Appropriate prescribing for older people

A.C. Drenth-van Maanen

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Appropriate prescribing for older people

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(met een samenvatting in het Nederlands)

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Prof.dr. A.C.G. Egberts

Copromotoren

Dr. P.A.F. Jansen

Dr. R.J. van Marum

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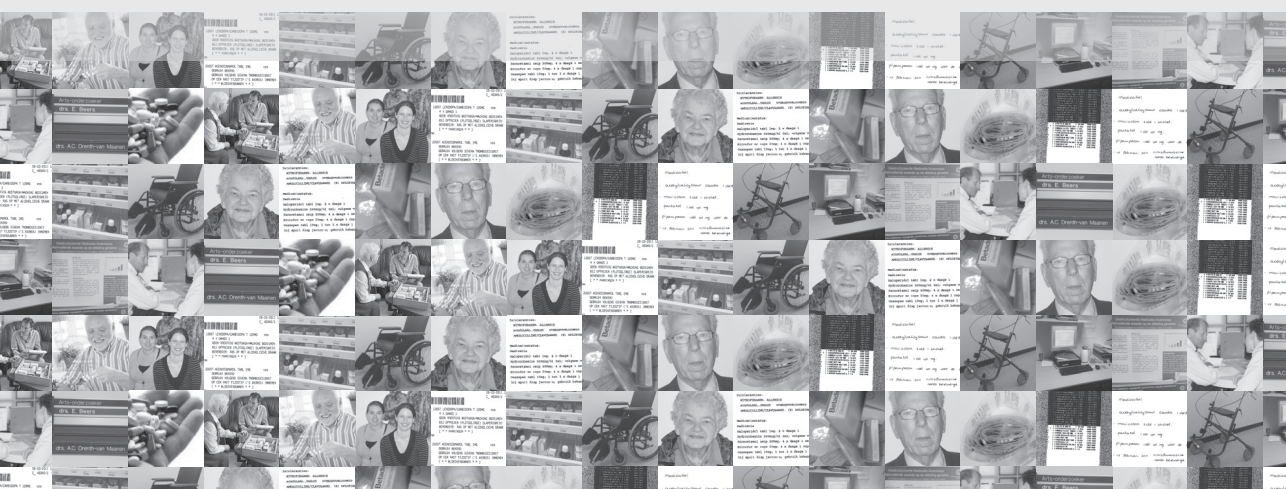
General introduction



Background

Appropriate prescribing refers to the results of a process of pharmacotherapeutic decision-making that maximises net individual health gains within society's available resources.[1] This definition implies that patient outcomes determine whether prescribing has been appropriate or not. This differentiates appropriate prescribing from rational prescribing which refers to the process of evidence based prescribing decision making.[2] If, for example, a patient develops a gastro-intestinal bleeding on ibuprofen, prescribed for gout in the big toe, the prescription was rational but turned out to be inappropriate for this individual patient.
The frequency of inappropriate prescribing, where the benefit-risk ratio results in negative patient outcomes, increases in cases of irrational prescribing. In 2004, Pirmohamed et al. showed that in England 6.5% of hospital admissions were related to an adverse drug reaction.[3] In 2008, Leendertse et al. published the results of a similar study in the Netherlands, the HARM study.[4] They found that 5.6% of all unplanned hospital admissions were medication-related. Almost half (46%) of these admissions were potentially preventable. The mean age of patients with a potentially medication related hospital admission was 70 years.

Susceptibility of older people for inappropriate prescribing

Several risk factors for medication-related hospital admissions were identified from the HARM study: impaired cognition, polymorbidity (≥4 diseases), dependent living situation, polypharmacy (≥5 medications, chronically used), impaired renal function, and nonadherence to medication regimen. The prevalence of all these risk factors is highest among older people (Figure 1). For example, among older people, the use of polypharmacy occurs frequently. In 2009, 39% of the Dutch population between 65 and 74 years old, and more than half of all people over 75, used five or more medications and almost 20% of people aged 75 years or above were prescribed ten or more different medications.[5] Although polypharmacy is often indicated, it makes it more complex for physicians to balance the benefit-risk ratio on the individual patient level, since outcomes of prescribing are more difficult to predict due to increased frailty, polymorbidity, and interactions. Causality of adverse events is also more difficult to determine in cases of polypharmacy. Furthermore, in patients receiving polypharmacy, often multiple prescribers are involved, who are insufficiently familiar with each other's prescribed medications.[6] Older people are also at increased risk of inappropriate prescribing because pharmacokinetics, pharmacodynamics, safety, and efficacy change over time and may vary significantly between individuals of the same age. For example, impaired renal function, which is present in up to 35.8% of people aged 64 years or older, compared to 7.2% in people aged 30 or older,[7] affects the

pharmacokinetics of many medications significantly. In case of impaired renal function, dose adjustments are required in medications that are excreted mainly by the kidneys in order to prevent accumulation of these medications or their active metabolites. Unfortunately, accurate detection of impaired renal function is difficult in older people. Serum creatinine measurements are traditionally used to assess renal function.[8] However, since creatinine is a waste product of muscle mass, it's reliability declines in people with a deviating muscle mass, as is the case in older, frail, malnourished or obese people. Furthermore, physicians often have insufficient knowledge of which medications require dose adjustments in case of impaired renal function.[9-18]

Finally, older people frequently transfer between health care settings. Each transition creates an additional risk for medication errors due to conflicting information between different sources and/or insufficient communication between health care providers and patient. Several efforts have been accomplished to implement transitional pharmaceutical care programs to improve continuity of pharmaceutical care between health care settings.[19-25]

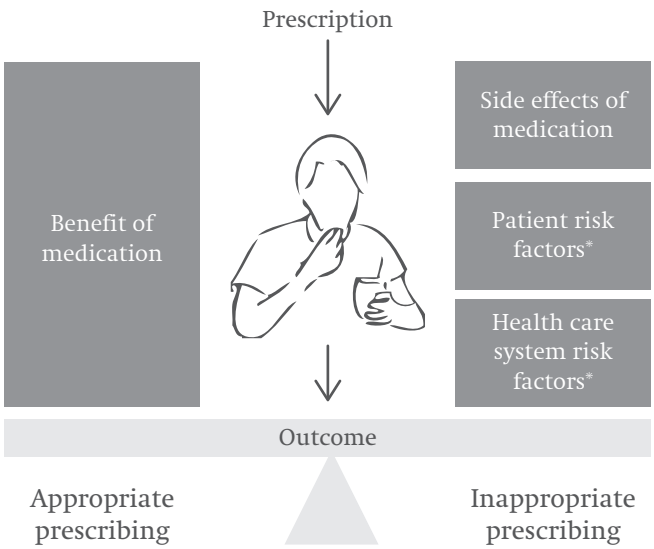


Figure 1 Susceptibility of older people for inappropriate prescribing

*Patient risk factors, e.g.:
- dependent living situation
- polypharmacy
- nonadherence
- altered pharmacokinetics and pharmacodynamics:
  - impaired renal function
  - polymorbidity
  - impaired cognition
  - ....
- frequent falls
- slow walking speed
- frailty
- ....

**Health care system risk factors, e.g.:
- transfer between health care settings:
- insufficient pharmacommunication
- prescribing errors
- dispensing errors
- administration errors
- education
- ....

Another aspect that differentiates prescribing for older people from prescribing for younger people is the therapeutic aim. A therapeutic aim is the definition of the desired outcome and the specification of when this outcome should be achieved. Therapeutic aims shift from mainly curative in younger patients to other aims, such as life prolongation, maintenance of current state or function (quality of life), and palliative care in older patients. When formulating therapeutic aims for older patients, physicians have to consider the remaining life expectancy of the patient. To determine if a patient's life expectancy is long enough that he or she would benefit from a particular medication, the amount of time until benefit of this medication will be achieved has to be considered.[26] For medications used for primary or secondary prevention it may take years before benefit is achieved and therefore treatment with them might not be started or might even be discontinued in patients with a limited life expectancy. Shared decision making among physicians, patients and/or caregivers about therapeutic aims is important when deciding whether to stop, start, alter, or continue a medicine for an older patient. Thus, for an individualised approach to a patient's treatment, the physician does not only need to consider practice guidelines, but also the patient's life expectancy, the time until benefit of medications, and the patients' wishes. For example, the patient may wish to avoid invasive procedures, and his priority may be to live as long as possible in his home. In that case, the therapeutic aims may be maintenance of current state or function, and treatment of acute illness (such as treatment of pneumonia). As physicians have to consider all of these aspects when prescribing medications for older patients, appropriate prescribing for older people, especially frail older people with multimorbidity, is challenging, yet important.

Appropriate prescribing

Appropriate prescribing can be achieved through a continuous process of shared decision making with the patient, which consists of six steps (Figure 2):[27]

1) Definition of the patient's problem
   A patient usually presents a complaint or a problem. Making the correct diagnosis is important to start the appropriate treatment.
2) Specification of the therapeutic aims
   Before choosing a treatment the therapeutic aims must be specified. For example, when a patient has been diagnosed with colon cancer and an operation would be the best treatment, but the patient will probably suffer greatly from the operation, the physician and patient may choose to decide against the operation and choose for symptomatic treatment instead, in order to maintain functionality of the patient as long as possible.
3) Suitability of the selected intervention(s)
   The next step is to investigate whether and which non-pharmacological interventions are appropriate, and if a pharmacological intervention is necessary. If that is the case, a physician needs to make an evidence based selection of a medication, for example based on treatment guidelines. However, guidelines offer medication advice appropriate for the general population. Therefore, the physician subsequently needs to check if this medication advice is suitable for the individual patient. Suitability can be determined based on three aspects: (1) Are the active substance and the dosage form suitable for this patient? (2) Is the standard dosage schedule suitable? And (3) is the standard duration of treatment suitable? For each aspect, the medication can be checked for effectiveness and safety. A check on effectiveness includes a review of the drug indication and convenience of the dosage form. Safety relates to contraindications and possible interactions.
4) Writing of prescriptions and updating the medication list
   It is important to document all changes to the medication regimen and adjust the patient's medication list, in order for it to be readily available for the patient and other involved health care providers.
5) Informing the patient
   Patients need information, instructions, and warnings to provide them with knowledge to accept and follow the treatment and to acquire the skills to take the medication appropriately.
6) Monitoring the treatment outcome
   Monitoring the treatment outcome enables the physician to determine whether the initiated treatment really was appropriate, or whether additional action is required. Monitoring can be performed passively, by explaining the patient what to do if the treatment is not effective, inconvenient, or if side effects

occur. Monitoring can also be performed actively by making an appointment with the patient to determine whether the treatment has been appropriate. Ideally the process of appropriate prescribing is a continuous cycle.

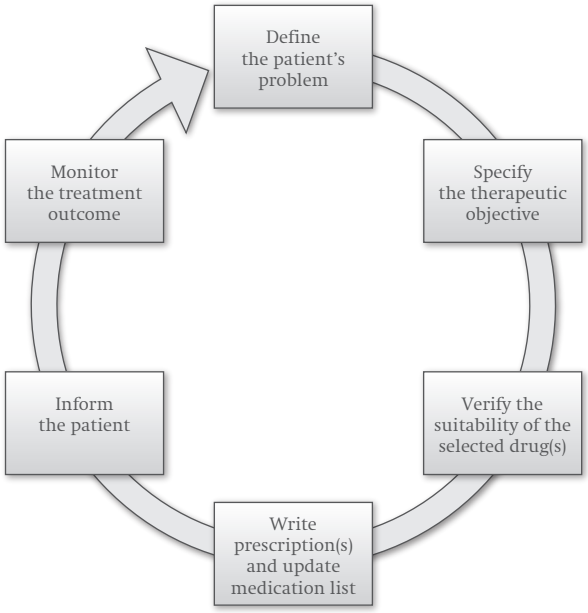


Figure 2 Appropriate prescribing

Objective of this thesis

The objective of this thesis is first to describe the frequency and nature of risk factors for inappropriate prescribing, with a focus on polypharmacy, transitional pharmaceutical care and impaired renal function, and second to develop and investigate the effectiveness of interventions to improve appropriate prescribing for older people.

Outline of this thesis

The second chapter of this thesis concentrates on polypharmacy. It describes the Prescribing Optimization Method (POM), a tool to improve appropriate prescribing, and summarises the main problems recognised with appropriate prescribing, especially in older patients receiving polypharmacy. The aim of this chapter is to

determine if the POM, applied to case histories of older patients with polypharmacy, improves appropriate prescribing by general practitioners.
The third chapter focuses on transitional pharmaceutical care. Patient transitions between health care sectors are a well-known risk factor for medication errors. The chapters 3.1 and 3.2 have a focus on transitional pharmaceutical care at hospital admission. Chapter 3.1 investigates how many discrepancies can be revealed through Structured History taking of Medication use (SHIM) compared to usual care medication history taking at hospital admission of geriatric patients, and if these discrepancies are clinically relevant. In Chapter 3.2 the same research question is investigated in another setting, i.e. an old age psychiatric clinic. Chapters 3.3 and 3.4 focus on transitional pharmaceutical care at hospital discharge. Discrepancies between intended medication use at hospital discharge and actual medication use by the patient may result from miscommunication between the hospital physician and the patient, and/or from miscommunication between the hospital physician and the next health care provider. Chapter 3.3 studies the effect of a discharge medication intervention, which combines patient counselling at discharge with a written structured medication overview for both patient and the next health care providers, on the incidence and nature of discrepancies between the intended medication use at discharge and the actual medication use by the older patient. Chapter 3.4 investigates whether this intervention improves the implementation of changes to the patient files of general practitioners and community pharmacists.
The fourth chapter has an emphasis on impaired renal function. In chapter 4.1 the objective is to investigate which method can be used best to identify impaired renal function in older people. Therefore, the most widely used formulas to estimate renal function (Cockcroft-Gault, Modification of Diet in Renal Disease (MDRD), and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI)) are compared to one another using sinistrin clearance as the criterion (reference) standard in a sample of older patients. Then, in chapter 4.2 the objective is to determine the prevalence, potential clinical relevance, and determinants of adherence with the Dutch dosing guideline in patients with impaired renal function discharged from the hospital.
Finally, in the general discussion the results of the different studies are discussed and recommendations for further research and improving appropriate prescribing for older people are provided.

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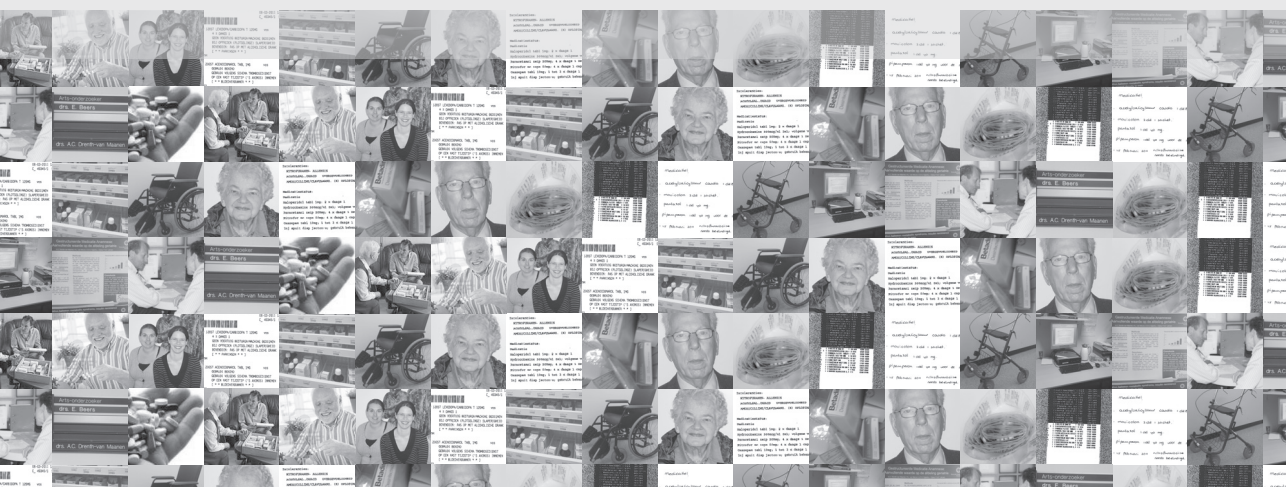
2

Prescribing for older people receiving polypharmacy



2.1

Prescribing Optimization Method for Improving Prescribing for Elderly Patients Receiving Polypharmacy

Results of Application to Case Histories by General Practitioners

A. Clara Drenth-van Maanen, Rob J. van Marum, Wilma Knol, Carolien M.J. van der Linden and Paul A.F. Jansen

Drugs and Aging, 2009, 26, 1170-229; 8, 687-701

Abstract

Background: Optimizing polypharmacy is often difficult, and critical appraisal of medication use often leads to one or more changes. We developed the Prescribing Optimization Method (POM) to assist physicians, especially general practitioners (GPs), in their attempts to optimize polypharmacy in elderly patients. The POM is based on six questions: (i) is undertreatment present and addition of medication indicated; (ii) does the patient adhere to his/her medication schedule; (iii) which drug(s) can be withdrawn or which drugs(s) is (are) inappropriate for the patient; (iv) which adverse effects are present; (v) which clinically relevant interactions are to be expected; and (vi) should the dose, dose frequency and/or form of the drug be adjusted?

Objective: The aim of this study was to evaluate the usefulness of the POM as a tool for improving appropriate prescribing of complex polypharmacy in the elderly.

Methods: Forty-five GPs were asked to optimize the medication of two case histories, randomly chosen from ten histories of geriatric patients admitted to a hospital geriatric outpatient clinic with a mean −SD of 7.9 − 1.2 problems treated with 8.7 − 3.1 drugs. The first case was optimized without knowledge of the POM. After a 2-hour lecture on the POM, the GPs used the POM to optimize the medication of the second case history. The GPs were allowed 20 minutes for case optimization. Medication recommendations were compared with those made by an expert panel of four geriatricians specialized in clinical pharmacology. Data were analysed using a linear mixed effects model.

Results: Optimization was significantly better when GPs used the POM. The proportion of correct decisions increased from 34.7% without the POM to 48.1% with the POM ($p = 0.0037$), and the number of potentially harmful decisions decreased from a mean −SD of 3.3 − 1.8 without the POM to 2.4 − 1.4 with the POM ($p = 0.0046$).

Conclusion: The POM improves appropriate prescribing of complex polypharmacy in case histories.

Background

Incidence of Polypharmacy

Long-term use of medication is often associated with the prescription of more than one medicine. In the Netherlands, 17% of all people who take medication long term take more than five different drugs.[1] Half of these patients are aged >70 years. In general, elderly individuals take 3- to 4-fold more medications than the general population. These drugs are mainly prescribed for diabetes mellitus, hypertension and cardiovascular disease.

Consequences of Polypharmacy

Polypharmacy is difficult to monitor, especially in the elderly, because of pharmacokinetic and pharmacodynamic changes. Age-related pharmacokinetic changes are found in the following areas:[2]

1. Absorption: various studies of the effect of aging on drug absorption show conflicting results. Therefore, from a clinical perspective, age-related changes in absorption are not of significant importance.
2. Distribution: geriatric patients have relatively more body fat than younger adults. This leads to an altered distribution of drugs over the different body compartments, resulting in higher plasma concentrations of hydrophilic drugs and delayed breakdown of lipophilic drugs.
3. Metabolism: aging is associated with decreased first-pass metabolism, probably because of a reduction in liver mass and blood flow. Consequently, the bioavailability of drugs undergoing extensive first-pass metabolism can be significantly increased. However, pro-drugs need to be activated in the liver and such activation might be slowed in the elderly.
4. Excretion: reduction in renal function affects the clearance of many water-soluble drugs. This is particularly important in the case of drugs with a narrow therapeutic index, such as digoxin and lithium.

The most important pharmacodynamic change is altered receptor function, mainly because of a decreased number of receptors. This results in higher sensitivity for drugs acting on the CNS, such as antidepressants and antipsychotics.[2]

Although polypharmacy is frequently unavoidable, the study performed by Frazier[3] showed that polypharmacy is a significant risk factor for hospitalization. The HARM (Hospital Admissions Related to Medication) study[4] showed that, in the Netherlands, 5.6% of all acute hospital admissions and twice as many acute hospital admissions for elderly individuals are the result of medication-related problems.

Polypharmacy is associated with a number of problems. First, the risk of adverse events increases exponentially with the number of drugs taken.[4-6] However,

polypharmacy is often necessary to prevent adverse events (e.g. patients taking NSAIDs may also need to take drugs that protect their stomach against ulcers). A European study of 1601 elderly patients from six countries showed that 46% of patients had at least one potential clinically significant drugdrug interaction.[5] Other possible interactions the physician must be aware of are drug-disease, drug-food, drug-alcohol, drug-herbal product and drug-nutritional status interactions. [6] Secondly, polypharmacy is associated with underprescribing.[7] More than 40% of elderly patients are undertreated,[8] with the main areas of undertreatment being heart failure and myocardial infarction, osteoporosis, atrial fibrillation, pain and depression.[9] Thirdly, adherence decreases as the number of daily doses increases: adherence to once-daily administration regimens is 79%, compared with 69% for twice-daily administration regimens, 65% for three-times daily administration regimens and 51% for four times daily administration regimens. [10] Approximately 20–50% of all patients are non-adherent to medical therapy.[11] Elderly patients are adherent to approximately three out of four of their medications, a rate that is similar to that in younger patients.[11-13] Fourthly, use of inappropriate medications increases sharply as the total number of medications to be taken increases.[14] This overtreatment increases the risk of morbidity and mortality in the vulnerable elderly.

