ADVERSE DRUG REACTIONS
IN INDIVIDUAL PATIENT CARE
documentation and prevention of represcription

Carolien M.J. van der Linden

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voor mijn ouders

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1

General introduction

Optimisation of pharmacotherapy

Safe and effective pharmacotherapy remains one of the greatest challenges in medicine, but it is often difficult to achieve the right balance between preventing and/or treating diseases with drugs and avoiding medication-related harmful effects.[1] The risks and benefits of individual drugs are evaluated at a population level in the pre- and post-marketing phases of drug development by pharmaceutical industry and regulatory authorities, based on information obtained from pharmacokinetic studies and clinical trials investigating a single drug in selected populations. However, many trials have restrictive inclusion and exclusion criteria, and older persons are often under-represented, even though many older people use several medications for multiple health problems.[2,3] Yet these elderly people may benefit from drug treatment as much or even more (i.e., number needed to treat the same or lower) than younger people, but they are more vulnerable to the harmful effects of medication because they are on polypharmacy, have comorbid conditions, and have altered pharmacokinetics and pharmacodynamics. Adverse drug reactions (ADRs) are an important cause of morbidity and mortality, especially in elderly patients.[4]

Adverse drug reactions

Definitions

Any substance that is capable of producing a therapeutic effect can also produce unwanted or adverse effects. The term "adverse reaction" must be distinguished from "adverse event". An adverse reaction is an adverse outcome that can be attributed to some action of a drug; an adverse event is an adverse outcome that occurs while a patient is taking a drug, but is not or not necessarily attributable to it. The term adverse reaction implies that the effect of the drug is causally related with the unwanted reaction. The WHO's definition of an ADR, which has been in use for about 40 years, is "a response to a medicine which is noxious and unintended, and which occurs at doses normally used in man".[5] The word noxious though, is vague and it may include all adverse reactions, no matter how minor they are. Edwards and Aronson proposed another definition: "An appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product."[6]

Causality

It is not always easy to establish the causality of an ADR because of the complex nature of adverse events, multiple treatments, and individual clinical variability.[7] The most commonly used approach to establish causality is based on the clinical judgement of an expert panel or "global introspection"; however, this process is subjective. To overcome this, several algorithms have been proposed for the reproducible

assessment of causality, all of which make use of a combination of five commonly used criteria for causality assessment: challenge, dechallenge, rechallenge, previous bibliographic description, and aetiological alternatives. Macedo et al. compared the causality assessments of an expert panel and 15 published algorithms and found algorithms to have a high sensitivity (average 93%) but low specificity (average of 7%).[8]

Frequency and risk factors

The reported frequency of ADRs is highly variable, probably because studies differ in their definition of an ADR, in the methods used to gather information about ADRs (e.g., intensive monitoring, spontaneous reporting), and in the study setting and design. A review article from 2000 reported the incidence of ADRs in hospitalised patients to vary between 1.9% and 37.3%.[9] Krähenbühl-Melcher et al. found ADRs to affect 6.1 per 100 hospitalised patients and also showed a high variability (range 0.17–65%) among the 46 studies retrieved for their review article.[10] Important risk factors for adverse drug events or reactions included polypharmacy, female sex, drugs with a narrow therapeutic range, renal elimination of drugs, age>65 years, and use of anticoagulants or diuretics. Factors believed to increase the risk of ADRs in elderly patients are polypharmacy, increased drug–drug interactions, and changes in pharmacokinetics and pharmacodynamics.[11]

Consequences

The majority of ADRs are probably of moderate risk to the patient, but some have serious consequences and lead to hospital or death.[12] A meta-analysis by Lazarou et al. showed an overall incidence of fatal ADRs of 0.32% (95% CI 0.23-0.41) among hospitalised patients.[13] The Hospital Admissions Related to Medication (HARM) study showed that, in the Netherlands, 5.6% of all acute hospital admissions are the result of medication-related problems. Individuals who were especially at risk of medication-related admissions were elderly patients who used several medications, who were cognitively impaired, or who did not adhere to their pharmacotherapy regimen.[14] In a prospective study of an elderly Italian population, Franceschi et al. found that 5.8% of all hospital admissions were related to ADRs.[15] In a review of 17 observational studies of potentially preventable hospital admissions related to medication, Howard et al. found certain groups of drugs to be associated with hospital admissions.[16] These groups of drugs corresponded with the high-risk medications mentioned in the HARM-study and in the study by Franceschi et al., namely anticoagulant and antiplatelet drugs, NSAIDs, diuretics, RAS inhibitors, medications that act on the central nervous system, glucose lowering medicines, corticosteroids, and opioids. ADRs that resulted in hospital admission were mainly gastrointestinal bleeding, trauma, electrolyte disorders, impaired renal function, derangement of diabetes, and constipation.

Preventability

ADRs are either non-preventable (e.g., a side effect that could not have been predicted) or preventable. Numerous definitions and algorithms have been developed to assess preventability. In their review, Hakkarainen et al. identified 18 unique instruments for determining the preventability of adverse drug events, varying from implicit instruments that loosely define preventability to explicit algorithms with clearly defined criteria for preventability.[17] All instruments shared the same basis for defining preventability, namely, whether an error or substandard care had resulted in adverse drug events. However, there was limited evidence to support the validity of these instruments and their reliability varied significantly. A frequently used and much modified algorithm is that of Schumock-Thornton.[18] This algorithm assesses prescribing errors, which can be defined as dosing errors or therapeutic errors, such as medication not indicated (based on patient history), medication contraindicated, recorded medication allergies, drug-drug interaction (included only if the interaction is inadequately monitored or if the medication involved in the interaction may never be combined), inadequate monitoring of therapy, therapeutic duplication medication, and underprescribing. Other causes of preventable medication-related problems are dispensing errors at the pharmacy and administration errors (errors made by caregivers or patients when administering medication, e.g. non-adherence to the medication regimen).

Almost half (46.5%) of the medication-related hospital admissions in the HARM-study were potentially preventable, as assessed with a modified version of the algorithm of Schumock and Thornton.[14] A meta-analysis of patients with preventable ADRs and the preventability of ADRs, identified 16 original studies involving outpatients with emergency visits or hospital admissions and 8 studies involving 24,128 inpatients. Overall, 2% (95% confidence interval (CI) 1.2 - 3.2%) of outpatients and 1.6% (95% CI 0.1 - 51%) of inpatients had ADRs, and approximately half of the ADRs were preventable.[19]

An important cause of preventable ADRs is the represcription of a drug that was previously withdrawn because it caused an allergy or another ADR in the patient.

Represcription after ADR

Patients expect their doctors and pharmacist to have a complete overview of their medication regimen, including past changes and reasons for them. While this seems reasonable, it is often not the case. Health professionals have to manage an increasing amount of clinical data in an increasingly complex practice environment. Furthermore, the decentralised and fragmented nature of the healthcare system contributes to the discontinuity of care when patients see multiple healthcare providers, none of whom have access to complete information about the patients' health care status.[20] To help professionals manage this increasingly complex practice envi-

ronment, James commented a new generation of support tools for clinical decision making that has been developed to "make it easy to do it right". These systems can integrate clinical data and, for example, generate reminders.[21]
In clinical practice we often see patients who have been represcribed medication that was withdrawn earlier because patients experienced an ADR during hospitalisation, an unfortunate example of the healthcare system failing to come up to patients' expectations as mentioned above. To prevent the represcription of drugs withdrawn because they caused an ADR, it is important that all ADRs are adequately detected and documented, and that this information is available to all relevant healthcare providers and the patient. In addition, physicians need to be alerted when represcription occurs.

Objectives of this thesis

The main objectives of this thesis were:
a) to investigate documentation of reasons for medication discontinuation and ADRs and to what extent drugs that have been withdrawn because of an ADR are represcribed, and
b) to investigate methods to prevent the represcription of withdrawn drugs, including the development and implementation of an electronic clinical decision support module and assessment of its feasibility.

Outline of this thesis

The research into ADRs and drug represcription, mainly in elderly patients, is described in two parts. The first part describes the documentation of ADRs and the frequency of represcription. We first investigated whether and how the reasons for medication discontinuation were documented in the medical records of patients on geriatric and internal medicine wards (chapter 2.1). We subsequently investigated the frequency of ADRs, the communication of information about ADRs to general practitioners and community pharmacists, and the rate of represcription of medicines withdrawn because of an ADR in geriatric patients (chapter 2.2). In chapter 2.3, we describe three patients who had a recurrence of a serious ADR because they had been represcribed a drug that had previously been withdrawn.
The second part of this thesis describes systems to prevent the represcription of medications withdrawn because of an ADR. In chapter 3.1, we review available systems that can prevent the represcription of drugs that previously caused an ADR. We developed an electronic clinical decision support module that compels doctors to document reasons for medication discontinuation and alerts them to unwanted represcription of drugs withdrawn because they caused an ADR (chapter 3.2). We also report preliminary results for the implementation of the module on a geriatric ward. In chapter 3.3, we describe the reasons for discontinuing medications during hospitalisation that were recorded with the electronic clinical decision support module used on geriatric and internal medicine wards and the alerts given when the medications are represcribed. The module was developed further to integrate information on ADRs into the information system of primary care centres, in order to prevent the represcription of withdrawn medicines in primary care. In chapter 3.4, we describe how these systems can be integrated, the barriers encountered to the integration, and its feasibility, as assessed by general practitioners. In the general discussion in chapter 4, we describe our findings in a broader perspective in relation to clinical practice and research and present suggestions for further research and clinical practice.

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2

Documentation of adverse drug reactions and frequency of represcription

2.1 Reasons for discontinuation of medication during hospitalisation and documentation thereof

a descriptive study of 400 geriatric and internal medicine patients

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Introduction

Medication is often changed or discontinued during hospital admission, and this is especially true for medications prescribed to elderly patients.[1] However, after discharge further changes to medication regimens are not always intentional and may be due to poor communication.[2] For example, in an earlier study, we found that adverse drug reactions (ADRs) detected during hospitalisation and requiring cessation of the causative drug were poorly communicated to primary care professionals (general practitioners (GPs) and pharmacists), leading to a rate of represcription of withdrawn medication of 27% during the first 6 months after discharge.[3] The study highlighted the need for better communication of reasons for discontinuation of medication. Adequate communication of these reasons can only exist on the condition that these reasons are well documented. Our experience in daily practice is that such documentation is often inadequate. The objectives of the current study were to evaluate the frequency of reasons for discontinuation of medication and the documentation thereof in hospitalised patients.

Methods

Two researchers (CMJL and EVG) studied the medical records (paper and electronic) of consecutive patients admitted to the geriatric (n=100) and internal medicine (n=100) wards of the University Medical Center Utrecht (UMCU) and the geriatric (n=100) and internal medicine (n=100) wards of the Catharina Hospital in Eindhoven (CHE), the Netherlands, to determine which medications were used before hospitalisation. Most prevalent medications were categorized in 11 therapeutic groups (table 1).

TABLE 1 **Categories of prevalent medications; 11 therapeutic groups**

- Analgetics
- Antibiotics
- Anticoagulants and Antiplatelet agents
- Antidiabetic agents
- Cardiovascular drugs
- Corticosteroids
- Gastro-intestinal drugs
- Inhalant agents in COPD
- Psychofarmaca (antipsychotics and antidepressant agents)
- Supplements (eg vitamins and minerals)
- Other

Discontinuation was defined as stopping or switching to another drug within the same therapeutic range. We distinguished discontinuation of medication prescribed before hospitalisation or prescribed during hospitalisation. Also, the moment of discontinuation (at the moment of hospitalisation, or later during hospitalisation) was documented. Prescribed and discontinued medications and dates of discontinuation were extracted from electronic prescription programs and then patient records were reviewed to determine whether the reasons for discontinuation of these medications at these dates had been recorded. Reasons for discontinuation were categorized as: 'adverse drug reaction', 'contraindication', 'no longer indicated', 'interaction', 'palliation', 'ineffective', 'no reason mentioned', 'at request of patient', or 'other'. Discontinuation of antibiotics after completion of a course and of potassium suppletion after normalization of serum potassium was interpreted as 'no longer indicated'.

Results

Mean age of 200 geriatric patients was 82 years, of 200 internal medicine patients 57 years. In the geriatric patients 61% were female, in internal medicine patients 50 % were female. The geriatric patients used a mean of 7.3 (range 0-24) medications at admission, the internal medicine patients 4.8 (range 0-20). The average number of discontinued medications was 4.9 (range 0-22) in geriatric patients and 2.8 (range 0-26) in internal medicine patients. In table 2 patient characteristics and numbers of medications on admission and of discontinued medications are mentioned grouped by ward and hospital.

Of all discontinued medications in geriatric patients, 50% were prescribed before admission and 50% had been started during hospitalisation. Among internal medicine patients, 35% of discontinued medications were prescribed before and 65% during hospitalisation. In geriatric patients the most frequently discontinued medications were cardiovascular drugs (18%), psychofarmaca (13%) and antibiotics (12%). The most frequently discontinued medications in internal medicine patients were cardiovascular drugs (16%) and gastrointestinal drugs (13%). In table 3 discontinued medications categorized and ranked by therapeutic group are represented.

TABLE 2 Patient characteristics, number of medications at admission and number of discontinued medication

	Hospital (number of patients)	Female (%)	Age: mean (SD)	Number of medications at admission: mean (SD)	Number of medications discontinued*: mean (SD)
Geriatrics	UMCU (100)	61	82.7 (6.9)	7.5 (3.7)	5.8 (5.1)
	CHE (100)	61	81.4 (6.3)	7.1 (4.4)	4 (3.5)
	UMCU+CHE (200)	61	82.1 (6.6)	7.3 (4.1)	4.9 (4.5)
Internal Medicine	UMCU (100)	50	53.7 (18.2)	5.0 (4.0)	3.1 (4.1)
	CHE (100)	50	60.2 (19.5)	4.6 (4.2)	2.4 (3.2)
	UMCU+CHE (200)	50	56.9 (19.2)	4.8 (4.1)	2.8 (3.7)

** Number of medications discontinued; at admission or during hospitalisation*

SD = standard deviation; UMCU = University Medical Center Utrecht; CHE = Catharina Hospital Eindhoven

TABLE 3 Frequencies of categories of discontinued medications

		GERIATRIC WARDS					
		CHE		UMCU		All	
Overall rank	Therapeutic group	Number	%	Number	%	Number	%
1	Cardiovascular drugs	77	19%	96	16%	173	18%
2	Psychofarmaca	75	19%	58	10%	133	13%
3	Antibiotics	52	13%	63	11%	115	12%
4	Supplements	53	13%	64	11%	117	12%
5	Gastro-intestinal drugs	29	7%	83	14%	112	11%
6	Others	41	10%	60	10%	101	10%
7	Analgetics	35	9%	49	8%	84	9%
8	Anticoagulants and Antiplatelet agents	27	7%	50	9%	77	8%
9	Inhalant agents in COPD	6	1%	28	5%	34	3%
10	Antidiabetic agents	2	0%	17	3%	19	2%
11	Corticosteroids	8	2%	14	2%	22	2%
	All	**405**	**100%**	**582**	**100%**	**987**	**100%**

Table 3 Continued »

TABLE 3 continued

Overall rank	Therapeutic group	INTERNAL MEDICINE WARDS CHE Number	CHE %	UMCU Number	UMCU %	All Number	All %
1	Cardiovascular drugs	43	18%	47	15%	90	16%
2	Gastro-intestinal	drugs23	10%	48	16%	71	13%
3	Others	43	18%	31	10%	74	13%
4	Analgetics	34	14%	31	10%	65	12%
5	Antibiotics	21	9%	45	15%	66	12%
6	Supplements	25	10%	35	11%	60	11%
7	Anticoagulants and Antiplatelet agents	22	9%	28	9%	50	9%
8	Psychofarmaca	14	6%	20	6%	34	6%
9	Corticosteroids	6	2%	11	4%	17	3%
10	Inhalant agents in COPD	6	2%	9	3%	15	3%
11	Antidiabetic agents	4	2%	4	1%	8	1%
	All	241	100%	309	100%	550	100%

Overall rank	Therapeutic group	ALL: UMCU AND CHE, GERIATRICS AND INTERNAL MEDICINE Geriatrics Number	Geriatrics %	Internal med Number	Internal med %	All Number	All %
1	Cardiovascular drugs	173	18%	90	16%	263	17%
2	Antibiotics	115	12%	66	12%	181	12%
3	Supplements	117	12%	60	11%	177	12%
4	Gastro-intestinal drugs	112	11%	71	13%	183	12%
5	Psychofarmaca	133	13%	34	6%	167	11%
6	Others	101	10%	74	13%	175	11%
7	Analgetics	84	9%	65	12%	149	10%
8	Anticoagulants and Antiplatelet agents	77	8%	50	9%	127	8%
9	Inhalant agents in COPD	34	3%	15	3%	49	3%
10	Antidiabetic agents	19	2%	8	1%	27	2%
11	Corticosteroids	22	2%	17	3%	39	3%
	All	987	100%	550	100%	1537	100%

CHE = Catharina Hospital Eindhoven; UMCU = University Medical Center Utrecht

In 39.8% of discontinued medications, no reason for discontinuation was documented (see Table 4).

TABLE 4 Reasons for discontinuation of medication; overall and subgroups 'medication used on admission' and 'medication prescribed during admission'

Reason	Medication used on admission	Medication prescribed during admission	All discontinued medication
No reason mentioned	373 (54.4%)	238 (28%)	611 (39.8%)
No longer indicated	52 (7.6%)	371 (43.6%)	423 (27.5%)
Palliation	45 (6.6%)	106 (12.5%)	151 (9.8%)
Contraindication	93 (13.6%)	47 (5.5%)	140 (9.1%)
Adverse drug reaction	58 (8.5%)	22 (2.6%)	80 (5.2%)
Ineffective	26 (3.8%)	40 (4.7%)	66 (4.3%)
At request of patient	2 (0.3%)	2 (0.2%)	4 (0.3%)
Interaction (drug-drug)	1 (0.1%)	0 (0%)	1 (0.1%)
Other	36 (5.2%)	25 (2.9%)	61 (4.0%)
All	686 (100%)	851 (100%)	1537 (100%)

Most frequently documented reasons for discontinuation were 'no longer indicated' (27.5%), 'palliation' (9.8%), 'contraindication' (9.1%), and 'ADR' (5.2%). In geriatric patients 'palliation' occurred more frequently as reason for discontinuation: 12.3% versus 5.5% in internal medicine patients. 'No longer indicated' occurred more often in internal medicine patients (32.5% versus 24.5%). Frequencies of other reasons for dicontinuation were not different between geriatric and internal medicine patients.
In both geriatric and internal medicine patients, discontinued medications were stopped in 84% and switched in 16%. Most prevalent reasons for switching were 'no reason mentioned' and 'ineffective' (see table 5).

