-313.

18. Reed Johnson F, Lancsar E, Marshall D, Kilambi V, Muhlbacher A, Regier DA, et al. Constructing experimental designs for discrete-choice experiments: report of the ISPOR Conjoint Analysis Experimental Design Good Research Practices Task Force. *Value Health* 2013;16:3-13.
19. Bridges JF, Hauber AB, Marshall D, Lloyd A, Prosser LA, Regier DA, et al. Conjoint analysis applications in health--a checklist: a report of the ISPOR Good Research Practices for Conjoint Analysis Task Force. *Value Health* 2011;14:403-13.
20. Hauber AB, Gonzalez JM, Groothuis-Oudshoorn CG, Prior T, Marshall DA, Cunningham C, et al. Statistical Methods for the Analysis of Discrete Choice Experiments: A Report of the ISPOR Conjoint Analysis Good Research Practices Task Force. *Value Health* 2016;19:300-15.
21. Heringa M, Floor-Schreudering A, Tromp PC, De Smet PA, Bouvy ML. Nature and frequency of drug therapy alerts generated by clinical decision support in community pharmacy. *Pharmacoepidemiol Drug Saf* 2016;25:82-9.
22. Preston CL, ed. Stockley's Drug Interactions (Online). London, United Kingdom: Royal Pharmaceutical Society, The Pharmaceutical Press 2016.
23. Borgsteede SD, ed. Commentaren Medicatiebewaking 2015-2016 (Commentaries medication surveillance). Houten, The Netherlands: Health Base Foundation 2015.
24. Sawtooth Software. The CBC System for Choice-Based Conjoint Analysis (version 8). Technical Paper Series. 2013.
25. Smith SG, Curtis LM, O'Conor R, Federman AD, Wolf MS. ABCs or 123s? The independent contributions of literacy and numeracy skills on health task performance among older adults. *Patient Educ Couns* 2015;98:991-7.
26. Malloy-Weir LJ, Charles C, Gafni A, Entwistle VA. Empirical relationships between health literacy and treatment decision making: a scoping review of the literature. *Patient Educ Couns* 2015;98:296-309.
27. Zikmund-Fisher BJ, Smith DM, Ubel PA, Fagerlin A. Validation of the Subjective Numeracy Scale: effects of low numeracy on comprehension of risk communications and utility elicitations. *Med Decis Making* 2007;27:663-71.
28. Dolan JG, Cherkasky OA, Li Q, Chin N, Veazie PJ. Should Health Numeracy Be Assessed Objectively or Subjectively?. *Med Decis Making* 2015.
29. Galesic M, Garcia-Retamero R. Do low-numeracy people avoid shared decision making?. *Health Psychol* 2011;30:336-41.
30. Ishikawa H, Takeuchi T, Yano E. Measuring functional, communicative, and critical health literacy among diabetic patients. *Diabetes Care* 2008;31:874-9.
31. Van der Vaart R, Drossaert CH, Taal E, ten Klooster PM, Hilderink-Koertshuis RT, Klaase JM, et al. Validation of the Dutch functional, communicative and critical health literacy scales. *Patient Educ Couns* 2012;89:82-8.
32. Fagerlin A, Zikmund-Fisher BJ, Ubel PA, Jankovic A, Derry HA, Smith DM. Measuring numeracy without a math test: development of the Subjective Numeracy Scale. *Med Decis Making* 2007;27:672-80.
33. Sawtooth Software. The CBC Latent Class Technical Paper (version 3). 2004, United States.
34. Trevena LJ, Zikmund-Fisher BJ, Edwards A, Gaissmaier W, Galesic M, Han PK, et al. Presenting quantitative information about decision outcomes: a risk communication primer for patient decision aid developers. *BMC Med Inform Decis Mak* 2013;13 Suppl 2:S7.
35. Garcia-Retamero R, Galesic M. Using plausible group sizes to communicate information about medical risks. *Patient Educ Couns* 2011;84:245-50.

36. Peters E, Hart PS, Fraenkel L. Informing patients: the influence of numeracy, framing, and format of side effect information on risk perceptions. *Med Decis Making* 2011;31:432-6.
37. Griffith JM, Lewis CL, Hawley S, Sheridan SL, Pignone MP. Randomized trial of presenting absolute v. relative risk reduction in the elicitation of patient values for heart disease prevention with conjoint analysis. *Med Decis Making* 2009;29:167-74.
38. Ahmed H, Naik G, Willoughby H, Edwards AG. Communicating risk. *BMJ* 2012;344:e3996.
39. Schapira MM, Fletcher KE, Gilligan MA, King TK, Laud PW, Matthews BA, et al. A framework for health numeracy: how patients use quantitative skills in health care. *J Health Commun* 2008;13:501-17.
40. Ubel PA. Beyond costs and benefits: understanding how patients make health care decisions. *Oncologist* 2010;15 Suppl 1:5-10.
41. Power TE, Swartzman LC, Robinson JW. Cognitive-emotional decision making (CEDM): a framework of patient medical decision making. *Patient Educ Couns* 2011;83:163-9.
42. McDermott R. Medical decision making: lessons from psychology. *Urol Oncol* 2008;26:665-8.
43. Lancsar E, Louviere J. Deleting 'irrational' responses from discrete choice experiments: a case of investigating or imposing preferences?. *Health Econ* 2006;15:797-811.
44. Ryan M, Watson V, Entwistle V. Rationalising the 'irrational': a think aloud study of discrete choice experiment responses. *Health Econ* 2009;18:321-36.
45. Internet: toegang, gebruik en faciliteiten (Internet; access, use and facilities), Accessed 27 October 2016. Available at: http://statline.cbs.nl/Statweb.
46. Pieterse AH, de Vries M, Kunneman M, Stiggelbout AM, Feldman-Stewart D. Theory-informed design of values clarification methods: a cognitive psychological perspective on patient health-related decision making. *Soc Sci Med* 2013;77:156-63.
47. Van der Weijden T, Pieterse AH, Koelewijn-van Loon MS, Knaapen L, Legare F, Boivin A, et al. How can clinical practice guidelines be adapted to facilitate shared decision making? A qualitative key-informant study. *BMJ Qual Saf* 2013;22:855-63.

Appendix 1: Latent class model fitting characteristics

Number of classes	Patients				Pharmacists			
	Log-likelihood	McFaddens pseudo rho^2	AIC	BIC	Log-likelihood	McFaddens pseudo rho^2	AIC	BIC
1	-2084	0.16	4179	4210	-1085	0.27	2180	2208
2	-1973	0.20	3968	4036	-989	0.33	2000	2062
3	-1882	0.24	3798	3903	-927	0.37	1888	1984
4	-1842	0.26	3730	3872	-874	0.41	1795	1925
5	-1817	0.27	3692	3872	-856	0.42	1771	1935

AIC = Akaike information criterion; BIC = Bayesian information criterion

Appendix 2a: Basic characteristics of assigned patients per class

		Class 1: 'stability focused' (n=62)[a]	Class 2: 'risk focused' (n=125)[a]	Class 3: 'certainty focused' (n=111)[a]	P[b]
Age	Mean (sd)	63.5 (9.5)	63.7 (10.5)	65.8 (8.6)	0.16
Gender	Male	37 (59.7%)	79 (63.2%)	70 (63.1%)	0.88
Educational level[c]	Low	14 (23.3%)	28 (22.4%)	37 (33.9%)	
	Medium	25 (41.7%)	45 (36.0%)	45 (41.3%)	0.07
	High	21 (35.0%)	52 (41.6%)	27 (24.8%)	
Number of medicines in use	Mean (sd)	4.9 (2.6)	4.7 (2.7)	4.7 (2.9)	0.90
Duration of use of cardiovascular medicines	> 5 years	50 (80.6%)	84 (67.2%)	81 (73.0%)	0.15
SNS	Mean (sd)	4.2 (0.8)	4.3 (0.8)	4.1 (0.9)	0.13
FCCHL total	Mean (sd)	3.0 (0.5)	3.0 (0.5)	2.9 (0.5)	0.22
FCCHL functional	Mean (sd)	3.0 (0.5)	3.0 (0.5)	2.9 (0.6)	0.20
FCCHL communicative	Mean (sd)	3.2 (0.6)	3.2 (0.6)	3.1 (0.5)	0.51
FCCHL critical	Mean (sd)	2.6 (0.7)	2.7 (0.7)	2.6 (0.7)	0.43

FCCHL = Functional Communicative and Critical Health Literacy Scales; sd = standard deviation; SNS = subjective numeracy scale

[a] Pharmacists assigned to the class for which they had the highest probability

[b] ANOVA for continuous variables, Pearson Chi square for categorical variables

[c] 4 missing

Appendix 2b: Basic characteristics of assigned pharmacists per class

		Class 1: 'risk focused' (n=54)[a]	**Class 2: 'stability focused' (n=55)[a]**	**Class 3: 'practicality focused' (n=69)[a]**	**P[b]**
Age	Mean (sd)	47.0 (10.6)	40.9 (11.9)	42.2 (10.6)	0.01
Gender	Male	33 (61.1%)	16 (29.1%)	28 (40.6%)	0.00
Years of practice in community pharmacy	0-5	4 (7.4%)	18 (32.7%)	14 (20.3%)	
	6-15	19 (35.2%)	14 (25.5%)	24 (34.8%)	0.02
	>15	31 (57.4%)	23 (41.8%)	31 (44.9%)	
Location of pharmacy	Village (up to 20,000 inhabitants)	24 (44.4%)	21 (38.2%)	26 (37.7%)	
	Town (20,00-150,000 inhabitants)	16 (29.6%)	23 (41.8%)	22 (31.9%)	0.55
	City (over 150,000 inhabitants)	14 (25.9%)	11 (20.0%)	21 (30.4%)	
Type of community pharmacy	Community health center (vs other)	32 (59.3%)	29 (52.7%)	31 (44.9%)	0.28

[a] Pharmacists assigned to the class for which they had the highest probability

[b] ANOVA for continuous variables, Pearson Chi square for categorical variables

Chapter 4.2

Understanding patient preferences for the management of drug-drug interactions

Mette Heringa
Annemieke Floor-Schreudering
Peter A.G.M. De Smet
Marcel L. Bouvy

Submitted

Abstract

Objective

The management of drug-drug interactions (DDI) involves a complex risk-benefit assessment, in which patients' preferences should be taken into account. The aim of this study was to examine the aspects influencing patients' preferences with regard to DDI management options.

Methods

Five focus groups with patients chronically using cardiovascular drugs were conducted. Key questions concerned preferences regarding DDI management options for a provided fictitious DDI. Thematic analysis of the verbatim transcripts was performed.

Results

Despite their limited knowledge with respect to DDIs, patients easily chose a management option for the presented DDI. When additional information was provided, preferences showed to be unsteadfast. Ten interdependent aspects influencing preferences were derived from patients' argumentations: risk perception, fear, acceptance of uncertainty, openness to change, willingness to take risk, trust in health care professional, financial & practical burdens, health condition, experience, and knowledge & assumptions. Most patients expressed great interest in being well informed, but were hesitant towards actual shared decision making.

Discussion and Conclusion

Patients' preferences regarding DDI management options were often determined by provided information. Preferences were dependent on an interplay of diverse aspects. Tailored provision of information and individualized counseling is needed for active patient involvement in DDI decision making.

Introduction

Clinical decision making on drug-drug interactions (DDIs) is complex. Health care professionals use DDI management guidelines which recommend one or more management options for every DDI. These options can include, for example, additional monitoring, switch to an alternative drug or dose adjustment. In daily practice, the choice between DDI management options is usually made by health care professionals, with limited patient involvement in decision making.

DDI management recommendations are generally developed in the tradition of evidence based medicine, with a focus on risk-benefit assessments. Although it is acknowledged that in essence evidence based medicine should also include the patient's perspective, in DDIs this is not often the case, yet [1, 2]. Frameworks like Grading of Recommendations Assessment, Development and Evaluation (GRADE) can guide the development and presentation of clinical guidelines [3, 4]. These frameworks have also been applied during the development of DDI management recommendations [5, 6]. The structured assessment in the GRADE framework includes a weighing of advantages and disadvantages. The uncertainty about or variability in how much patients value the involved health outcomes is one of the criteria included in the framework. In addition, the acceptability and feasibility of the intervention for the patient are part of the framework. These criteria may influence the strength of a recommendation, which in the GRADE framework is classified as weak (conditional) or strong.

In case of weak recommendations, the importance of shared decision making (SDM) is emphasized, as patient preferences may become a decisive factor [7]. Weak evidence and therefore weak recommendations are not unusual in case of DDIs and other drug therapy related problems. Whereas this suggests that patients should be involved in decision making, patients seem to be rarely involved in DDI management in daily practice. A potential explanation could be the complexity of DDI management, with at least two involved therapies and several management options with all their advantages and disadvantages.

For incorporating the patient's perspective in decision making on the individual level, awareness of potential preferences is needed. Having insight in the reasoning and values behind the preferences could be helpful for health care professionals to understand and interpret them. Knowledge in this field is conspicuously absent. Therefore, the aim of this study is to examine the aspects influencing patients' preferences regarding DDI management.

Methods

Patient selection and recruitment

Focus groups were conducted in five community pharmacies on different locations in the Netherlands. Patients were eligible when they were 18-85 years old, Dutch speaking, and healthy enough to participate in a focus group meeting in the pharmacy (according to the pharmacist). Moreover, patients had to have used cardiovascular drugs for over one year. This subgroup was selected to ensure that the patients were experienced drug users. Moreover, in this patient group the occurrence of DDIs is very frequent [8]. In each pharmacy patients with a specific user profile of cardiovascular medication were selected to increase group homogeneity in order to enhance interaction among participants. Selections were made based on the electronic patient records from the pharmacy information system, including drug dispensing history and coded chronic conditions. The five selected groups were: 1) patients with heart failure, using a loop diuretic; 2) patients with diabetes, using a renin-angiotensin system inhibitor; 3) patients using a platelet aggregation inhibitor, without heart failure or diabetes; 4) patients using lipid lowering drugs, without heart failure, diabetes, or use of antithrombotic drugs; 5) patients with hypertension using antihypertensive drugs, without heart failure, diabetes, or use of antithrombotic drugs.

Per pharmacy, a random sample of 60 selected patients were invited by letter. After one week patients were contacted by phone until at least eight patients had agreed to participate. These patients received a confirmation letter, a six-question questionnaire (basic characteristics including age, gender and educational level), and an informed consent form. Patients received a reminder phone call one day before the meeting. Questionnaires and informed consents were collected at the start of the meeting. After the meeting, participants received a 20 euro gift voucher.

Topic guide development

A topic guide was developed based on the research question and with feedback from researchers with experience in focus group research. The first focus group meeting was used as pilot, leading to the final topic guide, see Figure 1. The used DDI example was fictitious, but based on realistic DDIs and DDI management options [9, 10]. The options were chosen to include the domains of GRADE, including risks (both rare risks and common side effects), benefits and practical implications [3, 4].

Conduction of focus groups

The focus groups (one in the morning, four after working hours) were conducted in the community pharmacies and lasted two hours. The focus groups were run by three researchers / pharmacists: a moderator who had a training on focus group moderation (MH), an observer (making field notes), and a technical leader (at least one of the latter two was experienced in focus groups, being AF or MB). The participants did not know the moderator; she was introduced as a researcher in drug-drug interactions, interested in patients' opinions on DDI management in the context of patient centered care.

Data analysis

After every focus group the attending researchers discussed the results based on the field notes. Focus groups were audiotaped and transcribed ad verbatim. The analysis of the transcripts was performed in NVivo qualitative data analysis software (QSR International Pty Ltd. Version 11, 2015). Inductive thematic analysis with open codes was applied [11, 12]. One focus group was independently coded by MH and AF, and consensus on the coding scheme was reached. The other focus groups were coded by MH, and in case of doubt discussed with AF. Codes were thematically clustered into aspects influencing preferences. Applicability of these aspects to the coded fragments was continuously verified. Determined aspects and interpretation of findings were repeatedly discussed in the research team (MH, AF, PDS, MB) and verified with the data until consensus was reached. Reporting was conducted taking into account the Consolidated criteria for reporting qualitative research (COREQ) [13].

Ethics and confidentiality

The Institutional Review Board of the Division of Pharmacoepidemiology and Clinical Pharmacology of the Utrecht University approved the investigation and the work was conducted in compliance with its requirements. All participating patients signed informed consent and all data were anonymized during transcription.

Introduction & transition (engagement questions)

- Why do you join this meeting?
- Have you ever experienced a situation in which two medications did not go well together (or other problems with medications), and how was it managed?

Case description

Imagine: you suffer from pneumonia. Your doctor suggests starting an antibiotic for 10 days. The combination of the antibiotic and your cardiovascular drug can cause muscle pain. In rare cases even serious muscle problems can occur (with hospitalization and risk of permanent kidney damage).

What to do? (management options)

A. No action. Use the antibiotic and your cardiovascular drug concurrently
B. Switch to another cardiovascular drug
C. Switch to a second choice antibiotic
D. Use the antibiotic and your cardiovascular drug concurrently + two blood tests to detect emerging muscle problems

Key (exploration) questions

- In this example: which management option do you prefer and why?
- Would you like to have more information about the management options? Which one(s)?
- Considering the information on risks and benefits:
  - Which risks do you consider to be frequent?
  - Which risks do you consider to be serious?
- Which should, in your opinion, be the role of the health care professional and you in the management of drug-drug interactions?

Additional information *(provided stepwise and written down on flipchart)*

Characteristics of management options		***Option***
Risk of serious muscle problems with permanent muscle damage	3 out of 10.000	A
	1 out of 10.000	B, C, D
Chance of recovery from pneumonia without hospitalization	95 out of 100	A, B, D
	90 out of 100	C
Switch to another cardiovascular drug	Yes	B
	No	A, C, D
Blood sampling	Yes	D
	No	A, B, C
Moderate muscle pain	10 out of 100	A, D
	5 out of 100	B, C
Nonrefundable costs (to be paid by patient)	0 euro	A, B, C
	25 euro once	D

Figure 1: Focus group topic guide and case description

Results

Participants and focus groups

Five focus groups with 5, 8, 10, 7 and 8 participants were conducted in five different community pharmacies. Because after the first pilot focus group no substantial changes in the topic guide were needed, this focus group was included in the analysis. Data saturation was likely to be reached as no new aspects were derived from the last focus group. Sixteen participants were male and 21 female, their age ranged from 49 to 84. The educational level was diverse: 25 participants were low educated, eight medium, and five high. For patient characteristics per focus group, see Appendix 1.

Patients' preferences and decision making

The participants had little knowledge about the subject of DDIs. When confronted with the example, patients intuitively decided on their preference for a management option. They expressed hardly any need for additional information preceding their decision. Preferences, however, were not steadfast. After additional information was actively provided (Figure 1), many patients switched (repeatedly) to another option. Moreover, a few patients mentioned that their current preference could be different from the one in reality, because of the hypothetical nature of the example.

Aspects behind patients' preferences

Out of patients' rationales for their preferences, ten aspects were derived. The aspects were in the cognitive, emotional, personal and situational domain (Figure 2). The ten aspects were gradual concepts: they could be either low or high, positive or negative. The expressed preference was dependent on a complex interplay between the aspects. The aspects could apply to all characteristics of the management options (e.g. fear could –to a different extent- apply to pneumonia, to muscle damage, or to replacement of current medication). Moreover, there was high mutual interdependency between the aspects, e.g. a bad experience could lead to fear, which could lead to unwillingness to take risk, etcetera. The interdependency is reflected in the citations below.