Interventions to Improve Polypharmacy and its Harmful Effects

The growing population of elderly patients makes it important to optimize polypharmacy to prevent adverse drug reactions (ADRs), harmful interactions, overtreatment, undertreatment and non-adherence. Several interventions have been developed to improve prescribing. Beers and colleagues[15-17] developed criteria for defining groups of drugs or specific medications that should be regarded as ''potentially inappropriate'', but they were interested in reducing the prescription of potentially inappropriate medication rather than in addressing the problems of polypharmacy. Educating prescribers in appropriate prescription is effective but time consuming.[18] Hanlon et al.[19] developed the Medication Appropriateness Index (MAI) to measure the appropriateness of prescribing for elderly patients in relation to ten criteria for each medication prescribed. Although the MAI is useful for identifying ADRs, drug-drug interactions and overtreatment, it does not detect undertreatment. It is also very time consuming to use. The Screening Tool to Alert physicians to the Right Treatment (START) was developed to detect prescribing omissions but not the other problems mentioned previously.[20,21] Underprescribing can also be detected with the Assessing Care Of the Vulnerable Elder (ACOVE) criteria, a set of quality care indicators.[22] Pharmacist-led medication review is a structured evaluation of a patient's medicines, with the aim of reaching an agreement with the patient about drug therapy in order to optimize the impact of

medicines and minimize the number of medication-related problems. However, in a systematic review, pharmacist-led medication review did not reduce in-hospital mortality among older people and thus may not provide substantial clinical benefit.[23] Such reviews may nevertheless improve knowledge of drugs and drug adherence. Geriatric medication evaluation performed by both physicians and pharmacists led to a reduction in suboptimal prescribing for frail elderly patients.[24] Geriatric Evaluation and Management (GEM) care improved the appropriate use of medicines during hospital stay and after discharge.[25] Although GEM is effective, it is applicable only in a hospital setting and, therefore, reaches only a portion of the elderly using polypharmacy.

Objective

The above-mentioned considerations highlight the need for a useful and rapid method for optimizing prescribing of polypharmacy in general practice. Use of such a method should lead to fewer ADRs, fewer harmful interactions, less over-treatment, less undertreatment, better patient adherence and, ultimately, fewer hospital admissions because of inadequate pharmacotherapeutic treatment. To this end, we developed a method to optimize the prescription of polypharmacy in elderly patients by general practitioners (GPs) and tested whether the method led to prescribing behaviour comparable to that of an expert panel.

Methods

Prescribing Optimization Method

The Prescribing Optimization Method (POM) to assist physicians to optimize polypharmacy prescribing for the elderly population is based on six open questions. These questions should help physicians check whether their elderly patients are receiving the best pharmacotherapeutic treatment possible. Each of the questions is presented below with an overview (based on the available literature) of the most frequent and clinically relevant problems, together with suggestions to improve prescribing.

Is the Patient Undertreated and is Additional Medication Indicated?

Although it may not seem logical to ask about possible undertreatment when one is concerned about polypharmacy, some health problems are undertreated. The most common areas of undertreatment are presented in table I.[8-10] Appropriate interventions, as stated in the POM, are based on Dutch guidelines, such as the General Practitioner Guidelines and the National Interdisciplinary Guidelines,[26-29] which in turn are based on evidence from the literature.

Table I Commonly undertreated conditions or settings and medications advised by guidelines[8-10]

Condition/setting	Medication
• Angina pectoris	β-receptor-blocking drug
• Atrial fibrillation	Cumarins, when contraindicated acetylsalicylic acid
• Cardiovascular disease[a]	Acetylsalicylic acid, in case of over-sensitivity clopidogrel
• Cardiovascular disease[a] + LDL>2.5	Statin
• Cerebral infarction/TIA	Consider antihypertensive treatment, even if blood pressure is normal
• COPD	Inhalational anticholinergics/β2-agonists
• Corticosteroids used >1 month	Medication to prevent osteoporosis
• Depression	Antidepressent
• Diabetes mellitus	Statin
• Diabetes with proteinuria	ACE inhibitor
• Heart failure	ACE inhibitor, if necessary β-receptor-blocking drug
• Hypertension	Antihypertensive treatment
• Insufficient daylight	Vitamin D
• Myocardial infarction	Acetylsalicylic acid, ACE inhibitor, β-receptor-blocking drug
• NSAID	Drugs to protect the stomach
• Opioids	Laxatives
• Osteoporosis	Medication to treat osteoporosis
• Pain	Analgesics

[a] Caused by atherothrombotic processes with clinical manifestations such as myocardial infarction, angina, cerebral infarction, TIA, aortic aneurysm and peripheral arterial disease.
LDL = low-density lipoprotein; TIA = transient ischaemic attack.

Does the Patient Adhere to His/Her Medication Schedule?

To identify problems with adherence, one could simply ask patients which medications they forget or do not take regularly and explain that they are not the only people who forget their medicine. Another way is to use objective measurements, such as blood pressure in the case of antihypertensive treatment. Medication delivery data from the pharmacy may also help to detect lack of adherence. It is important to discuss with the patient reasons for non-adherence and possible ways to improve it.[30]

Which Drug(s) can be Withdrawn or Which Drug(s) is (are) Inappropriate for this Patient?

The aim of this question is to recognize overtreatment and to identify drugs with a (relative) contraindication. The indication for a drug is often based on guidelines. However, even if a drug is indicated, in specific cases the guidelines can be ignored. For example, in elderly patients, time until benefit and life expectancy are important factors to consider.[31] At the same time, age in itself is not a reason to omit drug therapy. A list of contraindicated drugs is provided in table II.

Table II Conditions and possible contraindicated drugs[17]

Condition	Contraindicated drug
COPD	Long-acting benzodiazepines, non-selective -receptor-blocking drugs (propranolol, carvedilol, labetalol, sotalol)
Dementia	potent anticholinergic agents[a]
Heart failure	verapamil, diltiazem, short-acting nifedipine, NSAIDs, rosiglitazone
Lower urinary tract syndrome	anticholinergic agents[a]
Gastric ulcer or gastritis	NSAIDs
Narrow angle glaucoma	potent anticholinergic agents[a]
Constipation	verapamil, diltiazem, anticholinergic agents[a]
Postural hypotension	tricyclic antidepressants
Parkinson's disease	metoclopramide, all antipsychotics except clozapine and quetiapine
Hyponatriemia (SIADH)	SSRIs
Falls	psychoactive drugs

[a] spasmolytics, tricyclic antidepressants, anticholinergic antiparkinsonic drugs SIADH – syndrome of inappropriate antidiuretic hormone secretion

Which Adverse Effects are Present?

ADRs are common in elderly people because of changes in pharmacokinetics and pharmacodynamics. A list of drugs with a narrow therapeutic index, and their accompanying adverse effects, is presented in table III.[27] It is important to ask patients about adverse effects because they often do not mention them otherwise.[32] Naranjo's method can be used to determine the probability of an ADR.[33]

Which Clinically Relevant Interactions are to be Expected?

It is important to establish whether there are clinically relevant pharmacokinetic and pharmacodynamic interactions. Frequently occurring drug-drug interactions and food-drug interactions mentioned in the literature are listed in table IV.[5,34,35]

Table III Common adverse effects of drugs[27]

Drug	Adverse effect
anticonvulsants	drowsiness
anti-parkinsonic drugs	hallucinations, postural hypotension
antipsychotic drugs	drowsiness, extrapyramidal syndrome
cumarins	bleeding
digoxin	nausea, bradycardia
lithium	delirium, nausea, ataxia, drowsiness
opioids	drowsiness, constipation
sulfonylurea anti-diabetics	hypoglycemia
tricyclic antidepressants	drowsiness, postural hypotension
verapamil, diltiazem	bradycardia, hypotension, constipation

Table IV Clinically relevant interactions[5, 34, 35]

Drug	Interaction	Effect
ACE inhibitors	NSAIDs, potassium-sparing diuretics	Decreased renal function, hyperkalaemia
Antidepressants	Enzyme inducers[a]	Reduces antidepressant effect
Antihypertensives	Vasodilators, antipsychotics, tricyclic antidepressants	Increased antihypertensive effect
	NSAIDs	Decreased antihypertensive effect
β-adrenoceptor antagonists	Antihyperglycaemic drugs	Masks hypoglycaemia
	Fluoxetine, paroxetine (especially in combination with metoprolol and propranolol)	Bradycardia
Corticosteroids (oral)	NSAIDs	Gastrointestinal ulcers
	Enzyme inducers[a]	Decreased corticosteroid effect
Coumarins	NSAIDs, metronidazole, miconazole	Bleeding
	Rifampicin	Decreased anticoagulation control
Digoxin	NSAIDs, diuretics, quinidine, verapamil, diltiazem, amiodarone	Digoxin intoxication

Table IV Continued

Drug	Interaction	Effect
Lithium	NSAIDs, thiazide diuretics, antipsychotics	Lithium toxicity
Phenytoin	Enzyme inhibitors[b]	Increased toxicity
Sulfonylurea antihyperglycaemics	SSRIs, chloramphenicol, coumarins, phenylbutazone	Hypoglycaemia
SSRIs	Diuretics, NSAIDs	Hyponatraemia, gastric bleeding
Tetracycline	Antacids, iron	Decreased availability

[a] Important enzyme inducers: carbamazepine, rifampicin, phenobarbital, phenytoin and hypericum (St. Johns wort)[c].

[b] Important enzyme inhibitors: verapamil, diltiazem, amiodarone, fluconazole, miconazole, ketoconazole, erythromycin, clarithromycin, sulfonamides, cimetidine, ciprofloxacin, and grapefruit juice[c].

[c] Because of their enzyme inhibitor and inducer activities, respectively, patients should be advised not to drink grapefruit juice or to take hypericum if they are using any of the following drugs: quinidine; astemizole, terfenadine; alprazolam, diazepam, midazolam, triazolam; diltiazem, felodipine, nifedipine, verapamil, lercanidipine, nitrendipine; indinavir, nelfinavir, ritonavir, saquinavir; estradiol, hydrocortisone, progesterone, testosterone; ciclosporin, tacrolimus; clarithromycin, erythromycin; atorvastatin, simvastatin; and aripiprazole, buspirone, dexamethasone, docetaxel, domperidone, fentanyl, haloperidol, irinotecan, propranolol, risperidone, salmeterol, tamoxifen, paclitaxel, vincristine or zolpidem.

SSRIs = selective serotonin reuptake inhibitors.

Should the Dose, Dose Frequency and/or Form of the Drug be Adjusted?

The dose of prescribed drugs often needs to be adjusted if, for example, a patient's renal function is poor. Decreased renal function is very common among the elderly. In most people aged >80 years, renal function has declined by ‡50%.[36] The best way to determine renal function is to measure inulin clearance. However, this method is cumbersome, time consuming and, therefore, not possible to perform as a routine assessment of renal function. Hence, a number of estimation formulas have been developed. The two most frequently used formulas are the Modification of Diet in Renal Disease formula and the Cockcroft-Gault formula.[37] They are easy to use in clinical practice; however, they perform less accurately in people with a very high or low body mass index.[38] A list of drugs which require dose adjustment in patients with decreased renal function is presented in table V. This question also serves to raise awareness of the possibility of decreasing administration frequency or combining drugs in a single preparation in order to improve adherence.

Table V Adjustment of dose in renal insufficiency[39,40]a

Drug	
ACE INHIBITORS	
captopril	Clcr 10-30 ml/min: start with 12.5-25 mg once daily. Adjust dose based on effect until 75-100 mg/day
enalapril	Clcr 10-30 ml/min: start with max. 5 mg/day. Adjust dosage based on effect until max. 10 mg/day
lisinopril	Clcr 10-30 ml/min: start with max. 5 mg/day. Adjust dosage based on effect until max. 40 mg/day
perindopril	Clcr 30-50 ml/min: max. 2 mg/day; Clcr 10-30 ml/min: max. 2 mg every two days
quinapril	Clcr 30-50 ml/min: start with 5 mg/day; Clcr 10-30 ml/min: start with 2.5 mg/day. Adjust dosage based on effect.
ramipril	Clcr 20-50- ml/min: start with max. 1.25 mg/day. Adjust dosage based on effect.
	Clcr 10-20 ml/min: insufficient data for sound advise
ANTIBACTERIALS	
CEPHALOSPORINS	
cefalexin	Clcr 10-50 ml/min: prolong interval to once per every 12 hours.
cefalotin	Clcr 50-80 ml/min 2 g every 6 hours; 30-50 ml/min 1.5 g every 6 hours; 10-30 ml/min 1 g every 8 hours.
cefamandole	Clcr 50-80 ml/min 2 g every 6 hours, in case of life-threatening infection 1.5 g every 4 hours;
	Clcr 30-50 ml/min 2 g every 8 hours, in case of life-threatening infection 1.5 g every 6 hours;
	Clcr 10-30 ml/min 1.25 g every 6 hours, in case of life-threatening infection 1 g every 6 hours.
cefazolin	Clcr 30-50 ml/min: 500 mg every 12 hours; 10-30 ml/min: 500 mg every 24 hours.
cefradine	Clcr 10-30 ml/min: contra-indicated
ceftazidime	Clcr 30-50 ml/min: 1 g every 12 hours; 10-30 ml min: 1 g every 24 hours.
MACROLIDES	
clarithromycin	Clcr 10-30 ml/min: 50% of normal dosage with normal dose frequency
PENICILLINS	
amoxicillin/clavulanic acid	Clcr 10-30 ml/min: standard dosage every 12 hours (orally, i.v. of .im.)
benzylpenicillin	Clcr 10-30 ml/min: dosage dependent of indication. Consider intended effect, risks of overdosage and underdosage.
piperacillin	Clcr 30-50 ml/min: max. 12 g per day in 3 or 4 doses; Clcr 10-30 ml/min: max. 8 g per day in 2 doses

Table V Continued

Drug	
ANTIBACTERIALS	
QUINOLONES	
ciprofloxacin	Clcr 10-30 ml/min: 50% of normal dosage
levofloxacin, ofloxacin	Clcr 30-50 ml/min: 50% of normal dosage; Clcr 10-30 ml/min: 25% of normal dosage
norfloxacin	Clcr 10-30 ml/min: prolong interval to once every 24 hours
SULFONAMIDES	
cotrimoxazole	Clcr 10-30 ml/min: decrease dosage by 50% or double dosage interval
sulfadiazine	Clcr 10-30 ml/min: 50% of normal dose
trimethoprim	Clcr 10-30 ml/min: first 3 d normal dose, then 50% of normal dose
Other antibacterials	
Nitrofurantoin	Clcr 10-50: contra-indicated. Risk of neuropathy and failure of therapy.
tetracycline	Clcr 10-30 ml/min: maintenance dosage 250 mg once daily
ANTIDOTES	
Methylnaltrexone bromide	Clcr 10-30 ml/min: body weight 62-114 kg 8 mg in standard dose frequency; bodyweight <62 or >114 kg 0.075 mg/kg in standard dose frequency
ANTIEPILEPTICS	
Carbamazepine	Clcr 10-30 ml/min: be alert to adverse effects
Gabapentin	Clcr 50-80 ml/min: 600-2400 mg/d Clcr 30-50 ml/min: 300-1200 mg/d Clcr 10-30 ml/min: 150-600 mg/d
Levetiracetam	Clcr 50-80 ml/min: 500-1000 mg twice daily Clcr 30-50 ml/min: 250-750 mg twice daily Clcr 10-30 ml/min: 250-500 mg twice daily
Oxcarbazepine	Clcr 10-30 ml/min: 50% of normal dose, then increase dosage slowly
Phentyoin	Clcr 10-30 ml/min: dose based on free concentration of phenytoin
Pregabalin	Clcr 30-50- ml/min: 50% of normal dose
	Clcr 10-30 ml/min: 25% of normal dose
topiramate	Clcr 10-50 ml/min: 50% of normal dose
Valproic acid	Clcr 10-50 ml/min: dose based on effect and adverse effects
ANTIHORMONE THERAPY	
Raloxifene	Clcr 10-30 ml/min: preferably do not use

Table V Continued

Drug	
ANTIHYPERGLYCAEMICS	
metformin	Clcr 30-50 ml/min: start with twice daily 500 mg Clcr 10-30 ml/min: contra-indicated
sulfonylureas (glibencalmide, glicazide, glimepiride)	Clcr < 50 ml/min start with half the dose
ANTIHISTAMINES	
cetirizine/levocetirizine/ hydroxyzine	Clcr 10-50 ml/min: 50% of normal dose
ANTIFUNGALS	
fluconazole	In patients taking more than once-daily doses: Clcr 10-50 ml/ min: normal starting dose, decrease maintenance dosage until 50% of normal dose
flucytosine	Clcr 30-50 ml/min: prolong interval to once every 12 h, then base on serum plasma concentration
	Clcr 10-30 ml/min: prolong interval to once every 24 h, then base on serum plasma concentration
ANTIHYPERLIPIDAEMICS	
Rosuvastatin	Clcr 30-50 ml/min: start with 5 mg/d, then increase dosage with 5mg/d until max 20 mg/d Clcr 10-30 ml/min: start with 5 mg/d, then if necessary increase until max 10 mg/d
ANTIPARKINSONIAN MEDICATIONS	
Pramipexole	Clcr 30-50 ml/min: start with 0.125 mg (=0.088 base) twice daily, then base on effect/adverse events
	Clcr 10-30 ml/min: start with 0.125 mg (=0.088 base) once daily, then base on effect/adverse events
ANTITHROMBOTICS	
Nadroparin calcium	Prophylactic: Clcr 10-30 ml/min: decrease normal dose by 25% Therapeutic: Clcr 30-50 ml/min: decrease normal dose by 25% Clcr 10-30 ml/min: contraindicated
tirofiban	Clcr 10-30 ml/min: 50% of normal dose
ANTIVIRAL MEDICATIONS	
aciclovir (oral)	Decrease dose used for herpes zoster treatment: Clcr 10-30 ml/ min: 800 mg three times daily.
amantadine	Start with 200mg, maintenance dosage: Clcr 50-80 ml/min: 100 mg once daily
	Clcr 30-50 ml/min: 100 mg every 2 d Clcr 10-30 ml/min 100 mg every 3 d

Table V Continued

Drug	
ANTIVIRAL MEDICATIONS	
famciclovir	Clcr 30-50 ml/min: normal dosage every 24 h Clcr 10-30 ml/min: 50% of normal dose every 24 h
foscarnet	Clcr 30-80 ml/min: dosage according to manufacturer schedule Clcr 10-30 ml/min: contraindicated
ganciclovir	Induction: Clcr 50-80 ml/min: 50% of normal dose every 12 h 30-50 ml/min: 50% of normal dose every 24 h 10-30 ml/min: 25% of normal dose every 24 h Maintenance: Clcr 50-80 ml/min: 50% of normal dosage every 24 h Clcr 30-50 ml/min: 25% of normal dosage every 24 h Clcr 10-30 ml/min: 12.5% of normal dosage every 24 h
oseltamivir	Clcr 10-30 ml/min: 50% of normal dose or normal dose but double interval
ribavirin	Clcr 10-50 ml/min: base dos on haemoglobin concentration
valaciclovir	Clcr 10-80 ml/min: adjust dose according to manufacturer schedule
β-Adrenoceptor antagonists	
Acebutolol, atenolol	Clcr 10-30 ml/min: 50% of normal dose
bisoprolol	Clcr 10-20 ml/min: start with 50% of normal dose. Then max. 10 mg/day
sotalol	Clcr 30-50 ml/min: max 160 mg/d Clcr 10-30 ml/min: max. 80 mg/d
CALCIUM CHANNEL ANTAGONISTS (DIHYDROPYRIDINES)	
barnidipine	Clcr 10-50 ml/min: contra-indicated
DIGOXIN	Clcr 10-50 ml/min: decrease initial dose by 50%, then change to 0.125 mg/d. Then adjust dose based on clinical symptoms.
DISEASE –MODIFYING ANTIRHEUMATIC DRUGS	
Chloroquine, hydrochloroquine	Clcr 10-30 ml/min: no general advice can be given
methotrexate	Clcr 50-80 ml/min: 50% of normal dose. Clcr 10-50 ml/min: base on serum plasma concentration
DIURETICS	
Amiloride	Clcr 30-50 ml/min: determine plasma potassium regularly Clcr 10-30 ml/min: contra-indicated
Bumetanide	Clcr 10-30 ml/min: start with normal dosage, if necessary increase dose based on effect and indication
Chlortalidone, chlorothiazide	Clcr 10-30 ml/min: contraindicated

Table V Continued

Drug	
DIURETICS	
Furosemide	Clcr 10-30 ml/min: start with normal dosage, if necessary increase dose based on effect and indication
Hydrochlorothiazide	Clcr 30-50 ml/min: start with 12.5 mg/d Clcr 10-30 ml/min: contraindicated
Spironolactone	Clcr 10-50 ml/min: determine plasma potassium regularly
Triamterene	Clcr 30-50 ml/min: 50% of normal dose, determine plasma potassium regularly Clcr 10-30 ml/min: contraindicated
GOUT MEDICATIONS	
allopurinol	Clcr 50-80 ml/min: 300 mg/d Clcr 30-50 ml/min: 200 mg/d Clcr 10-30 ml/min: 100 mg/d
Benzbromarone, probenicid	Clcr 10-30 ml/min: contra-indicated
colchicine	Clcr 10-50 ml/min: 0.5 mg/d
HISTAMINE H2 RECEPTOR ANTAGONISTS/ANTI-EMETICS	
Nizatidine, cimetidine, famotidine, ranitidine	Clcr 10-30 ml/min: 50% of normal dose once daily
Metoclopramide	Clcr 10-50 ml/min: 50% of normal dose
PSYCHOTROPICS	
Chloral hydrate	Clcr 10-50 ml/min: preferably do not use
Lithium	Clcr 30-50 ml/min: 50% of normal dose Clcr 10-30 ml/min: preferably replace by lamotrigine, carbamazepine or valproic acid
midazolam	Clcr 10-30 ml/min: base dose on effect and adverse events
risperidone	Clcr 10-50 ml/min: 50% of normal dose, then base on effect and adverse events
MUSCLE RELAXANTS	
Baclofen	Clcr 10-50 ml/min: start with 5 mg once daily, then adjust based on effect and adverse events.
NSAIDs	
All NSAIDs	Clcr <30 ml/min: consider if long-term use is indicated. Check renal function before and 1 week after starting as use of NSAIDs can cause acute renal failure
OPIOIDs	
Morphine	Clcr 10-50 ml/min: dose based on effect and adverse events. Be alert to accumulation of morphine-6-glucuronide
Tramadol	Clcr 10-30 ml/min: 100 mg twice daily

Table V Continued

Drug	
PARASYMPATHICOLYTICS	
Solifenacin	Clcr 10-30 ml/min: max 5 mg/d
Tolterodine	Clcr 10-30 ml/min: 1 mg twice daily
SKIN MEDICATIONS	
Tretinoic acid	Clcr 10-50 ml/min: 25 mg/m^2 body surface per day in two doses
TUBERCULOSTATICS	
Ethambutol	Clcr 10-50 ml/min: 50% of normal dose
VERTIGO MEDICATION	
Piracetam	Clcr 30-50 ml/min: 50% of normal dose Clcr 10-30 ml/min: 25% of normal dose
XANTHINE DERIVATIVES	
Pentoxifylline	Clcr 30-50 ml/min: 400 mg twice daily Clcr 10-30 ml/min: 400 mg once daily
OTHERS	
Memantine	Clcr 10-30 ml/min: max 10 mg/d
Vitamin D3 (colecalciferol)	Clcr <50 ml/min: replace with calcitriol

[a] Refer to The Nephron Information Center website to calculate Clcr.[37]
Clcr = creatinine clearance; IM = intramuscularly; IV = intravenously; max = maximum.