TABLE 5 Reasons for discontinuation versus stopping or switching

GERIATRIC WARDS					
Reason	**stop(n)**	**stop(%)**	**switch (n)**	**switch (%)**	**All**
No reason mentioned	316	38.1%	81	51.3%	397
No longer indicated	235	28.3%	7	4.4%	242
Palliation	119	14.4%	2	1.3%	121
Contraindication	89	10.7%	2	1.3%	91
Adverse drug reaction	47	5.7%	4	2.5%	51
Ineffective	7	0.8%	31	19.6%	38
At request of patient	0	0.0%	1	0.6%	1
Interaction (drug-drug)	1	0.1%	0	0.0%	1
Other	15	1.8%	30	19.0%	45
All	829	100%	158	100%	987
INTERNAL MEDICINE WARDS					
Reason	**Stop (n)**	**Stop (%)**	**Switch (n)**	**Switch (%)**	**All**
No reason mentioned	179	38.7%	35	40.2%	214
No longer indicated	161	34.8%	20	23.0%	181
Palliation	29	6.3%	1	1.1%	26
Contraindication	48	10.4%	1	1.1%	49
Adverse drug reaction	22	4.8%	7	8.0%	29
Ineffective	9	1.9%	19	21.8%	28
At request of patient	3	0.6%	0	0.0%	3
Interaction (drug-drug)	0	0.0%	0	0.0%	0
Other	12	2.6%	4	4.6%	16
All	463	100%	87	100%	550

Discussion

To our knowledge, this is the first study of reasons for medication discontinuation during hospitalisation. We found that in more than a third of the disontinued medications the reason was not documented in the patient records. Poor documentation and communication of reasons for discontinuing medication may result in the represcription of withdrawn medications, which could have adverse repercussions on the patients' health. Eguale et al. reported that reasons for discontinuation can be accurately recorded in an electronic prescription program in primary care.[4] We propose that reasons for discontinuation of medication should be recorded in electronic patient files, which are currently being introduced in the Netherlands and other countries.[5,6] To facilitate this, we are developing an electronic clinical decision support module that forces physicians to document these reasons. In addition, this module will make the information available to other relevant healthcare providers, for example GPs and pharmacies. A limitation of the present study is its small number of studied departments (internal medicine and geriatric wards) and hospitals (two). We believe that using an electronic prescription program with a clinical decision support module that incorporates reasons for discontinuation will improve documentation and communication of reasons why medication is withdrawn, leading to better pharmacovigilance at a patient level.

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2.2 Represcription after adverse drug reaction in the elderly

a descriptive study

Archives of Internal Medicine 2006;166:1666-67

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Introduction

Adverse drug reactions (ADRs) frequently occur in hospitalised elderly patients.[1] In geriatric medicine it is common practice to evaluate pharmacotherapy during hospitalisation, often leading to interventions in general and related to ADRs in specific. After discharge the general practitioner (GP) takes over responsibility for the pharmacotherapeutic management of the patient. This requires adequate transfer of information to primary care about these interventions and the reasons for it. The objective of this study was to measure the rate of represcription of drugs stopped because of an ADR.

Methods

We studied consecutively hospitalised patients on geriatric wards of the University Medical Center in Utrecht (n=105) and of the Tweesteden teaching hospital in Tilburg (n=110), the Netherlands. Mean age was 82 years (59-96), 67% female.
ADRs identified by the attending physician were extracted from medical files by two of the investigators (CvdL and MK).
Causality of ADRs was classified as definite, probable, possible or unlikely using Kramer's algorithm.[2] ADRs classified as unlikely were excluded for this study. ADRs were classified as serious in case of death or life-threatening events, requiring in-patient hospitalisation or prolongation of existing hospitalisation, or resulting in persistent or significant disability.[3]
For each ADR we studied whether it was mentioned in the discharge letter to the GP and whether the GP had incorporated provided information on ADRs in his own patient files. For those drugs that had been withdrawn during hospitalisation because of an ADR, we studied the represcription rate during 6 months following hospitalisation. Information on represcription was obtained from the patients' community pharmacies.

Results

In 32% of patients (69/215) 104 ADRs of at least possible causality were recorded. Forty ADRs (38%) were classified serious. Half (51%) of all ADRs (53/104) and 62% of serious ADRs (25/40) were mentioned in the discharge letter to the GP.
Represcription rate could not be studied for 18 patients, because they died during hospital stay or within 6 months after discharge. To our knowledge, no probable relation between ADRs and cause of death was present in these patients. In remaining 51 patients with 77 ADRs, medication that caused an ADR was withdrawn 64 times. For these drugs the represcription rate was 27% (17/64) (table 1).
Represcription rate was not markedly different for serious or non-serious ADRs, or for ADRs mentioned or not mentioned in discharge letter.

GPs incorporated provided information on ADRs in their own patient files in eight of 37 mentioned ADRs (22%). This was not done in a standardized way, except for three patients where it was documented in a special part of the patient record, for example the allergy section. None of the pharmacies was aware of occurred ADRs.

TABLE 1 **Represcription rate of drugs stopped during hospitalisation because of an ADR within six months after discharge**

	Represcription rate
Overall	27% (17/64)
Serious ADRs	22% (8/36)
Non-serious ADRs	32% (9/28)
ADRs mentioned in discharge letter	30% (11/37)
ADRs not mentioned in discharge letter	22% (6/27)

Discussion

Approximately a quarter (27%) of drugs withdrawn during hospitalisation because of an ADR, were represcribed within six months after discharge, irrespective of seriousness of the ADR. In addition, information transfer to GPs and documentation by GPs was poor. A limitation of the present study is the lack of information about the reasons to represcribe stopped medication, so we do not know whether represcription was contraindicated in all cases. Furthermore, we could not find information on recurrence of ADRs after represcription in most cases, partly because of the retrospective character of this study. The small number of studied objects is another limitation of our study. Larger prospective studies should be carried out to confirm our preliminary results. We are not aware of literature providing data on represcription of drugs stopped because of an ADR. One study showed the transfer of information on drugs to primary care was limited.[4] In a new and growing model of inpatient care in the United States, a hospitalist becomes the patient's attending physician during hospitalisation and the outpatient physician resumes supervision of the patient after discharge.[5] The loss of information on ADRs by poor communication between hospitals and primary care, as described in our study, may therefore be an emerging risk in the United States. We suggest better communication on ADRs between different health care echelons may reduce unnecessary represcription and thereby reduce the occurrence of ADRs. A national electronic medication file, as in development in the Netherlands, may improve medication surveillance.

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2.3 Recurrence of adverse drug reactions following inappropriate represcription. Better documentation, availability of information and monitoring are needed

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Abstract

Adverse drug reactions are a common, and often preventable, cause of hospital admission, especially in the elderly. They are also common during hospitalisation. In an earlier study, we showed that adverse drug reactions occurring during hospitalisation and requiring cessation of the presumed causative drug were poorly communicated to primary care (general practitioners and pharmacists), and that only 22% of the adverse drug reactions mentioned in discharge letters were incorporated into general practitioners patient files. The rate of represcription of medication withdrawn during hospitalisation because of an adverse drug reaction was 27% in the first 6 months after discharge. It is likely that poor documentation and communication contributed to this high rate of represcription. In this report we present three cases of recurrence of a serious adverse drug reaction due to represcription of a withdrawn medication. These cases highlight the need for a system to prevent the undesirable represcription of medications withdrawn because of an adverse drug reaction. We propose a system that systematically documents adverse drug reactions at a patient level, makes this information available to relevant healthcare providers and the patient, and flags represcription of the offending drug.

Introduction

Adverse drug reactions (ADRs), defined as "appreciably harmful or unpleasant reactions, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product",[1] are a common, and often preventable, cause of hospital admission, especially in the elderly.[2] They are also common during hospitalisation.[3] In an earlier study, we showed that ADRs occurring during hospitalisation and requiring cessation of the causative drug were poorly communicated to primary care (general practitioners (GPs) and pharmacists), and that only 22% of the ADRs mentioned in discharge letters were incorporated into GP patient files.[4] The rate of represcription of medication withdrawn during hospitalisation because of an ADR was 27% in the first 6 months after discharge. Poor documentation and communication probably contributed to this high rate of represcription. Although represcription of a drug after an ADR may sometimes be appropriate, we want to highlight the need for improved documentation and communication regarding ADRs and for a system for alerting doctors/pharmacists to the represcription of a previously withdrawn medication. We present three cases of recurrence of a serious ADR due to represcription of a withdrawn medication. In addition, we propose a system to improve the documentation and communication of ADRs and to optimise alerting in the event of represcription, independent of the healthcare setting.

Case reports

Case 1

A 53-year-old woman with a history of pneumonia, asthma, ulcerative colitis, and allergy to non-steroidal anti-inflammatory drugs (NSAIDs; 2 events in 15 years) complained of abdominal pain during the weekend. The GP on duty (not her GP) prescribed the NSAID diclofenac as suppository. Shortly after taking a single dose, the patient developed exanthema and became dizzy. Her husband called an ambulance and on its arrival the patient was hypotensive. She was treated with intravenous adrenaline and dexamethasone for suspected anaphylactic shock and admitted to hospital, where she made a rapid recovery. Her abdominal pain was caused by pancreatitis. The GP on duty had missed the information on her allergy to NSAIDs in her medical record. Moreover, although it was possible to register allergies in the hospital's electronic medication prescription programme, this was not done before, during, or after this hospitalisation.

Case 2

An 82-year-old man with a history of Parkinson's disease, transurethral resection of the prostate, cataract extraction, and Menière's disease suffered from urinary tract infection complicated by delirium, for which the GP prescribed haloperidol. Within a

few days the patient's extrapyramidal symptoms (EPS) worsened considerably and hospitalisation was necessary. His medication on admission was pergolide 1mg QID, selegiline 5 mg BID, levodopa/carbidopa 100/25 mg BID, and haloperidol BID (0.5 mg in the morning and 0.25 mg in the evening). During hospitalisation, haloperidol was withdrawn and the dosage of levodopa/carbidopa was increased to 100/25 mg QID, which diminished the EPS. The discharge letter from the hospital to the GP mentioned the aggravation of EPS with haloperidol and advised the prescription of clozapine or quetiapine instead of haloperidol in the event of delirium. However, 3 months after discharge, the same GP prescribed haloperidol for agitation, which again caused worsening of EPS. After consultation with the geriatrician, haloperidol was withdrawn and quetiapine was started. The patient's EPS improved and his agitation diminished. The GP reported he was not aware of the earlier advice not to represcribe haloperidol.

Case 3

An 85-year-old woman with a history of hypertension, diabetes mellitus, nodular struma, breast cancer (6 years previously), and mild hyperparathyroidism was referred to a geriatric ward by her GP because of delirium. She was taking insulin, digoxin, tamoxifen, amiloride, and hydrochlorothiazide. On admission, she had hypercalcaemia (3.06 mmol/l corrected for serum albumin); her renal function was normal. Hydrochlorothiazide was withdrawn because it may have contributed to hypercalcaemia and the patient was treated with intravenous hydration and pamidronate. Serum calcium decreased to 2.49 mmol/l and the delirium resolved. The discharge letter to the GP mentioned the probable contribution of hydrochlorothiazide to the development of hypercalcaemia. Over the next 10 months the patient was treated with cinacalcet and her serum calcium remained stable at 2.70 mmol/l. She was then readmitted to hospital because of delirium. On admission, the serum calcium concentration was 3.44 mmol/l and her renal function was impaired. The GP had represcribed hydrochlorothiazide, which might have contributed to the recurrence of hypercalcaemia. Discontinuation of hydrochlorothiazide and intravenous hydration led to a decrease in serum calcium and to resolution of the delirium.

Discussion

These case reports illustrate that poor documentation of ADRs and inadequate availability of this information to relevant healthcare providers, together with the lack of an automated alert for represcription of a previously withdrawn medication, may lead to the possibly inadvertent represcription of an offending medication and to the recurrence of ADRs.

The impact of the represcribed drugs is not entirely clear cut in our cases and multiple factors may have contributed to the ADRs. In case 1 we can not be entirely sure the

patient experienced an anaphylactic shock, although she was known with an allergy to NSAIDs. This allergy was not documented in the electronic medication prescription programme of the hospital and the GP on duty was not aware of this allergy. In this case insufficient documentation probably leaded to represcription. In case 2 patient's reaction to haloperidol with EPS was well documented in the hospital. Although the balance between movement and madness in Parkinson's disease is difficult, the clinical symptoms and time-course suggest a causative relation between haloperidol and aggravation of EPS. In this case the GP was advised not to represcribe haloperidol and represcription seems to result from insufficient or absent alerting. In case 3 multiple factors contributed to hypercalcaemia; hyperparathyroidism, hydrochlorothiazide and on readmission an impaired renal function. In this case the possible contribution of hydrochlorothiazide to hypercalcaemia was documented in the hospital and communicated to the GP but did not result in an advice to the GP. As in the other 2 cases, the information about the ADR was not communicated to the pharmacist. In this case the information was not available to all relevant healthcare professionals and alerting to possibly undesirable represcription was absent.

Represcription of drugs after an ADR may be appropriate and acceptable in some cases, for example when the dose had been too high, causing a toxic effect, when the ADR could have been prevented by the co-prescription of another drug, or when a previous susceptibility factor is no longer present. It may also be appropriate to use a lower dose in combination with a drug with the same treatment goal but with a different mechanism of action and different adverse effects.[5]

While pharmacovigilance is quite well developed as part of regulatory requirements for the pharmaceutical industry, it is primarily for product surveillance and liability and not for surveillance and therapeutic decision-making at a patient level. To improve pharmacovigilance at a patient level, we propose an electronic system to prevent the undesirable represcription of medications previously withdrawn for causing ADRs, or to propose measures to prevent recurrence of the ADR in case of represcription. This system has three essential elements.

❶ Documentation

All ADRs as defined above should be documented systematically and in a standardised manner. This registration minimally needs to consist of the name of the prescribing doctor; date of occurrence of the ADR; name, dose, and duration of the suspected drug; and description of the ADR. The causality and seriousness of the ADR should be documented. Causality should preferably be determined with an algorithm, for example Naranjo's or Kramer's algorithm,[6,7] and seriousness could be classified according to EMEA definitions: an ADR is serious if fatal, life-threatening, requiring inpatient hospitalisation or prolongation of existing hospitalisation, or resulting in persistent or significant disability.[8]

❷ Availability

The systematically documented information should be available and accessible to the patient and, with the patient's permission, to all relevant healthcare providers, including hospital specialists, GPs, and pharmacists.

❸ Alerting

Rescribed medication should be constantly monitored and the pharmacists/GPs/patients should be alerted if a previously withdrawn medication is represcribed.

The electronic clinical decision support module we are currently developing incorporates these elements, and future studies will test its usefulness in patient care, i.e., whether it prevents the represcription of previously withdrawn medications, and its cost-effectiveness. During the development of this module, we have paid particular attention to the timing and design of alerts, to minimize information overload and overriding, and to ensuring the confidentiality of patient data.

Conclusions

We present three cases that highlight the need for a system to prevent the undesirable represcription of medications withdrawn because of an ADR. This system should systematically document ADRs at a patient level, make this information available to relevant healthcare providers and the patient, and flag represcription of the offending drug. The effectiveness and cost-effectiveness of such a system would have to be determined, since we currently do not know how often ADRs occur because of inappropriate represcription after a previous ADR.

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3

Represcription after adverse drug reaction: systems for prevention

3.1 Systems that prevent unwanted represcription of drugs withdrawn because of adverse drug events

a systematic review

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Abstract

Introduction

Represcription of medication that was withdrawn after the occurrence of an adverse drug event (including allergy), is a recognised medication safety issue on a patient level. We performed a systematic review to identify systems (electronic and non-electronic) that can prevent the represcription of drugs withdrawn because of an adverse drug event, and the effects of these systems.

Methods

The review was performed using PRISMA and Cochrane guidelines. Pubmed and Embase were searched for articles describing systems that can prevent represcription of drugs that had been withdrawn for causing an adverse drug event. Information on the characteristics of the studies, systems, and -if present- results achieved with such systems, was extracted.

Results

Of 6793 articles screened 137 full-text articles were assessed for eligibility. Forty-five studies describing 33 systems (28 electronic) were included. The 5 non-electronic systems used allergy bracelets or allergy labels on hospital medical records or on drug orders. Systems differed in the way adverse drug events were documented and how users were alerted to drug represcription. Most systems functioned within a specific healthcare setting. Of 12 studies that compared pre- and post-intervention periods or wards with and without intervention, seven showed a reduction in represcription after adverse drug event.

Conclusions

Several systems have been developed that can prevent the represcription of drugs that elicited an adverse drug event, but the evidence that these systems are effective is limited.

Introduction

While medications usually improve patients' quality and/or duration of life, they can also cause considerable harm, especially if prescribing clinicians fail to take relevant patient characteristics, such as known allergies, into consideration.[1] In the Institute of Medicine's report "To Err is Human" from 1999, the death rate associated with medication errors was estimated at 7000 per year in the United States.[2] A subsequent report published in 2006 estimated that in the United States between 380,000 and 450,000 preventable adverse drug events (ADEs) occur annually in a hospital setting, at a cost of $3.5 billion.[3] An ADE is defined as: "an injury resulting from medical intervention related to a drug".[4] In a previous study, our group showed that ADEs that occurred and were documented during hospitalisation and which required withdrawal of the causative drug were poorly communicated to general practitioners (GPs) and not at all to pharmacists, and that only 22% of the ADEs mentioned in discharge letters were incorporated into GP patient files. The rate of represcription of medication withdrawn during hospitalisation because of an ADE was 27% in the first 6 months after discharge.[5] Poor documentation and communication probably contributed to this high rate of represcription. One condition, amongst others, that needs to be met to prevent prescription of medication to which patients earlier experienced an allergic reaction or another ADE, is that ADEs (including allergies) are well documented. In a study of 400 hospitalised patients, we found that the reasons for medication discontinuation were not reported in as many as 40% of the cases of medication discontinuation.[6] Khalil et al. [7] found in their study, that details of allergy were accurately reported in only 3 of 521 patients (0,6%), and that written records of ADEs were ineffective because insufficient information was recorded or because handwriting was illegible. Information technology consisting of computerised physician order entry (CPOE) and clinical decision support (CDS) has the potential to address the problem of unwanted represcription of drugs earlier withdrawn because of an ADE. We performed a systematic review to identify systems (electronic and non-electronic) that may prevent the represcription of drugs that caused ADEs at a patient level, and the effectiveness of these systems.

Methods

This review was performed using the PRISMA guidelines for systematic reviews and meta-analysis [8] and the Cochrane guidelines [9] where applicable.

Data sources and search strategy

Titles and abstracts in the Pubmed and Embase databases were searched from inception to November 2011 using the terms "drug" and "event", "allergy" or "hypersensitivity" combined with "systems", "surveillance" or "alerts", and synonyms. No limits were used in the searches. The search syntax used, is shown in Figure 1.

FIGURE 1 Search syntax in Pubmed and Embase

[title/abstract]	((drug OR drugs OR medicin* OR medication) AND (event* OR reaction* OR allergy OR allergies OR interaction* OR error* OR hypersensitiv* OR toxicit*))
AND	
[title/abstract]	overrid* OR decision support OR order entry OR medication alert OR alert system OR medication system OR reporting system OR information system OR surveillance OR e-prescribing system OR computer system OR alert OR alerts OR information management OR allergy documentation OR allergy register

Study selection and eligibility

Duplicate articles were excluded and the title and abstract of remaining articles were screened by one reviewer (MV) and confirmed by another reviewer (CvdL) using the following exclusion criteria: a) language other than English, German, French or Dutch, b) animal studies or non-human studies, c) study describing systems that do not function at the patient level, d) study not concerning ADEs, e) study describing a system not related to prevention of represcription, and f) review articles. Criterium c) means that the systems should be able to prevent prescription of a drug to a patient, when this drug was earlier withdrawn because of an ADE in this same patient. So, systems only enhancing reporting or documenting ADEs in a database were excluded. If the title and abstract were not sufficiently conclusive, full-text articles were retreived. All relevant full-text articles were then screened by LA (confirmed by CvdL) using the same exclusion criteria. References of included articles were screened for relevant articles.

Data extraction

One reviewer (LA) extracted information on the characteristics of the study (design, setting, population, and country) and of the systems studied (electronic or non-electronic, custom-designed or commercial), which was confirmed by CvdL. We also retrieved information about how ADEs were documented (by whom, when, voluntary or obligatory, automatic detection present or absent), how users were alerted to potential represcription of a discontinued drug (trigger, receiver, and possible actions after the alert), and to whom information on the ADEs was available. If present, data on results on represcription after the occurrence of an ADE were also extracted.