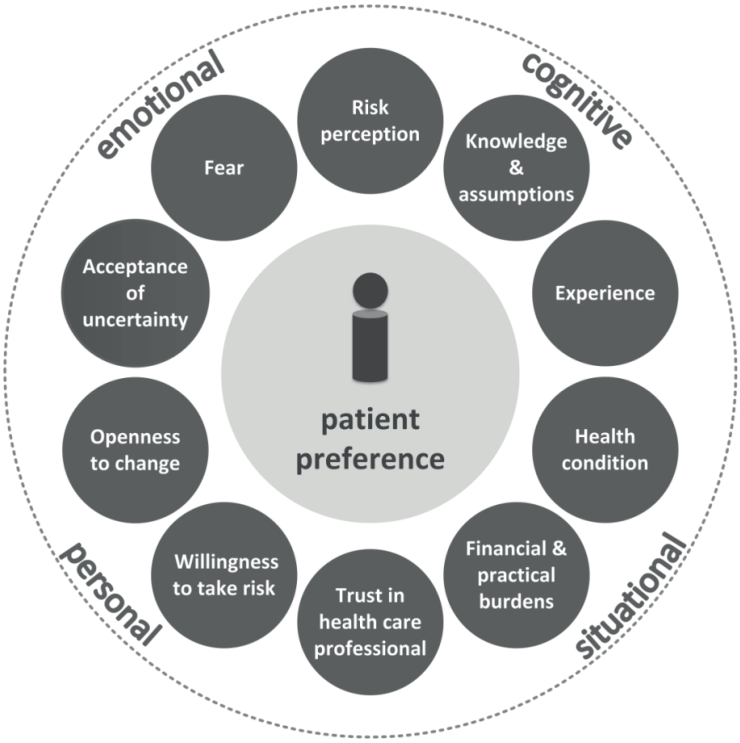


Figure 2: Aspects of patients' preferences regarding drug-drug interaction management options

Risk perception

The perception whether presented risks were high differed between participants. In the perception of the magnitude of the risk, both seriousness and incidence were included, and in some cases duration of the risk. Three considerations contributed to the perceived seriousness of a risk: whether you could die from it, whether it could cause permanent (organ) damage, and whether the potential effect was short lasting or long lasting:

> *If you have muscle pain for only one week, and when it's the only option, you take the risk. But when muscle pain becomes chronic, it is a whole different story.* [participant 5, group 1]

> *I assume you don't die from muscle problems, but you can die from pneumonia.* [participant 2, group 1]

The risk of 1 or 3 out of 10,000 was generally perceived as very small; the difference between them mattered to some, but not to all patients. A likelihood that pneumonia is cured of more than 90% was generally perceived as high. Whether the difference between 90% and 95% mattered was variably perceived, but often the difference was irrelevant to the participants.

> *I think 3 out of 10,000 is not a substantial risk. It leaves a lot of healthy people. It wouldn't keep me awake at night.* [participant 2, group 5]

> *I prefer the option with another [second choice] antibiotic; 5% difference [in curation rate] is negligible.* [participant 4, group 1]

To reduce the abstractness of risks, some participants compared them with rare events from other life areas (for example lotteries and earthquakes). In the interpretation of risks, a binary approach was often seen: either a focus on the ever-present possibility of being affected, or a focus on the extreme unlikeliness of being affected.

> *It is said an earthquake happens only once in 10,000 years – it could happen tomorrow [but that would be very coincidental].* [participant 7, group 3]

> *It could be my neighbor and me [who are affected by a risk of 3 out of 10,000].* [participant 2, group 1]

Fear

Fear concerned reoccurrence of events patients had already experienced as well as the occurrence of new health problems (especially the permanent renal damage and potentially fatal pneumonia from the presented example). Fear increased by information about potential risks.

> *I think it is a bit scary that many old people die from pneumonia.* [participant 2, group 1]

> *I'm scared. Eleven years ago, I got a mechanical heart valve, and I still live in fear.* [participant 6, group 2]

> *It would scare me off that it can cause permanent kidney failure.* [participant 3, group 5]

Acceptance of uncertainty

Uncertainty about outcomes was generally considered as unpleasant. Management options were assessed for the degree of certainty and whether the par-

ticipants felt in control. Having certainty, or being in control, was an important consideration for preferring blood testing. Mild adverse effects were perceived as more acceptable when the origin was known, thus providing certainty that they were not threatening. Opposite the wish for control and reassurance, was the realization that absolute certainty does not exist in life.

I prefer to be monitored. Then I am sure that things are going well. I think... I hope…. [participant 1, group 4]

You never know what is the best choice; when you are ill, you are at the mercy of the gods. [participant 7, group 2]

There's no guarantee that you won't be affected. [participant 5, group 5]

Openness to change

One of the management options included change of current medication. Many participants expressed strong attachment to their current medication, because they wanted to maintain the current stable situation. Some participants were open to change, but only when it was advised by their trusted physician. This openness for change was either related to the perception that the cardiovascular drug was not that essential, or by the perception that the importance of optimal treatment of the pneumonia could outweigh the initial resistance to the switch of the cardiovascular medicine.

I would be reluctant to switch the cardiovascular medicines. …..it's a balanced combination – you should just keep your hands off. [participant 2 group 1]

The heart is doing well by now. So, let them adapt the antibiotic. You are already used to the cardiovascular medicine and when you change it, other complications may occur. [participant 4 group 2]

Willingness to take risk

Risk played also a role in a person's willingness to take risk. Elimination of risk was generally motivated by the wish to prevent everything you could prevent. Low risk tolerance was motivated by the importance of health. Acceptance of risk was motivated by the fact that risk is everywhere in life.

Just try the combination – I'll be the guinea pig. [participant 3, group 1]

If you can potentially prevent something you should do so. Otherwise you play with people's health. [participant 1, group 1]

Trust in health care professional

Patients would take certain management options only under consideration when they were advised by their prescriber. Furthermore, the mere fact that a health care professional mentioned a certain situation as risky (e.g. the DDI), was for some patients reason not to take a risk, even when they assessed the risk themselves as negligible.

> *I am specifically told that the situation entails a risk. That triggers me and gets stuck in my mind.* [participant 3, group 5]

> *I won't mind [changing my lipid lowering drugs] when it is my cardiologist's advice. I trust him, and that's important for me.* [participant 6 group 2]

Financial & practical burdens

By most participants, health was seen as too important to save costs on monitoring like blood testing. The participants did, however, assume that some people would decline blood testing when they had to pay the costs themselves. Venipuncture itself was generally not perceived a burden as most participants were used to it.

> *Buckets of blood have already been sampled.* [participant 5, group 1]

> *I won't mind to pay 25 euros, I prefer to eliminate all risks.* [participant 3 group 5]

Health condition

Current health condition influenced patients' preferences. In general, suboptimal health led to increased risk averseness, in order to prevent further deterioration. The seriousness of the indication of the cardiovascular medicine also was taken into account by participants, especially with regard to the option to replace the cardiovascular medicine.

> *When your physical situation is less than optimal, you want to prevent any further deterioration.* [participant 3 group 4].

> *I always have muscle pain, so it doesn't matter [whether the risk of muscle pain is 5% or 10%].* [participant 2, group 3]

Experience

Former experiences - either related to health care or not - were part of the argumentation for current preferences. Both positive and negative experiences were

seen as forecast of future outcomes. Not only own experiences were taken into account, but also experiences of relatives and acquaintances.

> *In the past, I used some other medicines and I had a venipuncture. That will have had a reason. So I prefer the option with blood testing.* [participant 7, group 2]

> *Once, I have experienced serious side effects. I just don't want that ever again.* [participant 6, group 5]

> *My father-in-law suffered from pneumonia. He was in his bed, wheezing all the time, while using antibiotics. It took an entire week or even longer before the wheezing reduced.* [participant 3, group 3]

Knowledge and assumptions

Participants' knowledge about health and medicines influenced their preferences. The discussed knowledge included both correct information and incorrect assumptions. Some patients stuck to incorrect assumptions even when information falsifying their assumptions was presented.

> *There isn't any difference between this and that antibiotic, is there? I think an antibiotic is just antibiotic.* [participant 1, group 3]

> *It takes three days for a medicine to leave your body.* [participant 5, group 2]

> *When you are diagnosed with pneumonia, I think that your doctor wants to see you within a few days. When you tell him that you have serious muscle pain, he has all information he needs.* [participant 8, group 2]

The decision making process

In addition to their preference and rationale for a DDI management option, patients expressed their preferences for the DDI decision making process. Because of the unfamiliarity with DDI management, patients often referred to the medical decision making process in general. Key themes were trust, responsibility, expertise, and communication. Trust in the physician and a gap in expertise between physician and patient were main arguments for the preference to have the physician in the lead in DDI decision making. Nevertheless, most patients preferred to receive information about potential options. Some patients were interested in more active involvement in the decision making process, while others preferred to leave the decision completely to the health care professional (sometimes referring to the health care professionals' responsibility). A few patients explicitly recognized an own responsibility in (DDI) decision making. Trust in

the general practitioner with regard to decision making and in the pharmacist with regard to monitoring of medication safety was high.

Discussion

DDI management is a specialist field which is unfamiliar to most patients. Patients in our study could easily express their intuitive preferences for DDI management options, however these preferences were not steadfast. Preferences were influenced by ten interdependent aspects from the cognitive, emotional, situational and personal domain. In thinking on risk, the main considerations expressed were the seriousness, incidence and duration of the risk and whether to avoid any risk or to accept risks because of its inevitability.

It is well known that the understanding of risk measures is complicated and subject to many biases. Framing of outcomes affects choices: describing potential gains can lead to risk-averse choices; describing potential losses can lead to risk-seeking choices; however, effects seem to vary across situations and to depend on the exact presentation of information [14]. In our study, serious, but very small risks described in terms of loss were often perceived as relevant for the assessment (e.g. muscle damage in 1 or 3 out of 10,000). Curation rates (wins) of 90% and 95% were quite often perceived as comparable and therefore less relevant for the overall assessment. More in general, outcomes that give negative feelings –like health problems - lead to high risk estimates [15]. In addition, having to choose in health issues can cause stress, and hasty, irrational choices can be a way to cope with the decisional conflict [15].

We showed that patients' preferences for DDI management were dependent on a broad range of aspects, related to thinking (cognitive), feeling (emotional), character (personal) and current situation (situational). In general terms, the aspects we found were consistent with the aspects and domains which have been shown to be relevant in other investigations. This includes the combination of both cognitive and emotional aspects [15-17], and the wide range of aspects involved in risk perception [18]. Although several frameworks and models in the field of health decision making have been published, none of these models focuses on patients' reasoning. Models related to decision making generally cover the complete decision making process, while we focused on one of the steps: the 'preference construction' [15-17]. Frameworks for the development of clinical recommendation like GRADE focus on factors in the risk-benefit assessment rather than the underlying rationale or reasoning [3, 4]. Models for health

behavior and adherence have a focus on motivation and capability to undertake action [18-20]. In models related to SDM, process and knowledge are generally central factors, rather than aspects behind patients' preferences and perceptions [21-24]. For more details, see Appendix 2.

In situations with weak evidence (which is often the case in DDI management), guidelines advice SDM [7]. At the same time, it has been argued that the complex situation and uncertainty originating from weak recommendations could hamper SDM, because extensive professional guidance is inevitable [25]. However, recently it has been shown that even in the complex setting of an emergency department, SDM including risk communication is feasible [26, 27].

SDM in DDI decision making is not obvious yet, neither for patients, nor for health care professionals. In our study, patients were reluctant to take a more active role in DDI decision making, with a lack of expertise as one of their explanations. SDM is by definition tailored to the patients' needs – which can mean that some patients prefer limited patient involvement. We observed that patients often did not ask for information, but that their preferences changed when information was actively provided. To enable and foster SDM, provision of information to patients is essential. This is challenging, as a neutral presentation of information about risks and benefits without any framing is hardly possible [28]. Moreover, it has been shown that there is no clear relationship between patients' perception on being well informed and their actual knowledge [29], and that people generally do not realize to what extent their decisions are based on (in)correct assumptions [30]. Incorrect assumptions were common in patients' argumentations in our study.

SDM includes much more than provision of information. Health care professionals should be aware of patients' preferences, (treatment) goals and values. Our study showed that the range of aspects influencing preferences is broad. It will depend both on the patient and the present choice which aspects are decisive. SDM can be expected to be most appropriate for DDIs with several equivalent management options. But even for one-option DDIs (e.g. separation of dosing moments), patients could be asked how they think about the option. SDM is especially relevant when the DDI concerns long-term medication, and when variability in preferences can be expected (e.g. in case of change of current medication, or rare side effects, as seen in our example). For other drug therapy related problems, similar considerations can be applied.

Our study has strengths and limitations. A strength is that we presented an integrated situation involving both the DDI itself and its management options.

Therefore, advantages and disadvantages of the overall situation were assessed, consistent with the multifactorial complexity of the management of drug therapy related problems in daily practice.

A limitation is that the focus groups were about a hypothetical example. When patients are confronted with a DDI in real-life, their preference could be different. Moreover, only patients using cardiovascular medicines participated in the focus groups. In other patient groups or in real-life situations, patients can have other preferences, but it is unlikely that the underlying aspects will be different from the general aspects found in our study. The majority of participants were low educated, but this is consistent with the educational level of older cardiovascular patients in general. Finally, our study was an explorative investigation. For validation of the resulting aspects, additional research is needed.

Practice implications

In our study, patients did not ask for additional information themselves. However, their preferences changed when more information was actively provided. Therefore, health care professionals should invest in informing patients about drug therapy related problems in a way and extent appropriate for the individual patient. Health care professionals should realize that they may unintendedly influence patients' preferences when providing information about risks and benefits. Moreover, health care professionals should be aware that in addition to cognitive aspects, both emotional and personal aspects are important. These are preferably integrated in their consultations. In addition, potential burdens –like costs or venipuncture – should be discussed in decision making. For this kind of counseling, health care professionals need excellent communication skills.

Conclusion

Patients' preferences regarding DDI management options were determined by provided information and therefore unsteadfast. The preferences were dependent on the interplay of ten aspects, from the cognitive, emotional, personal and situational domain. The interdependency between the aspects was high, and many of them were related to risk assessment. Tailored provision of information and individualized counseling is needed for active patient involvement in DDI decision making.

Acknowledgements

We thank all patients who participated in this study. We thank the community pharmacists in whose pharmacies the focus groups took place. And we thank M. van Leeuwen, who coordinated the organization of the focus groups.

References

1. Schoemaker CG, van der Weijden T. Patient preferences versus evidence-based medicine: did the pioneers of evidence-based medicine take the patient's preferences into account?. *Ned Tijdschr Geneeskd* 2016;160:D24.
2. Greenhalgh T, Howick J, Maskrey N, Evidence Based Medicine Renaissance Group. Evidence based medicine: a movement in crisis?. *BMJ* 2014;348:g3725.
3. Guyatt GH, Oxman AD, Kunz R, Falck-Ytter Y, Vist GE, Liberati A, et al. Going from evidence to recommendations. *BMJ* 2008;336:1049-51.
4. Alonso-Coello P, Oxman AD, Moberg J, Brignardello-Petersen R, Akl EA, Davoli M, et al. GRADE Evidence to Decision (EtD) frameworks: a systematic and transparent approach to making well informed healthcare choices. 2: Clinical practice guidelines. *BMJ* 2016;353:i2089.
5. Floor-Schreudering A, Geerts AF, Aronson JK, Bouvy ML, Ferner RE, De Smet PA. Checklist for standardized reporting of drug-drug interaction management guidelines. *Eur J Clin Pharmacol* 2014;70:313-8.
6. Scheife RT, Hines LE, Boyce RD, Chung SP, Momper JD, Sommer CD, et al. Consensus Recommendations for Systematic Evaluation of Drug-Drug Interaction Evidence for Clinical Decision Support. *Drug Saf* 2015;38:197-206.
7. Neumann I, Santesso N, Akl EA, Rind DM, Vandvik PO, Alonso-Coello P, et al. A guide for health professionals to interpret and use recommendations in guidelines developed with the GRADE approach. *J Clin Epidemiol* 2016;72:45-55.
8. Heringa M, Floor-Schreudering A, Tromp PC, De Smet PA, Bouvy ML. Nature and frequency of drug therapy alerts generated by clinical decision support in community pharmacy. *Pharmacoepidemiol Drug Saf* 2016;25:82-9.
9. Borgsteede SD, ed. Commentaren Medicatiebewaking 2015-2016 (Commentaries medication surveillance). Houten, The Netherlands: Health Base Foundation 2015.
10. Preston CL, ed. Stockley's Drug Interactions (Online). London, United Kingdom: Royal Pharmaceutical Society, The Pharmaceutical Press 2016.
11. Braun V, Clarke V. Using thematic analysis in psychology. *Qualitative Research in Psychology* 2006;3:77-101.
12. Vaismoradi M, Jones J, Turunen H, Snelgrove S. Theme development in qualitative content analysis and thematic analysis. *Journal of Nursing Education and Practice* 2016;6:100-10.
13. Tong A, Sainsbury P, Craig J. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. *Int J Qual Health Care* 2007;19:349-57.
14. Trevena LJ, Zikmund-Fisher BJ, Edwards A, Gaissmaier W, Galesic M, Han PK, et al. Presenting quantitative information about decision outcomes: a risk communication primer for patient decision aid developers. *BMC Med Inform Decis Mak* 2013;13 Suppl 2:S7.
15. Power TE, Swartzman LC, Robinson JW. Cognitive-emotional decision making (CEDM): a framework of patient medical decision making. *Patient Educ Couns* 2011;83:163-9.
16. Witt J, Elwyn G, Wood F, Rogers MT, Menon U, Brain K. Adapting the coping in deliberation (CODE) framework: a multi-method approach in the context of familial ovarian cancer risk management. *Patient Educ Couns* 2014;97:200-10.
17. Witt J, Elwyn G, Wood F, Brain K. Decision making and coping in healthcare: the Coping in Deliberation (CODE) framework. *Patient Educ Couns* 2012;88:256-61.
18. Janz NK, Becker MH. The Health Belief Model: a decade later. *Health Educ Q* 1984;11:1-47.

19. Cane J, O'Connor D, Michie S. Validation of the theoretical domains framework for use in behaviour change and implementation research. *Implement Sci* 2012;7:37,5908-7-37.
20. World Health Organization. Adherence to long-term therapies: evidence for action. 2003, Geneva, Switzerland.
21. Moore JE, Titler MG, Kane Low L, Dalton VK, Sampselle CM. Transforming Patient-Centered Care: Development of the Evidence Informed Decision Making through Engagement Model. *Womens Health Issues* 2015;25:276-82.
22. Kaltoft M, Cunich M, Salkeld G, Dowie J. Assessing decision quality in patient-centred care requires a preference-sensitive measure. *J Health Serv Res Policy* 2014;19:110-7.
23. O'Connor AM, Tugwell P, Wells GA, Elmslie T, Jolly E, Hollingworth G, et al. A decision aid for women considering hormone therapy after menopause: decision support framework and evaluation. *Patient Educ Couns* 1998;33:267-79.
24. Malloy-Weir LJ, Charles C, Gafni A, Entwistle VA. Empirical relationships between health literacy and treatment decision making: a scoping review of the literature. *Patient Educ Couns* 2015;98:296-309.
25. Fried TR. Shared Decision Making--Finding the Sweet Spot. *N Engl J Med* 2016;374:104-6.
26. Hess EP, Hollander JE, Schaffer JT, Kline JA, Torres CA, Diercks DB, et al. Shared decision making in patients with low risk chest pain: prospective randomized pragmatic trial. *BMJ* 2016;355:i6165.
27. Stiggelbout AM, Jukema JW, Engelhardt EE, van den Bos C, Pieterse AH. Communicating risk to patients in the emergency department. *BMJ* 2016;355:i6437.
28. Peters E, Hibbard J, Slovic P, Dieckmann N. Numeracy skill and the communication, comprehension, and use of risk-benefit information. *Health Aff (Millwood)* 2007;26:741-8.
29. Sepucha KR, Fagerlin A, Couper MP, Levin CA, Singer E, Zikmund-Fisher BJ. How does feeling informed relate to being informed? The DECISIONS survey. *Med Decis Making* 2010;30:77S-84S.
30. McDermott R. Medical decision making: lessons from psychology. *Urol Oncol* 2008;26:665-8.

Appendix 1: Participant characteristics

Focus group	Participant	Gender	Age	Educational level[a]
1: patients with heart failure, using a loop diuretic	1	male	63	low
	2	male	74	low
	3	male	80	low
	4	female	65	low
	5	male	85	low
2: patients with diabetes, using a renin-angiotensin system inhibitor	1	male	82	low
	2	male	70	medium
	3	male	59	low
	4	male	72	low
	5	male	75	low
	6	female	69	low
	7	female	61	low
	8	female	75	low
3: patients using a platelet aggregation inhibitor, without heart failure or diabetes	1	female	78	low
	2	male	85	high
	3	female	57	high
	4	male	71	medium
	5	female	83	low
	6	male	78	low
	7	male	83	medium
	8	female	70	low
	9	female	76	medium
	10	female	79	low
4: patients using lipid lowering drugs, without heart failure, diabetes, or use of antithrombotic drugs	1	female	64	low
	2	female	70	medium
	3	male	68	high
	4	female	75	low
	5	female	67	low
	6	female	78	low
	7	female	70	low
5: patients with hypertension using antihypertensive drugs, without heart failure, diabetes, or use of antithrombotic drugs	1	female	67	high
	2	male	71	high
	3	female	64	medium
	4	female	67	low
	5	male	50	medium
	6	female	63	medium
	7	female	75	low
	8	female	78	low

[a] Educational level was categorized as low (primary education or lower secondary), medium (intermediate/higher secondary or intermediate vocational), or high (higher vocational/university).