Study Design and Setting

The usefulness of the POM was investigated using the case histories of ten geriatric patients admitted to the geriatric outpatient clinic of our hospital. These patients had a mean ± SD of 7.9 ± 1.2 problems treated with 8.7 ± 3.1 drugs. The cases were divided into five sets of two comparable cases. Forty-five GPs who were attending a postgraduate course in geriatric medicine were each asked to optimize the medications of two cases, the first in their usual manner and the second using the POM. The GPs were allowed 20 minutes for case optimization. Before using the POM, they attended a lecture lasting 2 hours on its use. They were also asked to record the time it took them to optimize therapy in both cases. The decisions made by the GPs were then compared with those of an expert panel, consisting of four geriatricians specialized in clinical pharmacology (R.M., W.K., C.L., P.J.). The expert panel was familiar with the POM but did not use it. They reached consensus on the pharmacotherapeutic changes that should be made in each case; the number of appropriate changes ranged from 5 to 13 per case. The GPs' decisions were evaluated anonymously, without the experts knowing which cases had been optimized using the POM. Decisions were subdivided into four categories: added

medication; discontinued medication; dose changes; and replaced medication. The decisions of the GPs were scored as appropriate or potentially harmful. Other possible decisions not proposed by the expert panel were, if appropriate, also scored as such. The appropriateness of other decisions was determined by consensus of the expert panel. Important considerations were expected effect, possible contraindications, expected adverse effects, possible interactions and correct dosage. Appropriate decisions were expressed as a percentage of the total appropriate decisions made by the expert panel. Potentially harmful decisions were further classified as follows: indicated drug not started; no or wrong adjustment of medication; drug not discontinued when the indication was no longer present; drug contraindicated; drug not effective; indication incorrect; and discontinuation of an effective drug.

Outcome Measures

The main outcome measure was the difference in the percentage of appropriate decisions made by the GPs without and with use of the POM. The secondary outcome measures were the difference in number of harmful decisions taken by the GPs without and with use of the POM, and the difference in time needed to optimize the medication list without and with use of the POM.

Statistical Analysis

Data were analysed with an independent sample t-test and a linear mixed effects model.

The linear mixed effects model was used to correct for the fact that each GP worked on two cases. It also corrected for the case sets used and the number of appropriate adjustments per cases (ranging from 5 to 13). Statistical analyses were performed in SPSS version 15 (SPSS Inc., Chicago, IL, USA) and S-PLUS_ (TIBCO Software Inc., Palo Alto, CA, USA).

Results

Of the 90 cases presented to the 45 GPs, six were excluded because it was unclear whether the POM had been used, four were excluded because the GP did not propose an optimized medication list and two were not received. Therefore, 78 medication histories were reviewed by the GPs, 39 without and 39 with use of the POM. The proportion of appropriate decisions increased from 34.7% without the POM to 48.1% with the POM (p= 0.004) [figure 1]. After correction for the case sets used and the possible number of appropriate adjustments per case, the difference between the two methods was 13% (95% CI 4.2, 21.6; p = 0.0037). In particular, use

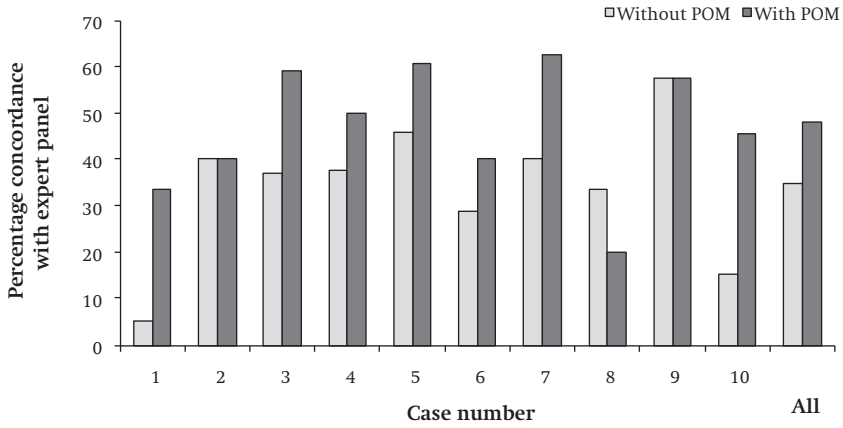


Figure 1 Percentage of concordance of appropriate decisions per case and in all cases with and without use of the Prescribing Optimization Method (POM)

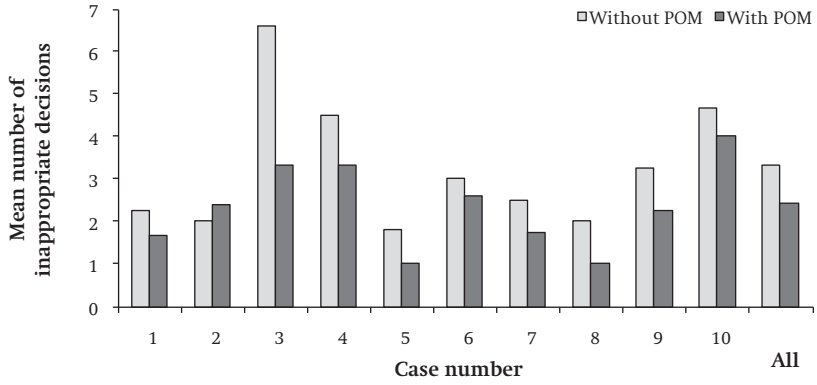


Figure 2 Number of potentially harmful decisions per case and in all cases with and without use of the Prescribing Optimization Method (POM)

of the POM led to increased prescribing of necessary medication. Concordance with the experts' opinion was 32% with the POM and 12% without the POM.

Use of the POM also led to a significant decrease in potentially harmful decisions (from mean ±SD 3.3 ± 1.8 without the POM to 2.4 ± 1.4 with the POM [95% CI -1.4, -0.3; p = 0.0046]) [figure 2]. The potentially harmful decisions made most frequently by the GPs are listed in table VI. The first eight of these are specifically mentioned

Table VI Potentially harmful decisions most frequently made by >50% of general practitioners

Class	Drug	Reason decision considered potentially harmful	Percentage with use of the POM	Specifically mentioned in the POM
Indicated drug not started	Coumarin	Atrial fibrillation	40	Yes
	Laxatives	Constipation	57	Yes
	β-receptor-blocking drugs	Decompensated heart failure, atrial fibrillation, and acute coronary syndrome	17	Yes
	ACE-inhibitor	Heart failure	25	Yes
	Vitamin D	Insufficient daylight exposure	53	Yes
	HMG-C0A reductase inhibitor (statin)	Diabetes	35	Yes
	Analgesics	Pain	44	Yes
	Prophylactic osteoporosis medication	Prednisone use	50	Yes
	Vitamin B12 (cyanocobalamin)	Pernicious anemia	50	No
No discontinuation of a drug	Miconazole	Indication ended	57	No
	Colchicine	Indication ended	50	No
	Calcium carbonate	Contraindication (poor renal function)	20	No
	Acetylcysteine	Lack of evidence supporting use	57	No
	Hydroquinine	Wrong indication	67	No
No or wrong adjustment of medication	Antihypergycaemics	Poor control	38	No
	Chronic obstructive pulmonary disease medication	Inappropriate schedule	37	No
	No replacement of digoxin by a β-adrenoceptor antagonist	Poor adherence, narrow therapeutic index	63	No
Discontinuation of an effective drug	Propranolol	Good effect on tremor	50	No

POM = Prescribing Optimization Method

in the POM. There was no statistically significant difference in the number of other decisions taken without (mean ±SD 3.7 ± 2.7) or with the POM (4.2 ± 2.1).

In addition, the number of drugs prescribed by both the expert panel and GPs decreased by >10% after drug revision, both with and without use of the POM.
Only 12 GPs reported the time they took to review the case histories. In these cases, more time was required to review a case when the POM was used (mean 8 minutes without the POM vs 16.7 minutes with the POM).

Discussion

This study shows that use of the POM by GPs improved appropriate prescription in elderly patients receiving complex polypharmacy. The aim of the POM is to improve appropriate prescribing by dealing with the known difficulties of polypharmacy, namely undertreatment, lack of adherence, overtreatment, ADRs, harmful interactions, and incorrect dose and administration regimens. We found that use of the POM specifically decreased undertreatment, which occurs in >40% of elderly patients.[9] Although other methods, such as START,[20,21] are also effective in detecting undertreatment, they do not address the other problems of polypharmacy mentioned previously.
The study had a number of strong points. Because the GPs were randomly assigned case histories to review with and without use of the POM, we could determine whether they performed better with the POM than without it. Moreover, by using ten different cases, we minimized the influence of a single case on the results. Since we not only evaluated the proportion of appropriate decisions but also the number of inappropriate decisions, we fully evaluated the additional value of the POM.
Potential limitations include the fact that the case review was done 'on paper' without contact with the patient. Therefore, the model was tested theoretically and the level of evidence obtained was not high. However, despite this shortcoming, the results of this study are promising. Another possible limitation is the fact that the expert panel was familiar with the POM. Although they did not specifically use this method, this knowledge could have caused a higher agreement between the expert panel and the GPs when they used the POM. Therefore, the value of the POM could have been overestimated. It is also possible that the GPs would have performed better in the second case because of the extra time taken and a learning effect from the first case. A limitation with regard to generalization of the study findings is that the POM is based on the Dutch situation and Dutch guidelines. Although these are often similar to international guidelines, small differences are possible. Another potential limitation is that the GPs did not have access to

reference materials that they could normally use in practice. It is likely that they would have performed better if they could have used reference material. However, all GPs had this disadvantage, regardless of whether they used the POM or not. Therefore, we do not think that access to reference books would have changed the outcome of this study significantly, particularly the improvement in under-treatment. A final potential limitation is selection bias. We recruited GPs who were to attend a course on geriatric medicine, and thus their knowledge of geriatric medicine could have been less thorough in some areas. On the other hand, it is also possible that the recruited GPs were more interested and alert to the specific problems in the elderly.

It is interesting that the cases that reached statistical significance in terms of an improvement in prescribing, i.e. cases 3 and 10, were the cases that needed the most alterations to the medication list. Thus, it would seem that the POM is especially useful when more changes need to be made to the medication list. Some decisions made by the expert panel were specifically mentioned in the lecture given on the use of the POM, such as the need for vitamin D if a patient does not have sufficient daily exposure to daylight. Surprisingly, this specific recommendation was followed in only 43.8% of the cases reviewed with use of the POM and in only 21.7% of the cases reviewed without the use of the POM. We would have expected a much higher percentage when the POM was used. It is possible that the GPs were not sufficiently familiar with the POM – training in its use consisted of only a 2-hour lecture – and consequently there is room for improvement.

A common error made by the GPs was not to replace vitamin D3 (colecalciferol) with calcitriol (the active form of vitamin D) in patients with decreased renal function. Vitamin D was not on the dose adjustment list for ''decreased renal function'' and we accordingly added it to the list in table V. The other changes made by the expert panel were too case specific to be translated into recommendations that would improve the POM (e.g. discontinuation of colchicine if the indication is no longer present).

Optimizing polypharmacy with the POM was twice as time consuming as optimization without the POM. This may be because the GPs were not familiar with the POM and, therefore, needed more time to read and interpret the method, and we expect that frequent use of the method will shorten the time taken to optimize the medication list. In our experience, it takes 10 minutes per medication to complete the MAI. Thus, with a mean of eight drugs per patient, physicians would need 80 minutes per case to optimize polypharmacy using the MAI. In our study, GPs reported taking a mean of approximately 17 minutes to optimize medications in each patient.

We would like to emphasize that the POM is meant to prevent the most frequently seen problems associated with pharmacotherapy – we do not pretend that it covers

all possible pharmacotherapeutic problems. We hope that the POM can be used by physicians as a practical tool to help them optimize complex polypharmacy in a short time. To this end, the POM could be incorporated into an electronic prescribing system that requires regular critical reviews and updates. The POM is suitable for use in a multidisciplinary team. The nurse practitioner could ask patients which medicines they actually take and what ADRs they experience, and the pharmacist could assist by determining interactions and by giving advice about the dose, dose frequency and formulation of the medicines. This would allow the GP to focus on drug indications and possible undertreatment. Even if medication optimization takes longer with the POM than without it, we think it is worthwhile taking this extra time because the results are significantly better.
It has yet to be determined whether optimization of polypharmacy with the help of the POM is clinically beneficial in terms of fewer adverse events, fewer hospital admissions, decreased morbidity and decreased mortality. We plan to investigate this in the future.

Conclusion

The POM improves appropriate prescribing of complex polypharmacy in case histories of elderly patients. Use of the POM leads to more appropriate prescribing decisions and fewer potentially harmful decisions.

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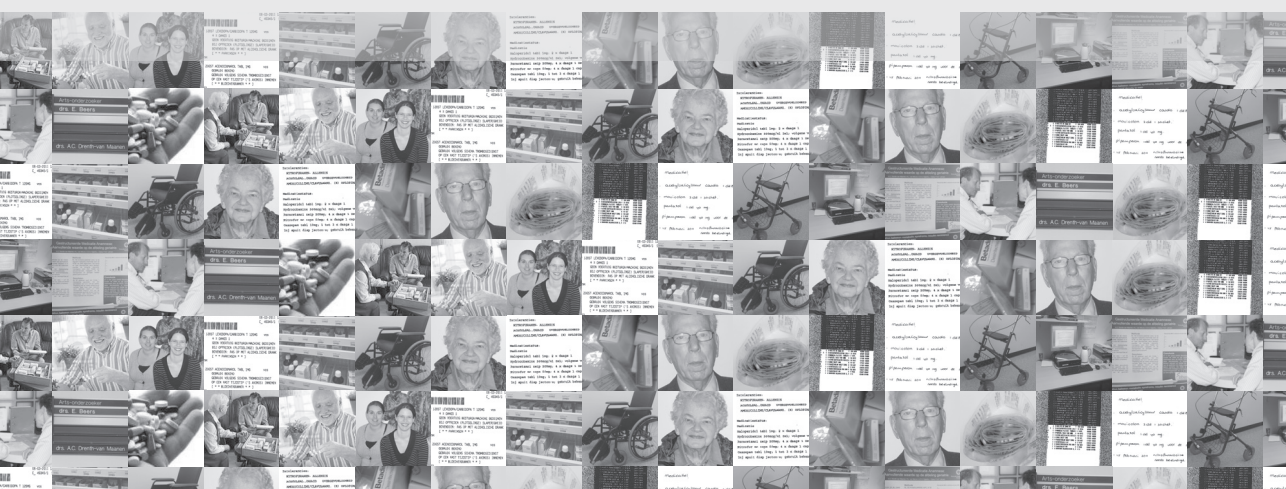
3

Transitional Pharmaceutical Care



3.1

Structured history taking of medication use reveals iatrogenic harm due to discrepancies in medication histories in hospital and pharmacy records

A. Clara Drenth-van Maanen, Jonne Spee, Rob J. van Marum, Toine C.G. Egberts, Larissa van Hensbergen and Paul A.F. Jansen

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(Letter to the Editor)

Abstract

Objectives – To evaluate whether Structured History taking of Medication use (SHIM) improves medication history taking at admission and if it has the potential to decrease medication-related harm during hospital admission.
Design - Prospective observational study.
Setting – Academic hospital.
Participants – One hundred patients admitted to the geriatric ward.
Intervention – SHIM, a structured interview.
Measurements – Comparison of the medication histories derived by SHIM to usual care (UC) medication history taking and community pharmacy listings. The number and type of discrepancies were registered. Discrepancies were assessed on potential clinical relevance. Actual clinical consequences during admission were retrospectively identified.
Results - In 92% of UC medication histories discrepancies were found, median 3 per patient. Discrepancies in prescription-only drugs were found in 78% of patients, median 2 per patient. The community pharmacy listings showed discrepancies in 88% of patients, median 3 per patient. Discrepancies in prescription-only drugs were found in 74% of patients, median 1 per patient. Of all discrepancies, 71% were potentially clinically relevant; 21% of patients experienced actual clinical consequences.
Conclusion – SHIM reveals discrepancies in medication history taking in almost all patients, admitted to the geriatric ward. Due to these discrepancies, approximately 1 in 5 patients experienced actual clinical consequences that could have been prevented by SHIM.

Introduction

Medication history errors can lead to prescribing errors. These may cause serious harm to patients and potentially high costs for the society.(1) Patient transfer across settings, e.g. from nursing home to hospital, leads to an increased likelihood of medication errors.(2) For example, errors in the medication history on hospital admission are found in 27 - 83% of patients.(3) Especially older patients are prone to medication errors.(4;5)

The medication reconciliation process has proven to be an effective way to reduce the number of prescribing errors.(6-8) This process consists of four steps. The first step is verification, i.e. the current medication list is assembled by using one or more sources of information (e.g. community pharmacy listings, general practitioner medical records, medication vials brought by the patient, the information provided by the patient and his/her family in patient counselling). The second step is clarification: the medication and dosages are checked for appropriateness for the patient. The third step is reconciliation, existing of the comparison of newly prescribed medications to the old ones and the documentation of changes to pharmacotherapy. The final step is transmission, in which the updated and verified list is communicated to the next care provider.(9)

Until now there has been no structured method for accomplishing the first step of the medication reconciliation process. In daily practice, the sources used to obtain a medication history vary widely and are highly dependent on the information provided by the patient. Furthermore, none of these sources alone, such as community pharmacy listings and general practitioner medical records, have proven to be completely accurate.(10) Also, none of the studies focusing on medication discrepancies at admission, have described the use of these sources in a structured way.(11-13) Moreover, the actual clinical consequences of the discovered discrepancies have not yet been studied.

To provide physicians with a method for medication history taking, we have developed a questionnaire, the Structured HIstory taking of Medication use (SHIM). The main objective of this study was to determine whether medication history taking by SHIM retrieves more information on actual medication use than usual care (unstructured medication history taking) and community pharmacy listings in patients admitted to the geriatric ward. Secondly, we have investigated whether discrepancies in medication history taking, revealed by SHIM, led to actual consequences during hospital stay.

Methods

Setting and study population

A prospective observational study was conducted from September 2008 until November 2008 and extended from February 2009 until August 2009 at the University Medical Centre Utrecht, a 1000-bed academic teaching hospital. All patients, admitted to the geriatric ward in those time windows, were eligible for inclusion. Exclusion criteria were discharge, death or terminal disease before SHIM could be accomplished, and severe cognitive impairment without the availability of a relative. Information was collected on participant characteristics, including age, gender, duration of hospital stay, residency, and type of admission (emergency versus planned). All patients or caregivers gave written consent after they were informed about the study. Patient data were sampled and stored in accordance with privacy regulations.