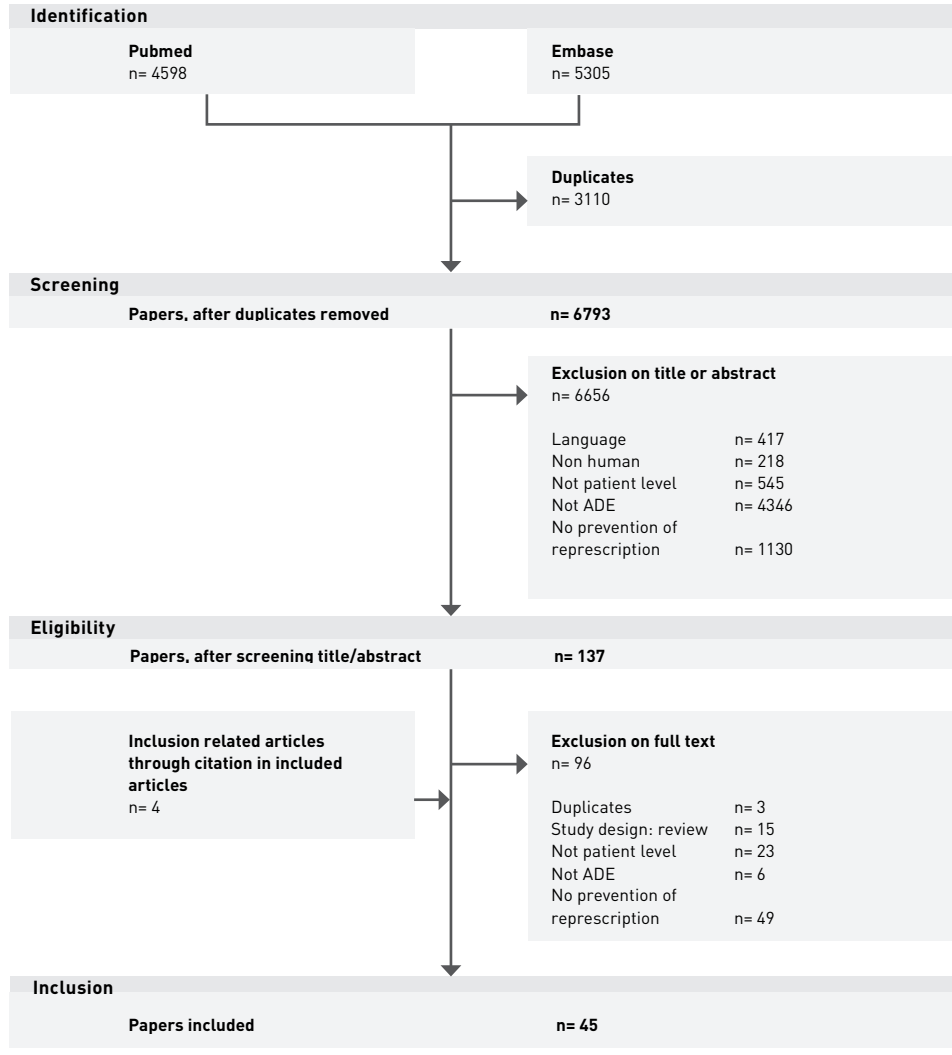
Data synthesis

Data were synthesised using narrative and tabular methods. As eligible studies were expected to differ substantially in terms of patient population, intervention and measurements methods, pooling of data was considered inappropriate. Results were judged benificial if a statistically significant ($p<0.05$) decrease in represcriptions after ADE was reported.

Results

A total of 9903 articles were identified in the initial search. After elimination of duplicate studies, 6793 articles were screened for exclusion criteria (see figure 2), leaving 137 full-text articles that were assessed for eligibility. Of these 137 articles, 96 articles were excluded, mainly because these studies describe systems that do not prevent represcription of drugs withdrawn because of an ADE. Forty-one articles were included; an additional four were included after screening of the reference lists of the included articles.

FIGURE 2 Search results with reasons for exclusion



Characteristics of the studies

The characteristics of the studies are shown in table 1.

TABLE 1 Characteristics of included studies

Characteristic	Number (%) of studies
Year of publication	
before 1990	4 (9%)
1990-2000	12 (27%)
after 2000	29 (64%)
Geographic location	
USA	29 (64%)
UK	5 (11%)
other in Europe	3 (7%)
Canada	3 (7%)
Asia	3 (7%)
Australia	1(2%)
Israel	1(2%)
Study design	
pre-post intervention	16 (36%)
descriptive	13 (29%)
retrospective	9 (20%)
interrupted time-series	2 (4%)
cohort studies	2 (4%)
trend analysis	1 (2%)
users interviews	1 (2%)
randomised controlled trial	1 (2%)
Age studied population	
not reported	30 (67%)
adults	12 (27%)
children	3 (7%)

Most studies (64%) were published after the year 2000. The studies concerning electronic systems were published between 1976 and 2011, those concerning non-electronic systems between 1967 and 2007. Of the 45 studies, 16 had a pre-post-intervention design, 13 were descriptive studies, 9 were retrospective studies, 2 were cohort-studies, 2 had a time-series design (interrupted or prospective), 1 was a trend analysis, 1 performed users interviews, and 1 was a randomised controlled trial. Most studies were performed in the United States (n=29, 64%), and the majority (n=30, 67%) did not report patient age; 12 studies (27%) involved adults and 3 (7%) children.

Characteristics of the systems

The 45 articles described 33 different systems, 28 (85%) of which were electronic.

Commercially available or custom-designed

Nine of the electronic systems (32%) were commercially available and 18 were custom-designed; one study did not report wether a commercial or custom-designed system was used. Eight studies investigated the Brigham Integrated Computing System (BICS) and five the Health Evaluation through Logical Processing (HELP) system. The characteristics of the studies and systems are shown in table 2 (electronic systems) and table 3 (non-electronic systems).

Setting

Most systems (21/33=64%) were used in an inpatient hospital setting. Five systems were used in general practice or outpatients outpatient departments, six systems were used in combined inpatient and outpatient settings, and one was used nationwide in Singapore.[10]

Documentation of ADEs

The systems differed in how ADEs were detected and documented. Eight of 28 electronic systems used automatic detection of ADEs, mostly on the basis of laboratory results and antidotes being ordered. In most cases, doctors or pharmacists recorded ADEs. Eleven of 33 systems recorded known ADEs at admission, and 6 recorded ADEs when the event occurred, when drugs were discontinued or when drugs were ordered. Studies on 12 systems did not mention the timing of ADE registration. The documentation of ADEs was obligatory in 12 systems, such that access to the electronic medication record was blocked until the patients' ADE history was reported.[11]

Availibility of information on ADEs

The information on documented ADEs was mostly available within one healthcare setting (11 systems). Six systems shared this information with different healthcare settings, one system offered an allergy card to the patient [11], and in one system the information on ADEs was registered in a central allergy database.[10] Nine systems did not describe to whom the information on ADEs was made available.

Alerts in case of represcription

In all systems a documented allergy triggered the alert in case of represcription. In 7 systems, also a cross-allergy triggered an alert, and in 5 systems other ADEs triggered an alert. Two systems incorporated a reverse allergy check: the current medication list was checked when a new allergy was reported. In the case of represcription after the occurrence of an ADE, 16 systems alerted the physician, 6 systems alerted the pharmacist, and 4 systems alerted both physician and pharmacist. In 16 systems, the receiver of

the alert could stop the medication order or override the alert (7 with mandatory reporting of the reason to override, 9 without or optional reporting of the reason to override). The 5 non-electronic systems used allergy bracelets or allergy labels on hospital medical records or on drug orders, and, as such, information about ADEs was available in the hospital setting.

Results on prevention of represcription after the occurrence of an ADE

Nineteen studies (1 involving a non-electronic system) investigated the effect of these systems for preventing drug represcription after an ADE, with two studies reporting results using BICS [12,13], and two studies reporting results using the HELP system.[14,15] Seven of these studies were retrospective or descriptive studies and did not present results for comparisons of pre- and post-intervention period or wards with and without intervention. In these studies, the frequency of allergy alerts ranged from 1.35% to 4.4% of drug orders, and override rates ranged from 44% to 97%. In the study by Dartnell et al. in which adverse drug reaction labels were attached to the cover of medical records, the culprit medicine was represcribed in 20% of identified ADEs.[16]

Twelve of the 19 studies reported pre- and post-intervention comparisons or compared wards with and without intervention implementation – seven studies reported that intervention was beneficial and 5 that it was not beneficial. None of the studies reported harmful results. The seven studies that reported benficial results concerned five systems. These systems had no striking shared characteristics.

In a study of the BICS used in a large tertiary care hospital the rate of medication errors in case of known allergy was reduced from 0.65 to 0.29 per 1000 patient-days after introduction of the BICS (p=0.009).[12] A study of the HELP system used in a 530-bed private tertiary care hospital investigated type B ADEs (aberrant effects that are not to be expected from the known pharmacological actions of a drug when given in the usual therapeutic dose; type A effects are predictable and dose dependent).[17] In this study by Evans et al., a previous allergy was documented in 23% of 56 type B ADEs during the first year of computerised surveillance without alerts.[15] In the following 2 years with computerised surveillance with alerts, none of the 8 type B ADEs was due to known allergy. The study by Park et al. [11], involved a ADE surveillance system in which reporting patients' ADE history was mandatory at admission. The rate of ADEs caused by re-administration of the suspected culprit drug decreased from 15% (8/54 events) to 1% (1/100 events) after introduction of the surveillance system. After implementation of integrated clinical information technology for CPOE in two hospitals, there were 109 prescriptions of medications to which the patient had a known allergy, compared with 833 such prescriptions before implementation of the system (odds ratio 0.14, 95% confidence interval 0.11-0.17, p<0.001).[18] Results of the studies on prevention of represcription after ADE are shown in table 2 (electronic systems) and table 3 (non-electronic systems).

TABLE 2 **Characteristics of studies and systems: electronic »** page 65 » 69

System name	CHARACTERISTICS OF THE SYSTEM								CHARACTERISTICS OF THE STUDY						Results On represcription after the occurrence of an ADE	Reference
		Documentation of the ADE				Alert in case of represcription						Population				
	C/H*	By whom	When	O/V^	Automatic detection^^	Trigger^^	Receiver#	Action	Availability ADE information	Country	Design	HealthCare System	N=Baseline/ intervention ##	Mean age	Gender %F	
BICS	H	Phy	At admission	O	√ lab results, antidotes	A CA RA	Phy	Stop / override alert +reason	Inside hospital	USA	1: Retrospective record analysis 2-5: Descriptive 6: Trend analysis 7: Retrospective Time series 8: Pre-post intervention	720-bed academic tertiary-care hospital	1: 1,150 patients 2-6: NR 7: 10,070/ 14,352 orders 8: 2,491/4, 220 admissions	1: 56 2-7: NR 8: 52.5 / 53.2	1: 68 2-7: NR 8: 50.9/ 54.3	1-6: No results 7: 10 'known-allergy-errors' in baseline period, 1 in intervention period, p<0.0001 8: Rate of errors because of known allergies decreased 56% from 0.65 to 0.29/1000 patient days, p=0.009	1: Hsieh ('04) 2: Kuperman ('03[a]) 3: Kuperman ('03[b]) 4: Kuperman ('01) 5: Kuperman ('98) 6: Abookire ('00) 7: Bates ('99) 8: Bates ('98)
HELP	H	Phy, Pha, N	At time of ADE	V	√ lab results, drug level in blood, antidotes, antihistamines, abrupt drug stop	A ADE	Pha	Pharmacist warns physician	NR	USA	9: Descriptive 10-13: Prospective pre-post intervention	520-bed private tertiary care hospital	9: 13,727 patients, 88,505 orders 10: 120,213/ 107,868 patient-days 11: 25,142 patients 12: 25,142/ 21,963 13: 878 patients	NR	9-12: NR 13: 60	9: 112 alerts on drug allergies 10: During the first year of computerised surveillance in 13/56 (23%) of type B ADEs a previous allergy was documented. In the following 2 years none of the 8 ADEs was due to known allergy. 12: Out of 373 ADEs 56 were type B in the first year of computerized surveillance without alerts. In the next year (with computer alerts) 8 of 560 ADEs were type B. (15% versus 1.4%, p<0.001) 11 and 13: No results	9: Hulse ('76) 10: Evans ('94) 11: Evans ('92) 12: Evans ('93) 13: Classen ('92)
MGH's CPOE	H	Phy	NR	NR	X	A	Phy	Stop / override alert +reason	NR	USA	2: Descriptive 3: Descriptive	General hospital	NR	NR	NR	No results	2:Kuperman ('03[a]) 3:Kuperman ('03[b])

System name	CHARACTERISTICS OF THE SYSTEM									CHARACTERISTICS OF THE STUDY						Results On represcription after the occurrence of an ADE	Reference
		Documentation of the ADE				Alert in case of represcription			Availability ADE information				Population				
	C/H*	By whom	When	O/V*	Automatic detection**	Trigger^^	Receiver#	Action		Country	Design	HealthCare System	N= Baseline/ intervention ##	Mean age	Gender %F		
LMR	H	Phy, N, Med Ass	NR	V	X	A	Phy	Stop /override alert	NR	USA	2: Descriptive 3: Descriptive	Outpatient practices	NR	NR	NR	No results	2:Kuperman ('03[a]) 3:Kuperman ('03[b])
VA Puget Sound	H	Phy, Pha, N, Dieticians	NR	V	√ antidotes	A	Phy	Stop /override alert (only without reason in low risk alert)	NR	USA	14: Prospective comparison '01 and '06 15: Descriptive	Teaching hospital, primary and tertiary care facilities, outpatient clinics, nursing home	14: 2001: 42,621 orders. 2006: 37,040 orders 15: NR	NR	NR	14: In 2001 0.25% (105/42,621) generated an allergy alert, of which 72 (69%) were overridden. In 2006 420 of 37,040 (1.13%) orders generated an allergy alert. Of these, 341 (81.2%) were overridden. 15: No results	14: Lin ('08) 15: Payne ('00)
Pocket script	C	Phy, Office staff	NR	V	X	A	Phy	Stop /change, or override alert	NR	USA	16: Interview users 17: Retrospective analysis	Small and medium-size group general practices	16: NR 17: 3,570,378 orders	NR	NR	16: No results 17: Allergy alerts accounted for 1.7% of all alerts (3874/233,537). 23% of allergy alerts were accepted.	16: Weingart ('09) 17: Isaac ('09)
SMR	C	Phy Pha	Before pre-scription	O	X	A	Phy	Stop/override alert +reason	18: Within healthcare facilities 19: NR	18: USA 19: CA	18: Descriptive 19: Retrospective cohort, pre-post intervention	18: Tertiary care academic health-care facility (incl. 3 hospitals, 40 health care centres, 120 outpatient clinics, 19: Paediatric hospital, 2 wards	18: NR 19: 6,674/ 5,786 patients	18: NR 19: 5.5 / 6.0	18: NR 19: 45 / 47	No results	18: Chaffee ('10) 19: King ('03)
MOXXI	C	Phy	Moment of discontinuing medication	NR	X	A	Phy Pha	Stop / change, or override alert +reason	Within setting	CA	Cluster randomized controlled trial	General practices	3,449 patients	67	61	No results	20: Tamblyn ('08)
PCMP	C	Phy, Pha, N, Other	At admission	V	X	A	Phy Pha N	Stop /override alert +reason	NR	USA	Retrospective	Academic hospital	49,887 orders	66	65	Allergy alerts were triggered for 643/ 49,887 (1.3%) prescriptions, of which 625 (97%) were overridden.	21: Hunteman ('09)
ADESS	H	Phy, N	At admission	O	X	A ADE	Phy	NR	Patient receives an allergy card	KR	Pre-post intervention	Hospital	20,564/ 55,432 admissions	51 / 53	47.5 / 48	Occurrence rate of re-administration of the agent previously suspected as culprit drug, decreased from 15% to 1%.	22: Park ('08)
CCCC	C	NR	NR	V	X	A	Phy	NR	NR	BE	Prospective controlled cross-sectional trial	intensive care unit of tertiary care hospitals	90 patients 2,510 orders	54 / 61.5	NR	1 med. error by known allergy on the computerized unit vs. 0 on the paper based unit	23: Colpaert ('06)
OMR	H	Phy, Pha, N	NR	V	X	A	Phy	Stop /override alert	Database is linked to inpatient, ambulatory and home care settings.	USA	Retrospective	5 Primary care practices and a teaching hospital	GPs: 24,034 orders	NR	70	352/24,034 (1.5%) of GP orders generated allergy alerts, of which 91.2% were overridden	24: Weingart ('03)
CEM	C	Pha	At admission	V	X	A ADE	Pha N	Warn physician	Information is sent to pharmacy	USA	Descriptive	Large healthcare system: hospitals and ambulant settings	NR	NR	NR	No results	25: Young ('01)
SMS PCW	C	NR	NR	NR	X	A	Phy Pha	SStop / override alert	Inside hospital	USA	Pre-post intervention	Two hospitals	1.452,346 / 1.390,789 medication orders	NR	NR	833 pre- versus 109 post-implementation prescriptions of medication to which the patient has a known allergy. OR 0.14(0.11-0.17), p<0.001	26: Mahoney ('07)

System name	CHARACTERISTICS OF THE SYSTEM									CHARACTERISTICS OF THE STUDY						Results On represcription after the occurrence of an ADE	Reference
		Documentation of the ADE				Alert in case of represcription			Availability ADE information	Country	Design	HealthCare System	Population				
	C/H*	By whom	When	O/V*	Automatic detection**	Trigger**	Receiver#	Action					Baseline/ intervention ## N=	Mean age	Gender %F		
CPOE MC	H	NR	NR	NR	X	A	Pha	NR	NR	USA	Retrospective	Outpatient setting of an academic centre	4,527 orders	NR	NR	No results	27: Varkey ('07)
MUPS	H	Pha (asked by nurse)	At admission	O	X	A CA ADE	Pha	Send printed advisory report to physician	Inside hospital	USA	Pilot, descriptive	Inpatient setting of an academic centre	NR	NR	NR	No results	28: Tatro ('79)
EADES	NR	All medical staff (reviewed by pha)	NR	V	X	A CA	NR	NR	Inside hospital	TW	Pre-post intervention	Academic hospital	108/394 ADE reports	NR	44/ 50	No results	29: Yen ('10)
MT	C + H	NR	NR	NR	X	A	Phy	Stop / override alert	Inside hospital	NL	Interrupted time-series design	Two wards in an academic hospital and two wards in another hospital	592/603 admis-sions 7,286 / 7,058 orders	65.5 / 65.1	54.7 / 56.6	No results	30: van Doormaal ('09)
GS	H	Phy	NR	V	X	No a-lert A	NR	NR	Hospitals are linked to a central allergy database	SG	Descriptive	Nationwide system	NR	NR	NR	No results	31: Tan (90)
EPS	C	Phy	Before pre-scription	O	X	A	Phy	Stop / override alert (reason optional)	Systems of pharmacy and hospital are linked	UK	32. Retrospective 33. Pre-post intervention	32. Tertiary care paediatric hospital 33. Renal outpatient clinic	32. 26,836 orders 33. 451 / 176 patients, 1,142 orders	32. NR 33. 8.8 / 8.9	32. NR 33. 40.2 / 35.6	32. 71/16,182 (4.4%) of alerts were allergy alerts, of which 45 (63.4%) were overridden. 33. No results	32: Jani ('11) 33: Jani ('08)
HELP AMP	H	Phy, Pha, N	At time of ADE	V	X	A CA	Phy	Stop/ override alert	NR	USA	Prospective study, pre-post intervention	Paediatric intensive care unit in academic hospital	809/ 949 patients	6.2 / 5.3	41.5 / 43.5	Each group 12 ADEs, with 1 being preventable secondary to known allergy	34: Mullet ('01)
CAIMP	H	NR	NR	NR	X	A	Phy	Stop/ override alert (+reason)	Program linked to patient records at hospital	USA	Prospective, pre-post intervention	Intensive care unit in teaching hospital	1,136/ 545 patients 942 orders in inter-vention period	47 / 48	41 / 41	146 pre- and 35 postimplement-ation orders of medications to which patients had reported allergies p<0.01	35: Evans ('98)
PIS	H	Phy, Pha	NR	O	X	A CA RA	Pha	NR	Inside hospital	USA	Descriptive	University medical centre	NR	NR	NR	No results	36: Mackowiak ('98)
U	H	Phy	NR	NR	X	A	Pha	NR	Online system hospital, pharmacy and general practices	USA	Descriptive	Hospital, GPs. phar-macists	NR	NR	NR	No results	37: Johnston ('80)
U	H	Phy	At admission	O	X	A	Phy	Stop/ override alert (not possible if alert is high risk)	Inside hospital	UK	Retrospective	Nephrology ward of a teaching hospital	1646 patients, 87,789 orders	54.4	41.8	37 prescriptions disallowed because of known allergy	38: Nightingale ('00)
U	H	NR	At admission	O	X	A CA	Phy	NR	Inside hospital	IL	Cohort study	2 Internal medicine wards of an academic hospital	641/709 patients	70.7 / 70.8	NR	Drug-allergy prescription errors were similar in handwritten and computerized department: 0.02 errors per patient.	39: Oliven ('05)
U	H	Phy, N	NR	V	X	A CA	Phy	NR	Inside hospital	DE	Cohort study, retrospective	University hospital	200 patients	59	52.5	20% of patients with ICD-10 coded allergy documentation versus 21.6% of patients with manual allergy documentation were prescribed the same culprit drug (p=1.0)	40: Benkhaial ('09)