Appendix 2: Existing models and frameworks related to decision making in health care

Type	Examples	Details	Relation to current study
Decision making process	CEDM framework (cognitive-emotional decision making) [15], CODE framework (coping in deliberation) [16, 17]	Frameworks covering the subsequent steps of the decision making process; includes both cognitive and emotional aspects.	The current research question is part of one step of the CODE framework: the 'preference construction' (and especially the appraisal related part).
Guidelines for developing clinical recommendations	GRADE (Grading of Recommendations Assessment, Development and Evaluation) evidence to decision frameworks [3, 4]	GRADE offers a systematic approach well-informed health care choices. The framework includes, among other factors, risk, benefit, practical implications and (variability in) patient values.	Compared to our current study, GRADE focuses on the actual factors included in the risk-benefit assessment rather than the underlying rationale or reasoning.
Health behavior including adherence	Leventhal's Health Belief Model [18], World Health Organization's five dimensions of adherence [20], theoretical domains framework [19]	Models related to (influencing) health behavior, which includes factors related to patients perceptions and decision making, but also motivation, self-efficacy and ability to undertake action.	Our study concerned patients' preferences, while these behavior related models are much broader, with a focus on patients' motivation and capability to undertake action.
Models related to shared decision making (SDM) and patient centered care	SDM models related to (quality of) process and decision aids, including the Ottawa decision support framework [21-24]	Models covering the complete process of patient centered decision making up to evaluation, and assessment of decision quality by a patient decision aid.	Compared to our current study, SDM related models have a focus on process and/or knowledge, rather than on including specific factors behind patients' preferences and perceptions.

5. General discussion

Introduction

Every action or omission of action in health care has a certain risk of harming one's health. The occurrence of patient harm caused by health care – including drug use - has been shown over and over again [1-4]. It has been acknowledged that a substantial part of patient harm is potentially preventable, and that a substantial part is medication related [3-6]. This has led to multiple recommendations directed at the prevention of drug therapy related problems (DTRPs). A DTRP can be defined as any undesirable event or risk thereof, experienced by a patient, that involves drug therapy and that actually or potentially interferes with the achievement of an optimal outcome. DTRPs are preventable when they are caused by errors in prescribing, dispensing or using drugs.

Clinical risk management (CRM) is a concept to prevent patient harm by risk-reducing strategies. It is a systematic approach including risk detection, assessment, management and evaluation [7-10]. The scope of this thesis is the CRM of drug therapy. This involves the complete drug chain: drug development and regulation, drug-related guideline development, drug prescribing, drug dispensing and drug use. CRM of drug therapy includes a broad range of strategies, actions, tools and measures. One of these are clinical decision support systems (CDSSs), which help health care professionals to detect DTRPs. CDSSs have been shown to reduce the number of DTRPs, for example the occurrence of drug-drug interactions, inappropriate dosing in patients with renal impairment, and the occurrence of adverse events [11-14]. The use of CDSSs also has drawbacks. Both the limited specificity and the limited sensitivity of current systems give rise to problems. The high alert rate in combination with the low alert specificity can lead to alert fatigue with the risk of missing important alerts [15, 16]. Despite the effort put in CDSS improvement, the progress with respect to increasing alert specificity is limited [17]. With regard to sensitivity, it has been shown that health care professionals detected a substantial number of DTRPs which were not detected by CDSSs [18, 19]. Continuous development of CDSSs is essential, firstly to improve their intrinsic performance in detecting DTRPs, and secondly for alignment with changes in society and clinical practice. The development of CDSSs should be seen in the broader perspective of the development of CRM. CDSSs are useful to support health care professionals, but they cannot fully take over the prevention of DTRPs. With the studies presented in this thesis we aimed to provide evidence to give direction to the further development of clinical decision support as a tool for CRM of drug therapy.

Evidence presented in this thesis

In this thesis, we presented studies related to improvement of clinical decision support in the field of drug therapy. In part 2 we showed the results of investigations into the current use of CDSSs in community pharmacy. We started in chapter 2.1 with the assessment of the electronic patient record (EPR), an important prerequisite for detecting DTRPs by CDSSs. We showed that in most EPRs data on medication or conditions were missing or incorrect, according to the information provided by the patient. Especially the registration of over-the-counter medication and chronic conditions was often incomplete. We showed that a more complete registration would have led to a substantial amount of drug therapy alerts by the CDSSs, which were missed in the current situation. In chapter 2.2 an overview of alerts generated by CDSSs in community pharmacy practice was presented. Almost half of the processed prescriptions led to one or more drug therapy alerts. Drug-drug interactions, drug-disease interactions and duplicate medication alerts were the most frequent alerts. The majority of alerts were concentrated in a minority of therapeutic drug groups and in a minority of patients. In chapter 2.3 we focused on one type of drug therapy alerts: the duplicate medication alerts. Our study showed that prescription modifications based on duplicate medication alerts were rare. However, the alerts were used as a trigger for other actions, e.g. updating the electronic patient record. Although these actions are in themselves useful, more specific alerting is possible.

In part 3 we presented the results of three improvement strategies for CDSSs. In chapter 3.1 we showed the feasibility of large scale implementation of advanced clinical decision support rules and point of care testing of renal function in community pharmacy. In chapter 3.2 it was shown that clusters of related drug interaction alerts were common and that using these clusters for alert generation substantially reduced the alert rate. This strategy could easily be extended to other alerts. In chapter 3.3 we presented another strategy to reduce the alert rate. We determined events which require a (re)assessment of a drug interaction, and we triggered alerts based on these events rather than for every repeat prescription. We demonstrated that this approach, by focusing on changes in the patient's situation, substantially reduced the number of repeat alerts.

Part 4 focused on choosing between management options of a detected DTRP. This choice requires an assessment of risks and benefits. In chapter 4.1 we showed that both among pharmacists and among patients, diverging preferences existed with regard to the management of drug-drug interactions. In chapter 4.2 we presented the results of an investigation of patients' reasoning underlying their preferences. The insight in the diverging preferences emerging from this chapter

can be incorporated in the development and application of recommendations on management of DTRPs.

Challenges and opportunities in CRM of drug therapy

The current implementation of CRM of drug therapy is challenged by developments within current CRM, developments in health care in general, and developments in society and technology. At the same time, some of the developments offer opportunities for improvement of CRM of drug therapy. Therefore, we first present an overview of developments relevant for the future, before we continue with a further elaboration of CRM of drug therapy.

- Because of the aging population, the number of patients with multimorbidity and polypharmacy increases [20, 21]. Aging of the population is associated with ***higher care needs***, while the availability of resources both in terms of finances and labor forces relatively decreases. It also is one of the reasons for public health policies that aim to shift activities from secondary care to primary care. This subsequently leads to increasing complexity in primary care and a need for more self-management of patients.
- In the past, every health care professional individually decided on the best therapy for a patient. To 'guarantee' a minimum quality of care, ***standardization*** and professional guidelines were introduced. However, rigid application of guidelines comes with problems, e.g., in case of multimorbidity and polypharmacy, conflicting recommendations occur [22, 23]. Moreover, checklists sometimes tend to be a goal rather than a tool. Health insurance companies and governmental authorities require extensive registration from health care professionals for reasons of accountability and control. This is time consuming, and therefore less time is available for actual provision of care. Dutch general practitioners (GP) united in a call to reduce bureaucratic administration and increase professional autonomy, which was widely supported by other health care professionals [24].
- More in general, the focus on quality, safety and accountability can be seen as an expression of the ***increasing risk averseness*** in current western society. An illustrative example can be found in a recent advice by VeiligheidNL, a Dutch Expert Organization for prevention of accidents. They advised in a national campaign to leave children more possibility for 'risky playing' in order to let them develop the capability to assess and handle risk (rather than protect them from every potential risk) [25]. A parallel can be seen with health care. In general, the introduction of protocols and procedures is favorable, but it should not decrease the ability of health care professionals to recognize, assess and manage risk themselves.

- The adoption of tools, especially computerized physician order entry (CPOE) systems in combination with CDSSs, is widespread in primary and secondary care practice. Despite their advantages, CPOE and CDSSs also have some drawbacks [26-29]. Automation can induce new types of errors, like selection errors [30]. For example: a pharmacy technician entered 'CHLOR25' in the system to select chlordiazepoxide 25 mg and accidentally chose from the resulting list chlortalidone 25 mg [30]. Moreover, with the increasing alert rates and the low specificity of alerts, the risk of ***alert fatigue*** and consequently overriding important drug therapy alerts increases [15, 16, 30-35].
- Most users will consider CDSSs indispensable. As with many technological developments (like navigation tools), high trust in these systems tends to lead to high dependency of these systems. Even more worrisome is the potential implicit assumption that managing CDSS alerts guarantees complete detection of DTRPs. This ***high trust in CDSSs*** could lead to decreased attention for other ways to detect DTRPs. CDSSs have been shown to be effective in detecting some categories of DTRPs (e.g. drug-drug interactions). However, even for well-detectable problems, the systems will never be perfect or complete. A small programming or user error can easily lead to missing alerts (e.g. in case of incomplete electronic patient records [36]). Moreover, several types of DTRPs cannot be detected by current CDSSs. Both for prescription modifications and for medication reviews it has been shown that a substantial part of the managed DTRPs were not detected by CDSSs, but by other means [18, 19, 37]. CDSSs predominately generate alerts based on explicit criteria, while several categories of DTRPs, like undertreatment and drug utilization problems, cannot easily be identified by these criteria [38].
- The ***amount of knowledge*** in the medical and pharmaceutical field increases exponentially: in Medline alone, about 4000 new publications come available every day. This includes knowledge on complex new medicines which are rapidly gaining market access, for example biologicals and cell therapy medicines [39]. Moreover, knowledge on existing medicines increases, for example about risk-modifying factors like interactions with genes or food [40, 41]. For the individual health care professional it is impossible to have all relevant knowledge in mind at the moment of decision making [42]. This problem is seen by health care professionals, but they generally do not recognize the extent of the problem [43]. Not using available knowledge can harm patients, for example when the dosage of chemotherapy is insufficiently adjusted to the body weight of obese patients [44].
- ***Big data*** is a development in which a huge amount of data from different sources and different domains are linked in order to identify patterns without

predefined hypothesis [45]. The data are used for other purposes than they were originally collected for. Big data in health care are seen as a promising development, especially in combination with machine learning. An example is IBM's supercomputer Watson, with specializations like Watson Care Manager and Watson for Oncology [45, 46].

- In the past, the limits of tools like CDSSs were set by the technological boundaries. Nowadays, performance and memory of systems are rarely a limitation, and all kinds of devices are available for both health care professionals and patients [47]. Challenges have shifted from technological issues to issues in the field of design, usability, privacy and transparency. New legislation at European level is introduced to protect patients' privacy [48]. Further extension of human rights, with the right to not be measured, analyzed or coached, and the right to meaningful human contact, has been proposed [49]. Long-term societal consequences of ***technological developments*** are difficult to predict.
- In current society, it is widely advocated that the relationship between health care professionals and patients should further change from paternalistic to partnership in order to reach optimal outcomes [50, 51]. In shared decision making (SDM), patients and health care professionals make health care decisions together, taking into account both scientific evidence and the patient's values and preferences [51-53]. Despite the overall acknowledgement of the relevance of SDM, it is not common practice yet. The availability of medical information for patients, especially by the internet, has stimulated patient empowerment. In addition to attention paid to SDM, ***patient participation*** is growing in regulatory decision making and guideline development on (inter)national level [54-57] .

CRM of drug therapy: the concept elaborated

To understand the consequences of the challenges and opportunities, CRM of drug therapy is assessed at three different levels: the (inter)national level, the local/regional level, and the individual (patient) level (Figure 1). At each level, all steps of CRM of drug therapy take place to some extent: risk detection, assessment, management and evaluation. CRM at (inter)national level (hereafter referred to as national level) is the domain of authorities, research institutions, professional associations, software suppliers, health insurance companies, health care inspectorates, etc. The second level is the regional/local level (hereafter referred to as local level) and concerns the organizational units of health care professionals and patients: e.g. hospitals, pharmacies, health centers, and local and regional associations in health care. Patient representatives increas-

ingly participate at both the national and local level. The third level of CRM is all about the individual patient. This level has three principal actors: the patient, the physician(s), and the pharmacist(s).

There is a close interplay between the levels. The main connections are indicated in Figure 1; however, other connections are present. In the following paragraphs, we will present the consequences of the described developments for the three different levels. For each level, we will focus on the four steps of CRM, including the interaction between the levels. Per step, bottlenecks and opportunities for improvement will be summarized, with a focus on the use of information and decision making rather than purely organizational aspects.

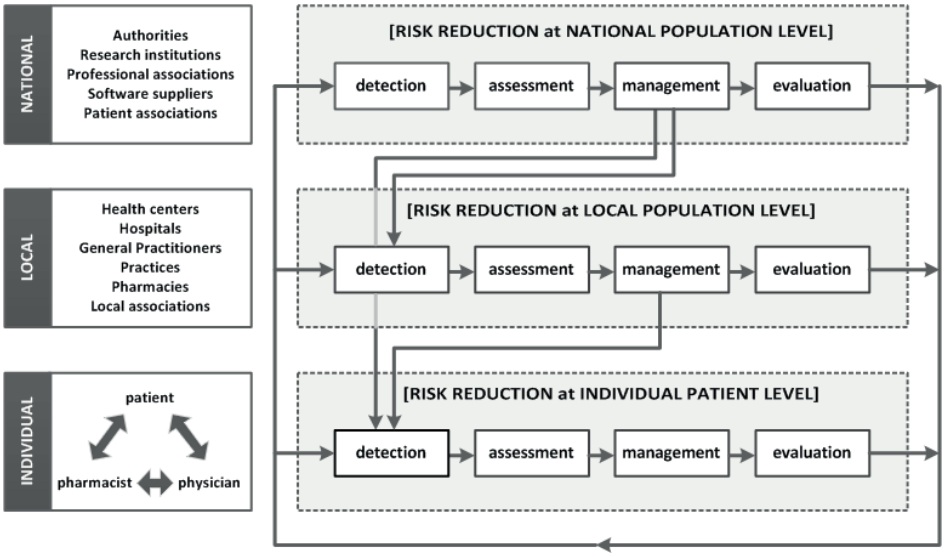


Figure 1: Clinical risk management of drug therapy: risk reducing strategies at three levels.

CRM – national level

The national level of CRM of drug therapy concerns the complete health care system. At this level, drugs are authorized for market access, recommendations for processes regarding safe drug use and clinical guidelines are developed, legislation about health care and drug dispensing (including its financing) is established, and research is conducted.

Risk detection at national level

Knowledge about the existence of a certain risk is a precondition for the development of risk reducing strategies. A first source of risk detection is clinical research, both pre-and post-authorization. Regulators increasingly require investigations to identify potential risks known to limit the safety of drugs, for example – from 2005 on – QT-interval prolongation [58]. In addition, mandatory post-marketing authorization programs (which can require post-authorization safety studies (PASSs)) intend to provide continuous follow up on the safety of medicines in daily practice – which may be very different from the controlled conditions of clinical research. Observational studies may identify potential rare risks, but provide information on associations rather than on causality. Every investigation is based on hypotheses, and therefore limited in its ability to discover the unexpected. Spontaneous reporting can detect additional risks which did not emerge in clinical and observational studies [59, 60]. Moreover, spontaneous reporting of errors in prescribing, dispensing or administrating drugs is useful for risk detection [30].

In addition to these methods, big data is an upcoming source of information on risks. With the methodology of big data, patterns – including rare events - can be identified without a prior hypothesis. This is both the strength and weakness of this method: unexpected relationships can be detected, but the causality needs thorough judgment [45, 46]. Well known is the example of an algorithm designed to predict complications or death resulting from pneumonia in hospital [46, 61]. The model assigned patients with asthma to an unexpected low risk category, because of their high survival rates. The initial model did not recognize that this counterintuitive result was caused by the extra medical attention and intensive treatment given to asthma patients with pneumonia. Although newer techniques have been developed to reduce this kind of problems, professional assessment of the outcomes is required.

The several ways to detect potential drug safety issues on population level complement each other, but are not always aligned, which lead to insufficient follow up of first signs of potential DTRPs. Further integration of research, reporting and big data could be helpful, because they often are separated pathways. Data from several sources should be made accessible for research purposes, for example data on file from manufacturers and data from specialist monodisciplinary (care related) registrations. This requires good privacy policy, which must be developed by thorough weighing of individual human rights and the potential patient harm caused by not using available data [62]. For example, new data protection directives of the European Union [48] may hamper the linkage of

clinical and dispensing data which is needed for more efficient risk detection. Coordination is needed for setting priorities, in which all actors – including patients – should be involved.

Risk assessment at national level

Not every detected potential drug therapy related risk is clinically relevant. Assessments are made by expert panels, although patients are increasingly involved. Assessments are generally based on the principle of evidence based medicine (EBM), with a focus on the clinical benefit-risk balance. For the development of clinical recommendations (including DTRP management), EBM-based guidelines are used, for example GRADE (Grading of Recommendations Assessment, Development and Evaluation) [63-65]. Despite these structured procedures and frameworks, which are widely adopted, substantial differences exist between the assessments from different professional and commercial organizations, for example with regard to drug-drug interactions [66, 67].

Many risks never turn into harm. Methods to distinguish between patients with and without a high risk are needed. One way is to identify patients who are in general susceptible to disturbance of delicate balances, e.g. vulnerable elderly. A second option is to identify patients who are more susceptible to specific risks, e.g. ultra-rapid CYP 450 metabolizers who are more likely to experience an effect of a CYP 450 inhibitor. Instead of incorporating single risk factors in risks assessments, a multifactorial risk assessment is proposed [68]: all potentially relevant risk-modifying factors should be included in one integrated assessment. An example is the Dutch risk score for gastric protection during use of non-steroidal anti-inflammatory drugs (NSAIDs), in which age, dose of NSAID, comorbidities, co-medication, and (dose of) gastric protection already in use are incorporated [69]. This risk score replaces the individual drug-drug interaction and drug-disease interaction assessments (e.g., the drug-drug interaction between NSAIDs and corticosteroids). Comparable multifactorial risk assessments are developed for, for example, the risk of QT-prolongation and Torsades de Pointes [70, 71]. For patient characteristics which are useful to include in multifactorial risk assessments, see Table 1.

Table 1: Patient factors relevant for multifactorial risk assessment

Patient factor	Examples / description
General characteristics	Age, gender
Medication	Prescription medicines, non-prescription medicines, herbal and nutritional products; with first starting date, intended period of use, type of prescriber, dosage regimen and indication
Diseases and conditions	Current and past conditions, including severity (e.g. stage of heart failure), and including conditions like dialysis, bariatric surgery, pacemaker, feeding tube
Clinical measurements	Blood pressure, pulmonary function, weight, height
Laboratory values	Renal function, hepatic function, electrolytes, HbA1c
Hypersensitivity	Allergies (immunological) and intolerances (non-immunological)
Pharmacogenetics	Genotype or phenotype related to drug use
Lifestyle parameters	Smoking, use of alcohol, fasting
Physical and cognitive disabilities	Poor hearing, poor vision, poor hand function, walking difficulties, swallowing problems, cognitive impairment
Compliance to therapy	
Living situation	Alone, home care, care home
Health-related events	Hospital admissions, occurred adverse events
Health literacy	
Patients views and experiences	Preferences, values, beliefs about medicines

In assessing a risk, the alternatives or management options should be taken into account in one integrated patient assessment. A risk in itself can be assessed as clinically relevant, for example a drug-drug interaction between an antibiotic for pneumonia and a chronic medicine leading to a risk of 0.05% of a very serious adverse event. However, when the only management option is to switch to another antibiotic and this antibiotic is 1 percentage point less effective, it could be questioned whether this management option should be considered as positive or not.

Especially in the assessment of very small risks, there can be tension between the perceived relevance at the population level and the perceived relevance at the individual patient level. An example is the risk of Torsades de Pointes by drug-related QT-prolongation, with a high number of people using QT-prolonging drugs, but a very low risk for the individual patient. This situation is comparable to medicines with a high number needed to treat, which may have beneficial outcomes on population level, but a low chance that an individual experiences the benefit. Even for health care professionals, interpretation of risk measures can be complex and influenced by framing (e.g., a difference in perception be-

tween risks presented in terms of loss like '5% mortality' and risks presented in terms of gain like '95% survival') [72, 73]. New risk measures may contribute to balanced thinking about risk-benefit assessments on population level, for example the time to benefit [74] and the so-called number unnecessarily treated [75]. Recommendations should not only be beneficial at population level, but also justifiable at individual level by a positive answer on the question: 'if applicable, would I recommend this to my (grand)mother?'.