Intervention

To determine the additional value of SHIM, we compared SHIM with UC and community pharmacy listings. UC medication history taking is based on an unstructured interview by the resident with the patient on admission; often information from letters by referring physicians is available, sometimes the patient's medication vials are also available or a medication history from the community pharmacy. The medication history, derived at admission by the resident, is written down in the medical chart. SHIM is based on multiple sources. (14;15) It consists of 21 questions (Table 1), focusing on the patients' current and recent medication use, practical problems concerning the intake of medicine, medication knowledge, and beliefs about medicine. SHIM is taken as a structured interview with the patient and, in case of cognitive impairment, a relative. To this end, a listing of the medications dispensed by the community pharmacy and the medication vials of the patient needs to be at hand. The usual care medication history was obtained from the resident's admission notes in the medical chart. The community pharmacy listings were requested from the patients' community pharmacy by faxing the patients' informed consent form.

SHIM was taken during hospital stay, if possible on the second or third day. For this purpose an appointment was made with the patient and, preferably, with a relative. SHIM was taken by a medical student (JS) and a research-physician, who is a clinical geriatrician and clinical pharmacologist in training (CD). The residents were not informed about the study to make sure that comparison with usual care would not be troubled.

Table 1 Structured History taking of Medication use (SHIM) questionnaire

Questions asked per drug on the medication list, provided by the community pharmacist:
1. Are you using this drug as prescribed (dosage, dose frequency, dosage form)?
2. Are you experiencing any side effects?
3. What is the reason for deviating (from the dosage, dose frequency, or dosage form) or not taking a drug at all?
4. Are you using any other prescription drugs, which are not mentioned on this list? (View medication containers)
5. Are you using non-prescription drugs?
6. Are you using homeopathic drugs or herbal medicines (especially st. Johns wort)?
7. Are you using drugs that belong to family members or friends?
8. Are you using any drugs 'on demand'?
9. Are you using drugs that are no longer prescribed?
Questions concerning the use of medicines:
10. Are you taking your medication independently?
11. Are you using a dosage system?
12. Are you experiencing problems taking your medication?
13. In case of inhalation therapy: What kind of inhalation system are you using? Are you experiencing any problems using this system?
14. In case of eye drops: Are you experiencing any difficulties using the eye drops?
15. Do you ever forget to take your medication? If so, which medication, why, and what do you do?
Questions concerning medication knowledge
16. Do you know why you should use this medication?
17. Do you know who prescribed this medication?
Questions concerning beliefs about medicine
18. Do you believe that your medication is health-improving?
19. Will you continue to use your medication?
20. Will you consult your physician in case of medication-related problems?
21. Would you like to comment on or ask a question about your medication?

Outcome

A discrepancy was defined as any difference between community pharmacy listings or UC, and SHIM. Discrepancies were classified into omission errors (drugs missed from the history by UC/community pharmacy, revealed by SHIM),

commission errors (drugs added to the history, which in fact were not used by the patient, as shown by SHIM), dose and/or dose frequency errors, and substitution errors. They were analyzed based on type, number, and potential clinical relevance. Non-prescription drugs were also taken into account.
Two geriatricians-clinical pharmacologists (RM, PJ) separately classified the potential clinical relevance of the discrepancies, based on the classification system by Cornish et.al.(16) Class 1 discrepancies were unlikely to cause patient discomfort or clinical deterioration, such as omission of non-prescription vitamins. Class 2 discrepancies had the potential to cause moderate discomfort or clinical deterioration, such as diarrhea, nausea, or moderate pain (solved by acetaminophen). Class 3 discrepancies had the potential to result in severe discomfort or clinical deterioration, such as gastro-intestinal bleeding, sedation, anaphylactic shock, or severe pain (not solved by acetaminophen). Cases of disagreement were discussed and consensus was reached.
Actual clinical consequences were studied retrospectively. Therefore, chart research was used to discover potential consequences. In order to find out if discrepancies continued to exist after discharge, or if they were corrected within three months after discharge, a medication delivery history from the community pharmacy was requested one year after discharge. This study was approved by the institutional review board.

Data analysis

Statistical analyses were performed in SPSS version 15 (SPSS Inc., Chicago, IL, USA). Descriptive statistics were applied to summarize the baseline characteristics, and to describe the number and type of discrepancies. Univariate regression analysis was used to determine the influence of the variables age, gender, number of drugs on admission, type of admission, use of non-prescription drugs and residency on the number of discrepancies. The variables that showed association with the number of discrepancies ($p<0.2$) were further analyzed using multivariate regression analysis.

Results

During the study period 132 patients were approached for inclusion. Ten patients chose not to participate, twenty patients were discharged before SHIM could be accomplished, and two patients were excluded because of cognitive impairment in combination with the absence of a relative. Therefore, 100 patients were included. In 27 cases the medication history could only be obtained through a relative, because of cognitive impairment.

The mean age of all participants was 82 years, and 61% was female. The use of polypharmacy was common, as the mean number of medications used at admission was 10 per participant. Furthermore, more than half of all admissions were emergency admissions (Table 2). Discrepancies between UC history taking and SHIM were found in 92% of patients. The median number of all discrepancies, including non-prescription drugs, was 3.0 (interquartile range 2.0-5.0) per patient. Omission was the most common discrepancy (Table 3). Discrepancies in prescription-only drugs were found in 78% of patients, median number 2.0 per patient (interquartile range 1.0-3.0).

Table 2 Baseline characteristics (N=100). Values are means unless otherwise indicated

Characteristic	Value
Age in years ± SD (range)	82 ± 8 (51-100)
Women (%)	61
Medications on admission ± SD (range)	10,2 ± 4,6 (1-24)
Length of hospital admission in days ± SD (range)	15,4 ± 8,4 (1-40)
Emergency admissions (%)	51
Patients using OTC-drugs (%)	83
Non-prescription drugs per patient ± SD (range)	2,0 ± 1,5 (0-6)
Residency (%)	
At home without caregiver	30
At home with caregiver	23
Sheltered housing*	16
Retirement home**	17
Nursing home	14

* independent, but with the possibility to make use of the facilities of a residential home, such as meal service

** elderly living in the same apartment building, with facilities such as meal service and limited nursing options

The community pharmacy listings showed discrepancies with SHIM in 88% of patients. The median number of discrepancies was 3.0 per patient (interquartile range 1.0-5.0). Discrepancies in prescription-only drugs were found in 74% of patients, median number 1.0 per patient (interquartile range 0.0-3.0).
Table 4 describes the influence of age, gender, number of medications at admission, type of admission (elective versus emergency), the use of non-prescription drugs,

Table 3 Discrepancies between usual care medication history taking, pharmacy listings, and SHIM

	UC vs SHIM		Community pharmacy listings vs SHIM	
	All	Prescription only	All	Prescription only
Number of patients with ≥ 1 discrepancies (%)	92 (92.0)	78 (78.0)	88 (88.0)	74 (74.0)
Median number of discrepancies per patient (IQR)	3.0 (2.0-5.0)	2.0 (1.0-3.0)	3.0 (1.0-5.0)	1.0 (0.0-3.0)
Total number of discrepancies	369	237	348	230
Number of omission discrepancies (%)	217 (58.8)	116 (48.9)	186 (53.4)	93 (40.4)
Number of dosage and/or dose frequency discrepancies (%)	113 (30.6)	87 (36.7)	96 (27.6)	71 (30.9)
Number of commission discrepancies (%)	31 (8.4)	26 (11.0)	65 (18.7)	65 (28.3)
Number of substitution discrepancies (%)	8 (2.2)	8 (3.4)	1 (0.3)	1 (0.4)

IQR = interquartile range

and residency on the number of discrepancies between UC or pharmacy listings and SHIM. The number of medications used at admission, emergency admissions, and the use of non-prescription drugs were positively associated with the number of discrepancies. The most vulnerable group for the occurrence of discrepancies at hospital admissions was the group of patients living at home without any care.
The potential clinical relevance of the 369 discrepancies were classified: 28% (105) was classified as class 1 (unlikely to cause patient discomfort or clinical deterioration), 56% (206) as class 2 (potential to cause moderate discomfort or clinical deterioration), and 16% (58) as class 3 (potential to cause severe discomfort or clinical deterioration). Figure 1 shows a flowchart of the course of the discrepancies. During hospital stay, 21 patients (21%) suffered one or more consequences due to these discrepancies. The most severe consequences were re-occurrence of hallucinations after omission of quetiapine, increase in blood pressure from 150/90 to 191/102 after omission of nifedipine, and chest pain after omission of isosorbide mononitrate. Discrepancies which caused actual consequences were not corrected in 29% of cases.

Table 4 Influence of baseline characteristics on medication discrepancies UC vs SHIM

	Number of discrepancies				Number of prescription only discrepancies			
	Univariate		Multivariate		Univariate		Multivariate	
Characteristic	Beta	p-value	Beta	p-value	Beta	p-value	Beta	p-value
Number of medications	0.43	<0.01	0.39	<0.01	0.32	<0.01	0.31	<0.01
Emergency admission	0.99	0.13	1.48	<0.01	0.81	0.12	1.21	<0.01
Residency								
Home without care	Ref		Ref		Ref		Ref	
Home with care	-2.45	<0.01	-1.65	0.03	-1.94	<0.01	-1.30	0.03
Sheltered housing	-1.15	0.25			-1.06	0.18	-1.30	0.05
Retirement home	-1.73	0.08	-1.52	0.06	-1.85	0.02	-1.64	0.01
Nursing home	-1.68	0.11	-1.57	0.07	-1.43	0.08	-1.20	0.08
Female gender	0.63	0.35			0.02	0.97		
Use of non-prescription drugs	2.11	0.02	1.04	0.15	–	–	–	–
Age	-0.03	0.53			-0.03	0.43		

At discharge, 203 discrepancies were still not corrected, of which 89 non-prescription drugs. However, 41 drugs were no longer indicated (e.g. antibiotics). Therefore, 73 discrepancies were still relevant and traceable after discharge. Of these discrepancies, 14 were corrected (19%), and 59 (81%) were not.

Obtaining the medication history by SHIM took 12.2 (SD 5.4) minutes (range 3-50).

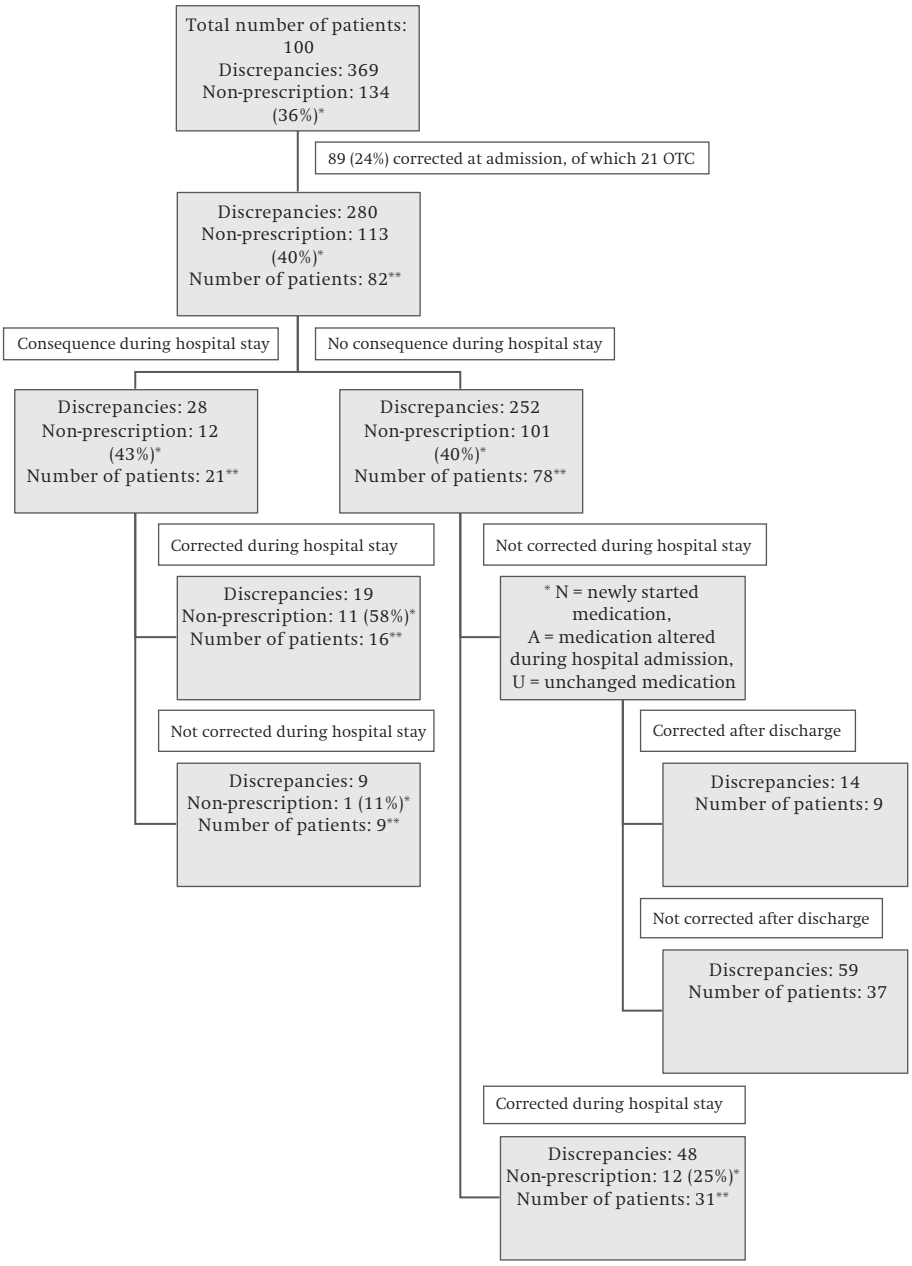

Figure 1 Susceptibility of older people for inappropriate prescribing

Discussion

This study shows that discrepancies between usual care and SHIM were found in 92% of patients; discrepancies between community pharmacy listings and SHIM were found in 88% of patients; 72% of these discrepancies were judged as potentially clinically relevant; 21% of patients experienced one or more consequences due to incorrect medication history taking on admission.

To the best of our knowledge, this is the first study to investigate actual consequences of observed discrepancies in patients during hospital stay. Other studies focused on the incident rate of consequences after discharge.(17) Since SHIM was successfully accomplished by both a medical student and a research-physician, SHIM does not need to be carried out by a physician. Nurses or pharmacy consultants can also be easily trained in taking SHIM, which could be cost-effective, considering the amount of discrepancies that can be prevented and the relatively short amount of time necessary.

The absence of a 'gold standard' makes it difficult to determine whether SHIM is a suitable method to obtain a correct overview of the actual pre-admission medication. However, combining different sources (medication vials, community pharmacy listings, interview with patient and/or carer) is the best possible way.(10) SHIM is the first method to combine these sources in a structured way.

We did not investigate whether uncorrected discrepancies had any consequences after discharge. Although many discrepancies were corrected during or after hospital admission, 59 out of 369 discrepancies (16%) were still relevant and continued to exist after discharge. Most of these discrepancies were prophylactic medication, such as folic acid, alendronate, or simvastatin, where consequences can only be expected in the long run. Our study population was too small for a reasonable follow-up of these patients.

Since this study was conducted on a geriatric ward with a particular interest in pharmacotherapy, the results of this investigation cannot be easily extrapolated to the general population. On the one hand, we expect the number of discrepancies to be lower in the general population, due to a lower prevalence of polypharmacy. On the other hand, since this geriatric ward specifically pays attention to pharmacotherapy, we would expect the number of discrepancies to be higher in the general population.

It is possible that the results of this study are overestimated, due to recall bias, since SHIM was accomplished after the medication history taking by the resident. Previous studies showed rates of discrepancies varying from 10-89%.(3;18-20) A possible explanation for the lower rates found in these studies, compared to this study, is that they were not conducted in a geriatric population, where the prevalence of polypharmacy is high. Polypharmacy is known to be an independent

risk factor for medication errors.(21) Furthermore, patients with cognitive impairment were excluded from these studies. Cognitive impairment could be a risk factor for the occurrence of medication discrepancies at admission. Additionally, there was considerable variation in the definition of discrepancies, which explains the large variation of discrepancies found in the previous studies. For example, some studies only included omission errors. Also, there was substantial heterogeneity in the methods used to obtain the comprehensive medication histories. For instance, one study relied solely on pharmacy listings.(22)

This study also shows that the number of discrepancies increased in cases of emergency admissions and use of polypharmacy. Omission was the most common type of discrepancy. This is in accordance with earlier studies.(5;16;18;23-27)

Most discrepancies were found in patients living at home without any care. Since these patients are the only ones in charge of their medication regimen, they probably do not have a well-registered medication overview. At hospital admission they are too ill to provide the physician with a correct medication history, and any accompanying relatives are unable to offer additional information. The availability of community pharmacy listings at admission could be a solution for this problem, however this study indicates that pharmacy listings alone are also an insufficient source of information.

Previous studies reported consequences in 5% of discrepancies, and we found the same rate.(28;29) However, these consequences occur in 21% of patients. This can be explained by the fact that the mean number of discrepancies per patient in our study is almost 4. It is remarkable that 43% of the actual consequences are caused by discrepancies in non-prescription drugs. This underlines the importance of including non-prescription drugs in taking the medication history. Consequences were mostly caused by discrepancies in drugs from the alimentary tract system and from the nervous system. The results of this study show that it is important to invest effort into obtaining an accurate medication history at admission.

Conclusion

This study shows that SHIM reveals discrepancies in the medication histories of almost all patients. Most of these discrepancies may cause patient harm. Community pharmacy listings alone are an insufficient source of information. Actual clinical consequences occur in one out of five patients, and almost half of these consequences are caused by discrepancies concerning non-prescription drugs. SHIM has the potential to prevent these problems and therefore is a successful first step in the medication reconciliation process.

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3.2

The use of a structured medication history for an accurate medication use at admission in the old age psychiatry: a prospective observational study

Meike C. Prins, A. Clara Drenth-van Maanen, Rob M. Kok and Paul A.F. Jansen

Abstract

Background: Implementation of medication reconciliation results in less adverse drug events (ADEs). The first step in medication reconciliation is the use of a structured interview about medication use. It is unknown whether a structured interview is of added value in the inpatient old age psychiatry.
Objective: We conducted a study in patients over 55 years, admitted to a psychiatric hospital, to examine the number of discrepancies in medication use revealed by the structured history of medication use (SHIM) checklist compared with the usual medication history taken at admission by the treating physician.
Study design: Prospective observational.
Setting: The inpatient old age psychiatry clinic of a large psychiatric teaching hospital in The Hague, the Netherlands.
Patients: All consecutive patients above 55 years of age admitted to the clinic from January until April 2011 were eligible for inclusion. 50 patients were included.
Intervention: The Structured HIstory taking of Medication use (SHIM) was performed in all included patients and compared to usual care in medication history taking.
Main outcome: Number of discrepancies found between the SHIM and usual care
Results: 100 discrepancies were found between the SHIM and the usual care (median 2,0 range 0-8). 78% (n=39) of the patients had at least one discrepancy. 69% were drug omissions. 82 % of the discrepancies were potentially clinically relevant. 14% of the discrepancies led to clinical consequences for the patient.
Conclusion: Medication history taking at admission to an old age psychiatry clinic can be improved. We believe that the SHIM has great value to create a complete and accurate overview of the medication used by the older patient admitted to a psychiatric hospital and to prevent clinically relevant ADEs.

Introduction

The presence of errors in medication histories is a classical problem concerning patient safety. Almost 60% of the medication histories at admission contain a discrepancy with the medication regimen used at home.[1-3] This causes problems during hospital admission: 25% of the prescription errors result from an erroneous medication history at admission.[4] These prescription errors may carry over to the next health care provider and thus affect patient safety, even after discharge.

A medication reconciliation process is known to reduce the number of medication discrepancies and adverse drug events (ADEs).[5-8] It consists of four steps: verification of medication charts, clarification of the medication and dosage (checked for appropriateness), comparing newly prescribed medication against old ones (documentation of changes to pharmacotherapy) and communication to the next health care provider.[5]

The first step in the medication reconciliation process consists of a structured interview on medication use. It is estimated that the sensitivity of such a structured interview in identifying the actual medication use by patients is 87-93%.[9] Especially older patients probably benefit from a structured medication interview at admission, since the prevalence of polypharmacy in older patients is high, and the risk of medication errors increases with the number of used medication.[10] Furthermore, older patients are more likely to receive prescriptions from multiple prescribers. Additionally, in case of cognitive impairment, patients may not be capable of reporting their medication correctly.

Structured history taking of medication use (SHIM) is developed to obtain an accurate pre-admission medication overview in older patients.[11] It combines a structured interview with the patient, and if needed also with the caregiver, with the information from community pharmacy listings and the medication vials brought by the patient. Comparing the SHIM with usual care in older patients admitted in a general hospital showed that 96% of the patients had at least one discrepancy with a mean of 3 discrepancies per patient. [11]

Reports about medication errors in inpatient old age psychiatry are scarce. Prevalence rates of overall medication errors described in studies vary widely due to differences in study design and denominators. [12,13] In the treatment of mental health problems prescription of medication might be vulnerable to errors due to different prescribers, patients' lack of insight and non-adherence.[14] To the best of our knowledge there are no studies that focus on improving medication history taking at admission in the old age psychiatry. If the results of the previously described study on the SHIM-method could be confirmed in the old age psychiatry setting, they would provide strong evidence for implementing SHIM in the inpatient old age psychiatry. Therefore, the main purpose of the present study is to

examine the number of discrepancies in medication use revealed by the SHIM compared with the usual practice of a medication history taken at admission in old age psychiatry patients.