LEGEND table 2 and 3

numbers mentioned in columns refer to the study references (right column)

	NR	Not reported		ADE	adverse drug event
*	C	Commercial; H= custom designed		RA	reverse allergy checking
**	√	present;	#	Phy	physician
	X	absent		Pha	pharmacist
^	V	Voluntary; O = Obligatory		N	nurse
^^	A	allergy	# #		if more than one intervention period: data
	CA	cross-allergy			are from last intervention period

SYSTEM NAMES in order of appearance

BICS	Brigham Integrated Computing System	OMR	Online Medical Record
HELP	Health Evaluation through	CEM	Clinical Event Manager
	Logical Programming	MUPS	Massachusetts General Hospital Utility
MGH's	Massachusetts General Hospital		Multi-programming System
CPOE	Computerised Physician Order Entry	EADES	electronic ADE management system
LMR	Longitudinal Medical Record	MT	Medicator + Theriak
SMR	Sunrise Clinical Manager	GS	Governmental System by the ministry
MOXXI	Medical Office for the Twenty First Century		of health
PCMP	PowerChart, Millennium Pharmnet	EPS	Electronic Prescribing System
ADE SS	ADE surveillance system	HELP/AMP	HELP + Antibiotics Management Program
SMS	Siemens Medical Solutions	CAIMP	Computerized Antiinfectives-Management
PCW	Pharmacy Clinical Workstation		Program
CPOE	Computerised Physician Order Entry system	PIS	Pharmacy information system
MC	Mayo Clinic	U	unknown
CCCC	Centricity Critical Care Clinisoft		

COUNTRIES

USA	United States of America	NL	The Netherlands
CA	Canada	SG	Singapore
KR	Korea	UK	United Kingdom
BE	Belgium	AU	Australia
TW	Taiwan	IL	Israel
		DE	Germany

TABLE 3 Characteristic of studies and systems: non-electronic » page 71

			Reference	41: Sister Liguori ('67)	42: Dartnell ('94)	43: Pilzer ('96)	44: Ismael ('07)	45: Mawby ('06)
			Results On represcription after the occurrence of an ADE	No results	In 31 (20%) of identified ADRs patients were represcribed the culprit medicine despite a ADR label.	No results	No results	No results
CHARACTERISTICS OF THE STUDY	Population	Gender %F		NR	NR	64	62.9 / 54	NR
		Mean age		NR	NR	NR Range 17-87	66.8 / 68.7	NR
		N=Baseline/ intervention ##		NR	587 records re-viewed	195 patients	186 / 250 patients	NR
	Setting			General hospital	Hospital	14 wards and one outpatient clinic of a hospital	436- Bed general hospital	2 Oncology wards of an university hospital
	Design			Pre-post intervention	Retro-spective	Descriptive	Two cross-sectional studies, pre-post intervention	Descriptive
	Country			CA	AU	USA	UK	UK
	Availability ADE information			Inside hospital	Inside hospital	Inside hospital	Inside hospital	Inside hospital
CHARACTERISTICS OF THE SYSTEM	Documentation of the ADE	O/V^		O	V	O	O	O
		How		Red bracelet for people with allergy: with patient name and medicine. Introduction of an allergy field on each drug order	ADE labels on the cover of medical records or drug charts	After an interview by the pharmacist a note was made in the medical record and the allergy label on front was corrected	White identification bracelets for every patient and red bracelets for allergic patients. Red allergy box on front of drug chart.	Allergy information on drug charts and note in medical record
		When		At admis-sion	During admis-sion	Within 24 hours after admis-sion	At admis-sion	Before pre-scription
		By whom		Pharmacy (gets infor-mation from Phy and N)	Phy Pha N	Pha	N (brace-lets) Pha (allergy box)	Phy
	System method			Allergy brace-lets and allergy field on drug order	ADE labels	Interview by phar-macist	Bracelets and allergy box on drug charts	Allergy infor-mation on drug charts and note in medical record

Discussion

We identified 45 articles that described 33 systems that can prevent the represcription of drugs that were withdrawn because they caused an ADE. Five of these systems were non-electronic and 28 electronic. The non-electronic systems used allergy bracelets or allergy labels on hospital medical records or on drug orders. The systems differed in the way ADEs were documented (when, by whom, obligatory or voluntary) and in the alerts that occurred if drugs were represcribed after an ADE. The represcription alerts were mostly triggered by allergies and cross-allergies only and not by other ADEs. In 11 systems the information on ADEs was available in one setting only, in 6 systems the information on ADEs was shared with different healthcare settings. None of the studies on non-electronci studies showed results comparing pre- and postintervention. Twelve of the studies on electronic systems reported pre- and post-intervention comparisons or compared wards with and without intervention implementation, with 7 studies reporting beneficial results. These studies differed substantially in terms of patient population, intervention and measurements methods, which made it difficult to compare results of the studies. Only 9 studies were primarily designed to measure results on prevention of represcription after the occurrence of an ADE.

Preventable ADEs, of which known allergic reactions represent an important fraction, frequently occur. In a study of inpatient medication errors, 8% of errors were preventable because it was known at the time of prescription that the patient was allergic to the medication being ordered.[19] In a comparable study involving outpatients, 13% of ADEs were caused by patient receiving medications to which they had a known allergy.[20] One study even recommended the development of a computer systems that can prevent reactions due to known allergies.[21] The current study reviewed systems that can help to prevent the represcription of drugs withdrawn because they caused an ADE.

Differences in the terminology used to describe the various systems made it difficult to search the literature. Furthermore, many of the studies retreived investigated surveillance systems from a much broader objective than only prevention of represcription of withdrawn drugs, for example the effect of a CPOE system on medication errors in general. It was not possible to fully follow PRISMA and Cochrane guidelines because of the strong heterogenity of the studies for example in design and outcome measures. More studies involved electronic systems. There might be a reporting bias in two ways; more recently there is more attention to the described problem, and more recent studies focus on electronic systems. A limitation of the current study is the fact that bias were not assessed in all studies.

To prevent represcription of drugs withdrawn because of an ADE at a patient level we suggest to improve quality of documentation of ADEs, preferably including causality assessment, which necessitates cooperation between physicians and pharmacists. Underreporting of ADEs is a known risk, and we suggest that the effect of compulsory documentation and timing is researched, with a view to minimising underreporting. Automatic detection of ADEs on the basis of laboratory results or antidotes orders might also be of help to prevent underreporting. As most systems only document and flag allergies, but not other types of ADEs, it is important to report all ADEs in patient files. Only two systems allowed reverse allergy checking which would seem a logical step optimise medication safety. Future systems should function in more than one setting and make information on ADEs and alerts available to all relevant healthcare professionals (general practitioner, pharmacist, specialist) and the patient. Another concern is the high rate of alert override rates in the case of allergy. Reasons to override mentioned by physicians in the selected studies are for example: 'patient previously tolerated medication' and 'benefit outweighed the risk'.[22] Van der Sijs et al. concluded in their review of drug safety order check studies that insufficient sensitivity and specificity of order checks results in high override rates.[23] We think the reasons to override an alert should be documented, so that pharmacotherapeutic choices can be evaluated retrospectively. Alerts should be given in a selective and effective way, preventing alert-fatigue and overriding.

Conclusions

Multiple systems, mostly electronic combining CPOE with DSS, have been developed to prevent the represcription of drugs withdrawn because of an ADE, but there is limited evidence that these systems are effective. Future systems should optimise the quality and frequency of ADE documentation, the availability of such information to all relevant healthcare providers, and the flagging of represcription of drugs withdrawn because they caused an ADE. Future research will have to show the value of these systems to patient care.

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3.2 An electronic system to document reasons for medication discontinuation and to flag unwanted represcriptions in geriatric patients

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Abstract

Introduction

Earlier studies have shown poor documentation of the reasons for medication discontinuation during hospitalisation. Communication of reasons for discontinuation, e.g. adverse drug reactions, to general practitioners and pharmacists was also found to be insufficient, leading tot a rate of represcription after an adverse drug reaction of 27% during the first 6 months after discharge.

Objective

The aim of this study was to develop and implement a user-friendly electronic clinical decision support system to document reasons for medication discontinuation in hospitalised geriatric patients and to flag potentially undesirable represcriptions.

Methods

The electronic clinical decision support module was developed using the Gaston framework. Pop-up windows force physicians to document reasons for medication discontinuation, and the system alerts physicians to the represcription of drugs withdrawn because of an adverse drug reaction. We interviewed users regarding the acceptability of the system.

Results

On a 20-bed geriatric ward, the electronic system documented 2,228 medication discontinuations and the reasons for them over 11.4 months and alerted physicians to represcription of drugs associated with an adverse reaction 20 times. The system was considered user-friendly.

Conclusions

This clinical decision support system fulfilled its aims of documenting the reasons for medication discontinuation and alerting physicians to potentially undesirable represcription of previously withdrawn drugs. It was found to be user-friendly.

Introduction

The need for pharmacovigilance was highlighted by the thalidomide disaster in 1961, which prompted international efforts to address drug safety issues. International and national pharmacovigilance centres for detecting and analysing previously unknown or poorly understood adverse effects of medicines were established, and standard sets of terms were developed to code these events, which facilitated the analysis of data related to the safe use of medical products. The Medical Dictionary for Regulatory Activities (MedDRA) is widely used.[1] Pharmacovigilance is part of the regulatory requirements of the pharmaceutical industry, where it is primarily for product surveillance and liability. It is not used for surveillance and therapeutic decision making at a patient level. Systems to improve surveillance of adverse drug reactions (ADRs) at a patient level often consist of spontaneous reporting systems, which tend to be associated with underreporting or reporting of allergic reactions to drugs but not other ADRs.

ADRs, defined as "a response to a medicine which is noxious and unintended, and which occurs at doses normally used in man",[2] are a common, and often preventable, cause of hospital admission, especially in the elderly.[3] ADRs are also common during hospitalisation.[4] Medication is often changed or discontinued during hospital admission, and this is especially true for medications prescribed to elderly patients.[5] Further changes to medication regimens after hospital discharge are not always intentional and may be due to poor communication between healthcare professionals.[6] In an earlier study, we showed that ADRs that occurred during hospitalisation and required withdrawal of the causative drug were poorly communicated to general practitioners (GPs) and not at all to pharmacists, and that only 22% of the ADRs mentioned in discharge letters were incorporated into GP patient files.[7] The rate of represcription of medication withdrawn during hospitalisation because of an ADR was 27% in the first 6 months after discharge. Poor documentation and communication probably contributed to this high rate of represcription. We have also found that reasons for medication discontinuation were not reported in as many as 39.8% of cases of medication discontinuation.[8]

We developed an electronic system for reporting reasons for medication discontinuation that alerted physicians to the represcription of drugs previously discontinued because of ADRs, with a view to improving pharmacovigilance at a patient level. The system was developed and tested using Gaston technology on the 20-bed acute geriatric ward in Catharina Hospital,[9] a 700-bed teaching hospital, in Eindhoven, the Netherlands.

Objectives

Electronic prescribing systems have the potential to facilitate pharmacovigilance. In combination with clinical decision support modules, prescribing systems could alert physicians to potential mismatches between the drug prescribed and patient

characteristics, such as use of interacting medication or an allergy. Such systems could also warn against the represcription of a drug previously withdrawn because of ADRs, thereby improving patient safety. Our goal was to develop a user-friendly electronic clinical decision support system to document reasons for medication discontinuation in hospitalised geriatric patients and to flag potentially undesirable represcription. In this preliminary study, we studied the reasons for discontinuing medications, the characteristics of the cases of represcription after ADR, and the acceptability of the electronic clinical decision support system.

Methods

We performed a pilot study on the 20-bed acute geriatric ward (median length of stay 14 days) of Catharina Hospital (a large teaching hospital in the Netherlands).

The electronic clinical decision support module was developed using the Gaston framework (company: Medecs, Eindhoven, the Netherlands).[9] Gaston methodology facilitates the development and implementation of computer-interpretable guidelines and guideline-based decision support systems, with the overall goal of improving the acceptance of these systems. Gaston uses medical protocols combined with patient-specific information to provide decision support in the event of potentially dangerous situations and advice on the best possible treatment. The Gaston framework consists of a guideline editor that enables healthcare providers (e.g., physicians, nursing staff, and hospital administrators) to define and maintain guidelines, and a decision support module that executes guidelines that were developed using the guideline editor. Gaston is able to provide various forms of decision support, such as generating reports or providing real-time alerts by means of pop-up windows. The decision support module takes into account patient-specific data such as medication prescriptions, laboratory data, and other diagnosis- and treatment-related information. These patient data are obtained from patient information systems such as electronic patient records (EPRs) and pharmacy or laboratory information systems using communication standards such as HL7, SQL or XML.

In this case, the system has been interfaced with the electronic prescribing system via a real-time application programming interface (API) that enables third parties to communicate with the EPR system by using the notion of 'events'. When an event is triggered in the EPR system (e.g., starting/stopping a medication), the relevant data (e.g., the name/code of the medication) are sent to the system, which is then able to process the data in combination with the entered protocols. When additional patient data are required, these data are automatically retrieved from the EPR system's database. As the interfacing part of the system is a separate module, the system can be relatively easily transferred to other EPR systems, which has been shown and described in other projects.[9]

The underlying Gaston framework, which was developed in the 1990s, has been developed into a real-time alerting system to guarantee fast response times. In addition, as mentioned above, the system can be interfaced wih an EPR system, using a real-time API, and can also retrieve additional patient data from a patient database when required. As a result, any pop-up window will appear within seconds and, therefore, the EPR user can receive the pop-up window or alert at the point of care. When such a real-time interfacing mechanism is not available, the system will not be able to perform real-time support at the point of care; instead, it must rely on other forms of decision support (e.g., placing alerts on working lists).

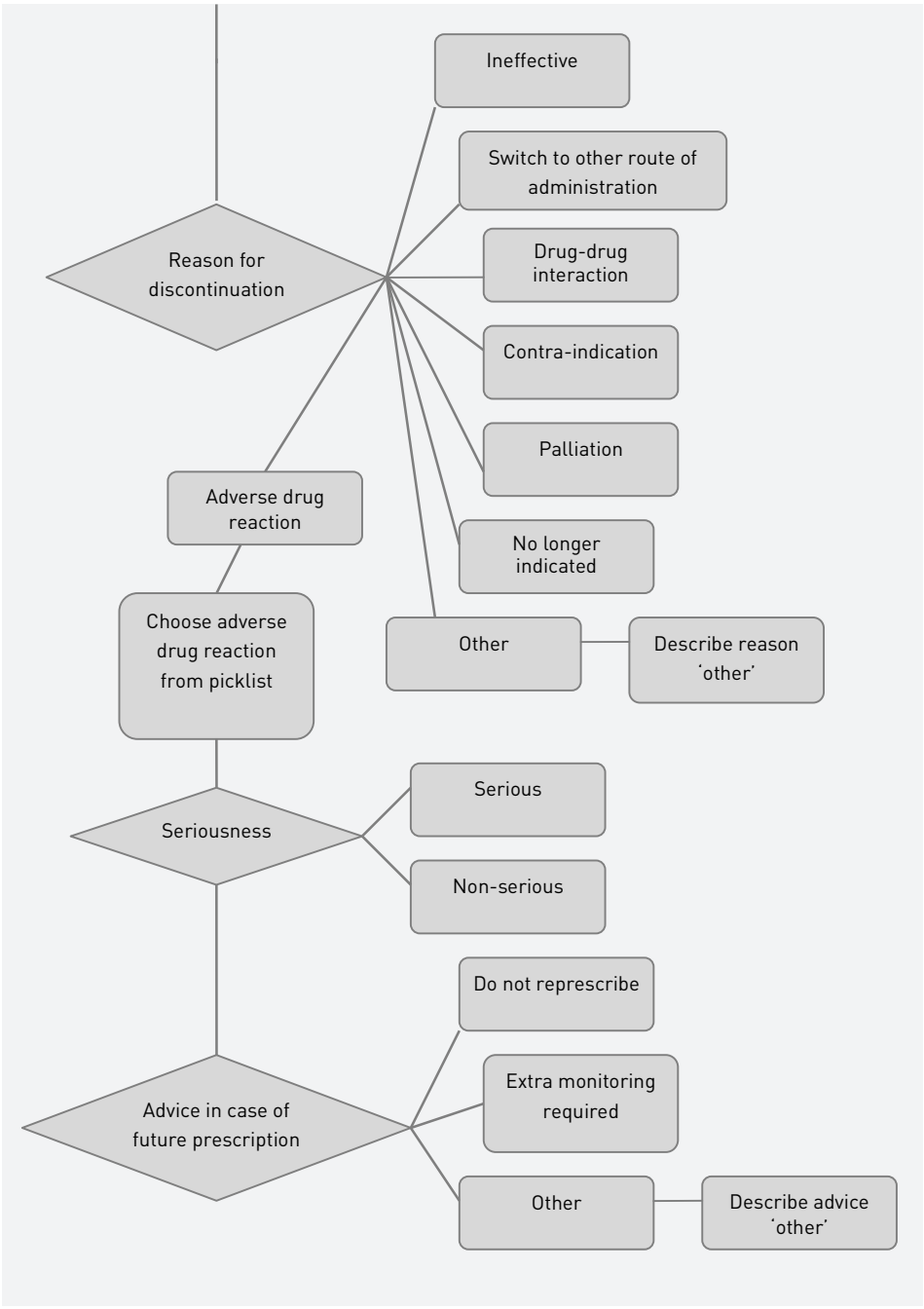
In this study, two guidelines were developed to run continuously in real-time alongside a (commercial) electronic medication prescription system. These guidelines contained the following steps:

Guideline 1:
Recording discontinued medication and documenting reasons for discontinuation:

1. Determine whether a medication is discontinued.
2. If it has, generate a pop-up window to register data on the discontinued medication (name of the drug, dose, dosing frequency, date of starting and stopping) and the reason of discontinuation (e.g., 'ineffective', 'no longer indicated', 'contraindication', 'adverse drug reaction', 'drug-drug interaction', 'palliation', 'switch to other route of administration' or 'other').
3. If the reason for discontinuation is not an ADR, the user is guided back to the electronic prescription system.
4. If the reason for discontinuation is an ADR, the user must:
   a) Select a description of the ADR, using a query function in the translated MedDRA-database. In this query function the clinician types characters of the ADR they want to document, leading tot a pick list of terms that incorporated these characters.
   b) Indicate whether the ADR is 'serious' (i.e. results in death, requires hospitalization or prolongation of existing hospital stay, or is life threatening), or 'non-serious', by selecting between these two options in the system.
   c) Indicate whether physicians can represcribe the same drug to the same patient in the future (by choosing between 'do not represcribe', 'extra monitoring required', or 'other' in the system).