In addition to the clinical benefit-risk balance, environmental factors may be involved. When effective drugs have a substantial but manageable risk, the assessment may depend on the presence of reliable structures to manage the risk in society. For example, in the Netherlands many drug-drug interactions with vitamin-K antagonists in outpatients are well manageable because of a national network of outpatient anticoagulation clinics which cooperate well with community pharmacies. However, even such a relatively well developed system may not cover all common situations, e.g., patients using vitamin-K antagonists going on holidays abroad.

In balancing risks, it is impossible to establish objectively which one should prevail. The outcome depends on the valuing of the different risks by the individual patient or health care professional. Research has shown that regulators, health care professionals, and patients make different assessments with regard to market approval [54-56, 76] and that patients and health care professionals can have different treatment preferences [77]. When there is (expected) variability in valuing of risks or outcomes, this has to be taken into account in guideline development. This also applies to variability in valuing of other advantages and disadvantages of management options, for example the need to change current medication, and the need to have additional check-ups (chapter 4.1). Taking into account variability does not only mean distinguishing between weak and strong recommendations in guidelines (like in GRADE), but also including a concrete description of the alternative management options for different preferences [78]. Although EBM is often considered as an objective clinical benefit-risk balance, patient preferences have always been an integral part of it [57, 79, 80].

Apart from the question how expert panels can make better risk assessments, it may be questioned whether decision making by expert panels is the best way of assessing risk relevance [81]. Several other options have been proposed. One of them is using the wisdom of the (professional) crowd [82, 83]. Although in experimental context the results were promising, reactions are hesitant [84]. The power of self-correction is high, but in health care, incorrect assessments can

have serious consequences. Another, more far-reaching option is to leave the assessment to computer algorithms. It was shown that dosing upper thresholds could be derived from (big) data by automatic algorithms [85] and that it is possible to predict the next medicine which will be prescribed to a patient [86]. Moreover, computer-aided diagnosing outperforms professionals under some conditions. However, algorithms cannot replace diagnosis by professionals (yet) [87]. In general, it has been suggested that in the future the best performance will be dependent on the best team of human and computer [88]. For applying computer assistance in risk assessment in health care, transparency must be realized in order to prevent the system from being a 'black box'. To what extent professionals would accept 'black box' systems and computer errors is questionable: on one hand trust in systems like car navigation is very high, on the other hand reactions to –for example - self-driving cars are twofold. The technological developments have been very fast. In the coming years we may thus expect a public debate on questions related to responsibility and accountability of self-learning CDSSs.

Risk management at national level

Available risk management strategies include stipulating conditions for drug use, providing information (either to health care professionals or patients), establishing and imposing procedures and regulations, and education. In addition to the authorized summary of product characteristics, numerous professional information resources are available. Regulators and professional organizations send notifications in case of newly established risks. In addition to the package leaflet, information can be provided to patients by several sources including standardized prescription label warnings (e.g. 'avoid exposure of the skin to direct sun light' on the label of doxycycline). Furthermore, publicity campaigns may help to raise general awareness on risks such as the combination of drugs and driving. Regulations and procedures mainly relate to defining responsibilities and to exchange of information – like the regulations on continuity of pharmaceutical care at hospital admission and discharge [89].

To implement guidelines and regulations, health care professionals should be aware of the existence, the content, and have the competences and resources to act on them. An efficient way to reach health care professionals with both information and regulations is implementing them in CDSSs.

With regard to CDSSs, the translation from guidelines to clinical decision support rules needs special attention [90]. For example, in textual guidelines, the difference between AND (cumulative) or OR (alternative) conditions is often un-

clear (i.e. should all listed conditions for an advice be met, or only one of them). In addition, descriptions like 'high dose' and 'long-term' should be translated into concrete parameters. Therefore, health care professionals and guideline developers should be involved in the development of algorithms in order to correctly parametrize the textual items [81].

CDSSs are mainly used for supporting protocoled care provision and for DTRP detection. When a multifactorial risk assessment as described above is realized, the same risk-modifying factors (table 1) should be integrated in the CDSS algorithms responsible for alert generation. Incorporation of age, laboratory values or co-medication has been shown to substantially increase the fraction of alerts leading to intervention [91-94]. When many factors are included in the risk assessment, change in any of the factors can lead to another outcome. Therefore, change - and not another prescription - should be the main trigger for alert generation. Relevant changes have to be defined per alert, taking into account the development of risk-modifying factors over time (e.g. differentiation of declining renal function versus impaired, but stable renal function). Sometimes, the absence of expected information should trigger alerts, e.g. unknown laboratory values or patients not showing up for medication refill. Also stopping medication is a relevant, but often unrecognized, trigger with respect to medication safety [95]. When alert generation in CDSS is change-based, there is no need for alerts triggered by recurrent prescriptions in unchanged condition (chapter 3.3). This approach leads to patient-centered alerting instead of the current prescription-based alerting, and to a substantial reduction of the alert rate.

Redefining alert triggers should go along with redistribution of CDSS alerts with respect to the moment of appearance: during the prescription or dispensing process (relevant at the desk or counter), in a continuously updated list (e.g. to be managed by the pharmacist), or periodically. Alerts must be shown in the process step where action must be taken. This approach will reduce the number of interruptive alerts in the prescribing or dispensing process. A related development concerns the need for alert prioritization when several alerts appear at the same moment. Health care professionals may not be able to manage all alerts at once, e.g. because therapy adjustments have to be implemented stepwise. Moreover, concurrent alerts may increase the risk of overseeing the most important ones. A prioritized presentation of alerts (or delay of less important ones to a later moment) should be based on the urgency of intervention, the expected short-term and long-term benefit, and the expected risk without intervention [96, 97]. CDSS alerts have been shown to cluster around certain drugs, patients, and potential adverse events (chapter 2.2). For example, combinations of diuret-

ics, RAS-inhibitors and digoxin will trigger several alerts regarding monitoring of potassium and renal function. These alerts cannot be prioritized, but can be combined based on the management advice (monitoring potassium and renal function). That would increase the efficiency (chapter 3.2) and it would rule out the possibility of contradictory advices, e.g. with regard to monitoring frequency.

We proposed several adjustments in the design of CDSS and the algorithms generating the alerts. With these adjustments, the alerts specificity can be substantially increased (up to 90% reduction in alert rate) with little or no decrease in sensitivity. By use of additional types of information (Table 1) for new types of alerts, the overall sensitivity of DTRP detection can even be expected to increase as well.

With all adjustments in CDSSs, maintenance, validation, implementation, user support, and evaluation should be guaranteed. Although alert generation is a central process in CDSSs, other aspects should not be overseen. CDSSs should support communication between health care professionals, and, ultimately, between health care professionals and patients. Currently, pharmacists may contact prescribers about a DTRP, and subsequently may learn that the physician has already managed the problem (for example by organizing additional monitoring). When pharmacists would have access to clinical data and physicians' assessments and management and vice versa, much efficiency would be gained. Furthermore, CDSSs should provide clear and individualized management recommendations. Along with the development of smarter alerting algorithms, the presentation of alerts should be optimized [98-103]. This is especially important when alerts are based on multifactorial assessments. In these situations, health care professionals need a good overview of all information related to the alert.

The performance of CDSSs is dependent on the quality of the EPR, which ideally should include all factors presented in Table 1. Although EPRs in the Netherlands are in general of reasonable quality, omissions regularly occur [104, 105]. For example, availability of data on renal function in community pharmacy is not optimal yet, despite legislation imposing physicians to inform pharmacists [106-108].

In CDSS development, clear choices are needed for potentially incomplete EPR, and associated assumptions. For example, when no pregnancy is recorded, should the system consider the patient as not being pregnant? The answer on this question should be dependent on the concerning risk: for prescribing or dispensing trimethoprim, the absence of pregnancy can be assumed, however, for prescribing or dispensing isotretinoin, the absence of pregnancy should be

explicitly checked with the patient. Legislation and ICT support have to facilitate data exchange between health care professionals. Correct and coded registration –supported by guidelines of professional organizations - is also required for reliable data exchange. As mentioned before, data-protection legislation will stir the debate about the balance between patients' privacy, and facilitating access to patient data.

Evaluation at national level

Evaluation of risk reducing strategies is an essential part of CRM. However, up to now, this receives limited attention in CRM of drug therapy. Even for widely adopted strategies like CDSSs for detection of drug-drug interactions, good quality evidence for reduced patient harm is conspicuously absent.

The result of risk reducing strategies can be assessed on several levels, from process to patient harm. Process evaluations for example show the uptake of recommendations following medication incidents [109]. Other types of evaluation include patients' understanding of prescription labels [110-112], or the extent of adherence to clinical recommendations [113, 114]. With regard to CDSSs, override rates [15, 16], performed interventions and DTRPs are the most investigated outcomes. A few studies focused on actual prevented patient harm, for example adverse events [14, 115]. Spontaneously reported incidents may also be seen as an outcome for evaluation. Reporting bias, however, may happen (e.g. after several publications concerning methotrexate intoxication, new incidents will – at least temporarily - be more likely to be reported).

In order to develop more effective risk-reducing strategies, more attention should be paid to their evaluation. Studies into the effectiveness of CDSSs should discriminate between accidental alert overrides, lack of intervention because of alert irrelevance and lack of intervention because of inappropriate judgment by the health care professional. Up to now, it has been shown that many CDSS alerts are overridden because they are assessed as irrelevant [15, 16]. However, in case of overrides, experts do not always agree with health care professionals' argumentation. Concurrently, performed interventions are not always considered clinically relevant by experts [15, 32, 116, 117].

In evaluation of CDSSs, the original purpose of alerts should be kept in mind. In chapter 2.2 we showed that duplicate medication alerts rarely led to therapeutic intervention, but that they were used to keep the EPR up to date. The latter is useful, but other strategies may better fit this purpose.

In conclusion, the evaluation step of CRM of drug therapy must be better anchored in the system to learn whether risk reducing strategies contribute to the intended goal: the reduction of patient harm.

In the context of evaluation, the value of good registration practice has to be emphasized. Registration should include both the process (considerations leading to the decision), the potential intervention, the agreement on follow up, and the eventual outcome. For decades, the importance of semantic interoperability for communication between systems has been stressed. However, with the increasing capabilities of computers to interpret natural language, and the realization that complete and correct coded registration in daily practice is a utopia, it is questionable whether the emphasis on coded registration will stand [118].

CRM – local level

The local level is the organizational level. The actors are hospitals, pharmacies, GP practices, nursing homes and their respective local monodisciplinary and multidisciplinary collaborations. Many of the preconditions for CRM have to be effectuated at this level, for example agreements on exchange of patient information and on local formularies. Compared to the other levels, this level is more process focused and less content focused. This is also the level where gaps in care provision become visible, and lead to innovation. That is why many activities intended to reduce the number of DTRPs have their origin and execution at the local level, for example medication reviews and integration of non-dispensing pharmacists in primary care practice [119, 120].

Risk detection at local level

At the local level, there is a focus on process related risks. This is due to the size of the local population, which is generally too small to recognize very small risks like adverse events or harm resulting from DTRPs. Detection of risk on a local level is often incident driven. In the quality systems of health care organizations, procedures are embedded to report (near) medication incidents, like incorrect drug dispensing or administration. Quality systems also lead to regular structural assessments which can be sources of information about risks.

For risk detection, especially outside the structural assessments, watchfulness of all health care professionals and their team members is needed. Therefore, organizations should establish a patient safety culture, with shared values, attitudes, and behavior of all staff to prioritize safety over efficiency and aiming to create a system that learns from errors and problems [121]. Just like CRM, the concept

originates from high risk sectors such as aviation [122]. Strategies to improve the safety culture tend to have a positive effect, but available evidence is very limited [123, 124]. Although Dutch GPs assessed the aspect 'culture and mentality which facilitates learning from incidents' as very important for increasing patient safety, they felt that it was not very much present in GP practices [125].

Risk assessment at local level

Risks are mainly assessed in regular meetings within or between health care organizations. Risks detected by incidents need to be assessed for the main causes and potential management strategies. This is again a benefit-risk balance: e.g., the number of process checks should be weighed against the expected safety gain. In addition to locally detected risks, risks detected on (inter)national or individual level can be a source of information. These risks could or could not be relevant at the local level. For example, when a national warning on confusion of two concentrations of insulin pen-fills has been spread, it depends on the local prescribing policy whether further measures are needed.

Risk management at local level

Managing risk at the local level is dependent on the implementation of protocols and procedures, both within and between institutions. They can include information exchange, registration of data in the EPR, use of CDSS, management of alerts, and patient counseling. Sufficient resources and competences are needed to complete these activities, including continuous education of all team members. Implementation of quality systems and procedures is only part of the story. Equally important is pro-active handling, needed to prevent 'gaps' in health care provision. In preventing gaps, inter-professional collaboration is considered as a precondition (although evidence is limited [126]). For collaboration between GPs and pharmacists, soft skills like communication, mutual respect, willingness to work together and recognition of roles have been shown to be important [126-128]. Although the national level can provide suggestions and tools for collaboration, the local health care professionals and organizations have to realize it.

Evaluation at local level

The daily evaluation of processes is generally part of the quality system in the health care practice, for example the daily final check of dispensed prescriptions by pharmacists. The added value of this kind of checks has been questioned, based on the in-process checks, current experience in daily practice, and lack of evidence [129]. Pharmacists and physicians evaluate agreements like local drug

prescribing policies in regular local pharmacotherapy meetings. Moreover, based on procedures and protocols in quality systems, regular evaluations take place, for example with regard to the CDSS settings which affect CDSS performance. In addition, indicators are used to assess quality of pharmacotherapy in institutions, for example indicators on medication safety in community pharmacy [130], where deviation of the benchmark can be a reason for further exploration of reasons and risks. Because of the presence of quality systems at local level, evaluation is more consequently embedded in the processes than at the other levels. However, evaluation sometimes is considered as an obligation accompanied by an administrative burden. It is important that national regulations do not hamper or demotivate health care professionals to use evaluation as a tool for improvement.

CRM – individual level

Incorrect use of medication by patients is the most important reason for inappropriate drug use (much more than inappropriate prescribing or dispensing) [131]. Therefore, the role of the patient can hardly be overrated. However, this does neither mean that attention to appropriate prescribing and dispensing is unnecessary, nor that we can blame the patient: health care professionals have a major responsibility in promoting and assuring correct drug use.

Risk detection at individual level

CDSSs are a major tool to detect DTRPs for individual patients. However, research has shown that only a minority of the prescription modifications by community pharmacists was triggered by CDSS [37]. And in medication reviews, DTRPs detected by CDSSs (by explicit criteria) were rather additional than replacing the CDSSs manually identified by pharmacists (by implicit criteria) [19]. Simply asking patients can uncover a broad range of problems, including adverse events, ineffectiveness, and administration problems (e.g. eye drops, breaking tablets) [120, 132-134]. Therefore, in every encounter between patient and health care professional, attention should be paid to this way of DTRP detection. Health care professionals' watchfulness leading to DTRP detection is often guided by 'gut feeling', which may seem difficult to explain rationally [135, 136].

To enable risk detection, the patient has a responsibility in providing relevant information in their contact with health care professionals. In addition, patients increasingly have the possibility to add data to the EPR themselves, for example regarding the use of over-the-counter medications, or about self-measurements

(blood glucose, weight, physical exercise etc.). The use of wearables and mobile health applications which are automatically connected to the EPR stimulates this development [137], and it provides the health care professional with new opportunities for patient monitoring and counseling. In addition to patients themselves, home care or caregivers could provide useful information. An example is the use of a list of explicit criteria for drug related risks including bruises and problems with managing intake of medicines, which can be easily noticed by care givers even with limited medical knowledge [138]. When a structure is created to share these finding with health care professionals, a useful additional safety net can be created.

Risk assessment at individual level

When a DTRP has been detected for an individual patient, three questions are relevant: is there really a DTRP, is the DTRP relevant for the patient, and are management options available to reduce the risk. The first question is especially relevant in case of DTRP detection by CDSSs. Sometimes, alerts are based on outdated information, e.g. a drug-drug interaction alert can be irrelevant, because the patient has discontinued the use of one of the drugs (chapter 2.1).

For the assessment of the relevance of a DTRP for an individual patient, sufficient clinical and non-clinical information is needed (Table 1). Special attention should be given to information on former patient harm, which is often overseen or unavailable (leading to, for example, frequent unintended restarts of drugs which were discontinued because of adverse events [139]). The risk assessment should include both the relevance of the problem and the feasibility of management options (e.g. the patient's capability of self-monitoring and self-management). Research has shown that health care professionals' non-adherence to clinical recommendations is often intentional and based on potentially valid reasons, including contra-indications and patient preferences [34, 114]. Reality is more complex than the alert generation in CDSSs, which use strict cut-offs (e.g. for renal function). However, the estimated glomerular filtration rate can be an underestimation or an overestimation of the actual value, depending on patient characteristics like stature, being bedridden, and drug use disturbing creatinine measurement [140-142]. This shows the need for clinical reasoning by a competent health care professional [143]. Following the medical field, the attention paid to this competence in pharmacy is growing fast.

Shared Decision Making (SDM) in CRM of drug therapy is mostly limited to problems related to compliance and drug administration. However, based on the weak evidence underlying many drug-drug interactions, SDM would

be expected to be useful [52, 144]. The existence of diverging preferences on drug-drug interaction management (chapter 4.1) also points in this direction. At the same time, SDM in this field is even more complex than in single treatment decisions, as in drug-drug interactions at least two therapies are involved, both with risks and benefits. However, examples of successful SDM in complex situations like an emergency department are available [53, 145]. In the end, SDM is by definition tailored to the patients' needs, which may mean that decision making is sometimes left to the health care professional. As patient needs and preferences can depend on received information (chapter 4.2), provision of information is crucial [146, 147]. Interpretation of risks has been shown to be subject to many biases, especially in patients with low health literacy [148, 149]. Low health literacy affects up to half of the general population and is associated with poorer health outcomes [112, 150-152]. So, for SDM, both providing clear and tailored information (including checking of understanding) and elucidation of patients' preferences are essential. Decision aids –integrated in guidelines and CDSSs - could be helpful tools in this process [78, 153-158].

When patients' preferences are explicitly included in decision making, the chosen management option could be different from the one the health care professional preferred for clinical reasons. Hence, a moral dilemma might arise. The judgment whether a decision is a good decision can be based either on the process, the medical impact, the outcome, the congruence with patients' values, or patient's regret. Therefore, it is not surprising that the question when a medical decision can be considered a good decision is under debate [153, 159, 160]. Ultimately, professional values are the main guide [161].

When a decision is made about the management of a DTRP, it is important that the decision, the reasoning, and the chosen management option including potential monitoring and roles and responsibilities are well documented. Also when a DTRP is assessed as irrelevant for an individual patient, it is important to record the considerations leading to that decision. Without careful record keeping, continuity of care provision is at stake. CDSSs should limit the options for undesirable ways of registration (e.g. registration of allergies in data fields which are not included in data exchange). Moreover, registration of alert management can be made mandatory in CDSSs. However, the administrative burden of coded registration should be minimalized, with a balance between the purpose of direct patient care and the purpose of local and national evaluation.

Risk management at individual level

The ultimate result of risk assessment is the decision whether or not to intervene, with agreement from all involved actors (physician, pharmacist, and/or patient). The main potential interventions are adjustment of drug therapy, patient counseling, and additional monitoring. Dependent on what already has been discussed with the patient during assessment of the problem, further consultation should be performed, e.g. counseling on intake schemes or monitoring. Of course, counseling should be tailored to the individual patient (chapter 4.2), as patients' needs and preferences in health care are highly diverse [162].

Counseling should not only include the current situation, but also potential future changes which contain risk. For example, in retrospective, the impact of a heat wave on a vulnerable patient with a delicate balance of electrolytes using diuretics and RAS-inhibitors is often clear. However, proactive management of these contextual, provocative factors is still unusual. One option (requiring sufficient patient self-management) is prospective counseling, for example by using 'sick day rules' to inform patients at risk about temporary cessation of certain medicines in case of fever, vomiting or diarrhea, in order to prevent acute kidney injury [163, 164].