Methods

Design and study participants

This study was conducted at the inpatient old age department of a large psychiatric teaching hospital in The Hague, the Netherlands. The unit contains 116 beds and has more than 400 admissions per year. Between January and April 2011 all consecutive patients above 55 years of age admitted to the clinic were eligible for inclusion. Patients who had severe cognitive impairments (eg acute psychosis or dementia) and had no caregiver and patients discharged before inclusion were excluded. All patients or caregivers gave written informed consent before inclusion. Since the Medical Research Involving Human Subjects Act (WMO) did not apply to this study, approval of the medical ethical committee of our hospital was not required.

Data collection

All eligible patients were asked to participate in the study directly after admission. An appointment for the interview was made separately from the usual care. Patients or caregivers were asked to bring all medication vials to this appointment. Furthermore, the community pharmacist was requested to provide a listing of the dispensed medication in the last six months. The exact use of the medication was verified by the SHIM (table 1), the community pharmacist list and the medication vials. All interviews were performed by the same researcher (M.C.P.).

The medication history was taken by the treating physician at admission according to the usual practice in our hospital. The medication history was extracted from the electronic chart in the 'history at admission' section and not from the electronic prescribing system in order to avoid intentional discrepancies, based on alterations made in the medication regimen at admission. After the SHIM was performed the medication list, retrieved with the SHIM, was compared to the usual care medication history. The number and description of the discrepancies between the two were registered. In order to prevent the physicians of altering the way of taking the medication history the treating physicians were not informed about the aim of the study.

Table 1 Structured History taking of Medication use (SHIM) questionnaire[11]

Questions asked per drug on the medication list, provided by the community pharmacist:
1. Are you using this drug as prescribed (dosage, dose frequency, dosage form)?
2. Are you experiencing any side effects?
3. What is the reason for deviating (from the dosage, dose frequency, or dosage form) or not taking a drug at all?
4. Are you using any other prescription drugs, which are not mentioned on this list? (View medication containers)
5. Are you using non-prescription drugs?
6. Are you using homeopathic drugs or herbal medicines (especially st. Johns wort)?
7. Are you using drugs that belong to family members or friends?
8. Are you using any drugs 'on demand'?
9. Are you using drugs that are no longer prescribed?
Questions concerning the use of medicines:
10. Are you taking your medication independently?
11. Are you using a dosage system?
12. Are you experiencing problems taking your medication?
13. In case of inhalation therapy: What kind of inhalation system are you using? Are you experiencing any problems using this system?
14. In case of eye drops: Are you experiencing any difficulties using the eye drops?
15. Do you ever forget to take your medication? If so, which medication, why, and what do you do?
Other
16. Would you like to comment on or ask a question about your medication?

Outcome

The main outcome measure was the number of discrepancies between the SHIM and the usual practice of taking a medication history. Three types of discrepancies were defined: omission, addition and discrepancies in dosage or dose frequency of the medication.

Furthermore, the clinical relevance of the discrepancies was classified independently by a geriatrician-pharmacologist (P.A.F.J.) and a geriatrician-pharmacologist in training (A.C.D.M.) according to the classification of Cornish et al.[3] Cases of disagreement were discussed until consensus was reached. Based on ethical considerations, the treating physician was informed about the discrepancies retrieved with the SHIM in order to resolve or to be aware of the discrepancy. Alterations to the prescribed medication were monitored and categorized into implementation before or after

the SHIM. This categorization was counted for in the classification of the discrepancies. The electronic charts of participating patients were searched for possible ADEs, caused by the discrepancies. The causality of the ADE was estimated using the Naranjo Scale.[15]

Statistical analysis

Statistical analyses were performed using SPSS (version 18; SPSS Inc. Chicago, Ill). Normal distribution of the discrepancies was reached by log transformation. Linear regression was used to explore the relation between baseline variables and the number of discrepancies.

Results

During the study period of three months 99 patients were eligible for inclusion of which 50 patients were included. In total 49 patients were excluded, reasons for exclusion are shown in figure 1.

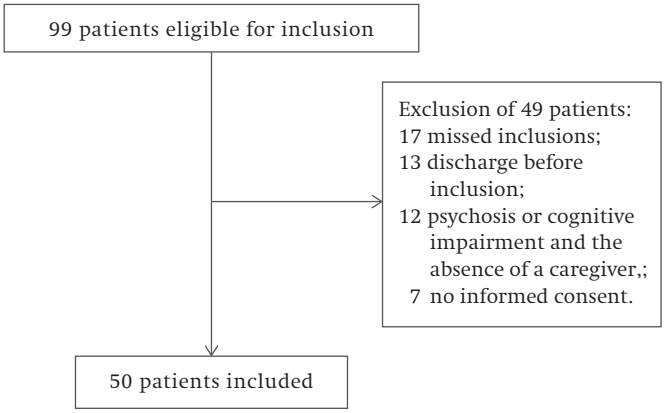

Figure 1 Inclusion process

Table 2 shows the patient characteristics of the 50 included patients. Fifty-two% of the study population was female, the mean age was 68,9 years old, the majority was admitted because of a major depression.
The SHIM was performed after admission at a mean of 6,46 days (range 0-14 days). The time used to take SHIM was 8 minutes (range 3-21 min). In 14 % of the cases the SHIM was performed with the help of a caregiver.

Table 2 Baseline Characteristics of 50 patients

Male gender (%)	24 (48)
Mean age in years (SD)	68,9 (8,3)
Mean number of medication on admission (range)	6.36 (0-15)
Admission diagnosis:	
- major depression (%)	23 (46)
- alcohol dependence (%)	6 (12)
- dementia / cognitive disorders (%)	6 (12)
- other: personality disorder, anxiety disorder, mania (%)	11 (22)
Residence:	
Home alone (%)	30 (60)
Home with caregiver or family (%)	15 (30)
Nursing home (%)	5 (10)
Medication use:	
Independent (%)	30 (60)
Dependent (%)	20 (40)

Main outcome

In total 100 discrepancies were found between the usual practice of taking a medication history and the SHIM. Thirty-nine patients (78%) had at least one discrepancy. Sixty-nine% were drug omissions. The types and number of discrepancies are described in figure 2.

Most discrepancies were found in medicines for somatic diseases (68%). They mainly concerned the following medication groups: gastro-intestinal medication (21%), vitamins on prescription (18 %), analgesics (15 %) and benzodiazepines (14%). Thirty-two% of the discrepancies concerned psychotropic medication of which 44% were benzodiazepines, 25% antidepressants and 15% antipsychotic medication. The minority (27%) of the discrepancies were corrected by the treating physician before the SHIM was taken.

According to the classification of Cornish et al., most discrepancies (82%) had the potential to result in moderate or severe discomfort or clinical deterioration (class 2 and 3). The number of psychotropic medication and medication for somatic diseases were equally divided in these groups. Discrepancies with clinical consequences and adverse drug events are shown in table 3.

Of the 41 discrepancies that could lead to severe discomfort 14 resulted in clinical consequences during the admission divided over 24% (n=12) of the study population. The clinical consequences comprised increased pain, constipation, detoxification-

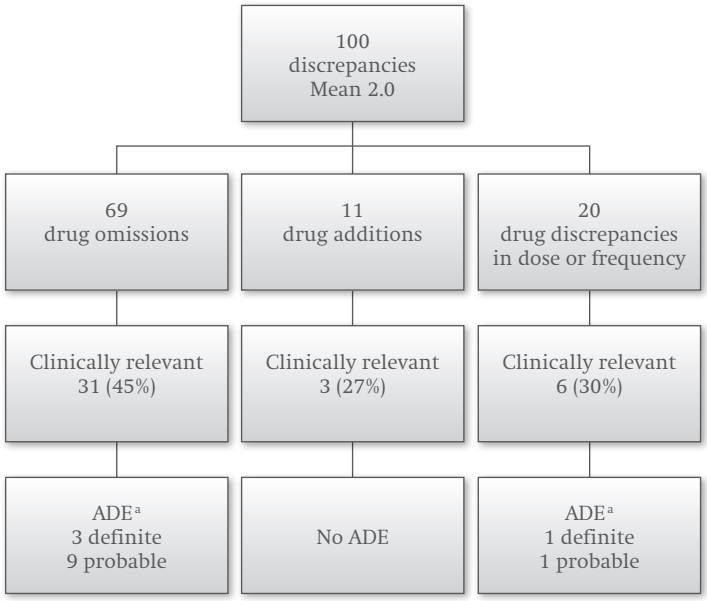

Figure 2 Number, type of discrepancies and clinical relevance

[a] Classification of causality according to the Naranjo scale[15]

rebound symptoms and hypertension (Table 3). One serious ADE occurred, namely a stomach perforation in a patient using an over the counter NSAID and cimetidine after both medications were omitted at admission. The patient had continued the unprescribed NSAID.

The amount of discrepancies was significantly increased by the amount of used medication and emergency admissions. Other factors like age, duration of hospital stay, dependent or independent medication use at home or residence did not predict the number of discrepancies (Table 4).

Table 3 The discrepancies with class 3 potentially severe clinical detoriation and actual clinical consequences and adverse drug events (ADE) (n = 14)

Type of medication	Type of discrepancy	ADE	Causality [a]
fentanyl	omission	recurrence of pain	probable
levodopa / carbidopa	Dose	parkinsonism	probable
oxazepam	dose	rebound symptoms	probable
acetaminophen	omission	pain	probable
lidocaine gel	omission	pain	probable
cimetidine	omission	stomach perforation	probable
oxazepam	omission	affective symptoms	probable
metoprolol	omission	hypertension	probable
risperidon	omission	progress psychosis	probable
acetaminophen/ codein	omission	pain	probable
oxazepam	dose	affective symptoms	definite
NSAID	omission	stomach perforation	definite
omeprazol	omission	naesea	definite
movicolon	omission	constipation	definite

[a] Classification of causality according to the Naranjo scale (15)

Table 4 Linear regression analysis

	B coefficient	95% confidence interval for B
Sex	0,104	- 2,44 to 0,452
Age	0,011	- 0,01 to 0,03
Emergency admission	0,373	0,03 to 0,71
Number of medication at admission	0,063	0,02 to 0,11
Number of somatic diseases	0,008	- 0,12 to 0,13
Duration of hospital stay	0	- 0,01 to 0,01
Time to interview with SHIM	0	- 0,05 to 0,05
Way of medication use	- 0,044	- 0,43 to 0,35

Associations between number of discrepancies and baseline variables

Discussion

This study showed that the actual use of medication at home of older patients, admitted at a psychiatric hospital, was largely discrepant with the medication history retrieved with the usual care. Compared to usual care the SHIM discovered in 78% of the cases discrepancies in medication use at admission (median 2,0 range 0-8). 82 % of the discrepancies were potentially clinically relevant. 14% of the discrepancies led to clinical consequences for the patient. Only 27% of the discrepancies were rectified by the physician shortly after admission. Polypharmacy and emergency admission were significant related to higher rates of discrepancies. The results of this study suggest that in an old age psychiatry inpatient clinic the frequency of discrepancies in medication at admission are at least as high as in previous studies conducted in general hospitals. Depending on the population studied, rates of discrepancies range from 54% in general medicine to 96% found with the SHIM in a geriatric hospital population.[2,3,11]

A large part of the discrepancies regarded non-psychotropic medication. There are no comparable studies in the inpatient old age psychiatry. These numbers can only be compared to studies that discuss prescription or medication errors as a whole in the inpatient old age psychiatry. Two studies each evaluating prescription errors as a whole in psychiatric hospitals in older patients reported a prescription error rate of 69,3% and 66,7% concerning non psychotropic medication.[17,18]) The high burden of somatic morbidity in older patients probably explains this observation.[13] Additionally, psychiatrists and physicians working in a psychiatric hospital might be less familiar with prescribing medication for somatic diseases. One third of the discrepancies are psychotropic medication, of which 44% benzodiazepines and 25% antidepressants. Fourteen % of the discrepancies led to clinical consequences during admission, in the study conducted with the SHIM in a geriatric department of a university hospital 5% of the discrepancies had clinical consequences.[11]

This is, to the best of our knowledge, the first prospective observational study in the inpatient old age psychiatry, which focuses on the first step of the medication reconciliation process. Also, this study investigates the actual clinical relevance, as well as the clinical consequences of discrepancies in the medication history. Furthermore, this study also assessed whether discrepancies were rectified during admission without intervention of the SHIM.

Several limitations apply to this study. The first limitation is the absence of a gold standard for obtaining an accurate medication history. Nevertheless, we believe that the SHIM combines the best available evidence for obtaining an accurate medication history. Second, SHIM was in most cases not conducted directly after admission, what ideally would be the case. Due to logistic limitations (one researcher) it took 6.5 days (range 0-14) before the SHIM was conducted. It is therefore possible that

the study results are influenced by recall bias. After a period of admission patients might forget what they used at home. This could have underestimated the number of discrepancies found in our study. Third, information bias due to a relatively low participation of a caregiver at the interview might decrease the reliability of the SHIM, especially since people with a major depression or alcohol dependency may suffer from concentration problems and thus memory problems. In 40 % of the study population a caregiver was involved with the medication use and in only 14 % of the SHIM's performed a caregiver participated in the interview. Fourth, the results of this study may not be easily generalizable, since it was conducted in a specific population in one psychiatric clinic for older patients. In addition, the presence of cognitive disorders and psychotic disorders in the study population was relatively low. In these patients the absence of a caregiver was the main reason for exclusion.

The amount of discrepancies found suggests that the usual care of medication history taking is insufficient. We believe that the SHIM has great value to create in a relatively short amount of time a complete and accurate overview of the medication used by the older patient admitted to a psychiatric hospital and thereby contributive in preventing clinically relevant ADEs.

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3.3

Effect of a discharge medication intervention on the incidence and nature of medication discrepancies in old patients

A. Clara Drenth-van Maanen, Ingeborg Wilting, Paul A.F. Jansen, Rob J. van Marum, Toine C.G. Egberts

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(Letter to the Editor)

Abstract

Background - Medication discrepancies after hospital discharge are common.
Objective - To investigate the influence of a discharge medication intervention on the incidence and nature of medication discrepancies after hospital discharge.
Study design – Prospective study with a control/intervention design from August 2010 to February 2011.
Setting – Acute care geriatric ward of a Dutch tertiary teaching hospital.
Participants – 85 patients, discharged in stable medical condition.
Intervention - Patient instruction and a structured medication overview for patient and next health care provider.
Main outcome measures - Medication discrepancies were assessed during a home visit one week after discharge and classified as intentional or unintentional. Unintentional discrepancies were classified as patient based and system based and assessed for potential harmfulness.
Results – 41 patients were included in the control group and 44 in the intervention group. The overall incidence of medication discrepancies did not differ between the two groups (13.5% control vs. 10.9% intervention; HR 0.82, 95% CI 0.52-1.93). There were fewer patient based unintentional discrepancies in the intervention group compared with the control group (2.4% vs. 0.8%; HR 0.34, 95% CI 0.21-0.94) but there were more system based discrepancies (1.2% vs. 2.6%; HR 2.16, 95% CI 0.87-5.24). Additionally, there were fewer intentional discrepancies in the intervention group (9.9% vs. 7.5%; HR 0.77, 95% CI 0.52-1.14), as did potentially harmful discrepancies (34.1% vs. 18.2% %; HR adj. 0.32, 95% CI 0.11-0.95).
Conclusion – The discharge medication intervention did not lower the incidence of medication discrepancies after hospital discharge, but it did influence the nature of the discrepancies (from mainly patient based to mainly system based) and fewer patients experienced potentially harmful consequences of these discrepancies.

Introduction

A patients' medication record is continuously subject to documentation, communication and interpretation by health care professionals and patients. Inadequate documentation, communication and interpretation can lead to medication discrepancies, which can adversely affect patient safety.[1-9] Medication discrepancies can be either intentional or unintentional. In the case of intentional discrepancies, the actual medication used by the patient differs from that recorded, for example, because the physician has modified the medication regimen, but not documented the modification. In the case of unintentional discrepancies, the medication used by the patient differs from that recorded, e.g. because of incorrect interpretation of the medication record by the patient, or due to administration or dispensing errors. Hospitalization is a major risk factor for discrepancies.[5,10-13] Three main causes are recognized for discrepancies after hospital discharge: inaccurate medication charts at admission, poor communication with the next health care provider, and insufficient patient involvement.[11-15]

Several studies and guidelines have focused on improving medication charts at admission and communication between health care providers.[2,16-21] Less attention has been paid to the active involvement of the patient. While hospitalized patients are often helped by hospital staff to prepare and take their medication, after discharge they are abruptly expected to manage their medication themselves.[11] It has been shown that active patient involvement with the discharge medication regimen improves their knowledge of their medication and leads to adjustments of discharge prescriptions, for example if a patient does not wish to continue using benzodiazepines at home.[22-24] However, studies of patient involvement in medication use have not investigated medication use after discharge from hospital, nor did they address inaccurate admission medication charts. Thus it is not clear whether the incidence and nature (i.e. causes and potential consequences) of medication discrepancies after discharge from hospital can be changed by a discharge medication intervention addressing the three causes of discrepancies.

The main objective of this study was to investigate the effect of a multicomponent transitional pharmaceutical care intervention that addresses all three main causes of unintentional discrepancies on the incidence and nature of medication discrepancies in a geriatric population after hospital discharge.

Methods

Setting and study population

The study was conducted on a 12-bed acute care geriatric ward of the University Medical Center Utrecht (UMCU), a tertiary teaching hospital in the Netherlands. All patients admitted to this ward from August 2010 to February 2011 were eligible for participation. Patients were excluded if they met one of the following criteria: transfer to another ward or hospital, discharge within 48 hours of admission or outside office hours, terminal disease at discharge, death during hospitalization, no informed consent, or severe cognitive impairment and no caregiver. The medical ethics committee of the UMCU considered that the Medical Research Involving Human Subjects Act (WMO) did not apply to this study.

Design

This prospective study had a control/intervention design. Patients that were admitted during the first three months formed the control group, and patients admitted in the subsequent three months formed the intervention group. Patients could not participate more than once in the same group. Information on age, gender, duration of hospital stay, type of admission (elective versus emergency), reason of admission, presence of a caregiver, and residence at admission and discharge was collected.

Transitional pharmaceutical care

At admission, the medication history of all patients was taken using the 'Structured HIstory taking of Medication use' (SHIM) method. Previous research has shown this to be an accurate method for recording the medication history,[21,25] and thus its use circumvents the first main cause of unintentional discrepancies, namely, inaccurate medication charts at admission, which might be carried over to the discharge medication record. In the control group, the discharge procedure was performed as usual, i.e. the day before discharge the resident printed the discharge prescriptions from the hospital's computerized physician order entry (CPOE) and faxed them to the community pharmacy for dispensing. These prescriptions contained information on the names, dosages, and dosage frequencies of the concerning medications; discontinued medications were not mentioned. On the day of discharge, a discharge letter with a copy of the discharge prescriptions was sent by post to the patient's primary care physician and given to the patient or his/her caregiver. In the intervention group, the multicomponent transitional care intervention was implemented, i.e. a pharmacy technician compared the discharge prescriptions with the admission medication chart, clarified undocumented differences with the resident, and subsequently documented them for both patient

and next health care provider in a structured medication overview (SMO). This overview contained additional information on the indication, intake instructions, discontinuation date if applicable, and reasons for initiation, changes, and discontinuation of medications. On the day of discharge, the SMO was faxed to the community pharmacist and the primary care or nursing home physician, with additional information on renal function, sodium and potassium values, and specific monitoring advice, if appropriate, and given to the patient and/or the caregiver. The pharmacy technician told the patient and/or caregiver about the names, dosages, indications, intake instructions, and possible adverse effects of all prescribed medications. Special attention was paid to alterations to the medication or intake regimen and, if relevant, the reasons why medications had been withdrawn.

Outcome

The primary outcome was the incidence and nature of discrepancies in actual medication use one week after discharge compared with the discharge medication prescriptions. The secondary outcome was the patients' and/or caregivers' knowledge of the prescribed medications.

All patients were visited one week after discharge by one of the researchers (CD or EM). First, discrepancies were assessed, using the SHIM. If present, the nature of these discrepancies was investigated by asking the patient and/or the caregiver, and if necessary the treating physician, nurse, or community pharmacist, about the changes. This information was used to classify the discrepancies as intentional or unintentional.

Discrepancies were considered intentional if the primary care physician had made post-discharge modifications in the medication record, if the patient intentionally deviated from the discharge medication record, or if the community pharmacist had corrected errors in the discharge receipts. All other discrepancies were considered unintentional, and these were classified as patient or system based. Examples of patient based unintentional discrepancies include unintentional non-adherence and unintentional continuation of discontinued medication.[26] Examples of system based unintentional discrepancies are dispensing errors, prescribing errors due to incorrect assimilation of the discharge medication record by the nursing home physician or the primary care physician, and administration errors by the home care or nursing home nurses. The potential harmfulness of unintentional discrepancies was assessed by two clinical pharmacologists (PJ and RM), using the classification system of Cornish et al.[5] Cases of disagreement were discussed until consensus was reached.