Thus, for each drug that is withdrawn, information is saved in the database (Microsoft Access 2002, Microsoft Corporation, Redmond, WA, USA) about the drug dose, dosing frequency, dates of starting and stopping, and reason for discontinuation, and in the case of an ADR, a description of the ADR and its seriousness, advice in case of future prescription, and details of the physician who withdrew the drug are also recorded. Guideline 1 is shown in figure 1.

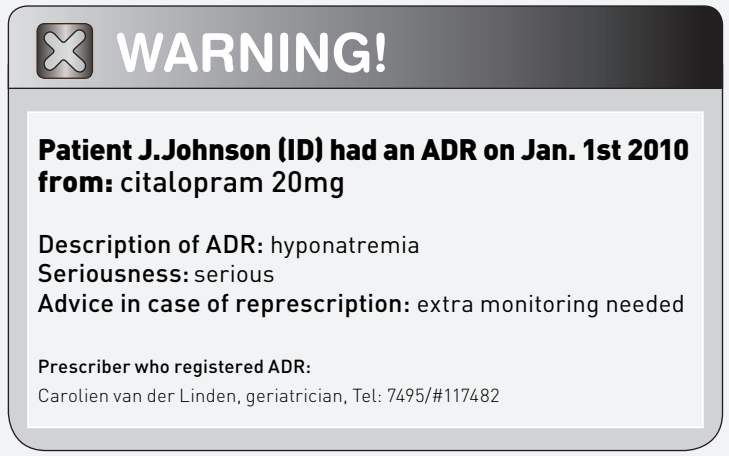
FIGURE 1 Guideline 1:
recording discontinued medication and documenting reasons for discontinuation



Guideline 2:
Signaling represcription of a drug previously discontinued because of an ADR:

1. For each prescribed medication, the database is checked to see whether the same generic drug was discontinued earlier in this patient's treatment because of an ADR (see Guideline 1).
2. If so, a warning appears in a pop-up window, detailing the name of the drug, the nature of the ADR, its seriousness, advice regarding represcription, and the name, function, and phone number of the physician who discontinued the drug. An example is shown in figure 2.

FIGURE 2 Pop-up appearing at the moment of represcription of medication associated with an adverse drug reaction (fictitious patient data)



Data on reasons for discontinuation and represcription after ADR were analysed using Microsoft Excel (2002 version, Microsoft Corporation, Redmond WA, USA).
All six physicians working on the study ward were trained to use the clinical decision support module in a 1-h session, after which the clinical decision support module was activated and physicians recorded the reasons for withdrawing individual drugs. Data on the patient ID, discontinued medication, and reasons for discontinuation were collected in a Microsoft Access database.
We interviewed users regarding the acceptability of the system using brief written surveys that contained questions about the clarity of all reasons for discontinuation provided in the system for selection, whether more explication was needed about the options, or whether a reason should be added. Other questions concerned the acceptability of a pop-up window appearing every time a medication was discontinued, and the time it took for the pop-up windows to appear. Furthermore there were

questions about the information that was asked for if the the user indicated an ADR was the reason to discontinue; whether every ADR they wanted to fill in could be found in the database and whether the time it took to complete the questions was acceptable. The time that the pop-up window took to appear was measured during paper patients rounds (weekly conferences of department physicians in which all hospitalised patients are discussed) using a manually operated stopwatch that measured the time between the moment 'stop drug' was clicked in the electronic prescribing system and the moment the pop-up window appeared.

Results

We performed a pilot study on the 20-bed acute geriatric ward of Catharina Hospital (a large teaching hospital in the Netherlands) in two periods (6 October 2009 to 26 February 2010, and 16 July 2010 to 31 January 2011), 342 days in total. In the period in between, the system did not function for multiple reasons, mainly because of changes in the electronic prescribing system due to the implementation of an updated version. During 11.4 months, 2228 medications were discontinued in 403 patients. Mean age of the patients was 84 years, 236 were female (59%), 167 male (41%). The most common reasons for discontinuation were 'no longer indicated' (56.7%), 'switch to other route of administration' (13.2%), 'palliation' (8.2%), 'ADR' (6.5%), and 'ineffective' (6.3%). 'Other' was indicated 144 times as the reason for discontinuation, meaning, for example, 'prescription error', 'temporary discontinuing before an operation' or 'medicament not available in hospital pharmacy'. (Table 1).

TABLE 1 Reasons for discontinuation of medication

Reason	Number	Percentage
No longer indicated	1263	56.7%
Switch to another route of administration	294	13.2%
Palliation	182	8.2%
Ineffective	140	6.3%
Adverse drug reaction	145	6.5%
Contraindicated	53	2.4%
Drug–drug interaction	7	0.3%
Other	144	6.4%
Total	2228	100%

The 145 ADRs occurred in 90 patients, i.e. 22.3% (90/403) of patients experienced one or more ADRs. The most frequently reported ADRs were renal insufficiency (23 times, 15.9%), extrapyramidal symptoms (11 times, 7.6%), electrolyte disorders (9 times, 6.2%), bradycardia (7 times, 4.8%) and diarrhoea (6 times, 4.1%).
The pop-up windows took a mean 1.6 seconds to appear (range 0.4-4.8 seconds), which was considered sufficiently fast by 75% of the users. Although 50% of users reported that it was time consuming to document ADRs, the time taken was considered acceptable because relatively few drugs were withdrawn because of ADRs.
There were 20 alerts to represcription of a drug previously withdrawn because of an ADR in 14 patients, and in 19 cases this represcription alert was given during the same hospital stay as when the drug was originally withdrawn. In the other case, the represcription alert was given in a subsequent hospital stay. The most frequently represcribed medications after ADR were diuretics (8), angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor antagonists (5), and laxatives (4). ADRs leading to discontinuation of these medications were renal insufficiency and diarrhoea. The advice given when the medication was withdrawn was 'extra monitoring required' (19 times) and 'do not represcribe' (1 time). One medication for which 'do not represcribe' advice was given was indeed not represcribed. This concerned severe hypokalemia after treatment with hydrochlorothiazide; after the represcription alert, another antihypertensive drug was chosen 3 months after the ADR. Nineteen medications for which 'extra monitoring required' advice were given were represcribed. In 16 of these 19 represcriptions (84.2%) extra monitoring was indeed effectuated. In three of 19 cases the advice to perform extra monitoring was not followed. Two of these cases concerned a patient to whom a drug was represcribed in a palliative phase. In one case a drug was discontinued because an ADR was presumed but discontinuation was not effective, so this drug was reprecribed. The response to represcription alerts is shown in tables 2 and 3.

TABLE 2 Actions taken after represcription alert and 'extra monitoring required' advice

Action	Number	Percentage
Represcribed in same dose with extra monitoring	10	52.6%
Represcribed in lower dose with extra monitoring	6	31.6%
Represcribed, no monitoring (switch to palliation)	2	10.5%
Represcribed because withdrawal was ineffective	1	5.3%
Total	19	100%

TABLE 3 Consequences of represcription after an ADR represcription alert

Consequences	Number	Percentage
No recurrence of ADR (alternative causes existent when withdrawn) *	8	42.2%
No recurrence of ADR	3	15.8%
ADR recurred due to another cause**	2	10.5%
Unknown because of hospital discharge	3	15.8%
Unknown because of palliation	2	10.5%
Status quo: withdrawal ineffective, represcription without change in symptoms	1	5.2%
Total	19	100%

** e.g., ACE inhibitors withdrawn at hospital admission because of renal insufficiency during dehydration*

** * renal insufficiency after represcription of diuretics recurred when the patient had viral gastroenteritis*

Discussion

Represcription of drugs after an ADR is a clinical problem [7] and can lead to the preventable recurrence of ADRs and even hospital readmission. Our electronic system enabled physicians to document reasons for drug discontinuation in a user-friendly way. Before we used this system, reasons for drug discontinuation were not documented in 39.8% of cases.[8] On the basis of our current findings, these non-documented reasons were probably 'no longer indicated' and 'switch to other route of administration'. The system alerted physicians to the potential represcription of a drug withdrawn because of an ADR. The advice documented after the medication was withdrawn was followed in 17 of 20 (85%) cases of represcription warnings after an ADR; in 15% of cases the physicians had a good reason not to follow the advice.

Eguale et al. investigated the accuracy of using orders for drug discontinuation and dose changes in an electronic prescribing system as a potential source of information on drug safety and effectiveness.[10] They assessed reasons for medication discontinuation recorded in the electronic prescription program of community-based primary care physicians (620 patients and 22 physicians) and compared them with treatment changes documented by physician-facilitated medical chart review. The results showed a high specificity (99.7%, 95%CI 95.5-99.9) and a moderate sensitivity (67%, 95%CI 54.1-77.7) with respect to the electronic prescribing system's ability to identify physician-initiated drug discontinuations and dose changes. Eguale et al. strongly recommend incorporating the reasons for discontinuation and dose change in electronic prescribing systems. Our system follows this recommendation and combines it with an alert for the potentially harmful represcription of a withdrawn drug.

A limitation of the current study is the fact that the ADRs are identified by the prescribers only, making underreporting of ADRs an actual risk. Another limitation its setting: a single ward of one hospital. Our next step will be to use the system on other wards, and to make the reasons for medication discontinuation, especially in the case of adverse events, available to relevant healthcare providers, such as primary care physicians and pharmacists. In this way, all prescribed medication can be monitored, and healthcare providers can be alerted if a previously withdrawn medication is represcribed. Future studies will have to show the value of this system to patient care, i.e. whether it prevents undesired represcription, recurrence of ADRs, and hospital admissions, and whether it is cost effective.

Conclusions

We developed and implemented a user-friendly system that documents reasons for medication discontinuation and alerts prescribers to potential represcription of previously withdrawn drugs. This may improve pharmacovigilance at a patient level.

Acknowledgements

The section 'Methods' was revised by Paul A de Clercq, Medecs.

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3.3 Documentation of reasons for medication discontinuation and alerts for represcription after adverse drug reaction

Submitted

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Abstract

Introduction

Studies have shown that reasons for medication discontinuation during hospitalisation are poorly documented and communicated to general practitioners and pharmacists. An earlier study showed that the rate of represcription of medication previously withdrawn because of an adverse drug reaction was 27%.

Methods

An electronic clinical decision support module, interfaced with the electronic prescription programme, was implemented on the geriatric and internal medicine wards of a large teaching hospital in the Netherlands. This module forced physicians to document reasons for medication discontinuation during hospitalisation, and alerted physicians to the represcription of drugs withdrawn because of an adverse drug reaction. Effects of these alerts were measured, and acceptability was investigated. Data were collected between February 2011 and June 2012.

Results

Over a study period of 600 studied days, 728 patients were hospitalised 830 times. They were treated by 12 physicians. In total, 3828 medications were discontinued, with the most frequently documented reasons for discontinuation being 'no longer indicated' (55.1%) and 'ineffective' (12.9%). Adverse drug reaction was recorded as reason for discontinuation 125 times (3.3%). There were 31 alerts for represcription of a drug previously withdrawn because of an adverse drug reaction. In most cases (87%), the advice that accompanied the alert was followed. The culprit drug was represcribed in 29 cases. In 18 of these 29 represcibed medications the adverse drug reaction did not reoccur, mainly because of extra monitoring. Most of the users considered it relatively easy to incorporate entering the data for the reason for medication discontinuation into their workflow.

Conclusions

This decision support system easily documents reasons for medication discontinuation, alerts physicians to prevent represcription or to perform extra monitoring of previously withdrawn drugs, and prevents reoccurrence of adverse drug reaction.

Introduction

Adverse drug reactions (ADR), defined as "a response to a medicine which is noxious and unintended, and which occurs at doses normally used in man"[1], are a common, and often preventable, cause of hospital admission, especially in the elderly.[2] ADRs are also common during hospitalisation.[3] Medication is often changed or discontinued during hospital admission, and this is especially true for medications prescribed to elderly patients.[4] A previous study showed that ADRs that occurred during hospitalisation and required withdrawal of the causative drug were poorly communicated to general practitioners (GPs), and that only 22% of the ADRs mentioned in discharge letters were incorporated into GP patient files. Moreover, none of the community pharmacists were informed about ADRs during hospitalisation and pharmacovigilance on individual base failed on this point. The rate of represcription of medication withdrawn during hospitalisation because of an ADR was 27% in the first six months after discharge.[5] Poor documentation and communication probably contributed to this high rate of represcription. The represcription of medication to which patients previously experienced an allergic reaction or another ADR can only be prevented if ADRs (including allergies) and other reasons for medication discontinuation are adequately documented. In a study involving 400 hospitalised patients, we found that reasons for medication discontinuation were not reported in as many as 40% of cases.[6] In their study, Khalil et al. found that allergy details were accurately recorded in only 3 of 521 patients (0.6%). The paper-based system used to record ADRs proved ineffective because of poor documentation, often as a result of a lack of information and illegible handwriting.[7] Information technology, such as computerized physician order entry (CPOE) and clinical decision support (CDS) has the potential to address the problem of inadequate documentation of reasons for medication discontinuation and unwanted drug represcription after the occurrence of an ADR. We developed and implemented an electronic CDS module that forced physicians to document reasons for medication discontinuation and flags represcription of a drug previously causing an ADR in the same patient. The objective of this study was to investigate reasons to discontinue medication, ADRs, alerts in case of represcription after ADR and effects of these alerts, and acceptability of the clinical decision support module.

Methods

Setting, design and study population

The electronic CDS module was first implemented on the 20-bed acute geriatric ward of a large teaching hospital in the Netherlands in October 2009 where it was used by the four residents and three geriatricians working on this ward. From October 2009 to January 2011 multiple minor changes were made to the electronic CDS module to optimize its ease of use and technical performance. The reasons

why medication was discontinued during this pilot period have been described before.[8] In February 2012, the new CDS module was also implemented on the internal medicine ward (with three residents and two internists) of the same hospital. In the current study, we analyzed data for all patients on the geriatric ward from February 2011 until June 2012, and on the internal medicine ward from February 2012 until June 2012.

Intervention: clinical decision support module

We developed an electronic CDS module using the Gaston framework.[9] Details of this module have been described elsewhere.[8] This CDS module is interfaced with the electronic prescribing system and has pop-up windows that appear when a medication is discontinued. These pop-up windows forced physicians to document reasons for discontinuation, showing a picklist of reasons containing 'ineffective', 'no longer indicated', 'contraindication', 'adverse drug reaction', 'drug-drug interaction', 'palliation', 'switch to other route of administration' or 'other' (free text). This picklist was composed using data from earlier descriptive research on reasons for medication discontinuation during hospitalisation.[6] If the reason for discontinuation is not an ADR, the user is guided back to the electronic prescription system. If ADR is picked as reason for discontinuation, the user is asked to select a description of the ADR using a query-function in translated Medical Dictionary for regulatory Activities (MedDRA)[10] database, to indicate whether the ADR is serious or non-serious, and to select an advice for future physicians on represcription of the same drug in the same patient (choice of 'do not represcribe', 'extra monitoring required' or 'other' (free text)). The system alerted physicians to the represcription of drugs earlier withdrawn because of an ADR in the same patient.

Acceptability

When a user selected 'stop drug' in the electronic prescription programme, a pop-up window appeared, asking for the reason for drug discontinuation. To measure the time the pop-up window took to appear, one of the investigators attended paper patients rounds that were conducted once weekly on both wards. This investigator (LMA Aussems, acknowledgements) used a manually operated stopwatch measuring the time between the moment 'stop drug' was clicked in the electronic prescribing system until the pop-up window appeared. Furthermore, all 12 users were given a brief written questionnaire on the acceptability of the system during a ward round, and completed questionnaires were collected a week later. The questionnaire contained questions about the clarity of reasons for discontinuation, whether the options were clearly explained, and whether other reasons should be recorded. Other questions concerned whether it was acceptable that the pop-up window appeared each time a medication was discontinued and whether the time it took for the pop-up window to appear was acceptable. Lastly, there were questions about the information users had to provide if they indicated that medication was discontinued because of an ADR, whether the database provided all possible ADRs, and whether the time it took to complete the questions was acceptable.

Main outcome measures

Main outcome measures were reasons to discontinue medication, ADRs, cases of represcription after ADR, reoccurrence of ADRs, and acceptability of the CDS module.

Data analysis

Data for patients on the geriatric and internal medicine ward, discontinued medications, reasons for discontinuation and represcription alerts were collected in a Microsoft Access database, and analyzed using Microsoft Excel.

Results

During the studied period, 728 patients were hospitalised 830 times (78 patients were hospitalised twice or more). The mean age of the patients was 79 years (range 19 to 103) and 441 of the 728 (60.6%) were women. Twelve physicians treated these patients and used the electronic CDS module. General data for the wards and patients are given in table 1.

TABLE 1 General data

Characteristic	Geriatric ward	Internal medicine ward	All
Studied period, days	486	114	600
Hospitalisations, no	608	222	830
Patients, no	518	211	728*
Male, no	199	89	287
Female, no	319	122	441
Age, mean (range), y	83(59-103)	67 (19-96)	79
Phycisians, no	7	5	12
Medical specialists, no	3	2	5
Residents, no	4	3	7

** one patient was hospitalised on both geriatric and internal medicine ward*

Discontinued medications

During the 830 hospitalisations, 3828 medications were discontinued (3202 on the geriatric ward and 626 on the internal medicine ward), giving a median discontinuation rate of 4.6 medications per hospitalisation. On the geriatric ward, most frequently discontinued medications were psychoactive drugs (antipsychotics, antidepressants, and sedatives; 629 withdrawals, 19.6%), cardiovascular medication (antihypertensives, diuretics, lipid-lowering agents; 490 withdrawals, 15.3%), and antibiotics (392 withdrawals, 12.2%). On the internal medicine ward, the most frequently discontinued medications were antibiotics (111 withdrawals, 17.7%), anticoagulants and platelet aggregation inhibitors (94 withdrawals, 15%), cardiovascular medication (78 withdrawals, 12.5%), and supplements (electrolytes, vitamins; 74 withdrawals, 11.8%).

Reasons for discontinuation

Most frequently documented reasons for discontinuation were 'no longer indicated' (2108 times, 55.1%) and 'ineffective' (495 times, 12.9%). ADR was indicated as reason for discontinuation 125 times (3.3%). 'other' was indicated as reason for discontinuation 386 times, specified as 'oral intake not possible' (55 times), 'prescription error' (52 times), and 'temporary discontinuation before surgery' (33 times). All reasons for medication discontinuation on the two wards are shown in table 2.

TABLE 2 Reasons for medication discontinuation on two wards

Reason, No. (%)	Geriatric ward	Internal medicine ward	All
No longer indicated	1660 (51.8)	448 (71.6)	2108 (55.1)
Ineffective	457 (14.3)	38 (6.1)	495 (12.9)
Switch to another route of administration	320 (10)	35 (5.6)	355 (9.3)
Palliation	212 (6.6)	3 (0.5)	215 (5.6)
Adverse drug reaction	101 (3.2)	24 (3.8)	125 (3.3)
Contraindication	93 (2.9)	29 (4.6)	122 (3.2)
Drug-drug interaction	13 (0.4)	9 (1.4)	22 (0.6)
Other	346 (10.8)	40 (6.4)	386 (10.1)
All	3202 (100)	626 (100)	3828 (100)

Adverse drug reactions

The 125 ADRs occurred in 105 patients (86 geriatric and 19 internal medicine patients); 13 patients experienced 2 or more ADRs. The most common ADRs were electrolyte disorders (23 times), mostly hyponatremia (11 times) and hypo- or hyperkalemia (10 times); other frequently occurring ADRs were gastrointestinal complaints (19 times), renal insufficiency (18 times), hypotension (9 times), cutaneous symptoms (7 times), and extrapyramidal symptoms (7 times). Because of a technical problem ADR was not described in 19 cases. The Frequency of ADRs on geriatric and internal medicine wards is shown in table 3.