Evaluation at individual level

Any management strategy of a DTRP has to be evaluated, either by the patient, the pharmacist, or the physician. In many cases, one question at the next visit to the health care professional is sufficient, e.g. whether the patient has experienced any symptoms of worsened chronic obstructive pulmonary disease after start of a beta-blocking agent. More exhaustive evaluation is needed when additional monitoring was scheduled, for example blood sampling in order to check renal function and electrolytes. Insufficient evaluation can lead to unnecessary persistence of problems or occurrence of events. Not recording the outcome of the evaluation (and not communicating it with other health care professionals) can lead to reoccurrence of problems. In addition to evaluation directly related to the management of a DTRP, evaluation could also take place at other moments, for example during a clinical medication review.

Two elaborated examples

In the foregoing, we presented the opportunities for improvement of CRM of drug therapy at the national, the local, and the individual level. In this last paragraph, we present two elaborated examples. The first example relates to a

proposed redesign of the nationwide system to improve clinical decision support. The second example illustrates how improved clinical decision support contributes to better patient care.

Example I: Redesigning the system to improve clinical decision support

Several gaps prevent CRM systems from optimal functioning. Not all available knowledge is well implemented in guidelines, and therefore it does not reach all health care professionals. Furthermore, not all guidelines are well incorporated in CDSSs. In the CDSSs, the result of available clinical decision support rules is suboptimal because of - among other things - incomplete EPRs. And, finally, the impact of the use of clinical decision support rules in daily practice is insufficiently evaluated. We propose a structure to overcome these gaps, by providing tailored information to all actors (Figure 2) [137, 165-167].

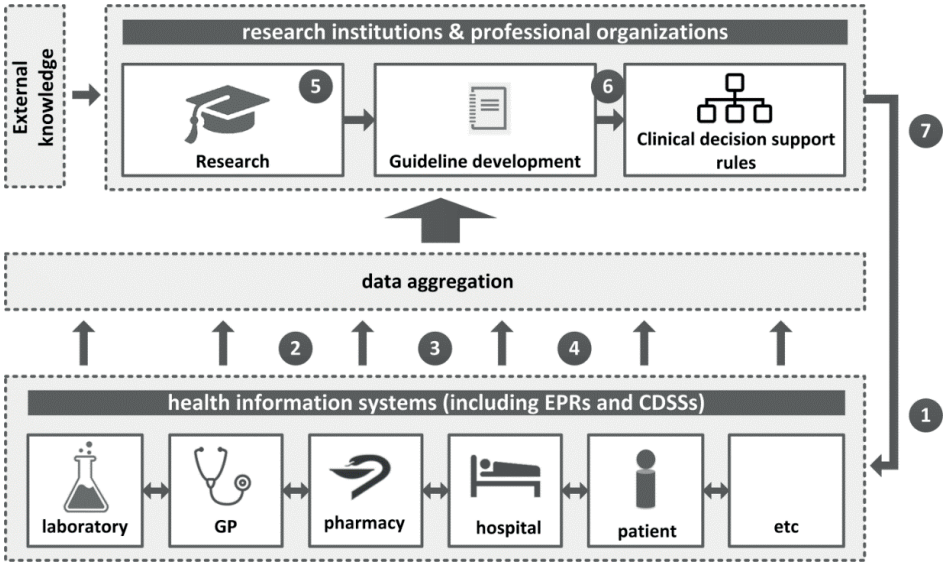


Figure 2: Closed knowledge loop (for numbered steps see text)

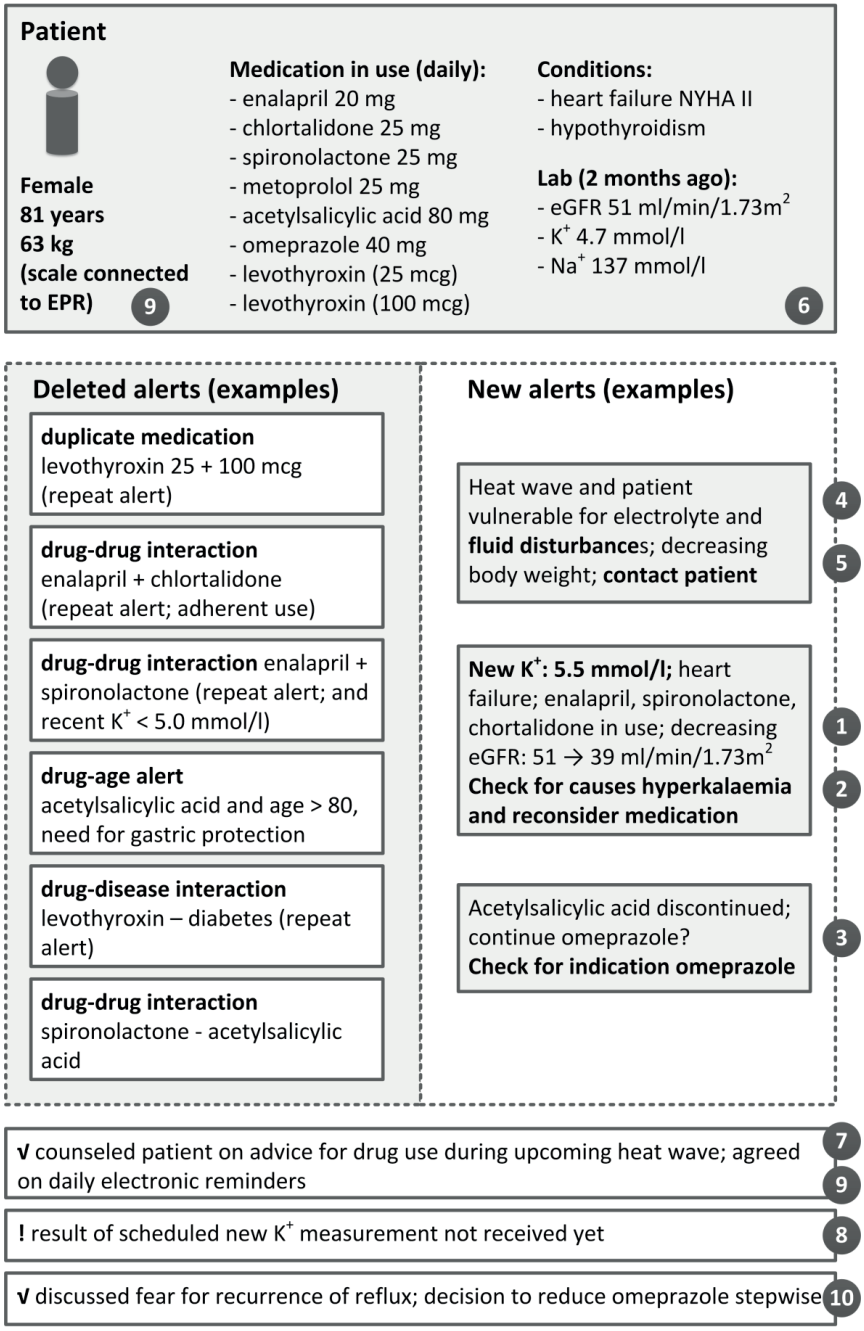
To illustrate the functioning of this closed knowledge loop, we look again at the need for gastric protection in patients using NSAIDs, for which a guideline-based multifactorial risk score is available (developed several years ago by the professional organizations) [69]. Based on the risk score, a clinical decision support rule can be implemented in the health information systems of health care professionals (step (1) in Figure 2). The clinical decision support rule advises gastric protection for NSAID users when at least two risk factors are present (including co-medication, diseases, age, and high dose of NSAID). However, the

relevance and cut-off is unclear for some risk factors, e.g. high dose of NSAID. The same holds for the management strategies, e.g. the optimal dose of a proton pump inhibitor. Moreover, lifestyle factors like smoking and alcohol use are not included in the guideline based risk score. In our proposed system, health care professionals and patients are actively asked by the system to provide information on these factors. In addition, they explicitly record whether or not (and why) they adhere to the recommendations for gastric protection (e.g. patient refuses addition of proton pump inhibitor) (2). Drug use and patient outcomes (e.g. gastrointestinal bleeding) are registered in the systems as well (3).The potentially relevant lifestyle factors - smoking and use of alcohol - are recorded by the health care professional or by direct patient questionnaires included in the system (4).

All data generated in clinical practice are aggregated and made available for research. Researchers evaluate the impact of the recorded patient characteristics and management options on the outcome (5). They, for example, detect that gastric protection is often prescribed to users of NSAIDs without risk factor, despite the disadvantages [168]. The new findings are incorporated in updated clinical decision support rules, which not only alerts on missing gastric protection, but also on the opposite: the use of gastric protection without indication (6). The updated clinical decision support rule is tested and implemented to close the loop, and a new cycle starts (7).

Example II: Better patient care by redesigned clinical decision support

This example illustrates how decision making for a patient benefits from redesigned clinical decision support. For this patient aggregation of alerts takes place because of polypharmacy (chapter 2.2). Figure 3a is a schematic representation of the result of redesigned clinical decision support for this patient, compared to a current CDSS. Ten requirements for CDSS redesign are shown in Figure 3b. Of the ten requirements, five are about the alert generating algorithms, and five are about other clinical decision support features. With clinical decision support meeting the ten redesign requirements, pharmaceutical care for this patient would be safer, more efficient and more patient-centered.



eGFR = estimated glomerular filtration rate; EPR = electronic patient record; NYHA = New York Heart Association

Figure 3a: Redesigned clinical decision support: the result for a patient

Ten requirements for redesign of clinical decision support systems

1. Base alerts on a multifactorial risk assessment, including all relevant risk-modifying factors.
2. Cluster all alerts about the same topic (advice-based alerting).
3. Trigger alerts by relevant changes in the patient's situation, and not by repeat prescriptions in unchanged conditions (change-based alerting).
4. Prioritize alerts and show them during the process step in which action should be taken: distinguish between urgent and non-urgent interventions.
5. Support pro-active counseling on relevant environmental changes, e.g. heat wave.
6. Base alerts on good quality (correct and complete) electronic patient records.
7. Support registration of alert management, including exchange between health care professionals.
8. Support evaluation of managed drug therapy related problems.
9. Support connection with patient devices, for counseling and clinical measurement (e.g. scale).
10. Support inclusion of patient's preferences and values in decision making (by information on potential variability of preferences, and by tools for (risk) communication).

Figure 3b: Requirements for redesign of clinical decision support systems

Implications and conclusions

CRM of drug therapy is relevant to avoid patient harm caused by medication. CRM consists of four steps: detection, assessment, management and evaluation of risk. In the context of drug therapy, these steps are relevant on three levels: the national level, the local level, and the individual patient level. Our research showed that on all levels further improvement is needed. Priority should be given to the following issues:

- In order to efficiently increase patient safety, measures to improve CRM of drug therapy should be prioritized based on potential impact. The impact may be estimated from the seriousness of the identified patient harm, its incidence, and its preventability. The impact should subsequently be weighed against the effort needed. For the majority of currently used measures to reduce patient harm, there is little evidence for their effectiveness. This implies that thorough evaluation of current and new methods and tools is needed, to provide evidence for their prioritization and effectiveness. Therefore, a nationwide structure for better use of knowledge must be realized (Figure 2). This structure should enable tailored provision of knowledge by clinical decision support rules to health care professionals. By a return loop, tailored

acquirement of information from clinical practice should enable evaluation and filling gaps in current knowledge.

- Incorrect use of medication by patients is the most important reason for inappropriate drug use, much more than inappropriate prescribing or dispensing [57]. Therefore measures to prevent DTRP should always take the patient perspective into account. This means that health care professionals have to invest in a continuous dialogue with patients about their drug use. This will enable them to understand how patients actually use drugs. Subsequently potential risks may be identified.
- CDSS redesign is needed. Two promising approaches are incorporating multifactorial risk assessments, and change-based alerting. In a multifactorial risk assessment, all risk-modifying factors are taken into account in one integrated approach. This enables risk stratification. Change-based alerting makes changes in the patient's situation (e.g. in treatment, co-morbidity or environmental conditions like a heat wave) the leading principle. When signs of potential upcoming drug-related harm [169] are detected, early intervention can be realized. Priority should be given to implementation of these approaches in CDSSs. Suppliers of health care information systems suffer from the 'dialectics of lead': automation was started early, especially in pharmacies, and the information systems do not meet current standards of flexibility. Resources spent on incorporating frequently changing regulations in the systems, cannot be spent to CDSS improvements. Coordination and collaboration between software suppliers, professional organizations and health care professionals is needed without further delay to adapt the systems to the continuously further developing profession.
- The shift towards patient centered care requires integrated risk assessments by clinical reasoning. Health care professionals should take into account both the detected problem and the potential solutions, in the context of the patient's overall health condition. The assessment should explicitly include patients' (clinical and non-clinical) goals, values and preferences. So, instead of assessing the clinical benefit–risk balance, health care professionals should assess the advantages and disadvantages for an individual patient. In this patient centered approach, situations may occur where other considerations prevail over the optimal clinical outcomes. Therefore, reconsideration of the definition of a good (medical) decision - based on professional values - is needed [161].
- Patients should be facilitated to participate in the decision making process as much as possible given their preferences and capabilities (which could result in a patient's preference to leave the decision completely to the health

care professional). In the complex context of CRM of drug therapy, tailored patient information, including risk communication, is essential. Studies are needed to determine conditions for positive effects of shared decision making in this field.

- Individualized decision making processes can be time consuming. Therefore, CDSS redesign should not only contribute to more accurate DTRP detection, but also to more efficiency. Health care professionals can save time by better risk stratification and subsequent targeted interventions.
- Improvements in clinical decision support should address privacy, accountability and transparency. When insufficiently addressed, these topics (e.g., the European data protection directive [48]) can interfere with further development of clinical decision support, and vice versa. With smarter CDSSs, transparency is essential to prevent the systems from becoming indispensable 'black boxes' where health care professionals completely rely on. Finally, the best performance is expected from the best combination of health care professional and computer, each with their own strengths.
- We showed that, irrespective of technological developments, watchfulness and integrated risk assessments by health care professionals are essential for CRM of drug therapy. Therefore, more attention should be given to continuous education of health care professionals with regard to competences like communication and clinical reasoning.

In conclusion, with increasing complexity and volume of health care, both competent health care professionals and CDSSs are essential for CRM of drug therapy. CDSSs can only meet current and future needs by continuous development. These developments are multidimensional and cover various fields, including technology, governance, research and education. The developments are complementary and all needed for the overall result. As the responsibility for CRM of drug therapy cannot be allocated to a single actor, at all levels a joint effort of all involved actors is needed. Based on their profession, pharmacists are united in their promise to put their pharmaceutical knowledge and abilities at the service of patient and society to support health and well-being. Pharmacists in every position in health care should be called on this responsibility, to contribute to CRM of drug therapy in order to reduce patient harm.

References

1. Pirmohamed M, James S, Meakin S, Green C, Scott AK, Walley TJ, et al. Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients. *BMJ* 2004;329:15-9.
2. Leendertse A, Egberts A, Stoker L, van den Bemt P. Frequency of and Risk Factors for Preventable Medication-Related Hospital Admissions in the Netherlands. *Arch Intern Med* 2008;168:1890-6.
3. Sturkenboom MC, Van Den Bemt PMLA, De Smet PAGM, Hek K. Eindrapport: Vervolgonderzoek Medicatieveiligheid. Erasmus Medical Centre 2017, Rotterdam, The Netherlands.
4. Kohn L, Corrigan J, Donaldson M, eds. To err is human; Building a safer health system. Washington, D.C. United States: National Academy Press 1999.
5. HARM-Wrestling Task Force (Expertgroep Medicatieveiligheid). HARM-WRESTLING. Een voorstel van de Expertgroep Medicatieveiligheid m.b.t. concrete interventies die de extramurale medicatieveiligheid op korte termijn kunnen verbeteren. Ministerie van Volksgezondheid, Welzijn en Sport 2009, The Hague, The Netherlands.
6. Audit Commission for Local Authorities and the National Health Services in England and Wales. A spoonful of sugar. 2001, London, United Kingdom.
7. Misson JC. A review of clinical risk management. *J Qual Clin Pract* 2001;21:131-4.
8. Hudson PT, Guchelaar HJ. Risk assessment in clinical pharmacy. *Pharm World Sci* 2003;25:98-103.
9. Reason J. Human error: models and management. *BMJ* 2000;320:768-70.
10. De Smet PA. Clinical risk management of herb-drug interactions. *Br J Clin Pharmacol* 2007;63:258-67.
11. Awdishu L, Coates CR, Lyddane A, Tran K, Daniels CE, Lee J, et al. The impact of real-time alerting on appropriate prescribing in kidney disease: a cluster randomized controlled trial. *J Am Med Inform Assoc* 2016;23:609-16.
12. Curtain C, Peterson GM. Review of computerized clinical decision support in community pharmacy. *J Clin Pharm Ther* 2014;39:343-8.
13. Ojeleye O, Avery A, Gupta V, Boyd M. The evidence for the effectiveness of safety alerts in electronic patient medication record systems at the point of pharmacy order entry: a systematic review. *BMC Med Inform Decis Mak* 2013;13:69.
14. O'Sullivan D, O'Mahony D, O'Connor MN, Gallagher P, Gallagher J, Cullinan S, et al. Prevention of Adverse Drug Reactions in Hospitalised Older Patients Using a Software-Supported Structured Pharmacist Intervention: A Cluster Randomised Controlled Trial. *Drugs Aging* 2016;33:63-73.
15. Nanji KC, Slight SP, Seger DL, Cho I, Fiskio JM, Redden LM, et al. Overrides of medication-related clinical decision support alerts in outpatients. *J Am Med Inform Assoc* 2014;21:487-91.
16. Van der Sijs H, Aarts J, Vulto A, Berg M. Overriding of drug safety alerts in computerized physician order entry. *J Am Med Inform Assoc* 2006;13:138-47.
17. Bryant AD, Fletcher GS, Payne TH. Drug interaction alert override rates in the meaningful use era: no evidence of progress. *Appl Clin Inform* 2014;5:802-13.
18. Van Doormaal JE, Rommers MK, Kosterink JG, Teepe-Twiss IM, Haaijer-Ruskamp FM, Mol PG. Comparison of methods for identifying patients at risk of medication-related harm. *Qual Saf Health Care* 2010;19:e26.

19. De Wit HA, Hurkens KP, Mestres Gonzalvo C, Smid M, Sipers W, Winkens B, et al. The support of medication reviews in hospitalised patients using a clinical decision support system. *Springerplus* 2016;5:871.
20. Divo MJ, Martinez CH, Mannino DM. Ageing and the epidemiology of multimorbidity. *Eur Respir J* 2014;44:1055-68.
21. Hovstadius B, Hovstadius K, Astrand B, Petersson G. Increasing polypharmacy - an individual-based study of the Swedish population 2005-2008. *BMC Clin Pharmacol* 2010;10:16.
22. Dumbreck S, Flynn A, Nairn M, Wilson M, Treweek S, Mercer SW, et al. Drug-disease and drug-drug interactions: systematic examination of recommendations in 12 UK national clinical guidelines. *BMJ* 2015;350:h949.
23. Boyd CM, Darer J, Boult C, Fried LP, Boult L, Wu AW. Clinical practice guidelines and quality of care for older patients with multiple comorbid diseases: implications for pay for performance. *JAMA* 2005;294:716-24.
24. Action committee 'Het Roer Moet Om'. Het Roer Moet Om (It Must Change). Accessed June 2017. Available at: www.hetroermoetom.nu.
25. VeiligheidNL. Risicovol spelen. Hoeveel speelruimte geef jij je kind? ("Risky playing - How much space has your child"). Accessed June 2017. Available at: https://www.veiligheid.nl/risicovolspelen/.
26. Koppel R, Metlay JP, Cohen A, Abaluck B, Localio AR, Kimmel SE, et al. Role of computerized physician order entry systems in facilitating medication errors. *JAMA* 2005;293:1197-203.
27. Eslami S, Abu-Hanna A, de Keizer NF, de Jonge E. Errors associated with applying decision support by suggesting default doses for aminoglycosides. *Drug Saf* 2006;29:803-9.
28. Wetterneck TB, Walker JM, Blosky MA, Cartmill RS, Hoonakker P, Johnson MA, et al. Factors contributing to an increase in duplicate medication order errors after CPOE implementation. *J Am Med Inform Assoc* 2011;18:774-82.
29. Brown CL, Mulcaster HL, Triffitt KL, Sittig DF, Ash JS, Reygate K, et al. A systematic review of the types and causes of prescribing errors generated from using computerized provider order entry systems in primary and secondary care. *J Am Med Inform Assoc* 2017;24:432-40.
30. Cheung KC, van der Veen W, Bouvy ML, Wensing M, van den Bemt PM, de Smet PA. Classification of medication incidents associated with information technology. *J Am Med Inform Assoc* 2014;21:e63-70.
31. Van der Sijs H, Mulder A, van Gelder T, Aarts J, Berg M, Vulto A. Drug safety alert generation and overriding in a large Dutch university medical centre. *Pharmacoepidemiol Drug Saf* 2009;18:941-7.
32. Buurma H, De Smet PAGM, Egberts AC. Clinical risk management in Dutch community pharmacies: the case of drug-drug interactions. *Drug Saf* 2006;29:723-32.
33. Isaac T, Weissman JS, Davis RB, Massagli M, Cyrulik A, Sands DZ, et al. Overrides of medication alerts in ambulatory care. *Arch Intern Med* 2009;169:305-11.
34. Weingart SN, Toth M, Sands DZ, Aronson MD, Davis RB, Phillips RS. Physicians' decisions to override computerized drug alerts in primary care. *Arch Intern Med* 2003;163:2625-31.
35. Lugtenberg M, Pasveer D, van der Weijden T, Westert GP, Kool RB. Exposure to and experiences with a computerized decision support intervention in primary care: results from a process evaluation. *BMC Fam Pract* 2015;16:141.
36. Floor-Schreudering A, Heringa M, Buurma H, Bouvy ML, De Smet PA. Missed drug therapy alerts as a consequence of incomplete electronic patient records in Dutch community pharmacies. *Ann Pharmacother* 2013;47:1272-9.