The patients' knowledge of indications, intake instructions, adverse effects, and discontinuation date was investigated for each medication used by asking them whether they knew what the medication was for, whether they knew how to take

the medication (dosage, administration schedule), whether they knew if the medication had unwanted effects, and if so, what effects, and whether they knew when they could stop taking the medication. Answers were classified as correct or incorrect. Knowledge of the indication was considered correct if the patient or the caregiver mentioned the correct indication at a disease level and/or organ level (e.g. heart failure or medication for the heart). Knowledge of the intake instructions was considered correct if the patient or the caregiver mentioned the prescribed administration schedule, including intake advice (such as fasted). Knowledge of adverse effects was considered correct if the patient or the caregiver correctly mentioned one common adverse effect of the medication concerned. Knowledge of the duration of medication use (question 4) was only recorded if a discontinuation date had been given. This knowledge was considered correct if the patient/caregiver knew the exact discontinuation date.

Data analysis

The incidence and types of discrepancies between the control and the intervention groups were compared using descriptive statistics with subsequent calculation of the relative risk and 95% confidence intervals. Patients with and without post-discharge medication discrepancies were compared using Cox regression analysis. Baseline characteristics considered potential confounders were analyzed separately in the regression model.

The difference in patient knowledge of medications between the control and the intervention groups was compared using descriptive statistics. The relative risks with the 95% confidence intervals were calculated, stratified for newly prescribed, modified, and unmodified medications.

Statistical analyses were performed with SPSS version 15.0 (SPSS Inc., Chicago, IL, USA).

Results

Baseline characteristics

Eighty-five patients were included: 41 in the control group and 44 in the intervention group (Figure 1). Both groups were comparable with respect to mean age (83 years), gender (about one third men), and mean number of medications used at admission (10) (Table 1). The most frequent reason for admission was gastrointestinal disease in the control group and delirium in the intervention group (19.5% and 31.8% of patients, respectively), the mean hospital stay was 12 days in the control group and 16 in the intervention group ($p<0.05$), and 82.9% of medications were delivered weekly by the pharmacy in the control group and 61.4% in the intervention group ($p<0.05$).

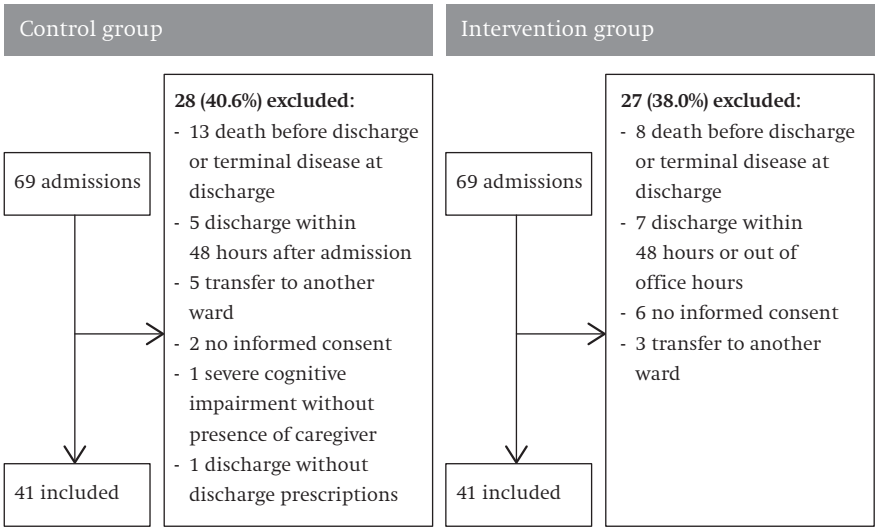

Figure 1 Inclusion Procedure

Incidence of medication discrepancies

In the control group, 583 discharge prescriptions were analyzed and 13.6% (n=79) contained discrepancies (Table 2); these discrepancies concerned 81% of patients (n=33). Of those who experienced discrepancies, 31% experienced a single discrepancy, 34% experienced two discrepancies, and 35% experienced three or more discrepancies (Figure 2).

In the intervention group, 611 prescriptions were analyzed and 11% (n=67) contained discrepancies; these discrepancies concerned 66% of patients (n=29). Of those who experienced discrepancies, 34% experienced a single discrepancy, 17% experienced two discrepancies, and 49% experienced three or more discrepancies (Figure 2). The number of patients with prescription discrepancies differed (81% vs. 66%), but not significantly, between the control and the intervention groups (adjusted HR 0.84 (95% CI 0.47-1.49) and nor was there a significant difference in the proportion of discrepancies at a prescription level (13.5% vs. 10.9%; HR 0.82, 95% CI 0.59-1.14).

Overall, the main discrepancies concerned changes to the intake regimen (19.7%; RR 2.46, 95% CI 1.47–4.04) or involved newly prescribed medication (15.6%, RR 1.95, 95% CI 1.25-3.03). There were few discrepancies concerning discontinued medications (1.0%; RR 0.13, 95% CI 0.03-0.42).

Table 1 Linear regression analysis

Characteristic	Control (N=41)	Intervention (N=44)
Age, years (SD)	83 ± 5	83 ± 7
Male gender, %	29.3	36.4
Independent medication use, %	19.5	18.2
Weekly delivery by pharmacy before admission, %	72.5	56.8
Weekly delivery by pharmacy after discharge, %	82.9	61.4
Presence of caregiver (at discharge and home visit), %	73.2	72.7
Living situation, %		
Community living	31.7	34.1
Community living with professional care	39.0	38.6
Residential home	22.0	18.2
Nursing home	7.3	9.1
Reason for admission, %		
Infection	12.2	25
Cardiovascular disease	7.3	6.8
Pain	14.6	9.1
Gastrointestinal disease	19.5	4.5
Delirium	7.3	31.8
Decreased mobility	7.3	9.1
Electrolyte disorder	7.3	2.3
Other	24.4	11.4
Emergency admission, %	48.8	65.9
Medications on admission, number (SD)	10.7 ± 4.0	10.1 ± 5.8
Medications at discharge, number (SD)	10.2 ± 3.6	9.9 ± 4.2
Length of hospital stay, mean number of days (SD)	12.3 ± 7.5	16.1 ± 7.6
Days until home visit since discharge, median (range)	7 (3-22)	8 (4-25)

Nature of medication discrepancies

Medication discrepancies were classified as unintentional and intentional. The unintentional discrepancies were subdivided into patient based and system based, and the potential harmfulness was assessed. The intentional discrepancies were subdivided into patient initiated, physician initiated, and community pharmacist initiated (Figure 3).

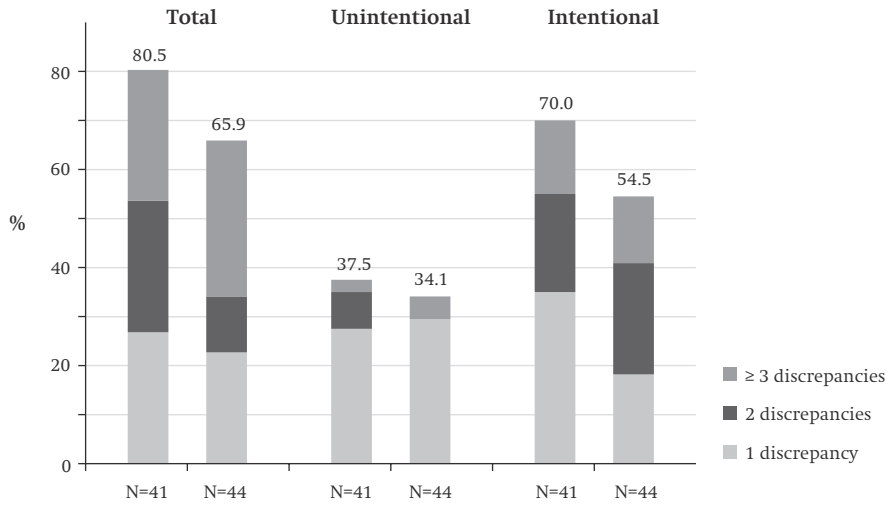

Figure 2 Patients with One or More Discrepancies after Discharge

The left bars represent the control group, the right bars the intervention group.

Unintentional medication discrepancies

Unintentional discrepancies were found in 3.6% (n=21) of the control group prescriptions and in 3.4% (n=21) of the intervention group prescriptions (HR 0.94, 95% CI 0.52-1.93). Of these discrepancies, 2.4% (n=14) were patient based and 1.2% (n=7) were system based in the control group compared with 0.8% (n=5) and 2.6% (n=16), respectively, in the intervention group. Common examples of patient based discrepancies were unintended continuation of the pre-admission medication schedule and unintended non-adherence to newly prescribed medication. Common examples of system based discrepancies were dispensing errors and prescribing errors, such as the prescription of calcium carbonate by the nursing home physician instead of calcium carbonate in combination with cholecalciferol. The observed difference in the incidence of patient based discrepancies and system based discrepancies was not significant (Table 2).

Overall, 3.3% (n=19) of the discrepancies in the control group prescriptions and 1.8% (n=11) of the discrepancies in the intervention group prescriptions were potentially harmful (Table 2). These prescriptions were intended for 14 patients in the control group and 8 patients in the intervention group (HR 0.32, 95% CI 0.11-0.95). Potentially harmful discrepancies included unintended discontinuation of dalteparin, unintended discontinuation of allopurinol, and use of non-prescribed ibuprofen.

Table 2 Medication Discrepancies

Discrepancies	Prescription level Number of prescriptions			Patient level Patients with 1 or more discrepancies		
	Control N=576	Intervention N=611	HR (95%-CI)	Control N=41	Intervention N=44	Adj. HR* (95%-CI)
Incidence						
Total	13.5% (78)	10.9% (67)	0.82 (0.59-1.14)	80.5% (33)	65.9% (29)	0.84 (0.47-1.49)
Nature						
Unintentional	3.6% (21)	3.4% (21)	0.94 (0.52-1.93)	39.0% (16)	34.1% (15)	0.87 (0.39-1.95)
Patient based	**2.4% (14)**	**0.8% (5)**	**0.34 (0.21-0.94)**	24.4% (10)	11.4% (5)	0.66 (0.21-2.08)
System based	1.2% (7)	2.6% (16)	2.16 (0.87-5.24)	17.1% (7)	22.7% (10)	1.04 (0.33-3.32)
Intentional	9.9% (57)	7.5% (46)	0.77 (0.52-1.14)	70.7% (29)	52.3% (23)	0.78 (0.41-1.45)
Patient initiated	2.3% (13)	1.5% (9)	0.65 (0.28-1.52)	19.5% (8)	13.6% (6)	0.88 (0.24-3.28)
Physician initiated	5.0% (29)	6.0% (37)	1.20 (0.74-1.96)	51.2% (21)	45.5% (20)	0.89 (0.44-1.79)
Pharmacist initiated	**2.6% (15)**	**0.0% (0)**	**0.01 (0.00-0.92)**	29.3% (12)	0% (0)	-
Severity						
Potentially harmful	3.3% (19)	1.8% (11)	0.88 (0.45-1.74)	**34.1% (14)**	**18.2% (8)**	**0.32 (0.11-0.95)**

*Adjusted for: age, gender, weekly delivery by pharmacy, reason of admission, and number of medications at discharge

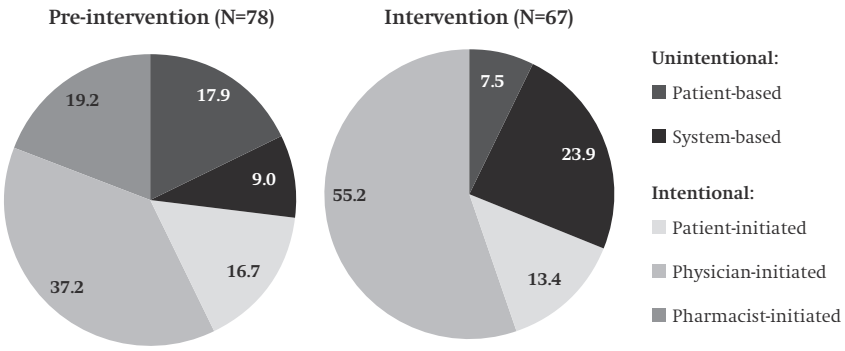

Figure 3 Nature of Discrepancies in Percentages

Intentional medication discrepancies

Ten percent (n=57) of the control group prescription discrepancies were intentional, patients initiated 2.3% (n=13), physicians 5.1% (n=29), and pharmacists 2.6% (n=15); 7.5% (n=46) of the intervention group prescription discrepancies were intentional: patients initiated 1.5% (n=9), physicians 6% (n=37), and pharmacists initiated none. Intentional discrepancies were less frequently found in patients in the intervention group, 52.3% (n=23) versus 70.7% (n=29), although significance could not be reached.

Patient knowledge

Patient knowledge of intake instructions was better in the intervention group than in the control group (87.4% vs. 55.8%; RR 1.57, 95% CI 1.43-1.69), with 16.5% and 7.1% of patients in these groups knowing about possible adverse effects (RR 2.32, 95% CI 1.50-3.63). The intervention did not significantly influence patient knowledge of the indication (67.3% control vs. 63.1% intervention) or discontinuation date (35.3% control vs. 41.7% intervention) of prescribed medications. Stratification for newly prescribed medication, modified prescriptions, or unmodified prescriptions did not alter these results.

Medication knowledge was not associated with medication discrepancies: discrepancies were found in 13.7% (n=31) of the prescriptions of patients with inaccurate and in 10.9% (n=63) of prescriptions of patients with accurate knowledge of medication intake instructions (p=0.26).

Discussion

The results of this study suggest that the multicomponent transitional pharmaceutical care intervention primarily influenced the nature of medication discrepancies: there was a shift in unintentional discrepancies from mainly patient based to mainly system based. Community pharmacists no longer needed to intervene because of errors in the discharge receipts, and fewer patients experienced potentially harmful discrepancies. Although the incidence of medication discrepancies decreased from 13.5% to 10.9% of the discharge prescriptions affecting 81% and 66% of the patients, respectively, the differences were not significant. The proportion of medication discrepancies in both groups (81% in the control group and 66% in the intervention group) was higher than that reported in previous studies. Coleman et al. found discrepancies in 14% of the study population, and Linquist et al. detected discrepancies in 56% of subjects.[11,27] However, both of these studies took place in non-geriatric departments in secondary care settings.

This is the first study to investigate the effectiveness of a multicomponent intervention on the incidence and nature of medication discrepancies after hospital discharge. We hypothesized that the intervention, which simultaneously addressed the three main causes of unintentional discrepancies (inaccurate medication charts at admission, poor communication with the next health care provider, and insufficient patient involvement), would mainly decrease the incidence of unintentional medication discrepancies after hospital discharge. The finding of a nonsignificant increase in system based unintentional discrepancies was not expected and might have been due to sender (hospital) and receiver (next health care provider) factors. The most important sender factor was a delay in sending the SMO, which was sent to the primary care physician and the community pharmacist on the day of discharge, whereas the discharge prescriptions had already been faxed to the community pharmacy a day before discharge in order to enable the community pharmacy to dispense the medications in time. In several cases, the SMO differed from the discharge prescriptions due to last-minute adjustments, resulting in misunderstandings and misinterpretations. The most important receiver factor was the limited ability of the next health care provider's computer system to process the information on discharge medication, such as discontinuation of medication, which resulted in drug dispensing errors and subsequently in errors in medication use by the patient. Hence, in order to further optimize transitional pharmacotherapeutic care, not only is unambiguous and timely communication of information to both patient and next health care provider essential to prevent unintentional medication discrepancies, but also correct processing of this information into the information systems of health care providers. Currently, physicians need to process information from other health care providers manually into their information

systems. Methods that facilitate processing of information, such as electronic communication or linking of information systems, may improve correct implementation of information into health care providers' information systems.
An important limitation of this study was that the main presenting ailment or condition was different in the control and the intervention groups (gastrointestinal disorders and delirium, respectively). Delirium could have adversely influenced the cognitive status of patients and their ability to provide accurate information about medication use. However, in most cases (both in the control and the intervention groups), the discharge and home interviews were conducted in the presence of both the patient and the caregiver who was in charge of the medication regimen in the home situation; only two patients admitted for delirium were interviewed on their own during the home visit (one control, and one intervention patient). Furthermore, the results of this study were corrected for the reason for admission, and so we think that this difference in admission diagnosis would have had a minimal effect on results. Lastly, the low number of study participants could also have influenced study outcomes.

Conclusion

Although a multicomponent transitional care intervention did not significantly decrease the incidence of medication discrepancies, it reduced the number of patients with potentially harmful discrepancies and altered the nature of the discrepancies from mainly patient based to mainly system based. In order to actually decrease the incidence of unintentional medication discrepancies, information should be sent to the next health care provider in a timely and unambiguous fashion, and this information should be correctly incorporated into their information systems.

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3.4

The effect of a transitional pharmaceutical care intervention at hospital discharge on the implementation of changes to patients' medication regimens into community pharmacists' and general practitioners' patient files

A. Clara Drenth-van Maanen, Geert J. Lefeber, Ingeborg Wilting, Paul A.F. Jansen, Rob J. van Marum, Toine C.G. Egberts

Abstract

Background – Community pharmacists (CPs) and general practitioners (GPs) often receive insufficient information on changes to the medication regimen made during hospitalisation. Consequently, these changes may not be implemented in primary care and patient safety may be compromised.

Objective – To investigate the effect of a transitional pharmaceutical care intervention at discharge on the implementation of changes to patients' medication regimens into CPs' and GPs' patient files.

Methods – A prospective study with a control/intervention design was conducted at a 12-bed acute care geriatric ward in a tertiary hospital in the Netherlands. In the intervention group a structured medication overview (SMO) was provided to the patient, the CP and the GP. On this overview, all changes to the medication regimen were clarified. The implementation of changes to the medication regimen into the CPs' and GPs' patient files was compared between the control and the intervention group.

Results – For the CP analyses 67 patients were included (30 control, 37 intervention). For the GP analyses 65 patients were included (30 control, 35 intervention). CPs implemented changes to the admission medication regimen in 84.0% of cases in the control group, compared to 84.1% in the intervention group (HR 1.00; CI 95% 0.83 – 1.21). GPs incorporated changes in 64.6% of cases in the control group, and in 67.5% of cases in the intervention group (HR 1.05, 95% CI 0.84-1.30).

Conclusions – A transitional pharmaceutical care intervention does not improve implementation of changes to the medication regimen into the CPs' and GPs' patient files. Linking of patient files and standardised processing instead of manual processing of SMO's may improve continuity of pharmaceutical care.

Introduction

During hospital admission the medication regimens of many patients require changes and consequently patients usually leave the hospital with a medication regimen that differs from that prior to admission.[1-4] One study reported that in 98% of patients the medication regimen is altered during admission and in 60% of patients five or more changes are effectuated.[5]

After hospital discharge these changes frequently are unintentionally not continued, due to insufficient communication between primary and secondary care and insufficient active patient involvement.[6] Information on the medication regimen is currently mainly communicated by the hospital through discharge letters for the general practitioners (GPs) and discharge receipts for the community pharmacists (CPs). These letters and receipts often do not contain information on reasons for changes to the medication regimen.[1, 7, 89]

Recently, a study has been published in which the informational preferences of GPs regarding discharge medication were investigated.[10] The main results of this study were that GPs considered information on the discharge medication regimen one of the most important items of information transfer, and they preferred to receive this information on the day of discharge by e-mail, containing whether and why medication had been stopped, initiated, and changed during hospitalisation.

Many studies have focused on improving transitional pharmaceutical care, for example by providing a structured medication overview (SMO) at discharge.[2, 6, 11-16] An SMO includes information on the intended medication regimen as well as information on changes to the medication regimen and reasons explaining these changes. However, these studies did not investigate whether medication changes are actually implemented into the patient files of CPs and GPs. Only two studies focused on the implementation of changes by CPs, with conflicting results.[17, 18] Lalonde et al. compared the discharge medication prescriptions to community pharmacy records of patients with or without medication discharge plans and they did not find an improvement of implementation of changes into the community pharmacy records when medication discharge plans were provided. Contrary, Paquette et al. found that the conformity rate with discharge medications improved significantly after the introduction of a new discharge prescription form. However, these two studies differed with respect to study population, usual care transitional care and the transitional care in the intervention. Continuity in pharmacotherapeutic care can only be ensured when CPs and GPs both receive complete and structured information on the discharge medication regimen, as well as implement this information into their patient files allowing it to be readily available in case of a new change to the medication regimen or a new transfer to another health care setting.[19]

The objective of this study was to investigate whether a transitional pharmaceutical care intervention at hospital discharge improves the implementation of changes to patients' admission medication regimens into CPs' and GPs'patient files.

Methods

Setting and study population

A prospective study with a control/intervention design was conducted at a 12-bed acute care geriatric ward of the University Medical Center Utrecht (UMCU), a tertiary teaching hospital in the Netherlands. All patients admitted to this ward between August 2010 and February 2011 were eligible for inclusion. Patients that were admitted during the first three months were included in the control group; patients admitted during the following three months were included in the intervention group. Patients were excluded if they met one of the following criteria: no discharge to home, discharge within 48 hours after admission or outside office hours, death before discharge or terminal disease at discharge, no discharge prescriptions, no changes to the medication regimen, no medication history received from the CP or GP and no informed consent. Patients could not be included more than once into the same group. The Medical Ethics Committee of the UMCU waived this study from review as the Dutch legislation does not require this for studies that do not affect the patient's integrity. CPs and GPs were unaware that the study was being conducted.