TABLE 3 Description of ADRs on geriatric and internal medicine wards

Adverse drug reaction, No	Geriatric ward	Internal medicine ward	All
Electrolyte disorders	19	4	23
Gastrointestinal complaints	15	4	19
Renal insufficiency	10	8	18
Hypotension	8	1	9
Cuteaneous symptoms	4	3	7
Extrapyramidal symptoms	7	0	7
Elevated liverenzymes	2	2	4
Edema	2	1	3
Sedation	1	2	3
Unknown	19	0	19
Other	12	1	13
All	99	26	125

The medications that caused the most ADRs were cardiovascular drugs (responsible for 56 ADRs, 44.8% of all ADRs), psychoactive medications (responsible for 15 ADRs, 12% of ADRs), analgesics (14 ADRs, 11.2% of ADRs), and antibiotics (10. 8% of ADRs). Of drugs causing ADRs, 70% were prescribed during hospitalisation; the remaining 30% were prescribed before admission. Twenty-nine (23%) of the ADRs were documented as being serious, mainly renal insufficiency and hypokalemia.

The advice 'do not represcribe' was selected for 22 ADRs (18%), 'extra monitoring required' for 88 ADRs (70%), and 'other' (mainly with the comment 'dependent on the effect of discontinuation') for 10 ADRs (8%). In five cases no advice was selected.

Alerts to represcription after ADR

During the study, 31 of the 125 (25%) medicines, that were previously withdrawn because of an ADR, were represcribed and alerts appeared. Four other alerts were incorrect due to a technical problem shortly after implementation of the CDS module. These alerts appeared although an ADR had not been the reason for discontinuation. The 31 'correct' alerts appeared in 17 patients. In seven patients two or more alerts to represcription appeared. Four of the ADRs with an alert to represcription were serious ADRs; the ADRS of the remaining 27 alerts were not serious. Two alerts gave the advice not to represcribe furosemide because it earlier caused hypokalemia. These two alerts appeared for the same drug in the same patient on two occasions during one hospitalisation. Despite the advice not to represcribe the drug, furosemide was represcribed but in combination with suppletion of potassium. The consequences of this treatment choice for the patient were not clear, because 1 day after the second alert the patient was switched to palliative treatment and died a few days later. Twenty-nine alerts gave the advice 'extra monitoring required'; in 2 cases the medication was not represcribed, in 25 cases it was represcribed with extra monitoring, and in 2 cases it was represcribed without extra monitoring. Monitoring mainly consisted of checking renal function, serum potassium (hypokalemia), blood pressure (hypotension), heartrate (tachycardia) and gastrointestinal symptoms. It was not clear why the advice for extra monitoring was not followed in the 2 cases. The ADR did not reoccur in 18 of 25 cases (72%) in which the advice to monitor was followed. Overall, the advice given by the alerts to represcription after ADR was followed in 27 of 31 cases (87%) (figure 1).

Acceptability

The time it took the pop-up window to appear was measured 127 times during 14 ward rounds on the geriatric ward (mean 4.8 seconds, range 2.2–10 seconds) and 51 times during 10 ward rounds on the internal medicine ward (5.9 seconds, range 2.8–11.4 seconds). All 12 users (five medical specialists and seven residents) completed the brief questionnaire about the acceptability of the system. Six of the 12 users (50%) found the checklist of reasons for medication discontinuation to be complete; the other 6 users suggested additional reasons, mainly 'temporarily not indicated' or 'erroneous prescription'. The information on the pop-up window alerting physicians to the represcription of a drug that previously caused an ADR was considered complete by all users. Results of the questionnaires are shown in table 4.

FIGURE 1 Alerts to represcription after ADR and the consequences

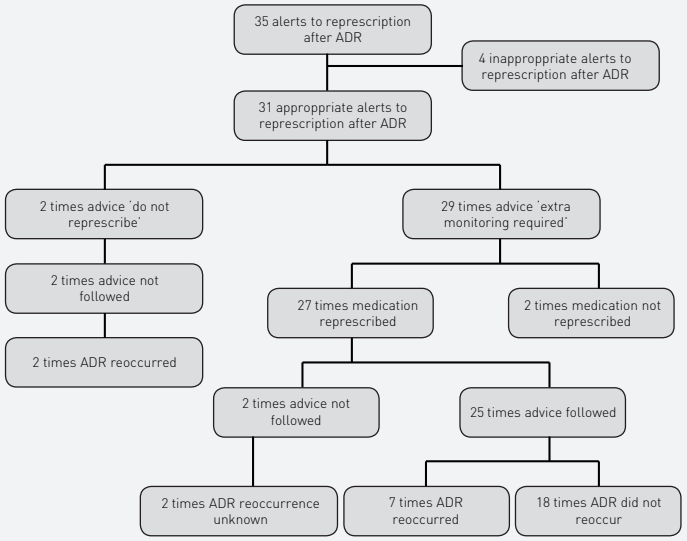

TABLE 4 Results of user questionnaires on acceptability

Question	Answers: n/N (%)
Are all reasons for discontinuation clear?	Yes: 11/12 (92) No: 1/12 (8)
Should a reason de added?	Yes: 6/12 (50) No: 6/12 (50)
Is it difficult to decide if a symptom is an ADR?	Yes: 10/12 (83) No: 2/12 (17)
Is it acceptable a pop-up window appears every time a medication is discontinued?	Not a problem: 1/12 (8) It is sometimes inconvenient, - but always enters a well considered reason: 7/12 (58) - and not always enters a well considered reason: 4/12 (33)
How do you experience speed of pop-up?	Just right: 1/12 (8) Sufficiently fast: 5/12 (42) Often long, is inconvenient: 6/12 (50)
What do you think of the time it takes to registrate an ADR?	No problem: 5/9* (56) Quite long but acceptable: 4/9 (44) Hindering workflow: 0/9
Do you always enter all medication used at home into the EPS at hospital admission?	Yes: 6/8** (75) Most of the time: 2/8 (25)

** three users never registrated an ADR, ** eight users enter medication at hospital admission*

Discussion

Key findings and interpretation

Physicians recorded reasons why medication was discontinued in patients on geriatric and internal medicine wards, using an electronic CDS module. The most common reason to discontinue medication was 'no longer indicated'. ADRs accounted for 3.3% of discontinuations. During the study, there were 31 alerts to represcription of a drug earlier withdrawn because of an ADR. The advice that accompanied the medication alert was followed in 87% of the cases. In 18 of 29 represcibed medications the ADR did not reoccur. Most of the users considered it relatively easy to incorporate this step (entering reasons for medication withdrawal) into their daily workflow.

Comparison with the literature

To our knowledge, this is the first study to investigate reasons for medication discontinuation in hospitalised patients. There are few data on the represcription of culprit drugs withdrawn previously because of an ADR. Davies et al. studied emergency re-admissions to hospital due to ADR.[11] From 955 studied patients 163 experienced an ADR during the index admission. Of these patients, 77 were re-admitted within 1 year, 16 for an ADR. Six of these 16 re-admissions were due to the same ADR as index admission. Zhang et al. found that 6853 of 37296 (18%) older (>60 years) patients experienced 10212 repeat ADRs,[12] and that repeat ADR-related hospitalisations in the elderly had consistently increased from 1980 to 2003. Repeat ADR in that study did not necessarily that the same ADR occurred after represcription of the same culprit drug earlier withdrawn. The authors found the most common drugs responsible for first-time and repeat ADRs to be cardiovascular drugs as we did.

Strengths and limitations

Before this module was used, the reason for medication discontinuation was not documented for nearly 40% of discontinued medications.[6] With the electronic CDS module, physicians were required to document reasons for discontinuation of each medication withdrawn in patients on a geriatric or internal medicine ward. A limitation of the current study is that the ADRs were identified by the prescribers only, making underreporting of ADRs an actual risk. Eighty-three percent of prescribers indicated it was somtimes difficult to decide if a symptom should be classified as an ADR. This probably indicates a lack of knowledge of ADRs. Likic et al. that the main cause of medication errors was physicians' poor knowledge of drug therapy.[13] The time medical curricula expend on education and training in especially geriatric pharmacology has not increased in the last decade even though increasingly more elderly patients are using complex polytherapy.[14] Another potential limitation is the time the pop-up window took to appear (mean 4.8 seconds, range 2.2-10 seconds), which was rated as inconvenient by 50% of the users and might be hinder future implementation of the system. Another limitation was the study setting: two wards in one hospital. Our

next step will be to make the reasons for medication discontinuation, especially in the case of ADRs, available to relevant healthcare providers, such as primary care physicians and pharmacists. In this way, all prescribed medication can be monitored, and healthcare providers can be alerted if a previously withdrawn medication is represcribed. Another limitation is the fact that 25% of doctors indicated they did not always enter all the medications patients used at home into the electronic prescription system, leading to an incomplete database of discontinued medications.

Recommendations

The time it takes the pop-up window asking for the reason for medication discontinuation to appear should be shortened. Because we propose that the reasons why medication is discontinued, including ADRs, should be documented and made available to all relevant healthcare professionals (general practitioner, pharmacist, specialist) and the patient, future systems should function in more than one setting. We suggest that the quality of ADR documentation should be improved, preferably by including a causality assessment, which necessitates cooperation between physicians and pharmacists. Future studies will have to demonstrate the value of this system to patient care, i.e. whether it prevents undesired represcription, reoccurrence of ADRs and hospital admissions, and whether it is cost effective.

Conclusions

We developed and implemented an electronic system for documenting reasons for medication discontinuation and for alerting prescribers to potential represcription of medicines previously withdrawn because of an ADR. ADRs did not reoccur in 18 of 29 represcribed medications, mainly because of extra monitoring. This may improve pharmacovigilance at a patient level.

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3.4 Integration of information on in-hospital adverse drug reactions in primary care information systems

a feasibility study

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Abstract

Introduction

Adverse drug reactions (ADRs) are common and are often preventable. One cause of preventable ADRs is the prescription of a drug that has been withdrawn because it caused an allergy or another ADR. Probable causes of represcription after an ADR include insufficient documentation of reasons for discontinuation, insufficient communication of ADRs to general practitioners (GPs) and community pharmacists, and lack of an alert to represcription of the drug.

Design and methods

An electronic clinical decision support (CDS) module that compels hospital doctors to document reasons for medication discontinuation, ADRs included, integrated information on ADRs into the information system of primary care centres and alerted doctors to the represcription of a drug withdrawn because it caused an ADR. We investigated the feasibility of this integration, using written structured questionnaires completed by GPs after they had been shown how the CDS system works during a short presentation.

Results

After demonstration of the CDS module, the 12 participating GPs rated all items with a median score of 2 or lower, meaning that they expected that the CDS module would be easy to use, useful, and have few barriers to acceptance. They intended to use it when implemented. Expected usefulness was awarded the lowest (best) score.

Conclusions

This study showed that GPs and a community pharmacist expected that a CDS module that integrated information about ADRs documented in a hospital into the primary care information system would be very useful and easy to use. The participants indicated that they intended to use the CDS module.

Introduction

Adverse drug reactions (ADRs) are common in hospitalised patients[1,2,3] and also frequently lead to hospital admission.[4,5] However, several studies have shown that a considerable part of these drug-related problems are preventable.[4,6,7] Preventable ADRs are estimated to occur in 2-3% of patients treated in ambulatory settings per year.[8] Preventable ADRs may be the result of a drug treatment procedure inconsistent with current knowledge of good medical practice, for example the prescription of a drug when its use is contraindicated, because of other concurrent medical conditions or because it interacts with other medications used by the patient,[9] or because the drug caused an allergy or other ADR when used previously. The represcription of previously withdrawn drugs occurs rather frequently. Lesar et al. found a rate of 4 errors per 1000 medication orders, and of the errors that could potentially cause adverse effects, 12.1% were due to known drug allergy.[10] In an earlier study we found that 27% of drugs previously withdrawn during hospitalisation because of an ADR were represcribed within 6 months.[11] Probable causes of represcription after an ADR were found to be insufficient documentation of reasons for discontinuation, insufficient communication of ADRs to general practitioners (GPs) and community pharmacists and lack of an alert to represcription after an ADR.[11,12]

It is widely accepted that electronic prescribing combined with clinical decision support systems can reduce avoidable ADRs,[13,14] and the specific functionalities needed to improve the safety and quality of drug management have been defined.[15] However, unlike other industries and organisations, healthcare organisations, have been slow in adopting information technology, possibly because such systems are perceived as interrupting doctors' workflow, are not proven to be beneficial, and are associated with organisational issues.[16] We have developed and implemented an electronic clinical decision support (CDS) module, interfaced with a hospital information system that compels in-hospital physicians to document reasons for medication discontinuation and alerts them to unwanted represcription of the medication after it caused an ADR. To prevent the primary-care represcription of medication previously withdrawn because of an ADR, relevant information needs to be available to GPs and community pharmacists, and there needs to be a system for automatically alerting prescribers if they attempt to represcribe withdrawn medications. In the current study, the CDS module was connected to the information system of a cooperative of 10 primary care centres. We describe the connection between this electronic CDS module, that documents adverse drug reactions in the hospital, to the information system of primary care centres, and investigated feasibility thereof.

Design and methods

Intervention

An electronic CDS module was developed and implemented on two wards of a large teaching hospital in the Netherlands. This module was interfaced with the electronic prescribing system and showed a pop-window at the moment medications were withdrawn. These pop-up windows compelled doctors to indicate why they had discontinued a medication; they could choose from a list of reasons, namely, 'ineffective', 'no longer indicated', 'contraindication', 'adverse drug reaction', 'drug-drug interaction', 'palliation', 'switch to other route of administration', or 'other' (free text). (These reasons were derived from a previous study for reasons for medication discontinuation.[12]) If the reason for discontinuation was other than an ADR, the user was guided back to the electronic prescribing system. If ADR was given as reason for discontinuation, the user was asked to select a description of the ADR, using a query function in the translated Medical Dictionary for regulatory Activities (MedDRA)[17] database, to indicate whether the ADR was serious or non-serious, and to select advice for other doctors who might attempt to represcribe the same drug in the same patient (choice of 'do not represcribe', 'extra monitoring required', or 'other' (free text)). The system alerted doctors to the represcription of drugs earlier withdrawn because of an ADR in the same patient. Details about this module and results on reasons for discontinuation, ADRs, and alerts in the case of represcription after an ADR in hospital have been reported earlier.[18]

In the current study, the CDS module was connected to the information system of a cooperative of 10 primary care centres in the city of Eindhoven, the Netherlands. Information about ADRs occurring in a virtual patient in hospital was sent to the test environment of the primary care information system, using an existing secured network (OZIS, a Dutch Open Healthcare Information System) sending EDIFACT messages (Electronic Data Interchange For Administration, Commerce and Transport developed under the United Nations)[19]. The EDIFACT message contained information on the ADR; its description (MedDRA), seriousness, advice in case of future represcription and the name and telephone number of the doctor who documented the ADR. This information was recorded in the patient's medical record at the general practice. Furthermore, the ADR was recorded as an intolerance in the GPs' and community pharmacists' information system, so that alerts were generated by the primary care information system if the drug was represcribed.

Feasibility

The CDS module was demonstrated to the participating GPs and a community pharmacist, who were also shown screenshots of the information integrated into the medical records and intolerance module, and of an alert generated in the case of represcription. After this short presentation, participants were given a written structured questionnaire. Since a validated questionnaire on this topic was not available, we developed one, using the technology acceptance model. This model, theorises that technology acceptance is determined by attitude, perceived usefulness and perceived ease of use.[20] We formulated questions about the expected usefulness and expected ease of use, as the GPs and pharmacist were not yet using the system. After intensive evaluation with help of an experienced researcher from the Netherlands Institute for Health Services Research (LvD, Acknowledgements), we added items on 'perceived barriers to acceptance' and 'intent to use'. The final questionnaire consisted of 4 items on expected ease of use, 4 items on expected usefulness, 5 items on intent to use, and 4 items on perceived barriers to acceptance, a total of 17 questions. Participants were asked to score each item on a 5-point Likert scale.[21] In a free text box at the end of the questionnaire, participants were asked to make any supplementary comments. After the questionnaires were completed, there was a discussion about the questions and comments for further development and implementation of the CDS module.

Data analysis

Questionnaire data were analysed using SPSS statistics 19.0. Descriptive data are reported as medians and range. A lower score on the 5-point Likert scale was in favour of feasibility, with a score of 3 being neutral, and a score of 4 or 5 expressing a negative view. There were too few participants to test the internal reliability of the questionnaire. The comments of the participants in the free text box and during the discussion afterwards were summarised qualitatively.

Results

Two investigators (CvdL and MNB) visited three primary care centres and demonstrated the CDS module to 12 GPs and 1 community pharmacist. All participants answered all questions. The median score of GPs for all items was 2 or lower (Table 1), indicating that GPs expected that the CDS module would be easy to use, useful, and have few barriers to acceptance. They intended to use the module when it became available.

The expected usefulness of the CDS module had the lowest score (i.e., rated the highest). The question (no 15) about consulting the hospital doctor who documented the ADR had a median score higher than 3, indicating that GPs would probably not contact the doctor. During the discussion, the GPs stated that the information shown in the alert was clear and that they had no need to consult the primary prescriber.

TABLE 1 GPs' scores (5-point Likert scale; n=12) for the feasibility of integrating information about in-hospital ADRs into the primary care information system.

	Median	Min	Max
Expected ease of use	**1.5**	**1**	**2.5**
1. I think the CDS module will be easy to use	1	1	2
2. It will be difficult for me to become skilful in using the CDS module	2	1	3
3. The information presented in the represcription alert is clear	1	1	2
4. The additional information documented in our patient file is easy to find	1	1	4
Expected usefulness	**1**	**1**	**2.25**
5. The use of this CDS module will improve medication safety in my patients	1	1	2
6. This CDS module will make me more alert to represcription after an ADR	1	1	3
7. The use of this CDS module will reduce the frequency of represcription of medicines causing an ADR	1	1	3
8. In general, using this CDS module will make me more aware of represcribing a medicine known to cause an ADR	1	1	4
Barriers to acceptance	**2**	**1.5**	**3.75**
9. I think it will take a lot of time to use this CDS module in my practice	2	2	3
10. I will take me some time to understand this CDS module	1.5	1	5
11. It will take a lot of time to search patient files for additional information after a represcription alert	2	2	4
12. Interpreting the resprescription alert seems difficult	2	1	4
Intent to use	**2**	**1**	**2.75**
13. If there an ADR, I will adjust my prescribing strategy	1	1	2
14. After an ADR alert, I will search the patient's file for more information	2	1	4
15. After an alert, I intend to consult the doctor who documented the ADR in the hospital	3	1	4
16. Do you think this CDS module would be useful for repeat prescriptions?	2	1	4
17. Would you like to use this CDS module in your practice?	1	1	2

The participating community pharmacist awarded a score of 2.25 to 'expected ease of use', 1 to 'expected usefulness', 2.5 to 'barriers to acceptance' and 2 to 'intention to use', all favouring the feasibility of the CDS module.
In the free text box, 5 of the 12 GPs commented that they thought that the CDS module would contribute to patient safety or to the quality of care. One GP wanted the module to be used on all wards, so that he would have information on ADRs from all hospital specialists. In the discussion, GPs recommended that the patients be told about the ADRs they experienced and to which drug, and that information on ADRs is included in the discharge letter and in discharge prescriptions.