37. Buurma H, de Smet PAGM, van den Hoff OP, Egberts AC. Nature, frequency and determinants of prescription modifications in Dutch community pharmacies. *Br J Clin Pharmacol* 2001;52:85-91.
38. De Smet PA, Dautzenberg M. Repeat prescribing: scale, problems and quality management in ambulatory care patients. *Drugs* 2004;64:1779-800.
39. Committee for Medicinal Products for Human Use (CHMP). Spherox. Spheroids of human autologous matrix-associated chondrocytes. European Medicines Agency 2017, London.
40. De Boer A, van Hunsel F, Bast A. Adverse food-drug interactions. *Regul Toxicol Pharmacol* 2015;73:859-65.
41. Swen JJ, Nijenhuis M, de Boer A, Grandia L, Maitland-van der Zee AH, Mulder H, et al. Pharmacogenetics: from bench to byte--an update of guidelines. *Clin Pharmacol Ther* 2011;89:662-73.
42. Weed LL. New connections between medical knowledge and patient care. *BMJ* 1997;315:231-5.
43. Taleb NN. The Black Swan. The Impact of the Highly Improbable. United States 2007.
44. Griggs JJ, Mangu PB, Anderson H, Balaban EP, Dignam JJ, Hryniuk WM, et al. Appropriate chemotherapy dosing for obese adult patients with cancer: American Society of Clinical Oncology clinical practice guideline. *J Clin Oncol* 2012;30:1553-61.
45. Ottes L. Big Data in de zorg (Big Data in Health Care). Scientific Council for Government Policy (Wetenschappelijke Raad voor het Regeringsbeleid, WRR) 2016, The Hague, The Netherlands.
46. The Royal Society. Machine learning: the power and promise of computers that learn by example. April 2017, London.
47. Baig MM, GholamHosseini H, Moqeem AA, Mirza F, Linden M. A Systematic Review of Wearable Patient Monitoring Systems - Current Challenges and Opportunities for Clinical Adoption. *J Med Syst* 2017;41:115,017-0760-1. Epub 2017 Jun 19.
48. European Union. Data protection directive 2016. Accessed June 2017. Available at: http://ec.europa.eu/justice/data-protection/.
49. Van Est R, Gerritsen JBA, Kool L. Human rights in the robot age: Challenges arising from the use of robotics, artificial intelligence, and virtual and augmented reality – Expert report written for the Committee on Culture, Science, Education and Media of the Parliamentary Assembly of the Council of Europe (PACE). Rathenau Instituut 2017, The Hague.
50. Stiggelbout AM, Van der Weijden T, De Wit MP, Frosch D, Legare F, Montori VM, et al. Shared decision making: really putting patients at the centre of healthcare. *BMJ* 2012;344:e256.
51. Elwyn G, Frosch DL, Kobrin S. Implementing shared decision-making: consider all the consequences. *Implement Sci* 2016;11:114.
52. Pollard S, Bansback N, Bryan S. Physician attitudes toward shared decision making: A systematic review. *Patient Educ Couns* 2015;98:1046-57.
53. Stiggelbout AM, Jukema JW, Engelhardt EE, van den Bos C, Pieterse AH. Communicating risk to patients in the emergency department. *BMJ* 2016;355:i6437.
54. Postmus D, Mavris M, Hillege H, Salmonson T, Ryll B, Plate A, et al. Incorporating patient preferences into drug development and regulatory decision making: Results from a quantitative pilot study with cancer patients, carers, and regulators. *Clin Pharmacol Ther* 2016;99:548-54.

55. Ho MP, Gonzalez JM, Lerner HP, Neuland CY, Whang JM, McMurry-Heath M, et al. Incorporating patient-preference evidence into regulatory decision making. *Surg Endosc* 2015;29:2984-93.
56. Britten N, Denford S, Harris-Golesworthy F, Jibson S, Pyart N, Stein K. Patient involvement in drug licensing: a case study. *Soc Sci Med* 2015;131:289-96.
57. Greenhalgh T, Howick J, Maskrey N, Evidence Based Medicine Renaissance Group. Evidence based medicine: a movement in crisis?. *BMJ* 2014;348:g3725.
58. ICH Harmonised Tripartite Guideline. The clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs E14. International conference on harmonisation of technical requirements for registration of pharmaceuticals for human use. Available at: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E14/E14_Guideline.pdf;.
59. Harmark L, van Hunsel F, Grundmark B. ADR Reporting by the General Public: Lessons Learnt from the Dutch and Swedish Systems. *Drug Saf* 2015;38:337-47.
60. Matos C, Harmark L, van Hunsel F. Patient Reporting of Adverse Drug Reactions: An International Survey of National Competent Authorities' Views and Needs. *Drug Saf* 2016;39:1105-16.
61. Caruana R, You Y, Gehrke J, Koch P, Sturm M, Elhadad N. Intelligible models for healthcare: predicting pneumonia risk and hospital 30-day readmission. *Proceedings of the 21st ACM SIGKDD International Conference* 2015:1721-30.
62. Jones KH, Laurie G, Stevens L, Dobbs C, Ford DV, Lea N. The other side of the coin: Harm due to the non-use of health-related data. *Int J Med Inform* 2017;97:43-51.
63. Alonso-Coello P, Schunemann HJ, Moberg J, Brignardello-Petersen R, Akl EA, Davoli M, et al. GRADE Evidence to Decision (EtD) frameworks: a systematic and transparent approach to making well informed healthcare choices. 1: Introduction. *BMJ* 2016;353:i2016.
64. Alonso-Coello P, Oxman AD, Moberg J, Brignardello-Petersen R, Akl EA, Davoli M, et al. GRADE Evidence to Decision (EtD) frameworks: a systematic and transparent approach to making well informed healthcare choices. 2: Clinical practice guidelines. *BMJ* 2016;353:i2089.
65. Guyatt GH, Oxman AD, Kunz R, Falck-Ytter Y, Vist GE, Liberati A, et al. Going from evidence to recommendations. *BMJ* 2008;336:1049-51.
66. Fung KW, Kapusnik-Uner J, Cunningham J, Higby-Baker S, Bodenreider O. Comparison of three commercial knowledge bases for detection of drug-drug interactions in clinical decision support. *J Am Med Inform Assoc* 2017 Feb 22:Epub ahead of print.
67. Vidal L, Shavit M, Fraser A, Paul M, Leibovici L. Systematic comparison of four sources of drug information regarding adjustment of dose for renal function. *BMJ* 2005;331:263.
68. De Smet PAGM. Nieuwe generatie medicatiebewaking. (Next generation clinical decision support). *Pharmaceutisch Weekblad* 2005;14:483-485.
69. Warle-van Herwaarden MF, Kramers C, Sturkenboom MC, van den Bemt PM, De Smet PA. Targeting outpatient drug safety: recommendations of the Dutch HARM-Wrestling Task Force. *Drug Saf* 2012;35:245-59.
70. Tisdale JE, Jaynes HA, Kingery JR, Mourad NA, Trujillo TN, Overholser BR, et al. Development and validation of a risk score to predict QT interval prolongation in hospitalized patients. *Circ Cardiovasc Qual Outcomes* 2013;6:479-87.
71. Vandael E, Vandenberk B, Vandenberghe J, Spriet I, Willems R, Foulon V. Development of a risk score for QTc-prolongation: the RISQ-PATH study. *Int J Clin Pharm* 2017;39:424-32.

72. Brett Hauber A, Fairchild AO, Reed Johnson F. Quantifying benefit-risk preferences for medical interventions: an overview of a growing empirical literature. *Appl Health Econ Health Policy* 2013;11:319-29.
73. Johnston BC, Alonso-Coello P, Friedrich JO, Mustafa RA, Tikkinen KA, Neumann I, et al. Do clinicians understand the size of treatment effects? A randomized survey across 8 countries. *CMAJ* 2016;188:25-32.
74. Van de Glind EM, Willems HC, Eslami S, Abu-Hanna A, Lems WF, Hooft L, et al. Estimating the Time to Benefit for Preventive Drugs with the Statistical Process Control Method: An Example with Alendronate. *Drugs Aging* 2016;33:347-53.
75. Legemate DA, Koelemay MJ, Ubbink DT. Number Unnecessarily Treated in Relation to Harm: A Concept Physicians and Patients Need to Understand. *Ann Surg* 2016;263:855-6.
76. Mol PG, Arnardottir AH, Straus SM, de Graeff PA, Haaijer-Ruskamp FM, Quik EH, et al. Understanding drug preferences, different perspectives. *Br J Clin Pharmacol* 2015;79:978-87.
77. Harrison M, Milbers K, Hudson M, Bansback N. Do patients and health care providers have discordant preferences about which aspects of treatments matter most? Evidence from a systematic review of discrete choice experiments. *BMJ Open* 2017;7:e014719.
78. Van der Weijden T, Pieterse AH, Koelewijn-van Loon MS, Knaapen L, Legare F, Boivin A, et al. How can clinical practice guidelines be adapted to facilitate shared decision making? A qualitative key-informant study. *BMJ Qual Saf* 2013;22:855-63.
79. Schoemaker CG, van der Weijden T. Patiëntvoorkeur versus evidence based medicine: hadden de pioniers van EBM oog voor wat de patiënt wil? (Patient preferences versus evidence-based medicine: did the pioneers of evidence-based medicine take the patient's preferences into account?). *Ned Tijdschr Geneeskd* 2016;160:D24.
80. Raad voor Volksgezondheid en Samenleving. Zonder context geen bewijs - over de illusie van evidence-based practice in de zorg. 2017, The Hague, The Netherlands.
81. Ebell M. AHRQ White Paper: Use of clinical decision rules for point-of-care decision support. *Med Decis Making* 2010;30:712-21.
82. McCoy AB, Wright A, Rogith D, Fathiamini S, Ottenbacher AJ, Sittig DF. Development of a clinician reputation metric to identify appropriate problem-medication pairs in a crowd-sourced knowledge base. *J Biomed Inform* 2014;48:66-72.
83. Bindoff IK, Peterson GM, Curtain C. Computer system to support medication reviews: a good but not new concept. *Int J Clin Pharm* 2014;36:218-9.
84. De Wit HA, Mestres Gonzalvo C, Janknegt R, Schols JM, van der Kuy PH. A fully automated medication review?. *Int J Clin Pharm* 2014;36:220-1.
85. Kawazoe Y, Miyo K, Kurahashi I, Sakurai R, Ohe K. Prediction-based threshold for medication alert. *Stud Health Technol Inform* 2013;192:229-33.
86. Wright AP, Wright AT, McCoy AB, Sittig DF. The use of sequential pattern mining to predict next prescribed medications. *J Biomed Inform* 2015;53:73-80.
87. Dromain C, Boyer B, Ferre R, Canale S, Delaloge S, Balleyguier C. Computed-aided diagnosis (CAD) in the detection of breast cancer. *Eur J Radiol* 2013;82:417-23.
88. Kasparov G. Deep Thinking. Where Machine Intelligence Ends And Human Creativity Begins. London, United Kingdom: Hodder & Stoughton General Division 2017.
89. ActiZ, GGZ Nederland, KNMG, KNMP, LEVV, LHV, NFU, NHG, NICTIZ, NPCF, NVZ, NVZA, Orde, V&VN. Richtlijn Overdracht van Medicatiegegevens in de keten. (Policy document: transfer of information on medication). 2008, The Netherlands.

90. Latoszek-Berendsen A, Tange H, van den Herik HJ, Hasman A. From clinical practice guidelines to computer-interpretable guidelines. A literature overview. *Methods Inf Med* 2010;49:550-70.
91. Eppenga WL, Derijks HJ, Conemans JM, Hermens WA, Wensing M, de Smet PAGM. Comparison of a basic and an advanced pharmacotherapy-related clinical decision support system in a hospital care setting in the Netherlands. *J Am Med Inform Assoc* 2012;19:66-71.
92. Czock D, Konias M, Seidling HM, Kaltschmidt J, Schwenger V, Zeier M, et al. Tailoring of alerts substantially reduces the alert burden in computerized clinical decision support for drugs that should be avoided in patients with renal disease. *J Am Med Inform Assoc* 2015;22:881-7.
93. Seidling HM, Klein U, Schaier M, Czock D, Theile D, Pruszydlo MG, et al. What, if all alerts were specific - Estimating the potential impact on drug interaction alert burden. *Int J Med Inform* 2014;83:285-91.
94. Duke JD, Li X, Dexter P. Adherence to drug-drug interaction alerts in high-risk patients: a trial of context-enhanced alerting. *J Am Med Inform Assoc* 2013;20:494-8.
95. Uijtendaal EV, Zwart-van Rijkom JE, van Solinge WW, Egberts TC. Serum potassium influencing interacting drugs: risk-modifying strategies also needed at discontinuation. *Ann Pharmacother* 2012;46:176-82.
96. Riedmann D, Jung M, Hackl WO, Stuhlinger W, van der Sijs H, Ammenwerth E. Development of a context model to prioritize drug safety alerts in CPOE systems. *BMC Med Inform Decis Mak* 2011;11:35.
97. Phansalkar S, van der Sijs H, Tucker AD, Desai AA, Bell DS, Teich JM, et al. Drug-drug interactions that should be non-interruptive in order to reduce alert fatigue in electronic health records. *J Am Med Inform Assoc* 2013;20:489-93.
98. Marcilly R, Ammenwerth E, Roehrer E, Pelayo S, Vasseur F, Beuscart-Zephir MC. Usability Flaws in Medication Alerting Systems: Impact on Usage and Work System. *Yearb Med Inform* 2015;10:55-67.
99. Russ AL, Chen S, Melton BL, Johnson EG, Spina JR, Weiner M, et al. A Novel Design for Drug-Drug Interaction Alerts Improves Prescribing Efficiency. *Jt Comm J Qual Patient Saf* 2015;41:396-405.
100. Zachariah M, Phansalkar S, Seidling HM, Neri PM, Cresswell KM, Duke J, et al. Development and preliminary evidence for the validity of an instrument assessing implementation of human-factors principles in medication-related decision-support systems--I-MeDeSA. *J Am Med Inform Assoc* 2011;18 Suppl 1:i62-72.
101. Payne TH, Hines LE, Chan RC, Hartman S, Kapusnik-Uner J, Russ AL, et al. Recommendations to Improve the Usability of Drug-Drug Interaction Clinical Decision Support Alerts. *J Am Med Inform Assoc* 2015;22:1243-50.
102. Melton BL, Zillich AJ, Russell SA, Weiner M, McManus MS, Spina JR, et al. Reducing prescribing errors through creatinine clearance alert redesign. *Am J Med* 2015;128:1117-25.
103. Slight SP, Eguale T, Amato MG, Seger AC, Whitney DL, Bates DW, et al. The vulnerabilities of computerized physician order entry systems: a qualitative study. *J Am Med Inform Assoc* 2016;23:311-6.
104. Buurma H, De Smet PAGM, Kruijtbosch M, Egberts AC. Disease and intolerability documentation in electronic patient records. *Ann Pharmacother* 2005;39:1640-6.
105. Floor-Schreudering A, de Smet PAGM, Buurma H, Egberts AC, Bouvy ML. Documentation quality in community pharmacy: completeness of electronic patient records after patients' first visits. *Ann Pharmacother* 2009;43:1787-94.

106. Koster ES, Philbert D, Noordam M, Winters NA, Blom L, Bouvy ML. Availability of information on renal function in Dutch community pharmacies. *Int J Clin Pharm* 2016;38:797-801.
107. Smits E, Houben E, de Smet PAGM, Szerencsi K, vanHerk-Sukel MPP, Herings RMC, et al. The Availability of Information on Impaired Renal Function in the Community Pharmacy, A Descriptive Pilot Study. *HSOA Journal of Nephrology and Renal Therapy* 2016;2:003.
108. Dutch Ministry of Health, Welfare and Sport (Ministerie van Volksgezondheid, Welzijn en Sport). Regeling van de Minister van Volksgezondheid, Welzijn en Sport van 25 juni 2007, nr. GMT/MVG 2780607, houdende uitvoering van bepalingen van de Geneesmiddelenwet. (Regulations of the Minister of Health attached to the Law on Medicines) 2007 (last update 2016):Artikel 6.10,Artikel 6.11.
109. Cheung KC, Wensing M, Bouvy ML, De Smet PA, van den Bemt PM. Self-reported uptake of recommendations after dissemination of medication incident alerts. *BMJ Qual Saf* 2012;21:1009-18.
110. Law AV, Zargarzadeh AH. How do patients read, understand and use prescription labels? An exploratory study examining patient and pharmacist perspectives. *Int J Pharm Pract* 2010;18:282-9.
111. Wolf MS, Davis TC, Curtis LM, Webb JA, Bailey SC, Shrank WH, et al. Effect of standardized, patient-centered label instructions to improve comprehension of prescription drug use. *Med Care* 2011;49:96-100.
112. Koster ES, Philbert D, Bouvy ML. Health literacy among pharmacy visitors in the Netherlands. *Pharmacoepidemiol Drug Saf* 2015;24:716-21.
113. Buurma H, Schalekamp T, Egberts AC, de Smet PAGM. Compliance with national guidelines for the management of drug-drug interactions in Dutch community pharmacies. *Ann Pharmacother* 2007;41:2024-31.
114. Arts DL, Voncken AG, Medlock S, Abu-Hanna A, van Weert HC. Reasons for intentional guideline non-adherence: A systematic review. *Int J Med Inform* 2016;89:55-62.
115. McCoy AB, Wright A, Krousel-Wood M, Thomas EJ, McCoy JA, Sittig DF. Validation of a Crowdsourcing Methodology for Developing a Knowledge Base of Related Problem-Medication Pairs. *Appl Clin Inform* 2015;6:334-44.
116. Buurma H, De Smet PAGM, Leufkens HG, Egberts AC. Evaluation of the clinical value of pharmacists' modifications of prescription errors. *Br J Clin Pharmacol* 2004;58:503-11.
117. Van der Sijs H, van Gelder T, Vulto A, Berg M, Aarts J. Understanding handling of drug safety alerts: a simulation study. *Int J Med Inform* 2010;79:361-9.
118. Roberts A. Language, Structure, and Reuse in the Electronic Health Record. *AMA J Ethics* 2017;19:281-8.
119. Hazen ACM, de Bont AA, Boelman L, Zwart DLM, de Gier JJ, de Wit NJ, et al. The degree of integration of non-dispensing pharmacists in primary care practice and the impact on health outcomes: A systematic review. *Res Social Adm Pharm* 2017:Epub ahead of print.
120. Kwint HF, Faber A, Gussekloo J, Bouvy ML. Effects of medication review on drug-related problems in patients using automated drug-dispensing systems: a pragmatic randomized controlled study. *Drugs Aging* 2011;28:305-14.
121. Blegen MA, Sehgal NL, Alldredge BK, Gearhart S, Auerbach AA, Wachter RM. Improving safety culture on adult medical units through multidisciplinary teamwork and communication interventions: the TOPS Project. *Qual Saf Health Care* 2010;19:346-50.
122. Lyndon A. Communication and teamwork in patient care: how much can we learn from aviation?. *J Obstet Gynecol Neonatal Nurs* 2006;35:538-46.