Transitional pharmaceutical care

In the control group, the discharge medication regimen was communicated according to usual care, i.e. the day before discharge the resident printed the discharge receipt from the hospitals' computerised physician order entry (CPOE), which was subsequently faxed to the community pharmacy for a 30-day dispensing. The discharge receipt contained information on the names, dosages and dosage frequencies of the medications that the patient was intended to use after discharge, including newly prescribed and altered medications; there was no emphasis on, or clarification of, changes made to the medication regimen. Medications used before or during admission but that were stopped during admission were not on the discharge receipt. On the day of discharge, a short summary of the hospital admission with a copy of the discharge receipt was sent by post to the general practitioner. In some cases, the short summary of the hospital admission contained information on changes made to the medication regimen. For example when a patient was admitted because of heart failure, the short summary may have contained information on changes made to medications prescribed for heart

failure. The patient also received a copy of the discharge receipt and the short summary of the hospital admission.
In the intervention group a pharmacy technician compared the discharge receipt to the medication used prior to admission, changes were verified with the resident and subsequently the pharmacy technician prepared for both patient and next healthcare provider a structured medication overview (SMO). The SMO contained information on the intended medication regimen after hospital discharge, including additional information on the indication, intake instructions, discontinuation date if applicable, and reasons for the initiation, alterations and discontinuations to the medication regimen (Appendix 1). On the day of discharge, the SMO was given and explained to the patient and sent to the GP and CP by fax, along with the short summary of the hospital admission for the patient and the general practitioner.

Outcome

The primary outcome was the implementation of changes to the patients' admission medication regimen into the patient files of CPs and GPs. This information was gathered by requesting a medication overview from the CPs' patient files within one week after discharge. Furthermore, a medication overview was requested from the GPs' patient files within one to two months after discharge. Each change to the medication regimen made during hospitalisation was checked with the medication overview from the CPs' and GPs' patient file. Changes to the patient's medication regimen were defined as newly started medications, discontinued medications, and alterations in dosages, dose frequencies, or formulations during hospital admission. A change was defined as implemented for newly started medications if they were on the medication overview, for altered medications if they were in the altered form on the medication overview, and for discontinued medications if they were no longer on the medication overview.
Secondary, it was investigated whether implementation of changes was influenced by the variables, type of change (start, stop, or alteration), type of GP practice (single GP, multiple GPs/health centre without pharmacy, health centre with pharmacy/GP with own pharmacy), weekly delivery by pharmacy (yes or no), and information system used by the CP.

Data analysis

Descriptive statistics were used to describe the baseline characteristics. Independent t-test for continuous variables, and chi-square test for categorical variables, was used to compare the control group and the intervention group at baseline. Cox regression analyses were applied to analyse the differences in implementation of changes to the medication regimen between the control group and the intervention group. Furthermore, the results were stratified for type of change, type of GP practice weekly delivery by pharmacy, and information system used by the CP.

Results

Baseline characteristics

During the study period 140 patients were admitted to the acute care geriatric ward. A total of 67 patients were included for the CP analyses: 30 in the control group and 37 in the intervention group and a total of 65 patients were included for the GP analyses: 30 in the control group and 35 in the intervention group (Figure 1).

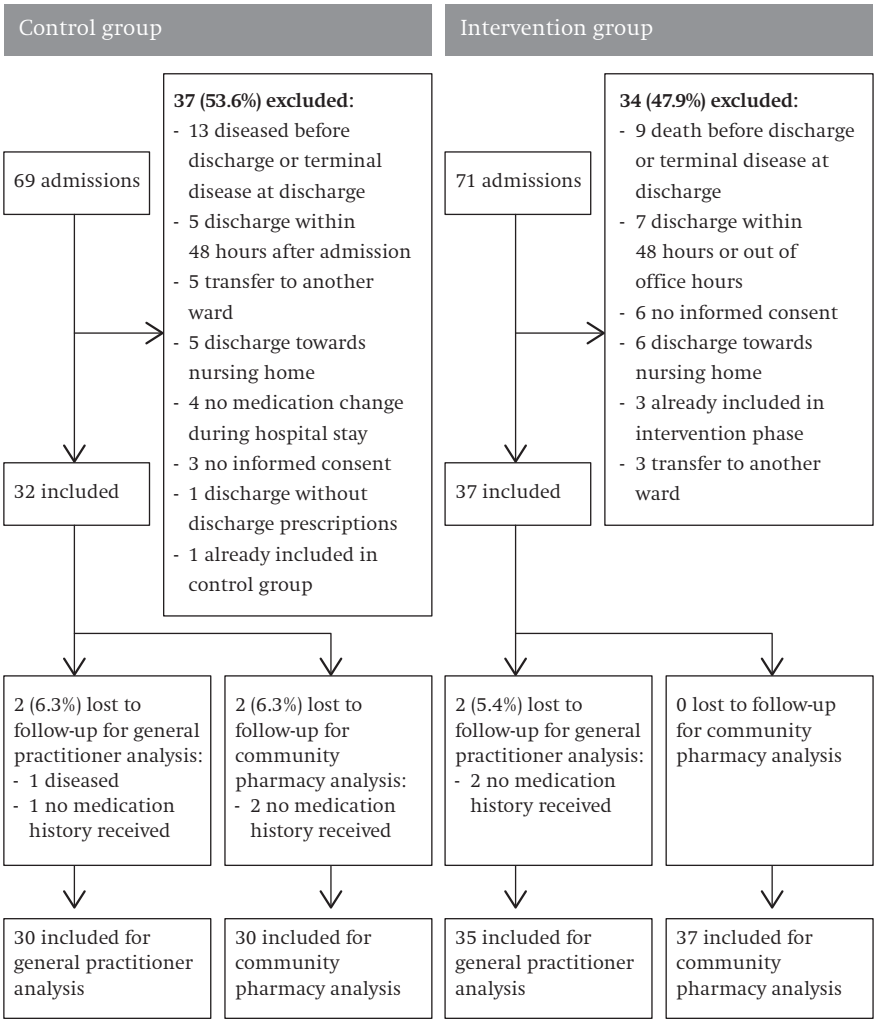

Figure 1 Inclusion Procedure

Table 1 shows that the baseline characteristics of the included patients for CP and GP analyses was similar in the control and the intervention group. The mean age of the included patients was 83 years, and more than 60% was female. On average, patients were discharged with 10 (control: range 5-19, intervention: range 4-21) medications and 7 (control, range 1-16) to 8 (intervention, range 1-20) changes to the medication regimen. Most changes concerned discontinued medications (>40%). The patients attended 49 different CPs, 22 in the control group and 27 in the intervention group. The patients were treated by GPs from 55 different GP practices, 28 in the control group, and 31 in the intervention group, 4 GP practices treated patients in both the control group, and the intervention group. In the control group 83.3% of the patients received their medications from the pharmacist in weekly trays with separate compartments for each day of the week and times of the day, compared to 62.2% in the intervention group (p=0.06).

Table 1 Patient, discharge medication, community pharmacy and general practitioner characteristics

Included for CP analyses			
Patient characteristics (number of patients)	**Control (n=30)**	**Intervention (n=37)**	**p-value**
Patient age, years (range)	83 (72-91)	83 (65-99)	0.97
Female gender, n (%)	20 (66.7)	23 (62.2)	0.70
Medications on admission, mean (range)	11 (3-20)	11 (3-24)	0.77
Discharge medication characteristics	Control	Intervention	p-value
Medications at discharge, mean (range)	10 (5-19)	10 (4-21)	0.99
Medication changes, mean (range)	7 (1-16)	8 (1-20)	0.39
Total changes, n (% of all medication*)	212/392 (54.1)	301/512 (58.8)	0.16
Type of medication change	83 (39.2)	113 (37.5)	
New, n (% of all changes)	41 (19.3)	57 (18.9)	0.71
Alteration, n (% of all changes)	88 (41.5)	131 (43.5)	0.91
Stop, n (% of all changes)			0.65
Community pharmacy characteristics	**Control**	**Intervention**	**p-value**
Number of CPs, total (range in number of patients per CP)	22 (1-4)	27 (1-4)	
Weekly tray delivery by pharmacy, n (% of all patients)	25(83.3)	23 (62.2)	0.06
CP information system	10 (33.3)	3 (8.1)	0.01
System 1, n (% of all patients)	18 (60.0)	31 (83.8)	0.05
System 2, n (% of all patients)	1 (3.3)	2 (5.4)	1.0
System 3, n (% of all patients)	1 (3.3)	1 (2.7)	1.0
System 4, n (% of all patients)			

Table 1 Continued

Included for GP analyses			
Patient characteristics (number of patients)	**Control (n=30)**	**Intervention (n=35)**	**p-value**
Patient age, years (range)	83 (72-91)	82 (65-99)	0.78
Female gender, n (%)	19 (63.3)	21 (60.0)	0.78
Medications on admission, mean (range)	10 (3-20)	10 (3-24)	0.56
Discharge medication characteristics	Control	Intervention	p-value
Medications at discharge, mean (range)	10 (5-19)	11 (4-21)	0.74
Medication changes, mean (range)	7 (1-16)	8 (1-20)	0.28
Total changes, n (% of all medication*)	209/388 (53.9)	286/487 (58.7)	0.15
Type of medication change	85 (39.9)	109 (38.1)	
New, n (% of all changes)	37 (17.4)	54 (18.9)	0.56
Alteration, n (% of all changes)	87 (42.7)	123 (43.0)	0.33
Stop, n (% of all changes)			0.37
General practitioner characteristics	**Control**	**Intervention**	**p-value**
Number of GP-practices, total (range in patients per GP)	28 (1-2)	31 (1-2)	
Type of GP-practice	5	4	0.72
Single GP, n (% of all patients)	19	20	0.80
Multiple GPs / Health Centre without pharmacy, n (% of all patients)	6	11	0.40
GP with own pharmacy / Health Centre with pharmacy, n (% of all patients)			

* All medication includes discharge medication and discontinued medication

Implementation of changes to the medication regimen into CPs' patient files

On average, CPs implemented 84.0% of changes to the medication regimen into the patient files in the control group, compared with 84.1% in the intervention group (HR 1.00, 95% CI 0.83-1.21; Table 2). There were no significant differences found after stratification for type of change, weekly tray delivery by pharmacy, and the information system used by the CP. Reasons for changes were not mentioned on the medication overviews received from the CPs.

Table 2 Implemented changes to the medication regimen into CPs' and GPs' patient files

Implemented changes CP patient files	**Control (n = 212 changes)**	**Intervention (n = 301 changes)**	**HR (95% CI)**
Total	178/212 (84.0%)	253/301 (84.1%)	1.00 (0.83-1.21)
Type of change			
Start	75/83 (90.4%)	107/113 (94.7%)	1.05 (0.78-1.41)
Stop	66/88 (75.0%)	95/131 (72.5%)	0.97 (0.71-1.32)
Alteration*	37/41 (90.2%)	51/57 (89.5%)	0.99 (0.65-1.51)
Weekly tray delivery by pharmacy			
Yes	154/183 (84.2%)	163/187 (87.2%)	1.04 (0.83-1.29)
No	24/29 (82.8%)	90/114 (78.9%)	0.95 (0.61-1.50)
Software system			
System 1	50/62 (80.6%)	17/18 (94.4%)	1.17 (0.68-2.03)
System 2	115/135 (85.2%)	230/274 (83.9%)	0.99 (0.79-1.23)
System 3	10/10 (100%)	3/6 (50.0%)	0.50 (0.14-1.82)
System 4	3/5 (60.0%)	3/3 (100%)	1.67 (0.34-8.26)
Implemented changes GP patient files	**Control (n = 209 changes)**	**Intervention (n = 286 changes)**	**HR (95% CI)**
Total	135/209 (64.6%)	193/286 (67.5%)	1.05 (0.84-1.30)
Type of change			
Start	49/85 (57.6%)	68/109 (62.4%)	1.08 (0.75-1.56)
Stop	61/87 (70.1%)	94/123 (76.4%)	1.09 (0.79-1.50)
Alteration*	25/37 (67.6%)	31/54 (57.4%)	0.85 (0.50-1.44)
Kind of GP practice			
Single GP	8/25 (32.0%)	21/28 (75.0%)	2.34 (1.04-5.29)
Multiple GPs/Health Center without pharmacy	89/144 (61.8%)	102/159 (64.2%)	1.04 (0.78-1.38)
Health Center with pharmacy/ GP with own pharmacy/ pharmacy medication overview received	38/40 (95.0%)	70/99 (70.7%)	0.74 (0.50-1.11)

* Change in dose or dose frequency/formulation

Implementation of changes to the medication regimen in GPs'patient files

In the control group GPs implemented 64.6% of all changes to the medication regimen into the patient files, compared with 67.5% of changes in the intervention group (HR 1.05, 95% CI 0.84-1.30; Table 2). Single GP-practices benefited most from the SMO, they implemented changes to the medication regimen in 75.0% of cases in the intervention group, compared with 32.0% in the control group (HR 2.34, 95% CI 1.04-5.29). Changes to the medication regimen were best implemented by GP-practices in health centres with a pharmacy and GPs with an own pharmacy: 95.0% in the control group and 70.7% in the intervention group (HR 0.74, 95% CI 0.50-1.11). In none of the cases reasons for changes were implemented in the patient files.

Discussion

Providing an SMO at discharge for CPs and GPs does not improve implementation of changes to the discharge medication regimen into their patient files, except for single GP-practices.

Numerous articles on improving transitional pharmaceutical care, which focus on improving the completeness of information provided to primary care health care providers, have been published.[6, 13, 14, 20-25] Only one study by Karapinar et al. focussed on the implementation of the provided information by CPs into their patient files.[26]The authors reported that CPs implemented 47% of changes made to the medication regimen. In the present study, we found that CPs in the control group implemented already 84% of changes to the medication regimen. However, in our study the vast majority of the analysed medications was dispensed into weekly trays, which may implicate that CPs are more closely involved with the medications regimens of these patients since they are responsible for the correct dispensing into the trays. As a result it is important for them to implement all changes to the medication regimen immediately after hospital discharge. Also, our study population was older and were prescribed more medications, which may also trigger CPs to be more alert to medication changes. Consequently, the studied populations in this study and the study by Karapinar et al. are not comparable. Furthermore, Karapinar et al. utilised a more strict definition of correct implementation. They defined correct implementation of changes as explicitly mentioned changes to the medication regimen on the medication overview from the CP. Thus, for example in case of discontinued medications, implementation was defined as correct when it was explicitly mentioned on the medication overview that a medication had been discontinued, while we defined cessation of dispensing as correct implementation.

Furthermore, one study investigated the implementation of information on adverse drug reactions into GPs' patient files.[7] This study reported that GPs implemented this information into their patient files in 22% of cases, and if so than mostly not in a standardised manner.

Although the focus of the present study was not on adverse drug reactions, the results also show that even explicitly provided information on changes to the medication regimen are scarcely documented in GPs' patient files.

The results of this study showed that in the control group GPs with close collaboration with the community pharmacy documented changes to the medication regimen best (95.0%). However, the provision of an SMO resulted in a (non-significant) decrease in documentation of changes to the medication regimen (from 95.0% to 70.7%), while particularly GPs working in a single practice documented changes considerably better (from 32.0% to 75%). A possible explanation for this observation is that based on practical considerations, the community pharmacy received the discharge receipt the day before discharge in order to enable them to dispense the medications in time. However, these discharge receipts were provided before the pharmacy technician compared the discharge receipts to the medication prior to admission. Therefore, in several cases the SMO differed from the discharge receipt due to last-minute changes and corrections, which may have caused confusion and consequently less or wrongly implementation of changes to the medication regimen.

This study was subject to several other limitations, which should be considered when interpreting the results. First, the SMO was sent to the CPs and GPs by fax instead of e-mail, their preferred method of communication.[10] However, fax is as good as e-mail for communication between health care settings and may not necessarily lead to less implementation of changes to the medication regimen.[27] Nonetheless, both communication methods require manual processing of the SMO, and subsequently both methods are prone to processing errors. Second, in the control group changes to the medication regimen as mentioned on the discharge receipt were not in all cases intended, such as medications that were temporarily discontinued during hospitalisation and restart was overlooked at hospital discharge. During home visits to the patient one week after discharge intentional discrepancies with the discharge medication regimen were interrogated and subsequently these cases of intentional non-implementation were not included in the database. Third, since the medication overview from GPs was requested within two months after hospital discharge, some changes to the medication regimen may have been reversed due to changes in the patients' medical situation, which possibly could have resulted in incorrect definition of non-implementation. On the other hand, GPs need time to implement changes to the medication regimen in their information systems, and consequently earlier requests for medication overviews may have also resulted in incorrect definition of non-implementation.

Furthermore, the implementation of changes by the CPs may have been better if they were given more than one week to implement these changes. However, since the majority of patients included in this study were depended on weekly tray dispensing from the pharmacy, we believe that changes in this population have to be implemented immediately. Moreover, in the ideal situation the medication overview from pharmacists is at any time up to date, especially at times of a new transfer to another health care setting.
Hence, we found that implementation of changes to the medication regimen was not performed in a standardised manner by both CPs and GPs. The implementation of most changes was only interpretable through repeat prescriptions, or the discontinuance of repeat prescriptions/dispensing in case of stopped medications. This may explain why we could not find an effect of the SMO on the implementation of changes in the patient files of CPs and GPs. When information is not processed in a standardised manner, significant parts of information may be lost, which seems to be the case in this study. Information systems should aid health care providers with standardised processing of information. Ideally, transitional pharmaceutical care occurs electronically with automatic processing of this information into the next health care providers' patient file. As such, incomplete or erroneous manual processing of information can be reduced and consequently transitional pharmaceutical care can be improved.

Conclusion

Optimising information on the discharge medication regimen as a single intervention does not improve implementation of changes to the medication regimen into the CPs' and GPs' patient files. Standardised implementation of SMO's by the CPs and GPs, as well as unambiguous and electronic communication by the secondary care physicians may enhance the implementation of changes to the medication regimen into CPs and GPs patient files.

Appendix 1 Structured Medication Overview

Structured Medication Overview at hospital discharge Geriatric ward UMC Utrecht

Patient: mr. Example	Adress: Medication street 12, Utrecht
Date of birth: 25-8-1920	Phone: 030-1234567
Social security number: 123456789	Community pharmacy: Old Pharmacy

Contra-indication(s): impaired thyroid gland function
eGFR:> 60 ml/min/1.73m^2 **Sodium:**138 mmol/l
Difficulty with swallowing of medications: no

Medication name	Dosage	Number of times daily	Administer route	Indication
Movicolon	1 sachet	1 sachet daily	Oral	Constipation
Euthyrox	50 µg	1½ tablet daily	Oral	Hypothyroidism
Hydrocortison	5 mg	8 h: 2 tablets 12 h: 1 tablet 18 h: 1 tablet	Oral	Dysfunctioning pituitary

Discontinued medications:

Medication name	Reason for discontinuation
Haloperidol	No longer indicated
Ciprofloxacin	No longer indicated
Oxazepam	No longer indicated
Furosemide	Was prescribed for edema, patient benefits more from support stockings

DD-MM-YYYY

Hospital pharmacy UMC Utrecht
Phone: 088-7556120
Fax: 088-7555996

Allergy/intolerance:nitrofurantoin
Potassium: 4.4 mmol/L **Smoking:** no **Alcohol:** 0-1 units/day
Probe: no **Monitoring advice:** none

N/A/U*	Reason for start/alteration Remarks	Stop date	Prescriber
N	Constipation	-	Dr. Physician, geriatrician
A	Insufficient effect of 1 tablet daily	-	Dr. Physician, geriatrician
U		-	Dr. Physician, internist

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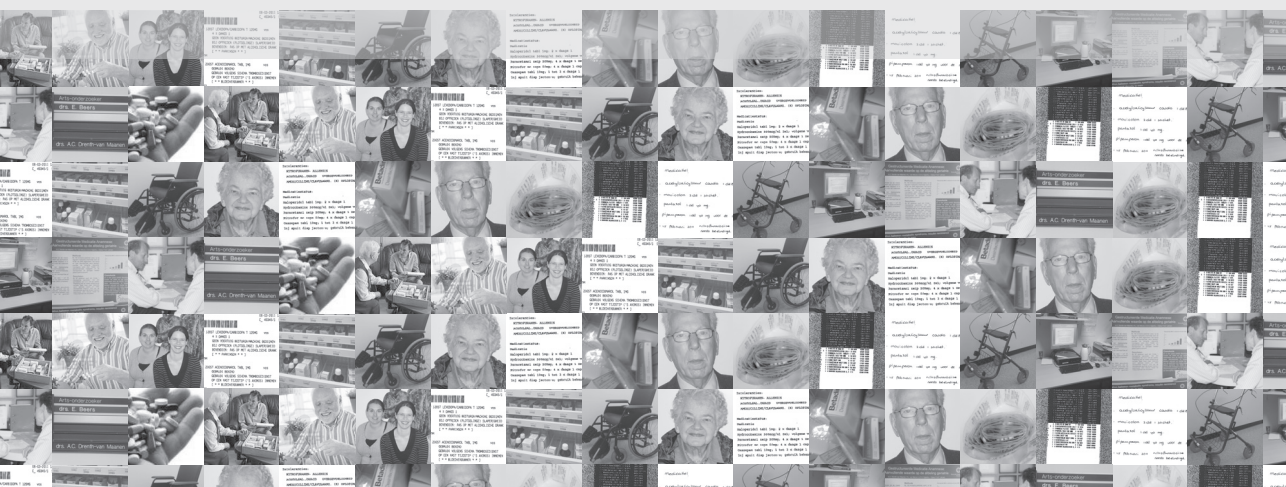
4

Prescribing for patients with impaired renal function



4.1

Renal function assessment in older people

A. Clara Drenth-van Maanen, Paul A.F. Jansen, Johannes H. Proost,
Toine C.G. Egberts, Arjan D. van Zuilen, Dawi van der Stap, Rob J. van Marum

Under review

Abstract

Aim –The Cockcroft-Gault (CG) and MDRD formula, and the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration), are often used to estimate GFR, which is important to identify patients with renal impairment. The objective was to determine the most accurate method for estimating GFR in geriatric patients.