Discussion

This study showed that GPs and a community pharmacist believed that a CDS module integrating information on ADRs documented in the hospital into the primary care information system would be very useful, easy to use, and have few barriers to acceptance. They all intended to use this CDS module when it became available. The participants gave expected usefulness the best score, probably because of expected improvements in safety, continuity, and quality of care. They expected the CDS module to be easy to use, probably because it would be integrated into the primary care information system with which they were already familiar, making special training redundant. The CDS module was first implemented in a hospital, thus surveillance of drug represcription was limited to that setting. Yet this information needs to be available to other care providers once a patient is discharged. In an earlier study, we showed that only 22% of GPs incorporated information on ADRs included in the hospital discharge letter into their own patient records. We also found that community pharmacists were never informed about ADRs that occurred in hospital. So, it seems necessary that information on ADRs is electronically sent and directly integrated in the primary care information systems, enabling alerting within this system. To enable alerting within the primary care information system the information on ADRs should be integrated within this system as an intolerance. To our knowledge this is the first time information documented in-hospital was directly integrated into a primary care information system in the Netherlands. Dutch hospitals and primary care settings use different information systems, and thus we encountered several problems when trying to integrate the two systems. Software suppliers from primary and secondary care systems seemed reluctant to "open" their systems for information exchange on ADRs, probably due to a lack of experience with this phenomenon and hence the absence of a commercial interest. Overcoming this reluctance required considerable time and effort, yet it resulted in the possibility to import the information about ADRs into the primary care information system. It should be remembered that we used a virtual patient, and that the integration of ADR information for real patients into the actual GPs' information system has yet to be realised. Another, more practical,

barrier is that the two systems use different medication codes. The CDS module used in the hospital initially used the Anatomical Therapeutic Chemical (ATC) classification system to identify the active substances of medications. To synchronise medication codes with the primary care information system, we had to recode information using SNK-codes; a Dutch classification system. Another barrier was that updates in the hospital information system influenced the functioning of our CDS module, which makes constant surveillance and maintenance necessary. A barrier to future use is that information was sent using the OZIS network, which will probably cease to exist in the coming year and will be replaced by another system, with hopes set on countrywide accessible electronic medication files.

A limitation of our study is the small number of participants and the fact that the internal reliability of the questionnaire could not be tested.

Further integration of community-based and in-hospital information systems, and closer cooperation between health care organisations and software suppliers is necessary. Our CDS module only communicates ADRs that occurred in-hospital to primary care, whereas in the future, information on ADRs that occurred in ambulatory care should be available in-hospital. As information system (either hospital based or in ambulatory care) updates may affect the functioning of the CDS, CDS systems should be tested after the information systems they are interfaced with are updated.[22]

Conclusions

A CDS module that integrated information on ADRs documented in-hospital into a primary care information system was considered very useful, easy to use, and with few barriers to acceptance by GPs and a community pharmacist. However, several barriers to software integration were encountered.

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4

General discussion

Introduction

Safe and effective pharmacotherapy, balancing between preventing and treating symptoms or diseases with drugs and avoiding medication-related harmful effects, is a great challenge in medicine, and an even greater challenge in geriatric medicine because these patients have multiple medical conditions and use multiple drugs. Hospitalisation is a critical phase in a patient's health history, because the patient may experience concurrent diseases, an exacerbation of existing disease, changes in renal and/or hepatic function, and adverse drug reactions (ADRs). During hospitalisation the patients' pharmacotherapeutic regimen is often altered. It may be necessary to add medication that is temporarily indicated because of concurrent disease or because undertreatment is present. Dose changes can be required because of ineffectiveness, or, for example, because of impaired renal function. The occurrence of an ADR, defined as "a response to a medicine which is noxious and unintended, and which occurs at doses normally used in man", may make it necessary to add a drug, or reduce the dose or withdraw the causative drug.[1] Following from the above, scrupulous medication reconciliation is needed during hospitalisation. However, the efforts put into optimising pharmacotherapy should not end at the moment when the patient is discharged from hospital, but should continue into primary care, with the accurate communication of the discharge summary, including discharge medications with reasons for changes, to primary care doctors and community pharmacists.[2]

In clinical practice, we see numerous patients who have been represcribed medications that had been withdrawn for causing an ADR during hospitalisation. This potentially harmful phenomenon was the incentive for the research presented in this thesis. ADRs are common in hospitalised patients. In a meta-analysis, van den Bemt et al. found the frequency of ADRs to vary between 1.9% and 37.3%.[3] ADRs are also a common cause of hospital admission, especially in the elderly.[4] ADRs are either non-preventable (e.g., a patient experiences a side effect to a medicine for the first time, an event which could not have been predicted), or preventable. Preventable ADRs can be due to inappropriate drug treatment that is not consistent with current knowledge of good medical practice, for example, prescription of a drug contraindicated because of a concurrent medical condition or because of a known interaction with other prescribed drugs.[5] Another cause of preventable ADRs is the represcription of a drug known to have previously caused an allergy or other ADR.

The main objectives of the studies described in this thesis were to a) investigate how reasons for medication discontinuation and ADRs are documented and the extent to which drugs that have been withdrawn because they caused an ADR are represcribed, and b) to investigate methods to prevent the represcription of drugs that previously caused an ADR, including the development, implementation, results, and feasibility testing of an electronic clinical decision support (CDS) module for clinical practice.

We found that the represcription of withdrawn drugs occurs rather frequently: 27% of drugs earlier withdrawn because of ADR were represcribed within 6 months (Chapter 2.2). Probable causes of represcription after ADR were found to be insufficient documentation of the reasons for discontinuation (Chapter 2.1), insufficient communication of ADRs to general practitioners and community pharmacists (Chapter 2.2), and the lack of an alert to represcription after an ADR. We developed and implemented an electronic CDS module that compels hospital physicians to document reasons for medication discontinuation and alerts them to unwanted represcription after an ADR (Chapter 2.3 and 3.2). We documented the reasons given for medication discontinuation and ADRs, and showed that the advice given in a represcription alert for drugs withdrawn for causing an ADR was followed in 87% of the cases (Chapter 3.3). To prevent represcription in primary care, the module was further developed to integrate information on ADRs with the information system of primary care centres. We investigated the feasibility of this among general practitioners (Chapter 3.4). To the best of our knowledge, this is the first attempt to integrate information on ADRs in two different information systems (one used exclusively in primary care, the other exclusively in hospitals).

In this final chapter, the results of the individual studies will be placed in broader perspective, focussing on the following major topics:

1. Detection of ADRs
2. Documentation of ADRs
3. Information transfer between healthcare settings

Lastly, we make suggestions for clinical practice and future research.

Detection of adverse drug reactions

To detect ADRs, doctors need to be aware that new or altered symptoms may indicate that a patient is experiencing an ADR. Moreover, the presentation of ADRs in older adults is often atypical and non-specific, which further complicates the recognition of ADRs.[6] While recognising well-known ADRs to established medications requires a thorough knowledge of the medication concerned, doctors need to be more "open-minded" when it comes to linking unexpected symptoms, possible ADRs, to recently marketed drugs. Doctors, pharmacists and nurses should be constantly vigilant to the development of ADRs, and the differential diagnosis in older patients taking multiple drugs should always include the possibility of an ADR. In our opinion, this vigilance is often limited, or even absent. The attitude that is needed to recognise ADRs requires detective-like qualities, but also an open mind. Furthermore, professionals need to be able to recognise symptoms in other fields than their own specialty, because ADRs frequently present with symptoms other than of the primarily treated disease. Medical doctors with a holistic approach like geriatricians and professionals educated with a broad perspective like pharmacists may be better equipped than professionals highly specialised in a limited area.

The lack of awareness of the development of ADRs may be due to insufficient knowledge of and training in pharmacotherapeutics. Likic et al. postulated that the main cause of medication errors is insufficient knowledge of drug therapy on the part of doctors and other health professionals.[7] Moreover, pharmacotherapy is becoming more and more complex, especially in older patients who have multiple medical conditions and who are treated with a large number of medicines.[8] Keijsers et al. reported that there is a considerable need to improve education in geriatric pharmacology among health professionals at both undergraduate and postgraduate levels, and that, in general, current curricula do not devote enough time to the teaching of pharmacology.[9] Several studies have shown that improving the pharmacological knowledge of doctors and nurses is an efficient way to reduce errors.[10] We think medical students should be taught about pharmacotherapy and in particular ADRs during the undergraduate phase, but that these topics should be brought to the attention of postgraduate doctors more often. In addition, closer cooperation with clinical pharmacists may facilitate the detection of ADRs. Leape et al. found that systematic review of all prescriptions by clinical pharmacists could prevent two-thirds of prescribing errors.[11] Another way to detect possible adverse events retrospectively is to use the Global Trigger Tool.[12] This tool provides an easy-to-use method for accurately identifying adverse events and measuring the rate of adverse events over time, using retrospective review of a random sample of inpatient hospital records using "triggers" (or clues) to identify possible adverse events. Triggers include vitamin K administration, use of antidotes, and raised serum levels of creatinine. Another potential strategy to improve the detection of ADRs is to identify those patients who are at high risk of an ADR and to target this group.[6] Onder et al. developed and validated a method to identify patients who are at increased risk of an ADR in a population of hospitalised older adults.[13] The number of drugs and a history of a previous ADR were the strongest predictors of ADRs, followed by heart failure, liver disease, presence of four or more comorbidities, and renal failure. Paying particular attention to high-risk groups of patients during medical training and in clinical practice could improve the recognition of ADRs.

The CDS module we described in this thesis probably contributes to the recognition of ADRs. It compels physicians to document the reason for discontinuation, which they can choose from a list, at the moment a drug is withdrawn. This forces doctors to consider the reason for discontinuation, ADR included, at least for one extra moment. However, this is not a comprehensive solution to the problem of underdetection, and, in a working environment of growing complexity, physicians and other healthcare professionals need to be supported more vigorously to enhance vigilance to ADRs.

Computerised CDS systems can probably provide healthcare professionals with this support, and can be of help to alert the possible presence of an ADR. In the study reported in chapter 3.1, we found several systems with automatic detection of ADRs at a patient level, mostly based on laboratory results (toxic levels of a drug in serum) and antidotes being ordered. Triggers such as those used in the IHI Global Trigger Tool could be integrated in these systems, and could, by combining laboratory results with prescribed medication (e.g. hyponatremia when a serotonin reuptake inhibitor is used), lead to a better detection of ADRs. When properly documented and coded, patients' symptoms and diagnosis, combined with prescribed medication, could be used to trigger alerts to possible ADRs. Another possibility is to alert doctors to the risk of a future ADR; for example, an alert when amiodarone is started and thyroid function has not been measured recently, or an alert to monitor kidney function and serum potassium levels after the prescription of an ACE-inhibitor. At hospital admission, doctors should ask patients about ADRs that they have experienced in the past. To ensure that this information is recorded, there are systems that block access to the electronic medication record until the patients' ADR history has been recorded.[14]

The performance of computerised CDS systems depends, among other conditions, on the availability and quality of data. Over the last years, much effort has been put into replacing hand-written clinical data with electronic versions. However, the information recorded in electronic patient files is often incomplete, entered in the wrong place, and often consists of free text, which makes these data unsuitable for use in CDS systems. Healthcare must now take the next step in improving the quality of data and make optimal use of computerised decision support systems.

Documentation of ADRs

Once detected, an ADR should be recorded in the patient's medical record so that this information can be taken into account when making pharmacotherapeutic choices after the occurrence of the ADR. To be as valuable as possible, the documented information is preferably structured and contains information on the causative drug, a description of the ADR, its seriousness and causality, and an advice for future prescribers. As mentioned in other chapters, it is difficult to establish causality of an ADR because of the complex nature of adverse events, multiple treatments, and individual clinical variability.[15] Several algorithms have been proposed for the reproducible assessment of causality. However, due to the lack of a well established gold standard, none of the existing causality algorithms is validated.[16] Most algorithms make use of a combination of five commonly used criteria for causality assessment: challenge (time relationship between ADR and medication administered), effect of de- and re-challenge, previous bibliographic description, and aetiological alternatives. Our CDS module asks physicians to choose a reason for medication discontinuation, for example an ADR, at the moment a drug is discontinued. At this moment, the effects of de- and re-challenge can not be known yet. Furthermore, completing a causality assessment was experienced as an interruption of the workflow, so, causality assessment was not part of the documented information in the final version of our CDS module. Regular contact between pharmacists and prescribing doctors may improve the quality of ADR information recorded and enable retrospective establishment of causality. In clinical practice we propose using four common major criteria to establish causality: previous description in the literature, plausible time relationship between the ADR and the start of medication administration, the absence of alternative causes, and the effect of dechallenge. Moreover, our CDS module might be improved by documenting ADRs at the level of the individual drug and drug group (e.g., penicillins).

Our CDS module supports the documentation of all ADRs, including, but not limited to allergies. In our review (chapter 3.1), we found that all 33 systems investigated alerted users to the represcription of a drug withdrawn for causing an allergy. In 7 systems, a cross-allergy also triggered an alert, and in only 5 systems did other ADRs trigger an alert. In currently available electronic hospital information systems, allergies can be documented, mostly in free text, and there is no designated place to document other ADRs. As allergies account for only a small proportion of all ADRs, we think that systems to document ADRs should not be limited to allergies.

Besides documenting ADRs to optimise pharmacotherapy at a patient level, doctors also have the responsibility to inform their national pharmacovigilance centre about clinically important adverse drug reactions, even if a well-recognised or causal link is uncertain. Spontaneous reporting remains the most important source of detecting ADRs. In the Netherlands, as in other Western countries, a growing number of ADRs are reported by patients.[17] To complement their spontaneous reporting system, the Netherlands Pharmacovigilance Centre Lareb started in 2006 its Lareb Intensive Monitoring (LIM) system, a non-interventional observational cohort study that uses patients as a source of information. The national centres are responsible for providing general information about drugs and for taking regulatory action. National centres send this information to the WHO worldwide database. This global information is analysed by the WHO Collaborating Centre for International Drug Monitoring (the Uppsala Monitoring Centre), using artificial intelligence in the form of a Bayesian Confidence Propagation Neural Network, which allows the analysis of all the variables in a report against the background information contained in the WHO database. Our electronic CDS module could, if an electronic connection can be realised, help to augment the number and improve the quality of ADRs reported to the Dutch national pharmacovigilance centre.

Information transfer between healthcare settings

Deficits in communication and information transfer at hospital discharge are common and may adversely affect patient care.[2] The systematic review by Kripalani et al. showed that few primary care doctors (12–34%) had the discharge summary available when a patient attended for the first time after discharge from hospital. Moreover, discharge summaries often lacked important information, such as discharge medications (2–40%). This is probably in part caused by the way in which hospital doctors approach hospitalisation, viewing it as a distinct period in a patient's life that ends at hospital discharge, as does responsibility for care, instead of viewing hospitalisation as a period of transition in the overall care of that patient. Furthermore, discharge summaries are probably seen as little more than a means of stamping "case closed", rather than as transition management documents.[2] We feel that hospital and primary healthcare professionals need to change their attitude to hospitalisation and not merely hand over responsibilities at the moment of hospital admission and discharge, but instead act together as a team in that patient's "health career".

In the study described in chapter 2.2, we showed that the transfer of information about ADRs is also poor, with general practitioners being informed about only 51% of ADRs that occurred during hospitalisation, and community pharmacists never being informed about ADRs that occurred in the hospital. The review reported in chapter 3.1 mainly confirms this finding with ADR information being shared with different healthcare settings in only 6 of 33 systems. To alert professionals to the undesired represcription of a drug that caused an ADR, in all settings, ADR information should be shared with all relevant healthcare providers – general practitioners, community pharmacists, other specialists, and the patient. However, it is often not enough to include this information in a discharge letter or summary to primary care professionals, as we found that ADR information was incorporated into the medical records of general practice patients in only 22% of the cases (chapter 2.2). Karapinar et al. found that sending medication overviews containing changes in pre-admission medication and/or clinical information to community pharmacists, only marginally increased the completeness of information about medication changes.[18] Lefeber et al., in a prospective intervention study, found that using a structured medication list including changed medication and reasons for changes at hospital discharge improved the quality of discharge medication information but did not improve information about medications in the information systems of general practitioners and community pharmacists.[19]

To provide optimal documentation of information about ADRs in primary care information systems, and to alert prescribers to the represcription of a drug withdrawn for causing an ADR, it seems important that all relevant information is sent electronically and directly integrated in the information systems of primary care services.

Although patients assume that essential information is shared between hospitals and primary care, this is often not the case. Moreover, these settings mostly use separate systems that do seldom link with each other.[20] Because of this, we invested considerable time and energy in gaining the cooperation of primary healthcare information services in order to connect the two systems, as reported in the study described in chapter 3.4. The reluctance on the part of software suppliers from primary and secondary care systems to "open" their systems for information exchange on ADRs might stem from a lack of experience with this phenomenon and hence the absence of a commercial interest.

In the Netherlands, as in many other countries, primary care practices, community pharmacies, hospitals, and other healthcare facilities all use electronic information systems, but these are typically different, separated, and are often purchased from different commercial information technology suppliers. These separate worlds contribute to the discontinuity of care in general and lead to problems in the continuity of pharmaceutical care in particular. Furthermore, information systems of pharmacies are primarily designed to facilitate the logistic process of medication dispension and not to document other relevant information, let alone support the optimisation of tailor-made pharmacotherapy at a patient-level by integrating these data. Healthcare professionals, software suppliers, regulatory authorities, and policymakers should start thinking beyond the boundaries of their own settings and have the responsibility to take up the challenge of approaching these separate worlds and integrating the information systems of these settings. Differences in incentives should be put aside to achieve a greater goal, the improvement of patient safety.

A national single patient record that is accessible to all healthcare providers could partly solve the problem of the discontinuity of care, pharmaceutical care included. However, plans for a national electronic health record in the Netherlands were put on hold after the Dutch senate voted against further implementation in 2011 mainly because of confidentiality and security issues. Since then, mostly regional, efforts have been made to improve the availability of data. At the moment, a national electronic infrastructure to enable healthcare professionals to request data from the medical records of patients in other institutions, is being developed, but is meeting with a lot of resistance. The oppponents of such systems consider that professional secrecy is at stake, and that the security of patient data is not yet guaranteed. Another way to provide doctors with access to a database containing vital information on patients is to use an implanted chip, such as the VeriChip approved by he United States Food and Drug Administration in 2002.[21] The use of such chips was and still is accompanied by ethical discussions on safety and privacy. The information available in a national patient record or on an implanted chip should also be accessible to the patients themselves. Ideally, patients participate in the discussion about their phar-

macotherapeutic regimen, and contribute to their own medication safety. To fulfill this participation, patients need to be well informed about the prescribed medications and, for example, about ADRs they experienced, which is a responsibility of doctors and pharmacists. However, patients may not have adequate health literacy or cognitive function to fully understand their medication regimens.[22]

Implications for research

The effectiveness of our CDS module in reducing the represcription of drugs withdrawn for causing an ADR has yet to be demonstrated, both in hospitals and in primary care. The integration of our CDS module into the information systems of all general practitioners and community pharmacists in our region would enable us to perform a randomised clinical trial. Because the number of drugs prescribed is a risk factor for ADRs, we could pre-stratify for the number of drugs being used at the time of hospital admission and, after obtaining informed consent, randomise hospitalised patients on the wards using the CDS module. No information about ADRs occurring in hospital would be sent via the CDS module to the GPs of the patients in the non-intervention group. However, it is not known when the risk of represcription of withdrawn drugs is the highest. In the study described in chapter 2.2, we investigated the represcription rate in the 6 months following hospital discharge, so to get comparable results we could choose the same time period. Represcription rates should be measured, categorized by medication class and related to the advice given by the doctors who had withdrawn the drug because of an ADR. Effort should be taken to estimate the potential harm of represcription and to find out why general practitioners or other doctors choose to ignore the prescribing advice given by the CDS module. Implementation of the CDS module in other hospitals and with sufficient financial support and manpower would enable a multicentre trial to be performed, which would provide more generalizable results.

However, regardless of whether the CDS module reduces the represcription of drugs after an ADR, it remains to be seen whether the reduction is clinically relevant, whether it is beneficial to patients. It is difficult to choose endpoints that represent relevant beneficial effects and for which statistically significant differences can be detected in a practically realisable study design. Possible endpoints are reduction in repeat ADRs, reduction in requests for medical help, reduction in (drug-related) hospital admissions, or improvement in (health-related) quality of life. Because the elderly population (which is at highest risk) is heterogeneous, it will probably be difficult to demonstrate statistically significant changes in clinically relevant endpoints. Moreover, it is often dificult to measure quality of life in individuals with comorbid conditions, given longitudinal changes in this outcome.