123. Verbakel NJ, Langelaan M, Verheij TJ, Wagner C, Zwart DL. Improving Patient Safety Culture in Primary Care: A Systematic Review. *J Patient Saf* 2016;12:152-8.
124. Morello RT, Lowthian JA, Barker AL, McGinnes R, Dunt D, Brand C. Strategies for improving patient safety culture in hospitals: a systematic review. *BMJ Qual Saf* 2013;22:11-8.
125. Gaal S, Verstappen W, Wensing M. What do primary care physicians and researchers consider the most important patient safety improvement strategies?. *BMC Health Serv Res* 2011;11:102.
126. Van Dijk L, Bouvy ML, De Bakker D, et al. Samenwerking tussen huisarts en openbaar apotheker: stand van zaken en mogelijkheden voor de toekomst. (Collaboration between general practitioner and community pharmacist: current practice and future perspectives). NIVEL 2016, Utrecht, The Netherlands.
127. Van C, Costa D, Abbott P, Mitchell B, Krass I. Community pharmacist attitudes towards collaboration with general practitioners: development and validation of a measure and a model. *BMC Health Serv Res* 2012;12:320,6963-12-320.
128. Ouwens M, Bosch M, Wensing M. De 'zachte kanten' van samenwerking in de eerstelijnszorg ('Soft factors' in collaboration in primary care). IQ Healthcare, Scientific Institute for Quality of Healthcare 2012, Nijmegen, the Netherlands.
129. Mertens BJ, Kwint HF, Bouvy ML, Van de Pol J. Eindcontrole kan efficiënter. Maak per apotheek onderscheid tussen hoog- en laagrisicopatiënten. (Final check of dispensed prescriptions can be performed more efficiently by differentiating between high risk and low risk patients). *Pharmaceutisch Weekblad* 2017;152:(20) 14.
130. Warle-van Herwaarden MF, Valkhoff VE, Teichert M, Koffeman AR, 't Jong GW, Sturkenboom MC, et al. Development and application of indicators for the reduction of potentially preventable hospital admissions related to medications. *Expert Opin Drug Saf* 2014;13:157-65.
131. Garfield S, Barber N, Walley P, Willson A, Eliasson L. Quality of medication use in primary care--mapping the problem, working to a solution: a systematic review of the literature. *BMC Med* 2009;7:50.
132. Williams M, Peterson GM, Tenni PC, Bindoff IK, Stafford AC. DOCUMENT: a system for classifying drug-related problems in community pharmacy. *Int J Clin Pharm* 2012;34:43-52.
133. Stafford AC, Tenni PC, Peterson GM, Jackson SL, Hejlesen A, Villesen C, et al. Drug-related problems identified in medication reviews by Australian pharmacists. *Pharm World Sci* 2009;31:216-23.
134. Notenboom K, Beers E, van Riet-Nales DA, Egberts TC, Leufkens HG, Jansen PA, et al. Practical problems with medication use that older people experience: a qualitative study. *J Am Geriatr Soc* 2014;62:2339-44.
135. Stolper E, van Bokhoven M, Houben P, Van Royen P, van de Wiel M, van der Weijden T, et al. The diagnostic role of gut feelings in general practice. A focus group study of the concept and its determinants. *BMC Fam Pract* 2009;10:17.
136. Vadillo MA, Kostopoulou O, Shanks DR. A critical review and meta-analysis of the unconscious thought effect in medical decision making. *Front Psychol* 2015;6:636.
137. Heintzman ND. A Digital Ecosystem of Diabetes Data and Technology: Services, Systems, and Tools Enabled by Wearables, Sensors, and Apps. *J Diabetes Sci Technol* 2015;10:35-41.
138. Sino CG, Bouvy ML, Jansen PA, Schop IM, Egberts TC, Schuurmans MJ. Signs and symptoms indicative of potential adverse drug reactions in homecare patients. *J Am Med Dir Assoc* 2013;14:920-5.

139. Van der Linden CM, Kerskes MC, Bijl AM, Maas HA, Egberts AC, Jansen PA. Represcription after adverse drug reaction in the elderly: a descriptive study. *Arch Intern Med* 2006;166:1666-7.
140. Eppenga WL, Kramers C, Derijks HJ, Wensing M, Wetzels JF, De Smet PA. Drug therapy management in patients with renal impairment: how to use creatinine-based formulas in clinical practice. *Eur J Clin Pharmacol* 2016;72:1433-9.
141. Eppenga WL, Kramers C, Derijks HJ, Wensing M, Wetzels JF, De Smet PA. Individualizing pharmacotherapy in patients with renal impairment: the validity of the Modification of Diet in Renal Disease formula in specific patient populations with a glomerular filtration rate below 60 ml/min. A systematic review. *PLoS One* 2015;10:e0116403.
142. Eppenga WL, Wester WN, Derijks HJ, Hoedemakers RM, Wensing M, De Smet PA, et al. Fluctuation of the renal function after discharge from hospital and its effects on drug dosing in elderly patients--study protocol. *BMC Nephrol* 2015;16:95.
143. Horsky J, Aarts J, Verheul L, Seger DL, van der Sijs H, Bates DW. Clinical reasoning in the context of active decision support during medication prescribing. *Int J Med Inform* 2017;97:1-11.
144. Neumann I, Santesso N, Akl EA, Rind DM, Vandvik PO, Alonso-Coello P, et al. A guide for health professionals to interpret and use recommendations in guidelines developed with the GRADE approach. *J Clin Epidemiol* 2016;72:45-55.
145. Hess EP, Hollander JE, Schaffer JT, Kline JA, Torres CA, Diercks DB, et al. Shared decision making in patients with low risk chest pain: prospective randomized pragmatic trial. *BMJ* 2016;355:i6165.
146. Hay JL, Orom H, Kiviniemi MT, Waters EA. "I don't know" my cancer risk: exploring deficits in cancer knowledge and information-seeking skills to explain an often-overlooked participant response. *Med Decis Making* 2015;35:436-45.
147. McDermott R. Medical decision making: lessons from psychology. *Urol Oncol* 2008;26:665-8.
148. Trevena LJ, Zikmund-Fisher BJ, Edwards A, Gaissmaier W, Galesic M, Han PK, et al. Presenting quantitative information about decision outcomes: a risk communication primer for patient decision aid developers. *BMC Med Inform Decis Mak* 2013;13 Suppl 2:S7.
149. Power TE, Swartzman LC, Robinson JW. Cognitive-emotional decision making (CEDM): a framework of patient medical decision making. *Patient Educ Couns* 2011;83:163-9.
150. Smith SG, Curtis LM, O'Conor R, Federman AD, Wolf MS. ABCs or 123s? The independent contributions of literacy and numeracy skills on health task performance among older adults. *Patient Educ Couns* 2015;98:991-7.
151. Van der Vaart R, Drossaert CH, Taal E, ten Klooster PM, Hilderink-Koertshuis RT, Klaase JM, et al. Validation of the Dutch functional, communicative and critical health literacy scales. *Patient Educ Couns* 2012;89:82-8.
152. Fagerlin A, Zikmund-Fisher BJ, Ubel PA, Jankovic A, Derry HA, Smith DM. Measuring numeracy without a math test: development of the Subjective Numeracy Scale. *Med Decis Making* 2007;27:672-80.
153. Kaltoft M, Cunich M, Salkeld G, Dowie J. Assessing decision quality in patient-centred care requires a preference-sensitive measure. *J Health Serv Res Policy* 2014;19:110-7.
154. Munro S, Stacey D, Lewis KB, Bansback N. Choosing treatment and screening options congruent with values: Do decision aids help? Sub-analysis of a systematic review. *Patient Educ Couns* 2016;99:491-500.

155. Pieterse AH, de Vries M, Kunneman M, Stiggelbout AM, Feldman-Stewart D. Theory-informed design of values clarification methods: a cognitive psychological perspective on patient health-related decision making. *Soc Sci Med* 2013;77:156-63.
156. Fagerlin A, Pignone M, Abhyankar P, Col N, Feldman-Stewart D, Gavaruzzi T, et al. Clarifying values: an updated review. *BMC Med Inform Decis Mak* 2013;13 Suppl 2:S8.
157. Peters E, Hart PS, Fraenkel L. Informing patients: the influence of numeracy, framing, and format of side effect information on risk perceptions. *Med Decis Making* 2011;31:432-6.
158. Ploug T, Holm S. Doctors, Patients, and Nudging in the Clinical Context--Four Views on Nudging and Informed Consent. *Am J Bioeth* 2015;15:28-38.
159. Hamilton JG, Lillie SE, Alden DL, Scherer L, Oser M, Rini C, et al. What is a good medical decision? A research agenda guided by perspectives from multiple stakeholders. *J Behav Med* 2017;40:52-68.
160. Editorial. Balancing the benefits and risks of choice. *Lancet* 2016;388:1129.
161. Royal Dutch Pharmacists Association (KNMP). Handvest van de apotheker (Charter Professionalism of the Pharmacist. Foundation to act professionally and ethically). 2012, The Hague, The Netherlands.
162. Motivaction. Wat werkt bij wie? Een doelgroepbenadering bij innovaties in zorg en preventie. (Targeting innovations in health care and prevention). 2009, Utrecht, The Netherlands.
163. Morris RL, Ashcroft D, Phipps D, Bower P, O'Donoghue D, Roderick P, et al. Preventing Acute Kidney Injury: a qualitative study exploring 'sick day rules' implementation in primary care. *BMC Fam Pract* 2016;17:91,016-0480-5.
164. Whiting P, Morden A, Tomlinson LA, Caskey F, Blakeman T, Tomson C, et al. What are the risks and benefits of temporarily discontinuing medications to prevent acute kidney injury? A systematic review and meta-analysis. *BMJ Open* 2017;7:e012674,2016-012674.
165. Heringa, M. A health knowledge ecosystem: towards participation of all healthcare actors in a self-reinforcing knowledge loop through advanced IT solutions. Presentation FIP Congress Bangkok 2014. Available at: http://www2.pharmakon.dk/pm/breve/FIP/ZOOM_2014/ZOOM_5_2014/Mette_Heringa.pdf;.
166. Schneeweiss S, Eichler HG, Garcia-Altes A, Chinn C, Eggimann AV, Garner S, et al. Real World Data in Adaptive Biomedical Innovation: A Framework for Generating Evidence Fit for Decision-Making. *Clin Pharmacol Ther* 2016;100:633-46.
167. Miriovsky BJ, Shulman LN, Abernethy AP. Importance of health information technology, electronic health records, and continuously aggregating data to comparative effectiveness research and learning health care. *J Clin Oncol* 2012;30:4243-8.
168. Xie Y, Bowe B, Li T, Xian H, Yan Y, Al-Aly Z. Risk of death among users of Proton Pump Inhibitors: a longitudinal observational cohort study of United States veterans. *BMJ open* 2017;7:e015735.
169. Olde Rikkert MGM, Melis RJF, Claassen JAHR, Ferrari MD, Lagro J, Tolner EA, et al. Waarschuwingssignalen voor acute verergering van chronische ziekten. (Signs of acute aggravation of chronic diseases). *Ned Tijdschr Geneeskd* 2015;159:A8150.

Summary

Summary

The occurrence of preventable patient harm caused by drug use has been shown over and over again. As explained in **part 1**, the general introduction, clinical risk management is a concept to prevent patient harm by risk-reducing strategies. It is a systematic approach including risk detection, assessment, management and evaluation. One of the risk-reducing strategies in clinical risk management of drug therapy is the use of clinical decision support systems (CDSSs), which help health care professionals to detect drug therapy related problems. However, both the limited specificity and the limited sensitivity of current CDSSs give rise to problems. Continuous development of CDSSs is essential, firstly to improve their intrinsic performance in detecting drug therapy related problems, and secondly for alignment with changes in society and clinical practice. With the studies presented in this thesis we aimed to provide evidence to give direction to the further development of clinical decision support as a tool for clinical risk management of drug therapy.

Part 2 of this thesis focuses on the current use of CDSSs in community pharmacy, in order to propose improvement strategies. In **chapter 2.1** we investigated the quality of the electronic patient record, an important prerequisite for detecting drug therapy related problems by CDSSs. The results showed that according to the information provided by the patient, most electronic patient records in community pharmacy were incomplete or incorrect. Especially the registration of over-the-counter medications and chronic conditions was often incomplete. For 38% of the patients, drug therapy alerts failed to appear because of missing information.

In **chapter 2.2** the nature, frequency and determinants of drug therapy alerts generated by CDSSs in community pharmacies are presented. Data from 123 community pharmacies were analyzed, including over 1.6 million prescriptions for over 80,000 patients. Forty three percent of the processed prescriptions led to one or more drug therapy alerts. Drug-drug interactions (15% of all prescriptions), drug-disease interactions (14%) and duplicate medication alerts (13%) were the most frequent alerts. The majority of prescriptions with alerts (80%) were clustered in a minority of patients (16%) and related to a limited number of therapeutic drug classes.

In **chapter 2.3** we focus on the management of one type of drug therapy alerts: the duplicate medication alert. Our study in 53 community pharmacies showed that in 32% of the 1,272 investigated alerts the pharmacists decided that one or more actions were needed. Actions included updating of the electronic patient

record (15%), and external actions like instructing the patient (14%) and/or modifying the prescription (2%). Alerts concerning first dispensing were more likely to be followed by external action than alerts concerning repeat prescriptions (40% vs 14%).

In **part 3** we present the results of three improvement strategies for CDSSs. **Chapter 3.1** shows the results of a large scale implementation in community pharmacy of advanced clinical decision support rules regarding safe use of antibiotics in elderly patients with (potential) renal impairment. Pharmacists had the possibility to perform creatinine point of care testing in case information on renal function was urgently needed and could not be retrieved from other sources. The management of 88,391 alerts by 351 pharmacists led to 1,532 prescription modifications (1.8%). Pharmacists performed 1,988 creatinine point of care tests (2.2%). Determinants for finding renal impairment by point of care testing were higher patient age and higher number of medicines in use.

In **chapter 3.2** we investigated to what extent clustering of related drug interaction alerts (drug-drug and drug-disease interaction alerts) would decrease the alert rate in CDSSs. We performed a retrospective analysis of drug interaction alerts generated by CDSSs in community pharmacies. We showed that there were three clusters of concurrently generated alerts with similar management recommendations. Using these clusters in alert generation reduced the alert rate within the clusters by 53%-70%. The overall drug interaction alert rate was reduced by over 10%. The approach can easily be extended to additional clusters.

In **chapter 3.3** we explored another strategy to reduce the alert rate. We first determined events which can require a (re)assessment of a drug interaction (e.g. changed dose, new comorbidity) by a two-step consensus process. Then, we simulated a situation where alerts were triggered based on these events rather than for every repeat prescription. This approach led to a 93% reduction of the alert rate for the ten selected drug interactions, corresponding with a 28% decrease of the overall drug interaction alert rate. So, by focusing on changes in the patient's situation, a substantial reduction of the number of repeat alerts can be realized.

Part 4 of this thesis focuses on choosing between management options for a detected drug therapy related problem. This choice requires an assessment of risks and benefits. **Chapter 4.1** shows the results of an investigation into pharmacists' and patients' preferences regarding drug-drug interaction management options. By a choice-based conjoint survey, we showed that preferences were diverging, both among pharmacists (n=178) and patients (n=298). Different groups attached

different value to the risks, benefits and practical considerations of the management options. Awareness of this variability of preferences (and possible incongruence between pharmacists and patients) can contribute to shared decision making in the management of drug therapy related problems.

In **chapter 4.2** we present the results of a focus group investigation about patients' reasoning underlying their preferences for the management of drug-drug interactions. Despite their limited knowledge with respect to drug-drug interactions, patients easily chose a management option for a presented fictitious drug-drug interaction. When additional information was provided, preferences showed to be unsteadfast. The preferences were dependent on ten aspects from the cognitive, emotional, personal and situational domain. The interdependency between the aspects was high, and many of them were related to risk assessment. Tailored provision of information and individualized counseling is needed for active patient involvement in decision making on drug therapy related problems.

Overall, **part 2** of this thesis shows that the current alert rate in CDSSs is very high and that improvement strategies are needed. These should be directed at the patients and therapeutic drug classes with the highest alert rates, taking into account all relevant patient and prescription characteristics in an integrated approach. **Part 3** shows that large-scale implementation of advanced clinical decision support including laboratory values is feasible. Moreover, two promising approaches for reduction of the alert rate were presented (alert clustering, and alert triggering by changes in the patient situation). These approaches deserve further investigation to assess their consequences and applicability in daily practice. **Part 4** of this thesis shows that preferences of patients and pharmacists with regard to the management of drug therapy alerts are divergent. This insight can be used for incorporation of the patient perspective in the development and application of management recommendations for drug therapy related problems.

In **part 5**, the general discussion, we argue that societal and technical developments (including big data, patient centered care and the aging population) give rise to challenges and opportunities in the field of clinical risk management of drug therapy. In the development of clinical risk management, priority should be given to measures with the highest yield by the lowest effort. Clinical risk management of drug therapy is relevant on three levels: the national level, the local level, and the individual patient level, all of which need improvement. A nationwide structure for better use of current knowledge is needed. This structure should also support the development of knowledge on the effectiveness of risk reducing strategies like the use of CDSSs. CDSS redesign is needed and

priority should be given to the implementation of two approaches: multifactorial risk assessments, and change-based alerting. In a multifactorial risk assessment, all risk-modifying factors are taken into account in one integrated approach. Change-based alerting makes changes in the patient's situation the leading principle, rather than generating repeat alerts for every repeat prescription for patients in stable condition. To realize CDSS redesign, better coordination and collaboration between software suppliers, professional organizations and health care professionals is urgently needed. Improvements in clinical decision support should also address privacy, accountability and transparency.

As incorrect use of medication by patients is the most important reason for inappropriate drug use, the patient perspective needs more attention. Patients should be facilitated to participate in the decision making process as much as possible, given their preferences and capabilities. Integrated risk assessments – which should include the patient perspective – and watchfulness by health care professionals are essential for safe drug therapy. Therefore, more attention should be given to education of health care professionals with regard to competences like communication and clinical reasoning.

In conclusion, both competent health care professionals and continuously developing CDSSs are essential for clinical risk management of drug therapy. A joint effort of all involved actors is needed, with a central position and responsibility for pharmacists in every position in health care.

Samenvatting

Samenvatting

Het gebruik van geneesmiddelen geeft altijd risico op geneesmiddelgerelateerde problemen zoals bijwerkingen. In de algemene inleiding, **deel 1** van dit proefschrift, introduceerden we klinisch risicomanagement als methode om geneesmiddelgerelateerde problemen te verminderen. Klinisch risicomanagement omvat het systematisch opsporen en beoordelen van risico's, en vervolgens het inzetten en evalueren van strategieën om die risico's te verlagen. Een veel gebruikte strategie is het toepassen van medicatiebewakingssystemen (clinical decision support systems) door artsen en apothekers. Deze computersystemen geven op basis van het patiëntendossier een waarschuwing bij een mogelijk geneesmiddelgerelateerd probleem. Een voorbeeld is een geneesmiddelinteractie: het gelijktijdig gebruik van twee geneesmiddelen die niet goed samen gaan. Anders dan in het ziekenhuis, worden waarschuwingssignalen voor geneesmiddelgerelateerde problemen in de eerste lijn (bij de huisarts of in de openbare apotheek) vaak afgehandeld door extra instructies aan de patiënt te geven. Hoewel medicatiebewakingssystemen een goed hulpmiddel zijn, geven de huidige systemen veel te veel waarschuwingssignalen: slechts een klein deel van de signalen leidt tot ingrijpen door de arts of apotheker. Tegelijkertijd kunnen lang niet alle geneesmiddelgerelateerde problemen met medicatiebewakingssystemen worden opgespoord. Met de onderzoeken die we in dit proefschrift presenteren, beogen we richting te geven aan de verdere ontwikkeling van de medicatiebewaking ter bevordering van veilig geneesmiddelgebruik.

Deel 2 van dit proefschrift beschrijft de huidige praktijk van de medicatiebewaking in openbare apotheken, als basis voor strategieën ter verbetering van de medicatiebewakingssystemen. **Hoofdstuk 2.1** gaat over het elektronisch patiëntendossier in de apotheek, aangezien een betrouwbaar dossier een randvoorwaarde is voor het opsporen van geneesmiddelgerelateerde problemen. We laten zien dat – op basis van door de patiënt zelf verstrekte informatie – de meeste dossiers in de openbare apotheek onvolledig of onjuist zijn. Met name de registratie van zelfzorggeneesmiddelen en chronische aandoeningen in de apotheek was vaak onvolledig. Daardoor zijn bij 38% van de patiënten waarschuwingssignalen gemist, die bij een volledig dossier wel opgetreden zouden zijn.

In **hoofdstuk 2.2** laten we zien hoe veel en welke waarschuwingssignalen in de huidige situatie door medicatiebewakingssystemen in de openbare apotheek worden gegenereerd. Daarvoor analyseerden we meer dan 1,6 miljoen receptregels voor meer dan 80.000 patiënten uit 123 apotheken. Bij drieënveertig procent

van de verwerkte receptregels traden één of meer waarschuwingssignalen op. De meest voorkomende signalen waren interactiesignalen (15% van alle receptregels), contra-indicatiesignalen (14%) en (pseudo)dubbelmedicatiesignalen (13%). Er trad een clustering van waarschuwingssignalen op: de meerderheid van de receptregels met een waarschuwingssignaal (80%) was afkomstig van slechts 16% van de patiënten, en had betrekking op een beperkt aantal geneesmiddelgroepen.

In hoofdstuk 2.3 hebben we ons gericht op de afhandeling van één specifiek type waarschuwingssignalen: de (pseudo)dubbelmedicatiesignalen. Deze signalen sporen het gelijktijdig gebruik van twee dezelfde of vergelijkbare geneesmiddelen op. Uit ons onderzoek in 53 openbare apotheken bleek dat de apotheker bij 32% van de 1.272 onderzochte signalen tot actie overging. Dit betrof onder andere het bijwerken van het elektronisch patiëntendossier (15% van de signalen), en externe acties zoals het instrueren van patiënten (14%) en het aanpassen van het recept (2%). Waarschuwingssignalen bij een eerste uitgifte van een geneesmiddel leidden vaker tot externe actie dan waarschuwingssignalen bij herhaalrecepten (40% versus 14%).

In **deel 3** van dit proefschrift komen drie verbeterstrategieën voor medicatiebewakingssystemen aan bod. In **hoofdstuk 3.1** onderzochten we de grootschalige implementatie in openbare apotheken van waarschuwingssignalen door medisch-farmaceutische beslisregels voor antibioticumgebruik bij ouderen met een (mogelijk) verminderde nierfunctie. Wanneer apothekers dringend informatie over de nierfunctie van een patiënt nodig hadden, en deze informatie nergens te achterhalen was, kon de nierfunctie in de apotheek worden gemeten (door een vingerprik). De afhandeling van 88.391 waarschuwingssignalen door 351 apothekers leidde tot 1.532 receptwijzigingen (1,8%). Apothekers voerden 1.988 nierfunctiemetingen in de apotheek uit (2.2%). Een verminderde nierfunctie werd met deze meting het vaakst gevonden bij patiënten met een hogere leeftijd en bij patiënten die meer geneesmiddelen gebruikten.

In **hoofdstuk 3.2** hebben we onderzocht in hoeverre het samenvoegen van gerelateerde waarschuwingssignalen kan bijdragen aan vermindering van het aantal signalen in de medicatiebewakingssystemen. Dit hebben we gedaan op basis van een database van in de praktijk opgetreden signalen. We toonden aan dat er drie clusters waren van waarschuwingssignalen die vaak tegelijkertijd optraden en bovendien een vergelijkbaar afhandelingsadvies hadden. Door slechts één signaal per cluster te genereren, nam het aantal signalen voor de geclusterde waarschuwingen met 53% tot 70% af. Het totaal aantal waarschuwingssignalen

nam af met ruim 10%. Deze aanpak is gemakkelijk op andere waarschuwingssignalen toe te passen.

In **hoofdstuk 3.3** hebben we een andere strategie onderzocht om het aantal waarschuwingssignalen te verminderen. We hebben voor tien geneesmiddelinteracties / contra-indicaties met een consensusprocedure vastgesteld op welke momenten (her)beoordeling nodig kan zijn (bijvoorbeeld bij een dosiswijziging of een nieuwe aandoening). Vervolgens hebben we een medicatiebewakingssysteem gesimuleerd dat alleen op deze momenten een waarschuwingssignaal gaf – en dus niet voor ieder herhaalrecept in een ongewijzigde situatie. Deze aanpak leidde tot 93% minder signalen voor de tien onderzochte geneesmiddelinteracties / contra-indicaties, wat in totaal resulteerde in 28% minder signalen. Door voor de signalering te focussen op veranderingen in de situatie van de patiënt, kan het aantal waarschuwingssignalen voor herhaalrecepten dus aanzienlijk worden verminderd.

Deel 4 van het proefschrift gaat over de afhandeling van waarschuwingssignalen: daarbij moet vaak een keuze gemaakt worden uit meerdere afhandelopties (bijvoorbeeld een geneesmiddel vervangen door een alternatief, of het uitvoeren van extra controles). Voor deze keuze moeten de voor- en nadelen van iedere optie worden afgewogen. In **hoofdstuk 4.1** laten we zien welke voorkeuren patiënten en apothekers hebben bij deze afweging van voor- en nadelen bij de afhandeling van een geneesmiddelinteractie. Uit het keuze-experiment dat we uitvoerden, bleek dat zowel onder apothekers (n = 178) als onder patiënten (n = 298) de voorkeuren sterk varieerden. Verschillende groepen hechtten in de afweging een verschillend belang aan risico's, effectiviteit, en praktische consequenties, variërend van nadruk op uitsluiten van zelfs de hele kleine risico's tot nadruk op het niet wijzigen van het bestaande geneesmiddelgebruik. Als zorgverleners zich beter bewust zijn van deze variatie (en van mogelijke verschillen tussen hun eigen voorkeur en de voorkeur van de patiënt), zullen ze beter in staat zijn de voorkeur van de patiënt te betrekken in de besluitvorming.

In **hoofdstuk 4.2** presenteren we de resultaten van een focusgroep-onderzoek naar de overwegingen van patiënten bij het kiezen tussen verschillende afhandelingsopties voor een geneesmiddelinteractie. Hoewel geneesmiddelinteracties voor de meeste patiënten onbekend terrein zijn, maakten patiënten gemakkelijk een keuze tussen de gepresenteerde afhandelopties voor een fictieve geneesmiddelinteractie. Wanneer aanvullende informatie werd gegeven, veranderden patiënten vaak van voorkeur. De voorkeuren waren afhankelijk van een wisselwerking van tien aspecten, uit de domeinen cognitie, emotie, persoonlijkheid,

en situatie. Er waren sterke onderlinge verbanden tussen de tien aspecten, en veel aspecten waren gerelateerd aan risico-inschatting. Begeleiding en informatieverstrekking op maat zijn nodig om patiënten actief te betrekken bij de besluitvorming over geneesmiddelgerelateerde problemen.

In het algemeen blijkt uit de resultaten van **deel 2** dat het aantal waarschuwingssignalen in de huidige medicatiebewakingssystemen zeer hoog is, en dat daarom verbeterstrategieën nodig zijn. Deze moeten gericht zijn op de patiënten en geneesmiddelgroepen met de meeste signalen, en rekening houden met alle patiënt- en receptkenmerken in een geïntegreerde beoordeling. **Deel 3** van het proefschrift laat zien dat grootschalige implementatie van medisch-farmaceutische beslisregels - oftewel geavanceerde waarschuwingssignalen - mogelijk is. Bovendien worden twee manieren beschreven om het aantal waarschuwingssignalen aanzienlijk te verminderen (het clusteren van signalen, en het signaleren op basis van veranderingen in de situatie van de patiënt). Nader onderzoek is nodig om te kijken wat de uitwerking van deze strategieën in de dagelijkse praktijk is. **Deel 4** laat zien dat zowel onder patiënten als onder apothekers de voorkeuren voor de afhandeling van waarschuwingssignalen divers zijn. Inzicht in deze variatie kan worden gebruikt voor het opstellen van betere afhandelingsadviezen voor de waarschuwingssignalen, en voor het betrekken van het patiëntperspectief in de besluitvorming in de dagelijkse praktijk.

In **deel 5** van dit proefschrift, de algemene beschouwing, stellen we vast dat doorontwikkeling van klinisch risicomanagement van geneesmiddelgebruik nodig is vanwege maatschappelijke en technologische ontwikkelingen (zoals big data, individualisering van zorg, en vergrijzing). Klinisch risicomanagement is relevant op drie niveaus: het nationale niveau, het lokale niveau, en het individuele patiëntniveau. Op alle niveaus is verbetering nodig is. Daartoe dient een landelijke structuur ontwikkeld te worden die bijdraagt aan beter gebruik van beschikbare kennis en aan betere evaluatie van risicoverlagende strategieën. Medicatiebewakingssystemen zijn toe aan herziening. Twee ontwikkelrichtingen verdienen prioriteit. De eerste is het toepassen van een meervoudige risicoschatting, waarbij alle relevante factoren uit het patiëntendossier (zoals labwaarden) in samenhang worden beoordeeld. De tweede aanpak is het signaleren op basis van verandering in de situatie van de patiënt - en dus geen signaal bij ieder herhaalrecept in een ongewijzigde situatie. Voor deze ontwikkelingen is betere samenwerking tussen softwareleveranciers, beroepsorganisaties en zorgverleners nodig. Bij de herinrichting van de medicatiebewaking dient ook voldoende aandacht geschonken te worden aan aspecten als privacy, transparantie, en verantwoording.

Aangezien onjuist medicijngebruik door patiënten de belangrijkste reden is voor geneesmiddelgerelateerde problemen, is meer aandacht nodig voor het perspectief van de patiënt. Patiënten dienen – met inachtneming van hun voorkeuren en mogelijkheden – daarom zo veel mogelijk betrokken te worden in het besluitvormingsproces. Zorgverleners dienen in de afweging van voor- en nadelen zowel medische als niet-medische factoren te betrekken. Voor veilig geneesmiddelgebruik blijft oplettendheid van zorgverleners van groot belang, naast de toepassing van technologische hulpmiddelen zoals medicatiebewakingssystemen. Dat vraagt om competentieontwikkeling bij zorgverleners, o.a. op het gebied van communicatie en klinisch redeneren.

Concluderend kan worden gesteld dat voor klinisch risicomanagement van geneesmiddelgebruik zowel competente zorgverleners als medicatiebewakingssystemen nodig zijn. Medicatiebewakingssystemen moeten worden doorontwikkeld en aansluiten bij maatschappelijke veranderingen. Daarvoor is samenwerking van alle betrokkenen vereist. Als geneesmiddeldeskundige hebben apothekers op alle posities in de gezondheidszorg hierin een verantwoordelijkheid.

Woord van dank

Woord van dank

Vijf jaar is voorbij: een zoektocht op divers terrein. Een traject dat langzaam begon, met parallel nog veel andere werkzaamheden. Maar het vorderde, en het geheel kon tot een goed einde worden gebracht. Ik ben daarvoor aan velen veel dank verschuldigd. Aan mensen die me de weg wezen bij de zoektocht, die me op nieuwe ideeën brachten, die een stukje met me mee liepen (al dan niet in cirkels), die kennis en ervaring met me deelden, met wie ik verhalen uitwisselde: die het de moeite waard maakten.

Een centrale plaats was daarbij uiteraard weggelegd voor mijn (co)promotoren Marcel Bouvy, Peter de Smet en Annemieke Floor. Hartelijk dank voor jullie begeleiding, geduld en vertrouwen. En voor de ruimte om voor een grote diversiteit aan onderzoeken en onderwerpen te kiezen: van multilevel-databaseanalyse tot conjointanalyse tot focusgroepen. Marcel: dank voor je hulp op alle onderzoeksniveaus, altijd vergezeld van een recent voorbeeld uit de apotheek, en met altijd energie om van ieder voorbeeld een nieuw onderzoek te maken. Peter: dank voor het steeds weer aandragen van nieuwe perspectieven en het meedenken over andere (diplomatieke) invalshoeken. Annemieke: dank voor je betrokkenheid, het meedenken op alle fronten, en de samenwerking in de vele onderzoeken.

De onderzoeken zijn tot stand gekomen in samenwerking met vele anderen. Willemijn Meijer, Hidde Siderius, Annet van der Heide en Hans Wouters zijn co-auteurs: veel dank voor jullie bijdrage! En dank aan alle anderen die hebben meegewerkt aan een of meerdere onderzoeken, bij de organisatie (Marsha van Leeuwen), de analyse (Bashir Rostai), het verkrijgen van de data (Petra Hoogland), en in welke andere vorm dan ook.

Daarbij horen zeker ook de -letterlijk- onnoemelijk vele openbaar apothekers en patiënten die hebben meegewerkt aan de gegevensverzameling, onder andere door bijeenkomsten te organiseren of bij te wonen en door vragenlijsten in te vullen. Veel dank daarvoor! Hopelijk bieden de onderzoeksresultaten aanknopingspunten voor de farmacie en patiëntenzorg van de toekomst.

Daarnaast veel dank aan alle collega's bij SIR, een bijzondere en fijne plek om (samen) te werken aan farmaceutische zorg, onderwijs en praktijkonderzoek. Allemaal hebben jullie in een of andere vorm bijgedragen: Adrianne, Anita, Anne-Margreeth, Bram, Caroline, Henk-Frans, Linda, Martine, Sanne, Sander, Sonia, Thessa en Valérie. En SIR bestaat niet zonder Academische Apotheek Stevenshof: ook dank aan alle collega's uit de apotheek, daar waar de connectie

tussen onderzoek en praktijk steeds weer gevonden wordt. En dank aan Henk Buurma: grondlegger van zowel dit promotietraject als SIR.

Het promotietraject heeft plaatsgevonden naast mijn werkzaamheden bij Stichting Health Base. Dank aan Jan-Kees Huyts, die de totstandkoming heeft gestimuleerd en ook tijdens het traject steeds alle ruimte heeft geboden. En dank aan alle andere collega's bij Health Base (en ook PharmaPartners) - waar medicatiebewaking wordt ontwikkeld en in de praktijk gebracht.

En passant heb ik ook nog de nodige tijd aan de Universiteit Utrecht doorgebracht. Dank aan iedereen die dat mogelijk heeft gemaakt, van formulieren tot databases tot ICT.

Verder dank aan de commissie van hoogleraren die het manuscript beoordeelde, bestaande uit Ton de Boer, Petra Denig, Han de Gier, Olaf Klungel en Bert Leufkens.

Bijna tot slot: dank aan de paranimfen. Chris Tromp, collega bij Health Base, met wie ik veel over de structuur en invulling van medicatiebewaking heb nagedacht, en mede-auteur van een van de artikelen. De andere, Jelte, broertje: vertegenwoordiging van de niet-farmacie - want gelukkig is de wereld groter. Dus dank ook aan die niet-farmaceutische wereld: vrienden en familie, Jelte & Martine (dank voor het mooie omslagontwerp!), Anco & Kyke, en - tot slot - Rani.

List of co-authors

List of co-authors of manuscripts presented in this thesis

Affiliations during the conductance of the research

Marcel L. Bouvy
Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht
SIR Institute for Pharmacy Practice and Policy, Leiden

Henk Buurma
SIR Institute for Pharmacy Practice and Policy, Leiden

Annemieke Floor-Schreudering
SIR Institute for Pharmacy Practice and Policy, Leiden
Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht

Annet van der Heide
Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht

Willemijn M. Meijer
Royal Dutch Pharmacists Association (KNMP), The Hague

Hidde Siderius
Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht

Peter A.G.M. de Smet
Departments of Clinical Pharmacy and IQ Healthcare, University Medical Centre St Radboud, Nijmegen
Royal Dutch Pharmacists Association (KNMP), The Hague

P. Chris Tromp
Health Base Foundation, Houten

Hans Wouters
Department of Pharmacotherapy, -Epidemiology & -Economics, Groningen University, Groningen

List of publications

List of publications

Publications presented in this thesis

- Heringa M, Siderius H, Floor-Schreudering A, De Smet PAGM, Bouvy ML. Lower alert rates by clustering of related drug interaction alerts. *J Am Med Inform Assoc* 2017;24:54-59.
- Heringa M, Floor-Schreudering A, Tromp PC, De Smet PAGM, Bouvy ML. Nature and frequency of drug therapy alerts generated by clinical decision support in community pharmacy. *Pharmacoepidemiol Drug Saf* 2016;25:82-9.
- Heringa M, Floor-Schreudering A, Meijer WM, De Smet PAGM, Bouvy ML. Nature and management of duplicate medication alerts. *J Am Med Inform Assoc* 2015;22:831-837.
- Floor-Schreudering A, Heringa M, Buurma H, Bouvy ML, De Smet PAGM. Missed drug therapy alerts as a consequence of incomplete electronic patient records in Dutch community pharmacies. *Ann Pharmacother* 2013;47:1272-1279.
- Heringa M, Floor-Schreudering A, De Smet PAGM, Bouvy ML. Clinical decision support and optional point of care testing of renal function for safe use of antibiotics in elderly patients: a retrospective study in community pharmacy practice. *Submitted.*
- Heringa M, Van der Heide A, Floor-Schreudering A, De Smet PAGM, Bouvy ML. Better specification of triggers to reduce the number of drug interaction alerts in primary care. *Submitted.*
- Heringa M, Floor-Schreudering A, Wouters H, De Smet PAGM, Bouvy ML. Preferences of patients and pharmacists with regard to the management of drug-drug interactions: a choice-based conjoint analysis. *Accepted for publication in Drug Safety.*
- Heringa M, Floor-Schreudering A, De Smet PAGM, Bouvy ML. Understanding patient preferences for the management of drug-drug interactions. *Submitted.*

Other scientific and professional publications

- Heringa M, Van de Steeg-van Gompel CH, Bouvy ML. Medisch-farmaceutische beslisregels en nierfunctiemeting in de openbare apotheek: wat levert het op? *Nederlands Platform voor Pharmaceutisch Onderzoek* 2017;2:a1638
- Hiddink EG, Heringa M. Signaal op Maat: Slimmer signaleren maakt medicatiebewaking veiliger en efficiënter. *De Jonge Apotheker* 2017;24:12-5.

- Heringa M. Herinrichting medicatiebewaking nodig voor betere zorgverlening door apotheker. Bewaking verbetert dankzij veel minder 'loos alarm'. *Pharmaceutisch Weekblad* 2016;151:16-7.
- Borgsteede SD, De Gier JJ, Eimermann VM, Tsoi KT, Heringa M (ed). Commentaren Medicatiebewaking, editions 2005-2017. Health Base, Houten, The Netherlands.
- Floor-Schreudering A, Heringa M. Eindrapportage Klinische relevantie van medisch-farmaceutische beslisregels inzake laboratoriumwaarden in openbare apotheken, SIR Institute for Pharmacy Practice and Policy, Leiden, December 2015.
- KNMP richtlijn medicatiebewaking *(in process)*. KNMP, The Hague, The Netherlands.
- KNMP richtlijn diabetes *(in process)*. KNMP, The Hague, The Netherlands.
- Harmsze AM, de Boer A, Boot H, Deneer VHM, Heringa M, Mol PGM, Schalekamp T, Verduijn MM, Verheugt FWA, le Comte M. Interactie tussen clopidogrel en protonpompremmers. *Ned Tijdschr Geneeskd* 2011;155:A2442.
- Heringa M, Wessels-Basten SJW, van Grafhorst JP, Ackerman EW. Met eenvoudige middelen naar een hoger niveau. Classificatie van interventies en consultaties verbetert FPZ in het ziekenhuis. *Pharmaceutisch Weekblad* 2005;37:1154-7.
- Czock D, Keller F, Heringa M, Rasche FM. Raloxifene pharmacokinetics in males with normal and impaired renal function. *Br J Clin Pharmacol* 2005;59:479-82.
- Heringa M. Review on raloxifene: profile of a selective estrogen receptor modulator. *Int J Clin Pharmacol Ther* 2003;41:331-45.

About the author

About the author

Mette Heringa was born on 21 April 1980 in Nijmegen, the Netherlands. She obtained her pharmacy degree *cum laude* at Utrecht University in 2004. From 2005 on, she worked at the Health Base Foundation in Houten. She conducted projects on several aspects of patient safety, including pharmacokinetic drug-drug interactions, drug use in patients with renal impairment, and drugs and driving. She worked on the development of advanced clinical decision support rules for community pharmacists and general practitioners. She was coordinator and final editor of the yearly published reference book *Commentaren Medicatiebewaking* on drug-drug interactions and drug-disease interactions.

From 2010 on, she combined her job at the Health Base Foundation with a position at the SIR Institute for Pharmacy Practice and Policy in Leiden. There, she contributed to the development of the guidelines for pharmaceutical care of the Royal Dutch Pharmacists Association. She developed and taught a post-graduate training on advanced clinical decision support rules for community pharmacists. She participated in several investigations on clinical decision support related to laboratory values in community pharmacy practice. In 2012, she started her PhD research 'clinical decision support in community pharmacy'. She will continue to work at the SIR Institute as a senior researcher.