Preventing the represcription of drugs that caused an ADR is only a minor aspect of pharmacotherapy optimisation. Elderly patients are most vulnerable to medication errors and medication-related problems. Patterson et al. reviewed 10 studies that described interventions to improve the appropriate use of polypharmacy for older people.[23] The authors of this Cochrane review stated that the evidence obtained from the combination of the studies was rather weak, and that it was unclear whether interventions to improve appropriate polypharmacy, such as pharmaceutical care, resulted in a clinically significant improvement. There is uncertainty about the effect of such interventions on hospital admissions and adverse drug events, and it could be argued that these are the critical outcomes for patients. However, the interventions appeared to be logical and beneficial in terms of reducing inappropriate prescribing and in reducing some medication-related problems, as well as in encouraging the proper use of medications and in promoting general health and education.

We propose that the CDS module to prevent the represcription of drugs after an ADR should be integrated in a multifactorial intervention to optimise pharmaceutical care (e.g., comprising critical medication reconciliation by pharmacists in collaboration with physicians at hospital admission and discharge, patient and healthcare professional education, and optimisation of communication pharmaceutical information between different healthcare settings), the effect of which will have to be demonstrated in future studies.

Implications for clinical practice

In this thesis, we confirmed that ADRs are relatively common (in the study reported in chapter 3.3 14% of hospitalised patients experienced one or more ADRs) and that the represcription of drugs withdrawn after an ADR is also common. Doctors and pharmacists should be constantly vigilant to the development of ADRs, in particular when prescribing high-risk drugs to vulnerable elderly patients, and document information on ADRs in a structured way. Until this information is automatically integrated with primary care information systems, hospital physicians should mention ADRs in their discharge letters to general practitioners and on every prescription or medication overview that is sent to community pharmacists. Information about ADRs that are detected and documented in primary care should also be sent to hospital doctors. To further improve the continuity of pharmaceutical care, healthcare professionals, policy makers, and information technology companies should take their responsibility and collaborate to bridge technical issues and differences in content. The further development of a national electronic health record deserves our support, since patient safety issues should outweigh commercial incentives and privacy concerns.
In this thesis, we focussed on ADRs, but the approach of improved and structured documentation and communication should not be limited to ADRs, but should be

broadened to at least pharmacotherapy in general. The first step of medication reconciliation is to assemble a list of medicines the patients really uses. This step is ideally taken at every patient consultation, and especially at the moment of hospitalisation. The effort required to obtain an accurate list may be substantial, including communication with community pharmacists, outpatient physicians, family members and caregivers, and time spent reviewing pill boxes with patients.[24] During hospitalisation, scrupulous medication reconciliation is needed, often resulting in multiple changes. Hospital discharge is another critical moment and much attention should be payed to the discharge medication overview. This overview should not only contain a list of prescribed drugs, but also indicate what changes were made in the medication regimen, the reasons for those changes, and advices for future prescriptions.

It remains a great challenge to provide patients, and especially vulnerable elderly patients, with the best possible pharmacotherapy, to find the balance that favours the beneficial effects of drugs. It requires the concerted effort and close cooperation of patients and all professionals involved.

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5

Summary and acknowledgements

5.1 Summary

Adverse drug reactions in individual patient care: documentation and prevention of represcription

Adverse drug reactions (ADRs) are common in hospitalised patients and also frequently lead to hospital admission, especially in the elderly. Several studies have shown that a considerable part of these drug-related problems are preventable. Preventable ADRs may be the result of a drug treatment procedure inconsistent with current knowledge of good medical practice, for example the prescription of a drug when its use is contraindicated. Another important cause of preventable ADRs is the represcription of a drug that was previously withdrawn because it caused an allergy or another ADR in the patient.

The main objectives of this thesis were to
a) to investigate documentation of reasons for medication discontinuation and ADRs and to what extent drugs that have been withdrawn because of an ADR are represcribed, and
b) to investigate methods to prevent the represcription of withdrawn drugs, including the development and implementation of an electronic clinical decision support module and assessment of its feasibility.

Chapter 1

Chapter 1 provides a general introduction uncluding objectives and outline of this thesis.

Chapter 2

Chapter 2 of this thesis describes the documentation of reasons for discontinuation of medication and ADRs, and frequency of represcription of drugs withdrawn because they caused an ADR.

In **chapter 2.2** we investigated the frequency of ADRs, communication thereof to general practitioners and community pharmacists, and frequency of represcription after ADR. In a descriptive study in 215 hospitalised patients geriatric wards of two hospitals in the Netherlands, 104 ADRs of at least possible causality were recorded in 69 patients. Only 51% of ADRs were communicated to general practitioners, and only 22% of the ADRs mentioned in discharge letters were incorporated into general practitioners' patient files. Moreover, none of the community pharmacists were informed about ADRs during hospitalisation. The rate of represcription of medication withdrawn during hospitalisation because of an ADR was 27% in the first six months after discharge.
Poor documentation and communication probably contributed to this high rate of represcription. The represcription of medication to which patients previously experi-

enced an allergic reaction or another ADR can only be prevented if ADRs (including allergies) and other reasons for medication discontinuation are adequately documented. In **chapter 2.1** we studied the documentation of reasons for medication discontinuation in 400 hospitalised (geriatric and internal medicine) patients in two hospitals. We found that reasons for medication discontinuation were not reported in as many as 40% of cases. Most frequently documented reasons for discontinuation were 'no longer indicated' (27.5%), 'palliation' (9.8%), 'contraindication' (9.1%), and 'ADR' (5.2%).
In **chapter 2.3** we describe three patients who experience recurrence of a serious ADR due to represcription of a withdrawn medication. These cases highlight the need for a system to prevent the undesirable represcription of medications withdrawn because of an ADR. We propose an electronic system and describe its essential elements to improve the documentation and communication of ADRs and to optimise alerting in the event of represcription, independent of the healthcare setting.

Chapter 3

Chapter 3 describes methods to prevent the represcription of withdrawn drugs, including the development and implementation of an electronic clinical decision support module and assessment of its feasibility.

Chapter 3.1 provides a systematic review describing existing systems that can prevent unwanted represcription of drugs withdrawn because of an ADR. Of 45 studies describing 33 systems (28 electronic and five non-electronic), 12 studies compared pre- and post-intervention periods or wards with and without intervention. Of these, seven studies showed a reduction in represcription after ADR. The seven studies that reported benficial results concerned five systems. Surprisingly, these systems had no striking shared characteristics.
We developed an electronic clinical decision support module that forces physicians to document reasons for medication discontinuation and alerts physicians to unwanted represcription after ADR. We describe this module that consists of two guidelines in **chapter 3.2.** The first guideline determines discontinuation of medication and forces physicians to choose a reason for medication discontinuation using a pop-up window. If the reason for discontinuation is not an ADR, the user is guided back to the electronic prescription system. If the reason for discontinuation is an ADR the user must select a description of the ADR (using a query function in a translated MedDRA-database), indicate whether the ADR is serious, and indicate an advice to physicians that plan to represcribe the same drug to the same patient. The second guideline alerts the represpription of a drug earlier withdrawn because of an ADR. We show preliminary results after implementation on a 20-bed geriatric ward.
The module was then also implemented on the internal medicine ward of the same hospital, results after implementation and acceptability are described in **chapter 3.3**.

In 830 hospitalisations 3828 medications were discontinued, with most frequently documented reasons being 'no longer indicated' (55.1%) and 'ineffective' (12.9%). ADR was indicated as reason for discontinuation 125 times (3.3%), and 31 alerts to represcription of a drug previously withdrawn because of an ADR appeared. The advices given by the alerts to represcription after ADR were followed in 27/31 cases (87%). Most of the users considered it relatively easy to incorporate entering the data for the reason for medication discontinuation into their workflow.
To prevent represcription outside the hospital the module was further developed to integrate information on ADRs into the information system of primary care centers.
In **chapter 3.4** we describe the connection between these systems and its feasibility, as assessed by general practitioners. Several barriers to software integration were enountered. The general practitioners considered the integration very useful, easy to use, and with few barriers for acceptance.

Chapter 4

Chapter 4 provides a general discussion of the results of the individual studies in this thesis placed in a broader perspective. Three topics are discussed: detection of ADRs; documentation of ADRs; and information transfer between healthcare settings. In addition, implications for further research and clinical practice are discussed.
It remains a great challenge to provide patients, and especially vulnerable elderly patients, with the best possible pharmacotherapy, and to find the balance that favours the beneficial effects of drugs. It requires the concerted effort and close cooperation of patients and all professionals involved.

5.2 Samenvatting

Samenvatting

Het gebruik van geneesmiddelen gaat frequent gepaard met bijwerkingen. Bijwerkingen leiden regelmatig tot ziekenhuisopname, met name bij ouderen. Meerdere studies hebben aangetoond dat een groot deel van deze bijwerkingen potentieel te vermijden is. Vermijdbare bijwerkingen kunnen het gevolg zijn van een behandeling die niet strookt met de huidige stand van zaken van medisch wetenschappelijke kennis, bijvoorbeeld het voorschrijven van een geneesmiddel terwijl dit gecontra-indiceerd is. Een andere oorzaak van vermijdbare bijwerkingen is het opnieuw voorschrijven van een geneesmiddel aan een patiënt, bij wie dat geneesmiddel eerder gestaakt is vanwege een bijwerking.

De doelen van dit proefschrift waren

a) documentatie van redenen van staken van geneesmiddelen, inclusief bijwerkingen, te onderzoeken, en na te gaan hoe vaak geneesmiddelen die eerder gestaakt werden vanwege een bijwerking opnieuw aan dezelfde patiënt werden voorgeschreven, en

b) onderzoek van methoden om represcriptie van eerder gestaakte geneesmiddelen te voorkomen, inclusief de ontwikkeling en implementatie van een elektronische beslissingsondersteunende module, de resultaten ervan en beoordeling van de uitvoerbaarheid van deze module.

Hoofdstuk 1 bevat een algemene introductie inclusief achtergrond, doelen en korte beschrijving van het onderzoek gepresenteerd in dit proefschrift.

Hoofdstuk 2

Hoofdstuk 2 van dit proefschrift beschrijft de documentatie van redenen van staken van geneesmiddelen, inclusief bijwerkingen, en de frequentie van represcriptie van geneesmiddelen die eerder gestaakt werden vanwege een bijwerking.

In **hoofdstuk 2.2** hebben we onderzocht hoe vaak bijwerkingen voorkwamen bij opgenomen geriatrische patiënten, of de informatie over deze bijwerkingen naar huisartsen en openbare apothekers werd doorgegeven, en hoe vaak geneesmiddelen opnieuw werden voorgeschreven na een bijwerking. In deze studie bij 215 opgenomen patiënten op twee afdelingen klinische geriatrie werden 104 bijwerkingen vastgesteld bij 69 patiënten. Slechts 51% van deze bijwerkingen werden gemeld in de ontslagbrief naar de huisarts, slechts 22% daarvan werd door de huisartsen verwerkt in hun eigen systeem. Openbare apothekers werden nooit geïnformeerd over de opgetreden bijwerkingen in het ziekenhuis. Van de geneesmiddelen die vanwege een bijwerking werden gestaakt, werd 27% binnen een half jaar opnieuw voorgeschreven aan dezelfde patiënt.
Aan deze hoge frequentie van represcriptie droegen waarschijnlijk slechte documentatie en communicatie bij. Eén van de voorwaarden voor de preventie van represcriptie

van geneesmiddelen die eerder een allergie of andere geneesmiddelenbijwerking veroorzaakten is dat bijwerkingen en andere redenen voor het staken van geneesmiddelen goed worden vastgelegd.
In **hoofdstuk 2.1** hebben we de documentatie van redenen voor het staken van geneesmiddelen onderzocht bij 400 opgenomen patiënten op afdelingen interne geneeskunde en klinische geriatrie in twee ziekenhuizen. Bij 40% van alle gestaakte geneesmiddelen was daarvoor in het dossier geen reden vastgelegd. De vaakst vastgelegde redenen voor staken waren 'niet langer geïndiceerd' (27,5%), 'palliatief beleid' (9,8%), 'contra-indicatie' (9,1%), en 'bijwerking' (5,2%).
In **hoofdstuk 2.3** beschrijven we drie patiënten die een ernstige bijwerking opnieuw ervaren door represcriptie van een middel dat bij hen eerder gestaakt werd vanwege dezelfde bijwerking. Deze patiënt-beschrijvingen benadrukken het belang van een systeem om represcriptie na een bijwerking te voorkomen. We beschrijven een elektronisch systeem dat de documentatie en communicatie van bijwerkingen kan verbeteren en kan bewaken op herstart in of buiten het ziekenhuis.

Hoofdstuk 3

In hoofdstuk 3 van dit proefschrift beschrijven we methoden om represcriptie van eerder gestaakte geneesmiddelen te voorkomen, inclusief de ontwikkeling en implementatie van een elektronisch beslissingsondersteunende module, en de beoordeling van de resultaten en uitvoerbaarheid van deze module.

In **hoofdstuk 3.1** geven we een overzicht van bestaande systemen die de ongewenste represcriptie na een bijwerking kunnen voorkomen. De 45 gevonden studies beschrijven 33 systemen (28 elektronische en 5 niet-elektronische). Twaalf van deze studies hebben onderzocht of de frequentie van represcriptie na een bijwerking daalde door afdelingen met en zonder het systeem, of periodes voor en na implementatie van het systeem te vergelijken. Zeven van deze 12 studies lieten een daling zien van represcriptie na een bijwerking. Deze zeven studies gingen over vijf systemen, die geen opvallende overeenkomsten hebben. We hebben een elektronische beslissingsondersteunende module ontwikkeld die artsen dwingt om redenen voor het staken van geneesmiddelen vast te leggen en artsen waarschuwt bij represcriptie na een bijwerking.
We beschrijven deze module die uit twee richtlijnen bestaat in **hoofdstuk 3.2**. De eerste richtlijn signaleert het staken van een geneesmiddel in het elektronisch voorschrijfsysteem en laat op het moment van staken een pop-up zien waarin de arts wordt gevraagd een reden voor staken te kiezen uit een gepresenteerde lijst. Als de gebruiker een andere reden dan een bijwerking aanklikt, wordt de gebruiker direct terug geleid naar het elektronisch voorschrijfsysteem. Als de gebruiker aangeeft dat de reden voor staken een bijwerking betreft, moet de gebruiker, met behulp van een zoekfunctie in een vertaalde MedDRA-database, aangeven wat voor verschijnsel is opgetreden.

Daarnaast wordt de gebruiker gevraagd aan te geven of de bijwerking ernstig is en wat zijn/haar advies is aan een arts die hetzelfde middel aan dezelfde patiënt wil voorschrijven. De tweede richtlijn zorgt ervoor dat een waarschuwing verschijnt op het moment dat een middel, dat eerder is gestaakt vanwege een bijwerking, opnieuw aan dezelfde patiënt voorgeschreven wordt. In dit hoofdstuk beschrijven we tevens de eerste resultaten van het werken met deze module op de afdeling klinische geriatrie van het Catharina Ziekenhuis.
De module werd daarna ook geïmplementeerd op de afdeling interne geneeskunde van hetzelfde ziekenhuis, en in **hoofdstuk 3.3** beschrijven we de resultaten van het werken met deze module op deze twee afdelingen en een evaluatie van het gebruik van de module door de gebruikers. Tijdens 830 ziekenhuisopnames werden 3828 medicijnen gestaakt. De meest voorkomende redenen voor staken waren 'niet langer geïndiceerd' (55,1%) en 'onvoldoende effect' (12,9%). 'Bijwerking' werd 125 keer (3,3%) aangegeven als reden voor staken en 31 keer verscheen een waarschuwing voor represcriptie na een bijwerking. De adviezen die werden gegeven in deze waarschuwing werden in 27 van de 31 (87%) gevallen gevolgd. De meeste gebruikers vonden dat het vastleggen van een reden voor staken met behulp van deze module gemakkelijk in te passen was in hun workflow.
Om represcriptie na een bijwerking niet alleen binnen het ziekenhuis te voorkomen, maar ook daarbuiten (in de eerste lijn) is de module verder ontwikkeld om informatie over bijwerkingen die in het ziekenhuis optraden te integreren in het informatiesysteem van eerste lijns gezondheidscentra. In **hoofdstuk 3.4** beschrijven we deze koppeling tussen de beslissingsondersteunende module en het informatiesysteem van eerste lijns gezondheidscentra en de problemen die we tegenkwamen bij het tot stand brengen van deze koppeling. Daarnaast beschrijven we de resultaten van een onderzoek naar de mening van huisartsen over deze koppeling. Na een demonstratie van de resultaten van deze koppeling gaven de huisartsen aan deze koppeling zeer nuttig te vinden, en gemakkelijk in gebruik.

Hoofdstuk 4

Tenslotte omvat hoofdstuk 4 een algemene discussie waarbij de resultaten van de individuele onderzoeken in dit proefschrift in een breder perspectief worden geplaatst. Drie onderwerpen worden besproken: de detectie van bijwerkingen, de documentatie van bijwerkingen, en de informatieoverdracht tussen verschillende gezondheidszorgsettings. Tot slot worden klinische implicaties en mogelijkheden voor toekomstig onderzoek besproken.
Het is een grote uitdaging om patiënten, in het bijzonder kwetsbare oudere patiënten, optimaal farmacotherapeutisch te behandelen waarbij een gunstige balans gevonden wordt tussen voor- en nadelige effecten van geneesmiddelen. Dit vraagt een grote gezamenlijke inspanning en goede onderlinge samenwerking van patiënten en alle betrokken professionals.

5.3 Dankwoord

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Nadat ik als klinisch geriater ben gaan werken in het Catharina Ziekenhuis hebben we mijn promotietraject een doorstart kunnen laten maken, uiteindelijk leidend tot een promotie aan de Technische Universiteit Eindhoven. Voor dit enigszins onconventionele promtotietraject heb ik mogen werken met het, in mijn ogen, ideale promotieteam: prof. dr. Erik Korsten, prof. dr. Toine Egberts, dr. Paul Jansen, en dr. René Grouls.
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Dit promotieonderzoek is het resultaat van een samenwerking tussen het Catharina Ziekenhuis, de Technische Universiteit Eindhoven en het Universitair Medisch Centrum Utrecht. Daarnaast werkten we samen met onder andere Medecs, Stichting Gezondheidscentra Eindhoven, Pharmapartners en andere instellingen.
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5.4 List of co-authors

Co-authors of manuscripts presented in this thesis

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5.5 List of publications

Publications related to this thesis

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(Submitted)

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5.6 About the author

About the author

Carolien van der Linden was born in Eindhoven on 10-10-1972, and grew up in Aalst-Waalre. After graduating from Sint Joriscollege in Eindhoven in 1991, she studied medicine at the University of Leuven in Belgium for one year. She continued her medicine study at Radboud University Nijmegen, where she graduated in 1999. Subsequently, she worked in Hilversum Hospital at the geriatric ward for one year. In 2000 she started her training in geriatrics. She fulfilled her residency in internal medicine at Hilversum Hospital, in geriatric medicine at the University Medical Center Utrecht, in old age psychiatry at the Institute for Mental Healthcare Oost-Brabant in Oss. She was registered as geriatrician in 2006. She has a special interest in gerontopharmacology and after a fellowship programme at the University Medical Center Utrecht she was registered as clinical pharmacologist in 2006.
The first preparations for the research presented in this thesis were made during her residency at the University Medical Center Utrecht, working under supervision of dr Paul Jansen. From August 2006 she has worked as a geriatrician at Catharina Hospital in Eindhoven where she has continued the research presented in this thesis from 2008. Since 2012 she has been a trainer of medical specialist trainees in geriatric medicine.

Notes