Methods - A cross-sectional study was conducted at the acute care geriatric wards and outwards of two hospitals in the Netherlands. Patients aged 70 years or above with an estimated (e)GFR below 60 ml/min/1.73m^2 were included. The CG, MDRD, and CKD-EPI formulas were compared to a criterion standard, sinistrin clearance. Renal function was classified into five stages according to the National Kidney Foundation Disease Outcomes Quality Initiative (NKF KDOQI) chronic kidney disease classification: stage 1, eGFR ≥ 90; stage 2, eGFR 60-89; stage 3, eGFR 30-59; stage 4, eGFR 15-29; and stage 5, eGFR < 15 ml/min/1.73m^2.

Results – Sixteen patients with a mean age of 82 years (range 71-87), 50% male and mean BMI 26 (range 18-36), were included. On average, all formulas slightly overestimated GFR: CG +0.05 (95% CI -28 to +28) ml/min/1.73m^2; MDRD +9 (95% CI -16 to +34) ml/min /1.73m^2; and CKD-EPI +5 (95% CI -20 to +29) ml/min/1.73m^2. In individual patients there were however large deviations. The formulas classified kidney disease correctly in 68.8% (CG), 43.8% (MDRD), and 68.8% (CKD-EPI) of the participants, respectively.

Conclusion – The CG, MDRD, and CKD-EPI estimate the GFR at mean rather well. However, in individual cases all formulas may misclassify kidney disease by one stage.

Introduction

When renal function declines, many drugs or their active metabolites that depend on renal excretion may accumulate, which necessitates dosage adjustment in order to prevent adverse drug reactions.(1) This is especially important in old people, who are more vulnerable to adverse drug reactions due to an increased prevalence of renal impairment, polypharmacy, and frailty. (2-4)
The criterion standard to assess renal function is to measure glomerular filtration rate (GFR) by determining the clearance of exogenous markers, which are completely filtered by the glomerulus, not secreted or reabsorbed in the renal tubule, stable and not metabolised.(5) However, these are expensive and cumbersome methods, and consequently not suitable for daily practice. Physicians need a quick, simple, and inexpensive method to validly estimate GFR. Various methods have been developed for this purpose. The most widely used methods are the Cockcroft-Gault (CG) and Modification of Diet in Renal Disease (MDRD) formulas. CG and MDRD estimate GFR based on serum creatinine concentrations, age, gender, and, in case of CG also weight, in case of MDRD also race.(6,7) More recently, the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) formula has been developed, which is based on serum creatinine concentrations and age.(8)
Multiple studies have been conducted to compare the CG and MDRD to a criterion standard in the geriatric population, with conflicting results.(9-16)(3) The CKD-EPI has recently been the subject of investigation in the geriatric population, in addition to the CG and the MDRD.(17) The authors of this study concluded that the MDRD or CKD-EPI formulas should be preferred. However, they did not investigate which of these formulas classified renal impairment category best. The aim of this study was to compare the accurateness of the CG, the MDRD and the CKD-EPI in classifying renal impairment in a geriatric population by using a criterion standard.

Methods

Design and setting

A cross-sectional study was conducted at the acute care geriatric wards and outwards of the University Medical Center Utrecht, an academic teaching hospital, and the Jeroen Bosch hospital 's-Hertogenbosch, a non-academic teaching hospital, in The Netherlands. The Medical Ethics Committee of the University Medical Center Utrecht reviewed and approved this study.

Study population

All patients, admitted to these wards or attending the outwards from January 2010 until December 2010, were eligible for inclusion if they were aged 70 years or above, in stable medical condition, cognitively able to give informed consent, and with an estimated GFR by the 4-variable version of the MDRD of 60 ml/min/1.73m^2 or less. All participants gave written informed consent.

Study procedures

The study procedure took eight hours for each included participant. First, information was collected on patient characteristics, including: age, gender, weight, height, race, co-morbidities, and medication use. Body height (in centimetres) and weight (in kilograms) were used to calculate the body mass index (BMI): weight / (height * height), and body surface area (BSA): 0.007184 * weight$^{0.425}$ * height$^{0.725}$.(18) Then an infusion tube was inserted into a cubited vein for blood withdrawal and infusion of the sinistrin. The Inutest 'single shot method' (Inutest®, 5 g of sinistrin per 20 mL; Fresenius Kabi, Graz, Austria) was used to measure the actual GFR. The active compound of Inutest is sinistrin, an analogue of inulin with greater water solubility.(19)

Serum creatinine concentrations were determined just before the 2500 mg sinistrin bolus infusion. The measurements were performed using the kinetic Jaffé method (rate-blanked) on an ARCHITECT ci8200sr analyser (2012 Abbott Laboratories. Abbott Park, Illinois, U.S.A.). At 10, 20, 30, 60, 90, 120, 240, and 480 minutes after the sinistrin infusion, venous blood samples were taken. Sinistrin concentrations were measured in all plasma aliquots, also in the plasma aliquot before sinistrin infusion. Because quantification of sinistrin in serum is limited by its physiological fructose content, which interferes with the natural fructose content of serum, it has to be determined as a serum blank.(20) Sinistrin concentration measurements were performed by colorimetric assessment using a Colorimeter Starrcol.

GFR measurement

To calculate the GFR the area under the curve of the sinistrin concentration-time curve was determined.(21) According to the manual of Inutest, the sinistrin concentration-time curves should be individually analysed by a two-compartment model.(19) However, previous research has shown that this may lead to imprecise estimates of the individual pharmacokinetic parameters and that a population analysis estimates individual pharmacokinetic parameters better than individual analysis.(22) Therefore a population approach was applied to obtain individual parameter estimates. Modelling was done using the non-linear mixed effects modelling software NONMEM VI version 2.0 (Icon Development Solutions, Hanover,

MD). The ADVAN 3 and TRANS4 subroutines were used to describe the data with a linear two-compartment model, with parameters CL (clearance), V1 (central volume), Q (intercompartmental clearance), and V2 (peripheral volume). The first-order conditional estimation method (FOCE) was used to obtain the parameter estimates. Additive, proportional and combined residual error models were tested (the residual error comprises the interindividual variability and the intraindividual variability). Interindividual variability on each parameter was modelled assuming a log-normal distribution. The selection of the two-compartment model (instead of one-, three-, or more compartments) was based on the likelihood ratio test, parameter estimates and their relative standard errors, residual error values and goodness-of-fit plots.

GFR estimation

The primary outcome was to assess which formula estimates the GFR best according to the National Kidney Foundation Disease Outcomes Quality Initiative (NKF KDOQI) chronic kidney disease classification.(23) This classification distinguishes 5 stages: stage 1, kidney damage with eGFR ≥ 90 ml/min/1.73m^2; stage 2, kidney damage with eGFR 60-89 ml/min/1.73m^2; stage 3, eGFR 30-59 ml/min/1.73m^2; stage 4, eGFR 15-29 ml/min/1.73m^2; and stage 5, eGFR < 15 ml/min/1.73m^2. For this study kidney damage was not assessed.

GFR was estimated according to the following formulas:

- CG (ml/min):(7)
  [(140-age in years) x weight (kg)] / [72 x serum creatinine (Scr) (mg/dl)*] (x 0.85 if woman);
- 4-variable version of the MDRD (ml/min/1.73m^2):(6)
  186 x Scr (mg/dl)$^{-1.154}$ x (age in years)$^{-0.203}$ x 0.742 (women) x 1.2 (dark race);
- CKD-EPI (ml/min/1.73m^2) if serum creatinine concentrations are >0.9 mg/dl (male) and >0.7 mg/dl (female):(8)
  Men: $141 \times (\text{Scr (mg/dl)} / 0.9)^{-0.411} \times (0.993)^{\text{Age}}$
  Women: $144 \times (\text{Scr(mg/dl)} / 0.7)^{-0.329} \times (0.993)^{\text{Age}}$.

*To give results in μmol/l multiply Scr by 88.4

In order to compare the estimated and measured GFRs, and to classify the results according to the NKF KDOQI classification system, the sinistrin clearance and the CG were normalised per 1.73m^2.

Data analysis

The relation between different methods of GFR assessment was explored using Bland Altman plots. The Bland Altman approach depicts the mean difference and 95% confidence intervals of the differences, represented by the limits of agreement (mean difference ± 2 standard deviations of differences).(24) Because the GFR measurements are more likely to be closer to the real GFR than the predicted estimates by the formulas, the measured GFR on the *x* axes was used instead of the mean of both methods.

Also, the mean absolute difference for each formula was determined by first calculating the absolute difference per patient (|eGFR-mGFR|) and then calculating the average of the absolute differences.

Results

Baseline characteristics

During the study period, 139 patients were approached for participation; 31 patients signed the informed consent form. Eventually, 24 patients completed the study procedures; two patients withdrew consent before the start of the study procedures, and five patients had to be excluded due to practical problems. In the dataset consisting of 24 patients, the results of eight patients did not meet the high standards of criterion standard GFR measurements. Two concentration profiles included a very high concentration of 1601 μg/ml and 2449 μg/ml at ten and twenty min, respectively, resulting in an unreliable estimate of V1. If these two concentrations were excluded, the GFR could not be measured reliably. Therefore these patients were excluded from the analysis. In four profiles, concentrations were zero due to the applied correction in the chemical assay. Since inclusion or exclusion of these concentrations resulted in significant differences in the estimated GFR, and it was not clear which of these GFRs was most reliable, these patients were excluded from further analysis. In two patients, the estimated values for V1 were close to 1 litre, which does not seem physiologically plausible; these patients were excluded from the final analysis.

This left 16 patients for whom all measured plasma concentrations and calculated pharmacokinetic parameters were considered reliable. Table 1 shows that the mean age of the included patients was 82 years (range 71-87), 8 participants (50%) were male, and mean BMI was 26 (range 18-36).

Table 1 Baseline characteristics

Characteristic	N=16
Age in years, mean (range)	82 (71-87)
Male gender, n (%)	8 (50)
Caucasian, n (%)	16 (100)
BMI, mean (range)	26.4 (18-36)
Height in meters, mean (range)	1.64 (1.48-1.75)
Weight in kilograms, mean (range)	71 (47-103)
Serum creatinine concentration in μmol/l, mean (range)	128 (80-292)
Number of medications, mean (range)	9 (3-15)
Number of comorbidities, mean (range)	5 (2-8)

Glomerular filtration rate

Figure 1 shows that on average, all formulas slightly overestimated GFR: CG +0.05 (95% CI -28 to +28) ml/min/1.73m^2 (+7.2% (95% CI -62.6 to +77.1%)); MDRD +9 (95% CI -16 to +34) ml/min /1.73m^2 (+29.1% (95% CI -45.6 to +103.9%)); and CKD-EPI +5 (95% CI -20 to +29) ml/min/1.73m^2 (17.8% (95% CI -51.3 to +86.9%)).

The formulas predict GFR similarly in both male and female participants (results not shown). Furthermore, Figure 1 suggests that CG tends to overestimate GFR in patients with morbid obesity (BMI > 30), and to underestimate GFR in patients with underweight (BMI < 19).

The mean absolute difference was highest for the MDRD formula, 12.1 ml/min/1.73m^2, compared with 10.8 ml/min/1.73m^2 for CG and 9.4 ml/min/1.73m^2 for CKD-EPI.

Figure 2 shows that the participants had kidney disease varying from stage two to four. The CG formula classified the kidney disease stage correctly in eleven participants (68.8%), the MDRD formula made a correct classification in seven participants (43.8%), and the CKD-EPI in eleven participants (68.8%). All incorrect classifications differed one stage (CG one higher, four lower, MDRD eight higher, one lower, CKD-EPI four higher, one lower) from the actual disease stage. This could result in incorrectly classifying a patient as having an impaired renal function, or vice versa. Combining the estimates of the three formulas did not improve classification (results not shown).

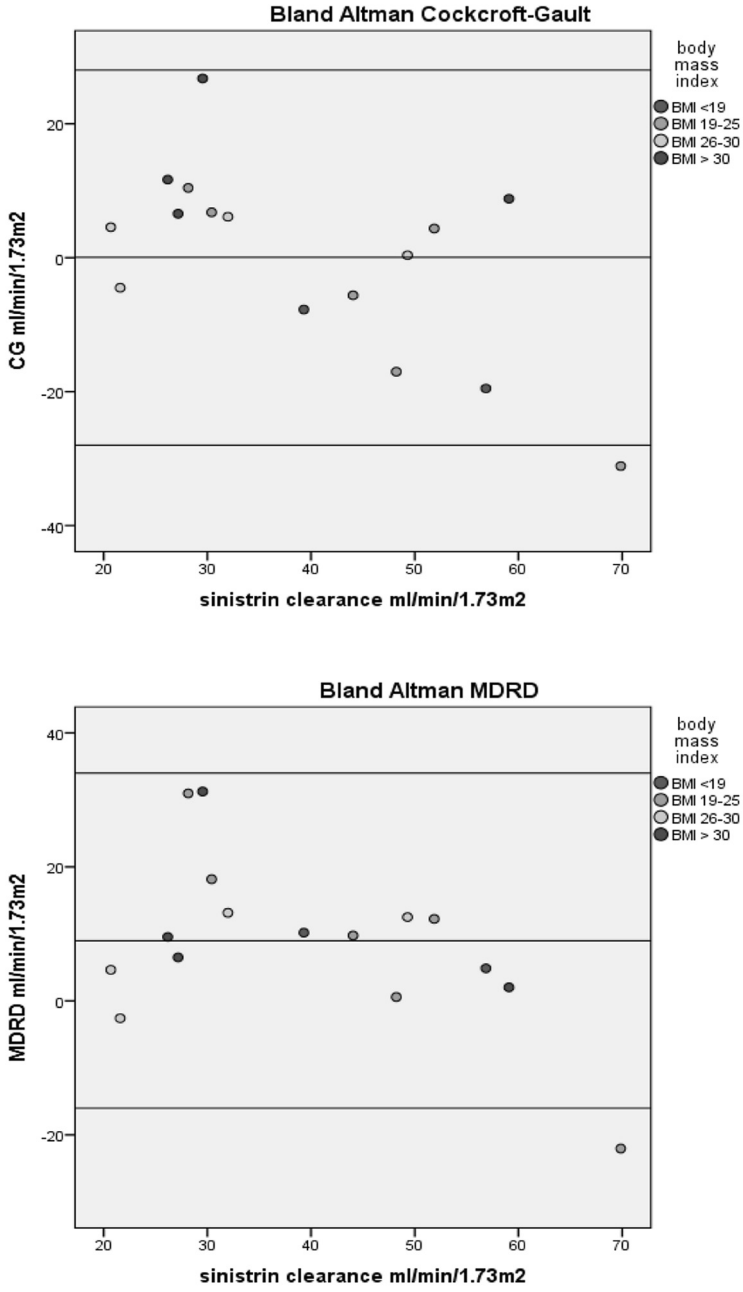


Figure 1 Bland Altman plots CG, MDRD, and CKD-EPI

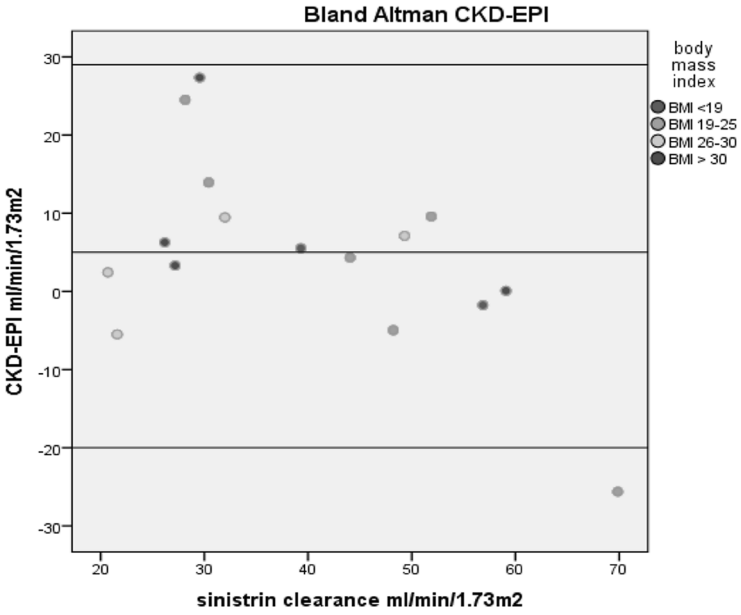


Figure 1 Continued

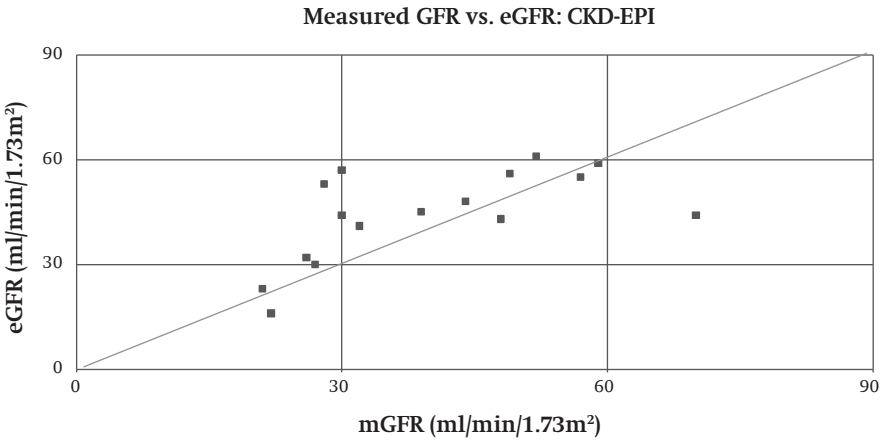


Figure 2 Measured GFR vs. eGFR

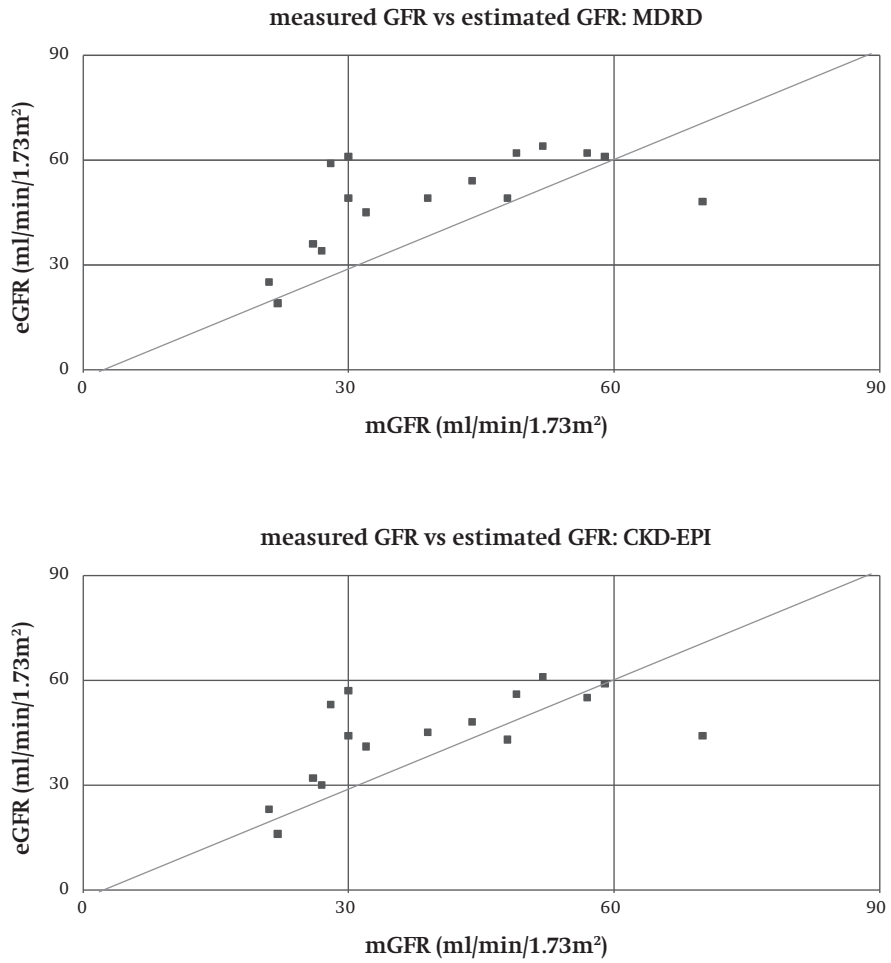


Figure 2 Continued

Discussion

The results of the present study indicate that at mean the CG, MDRD, and CKD-EPI estimate the GFR rather well in a geriatric population. However, in individual cases all formulas may misestimate the GFR by up to 31 ml/min/1.73m^2 (103%), thereby misclassifying kidney disease by one stage in more than 30% of the

participants. Both underestimation, as well as overestimation, occurred in all formulas. The CG and CKD-EPI classified renal impairment category best. The mean absolute difference was smallest for CKD-EPI.

This study compared the CG, MDRD, and the CKD-EPI formulas to a criterion standard in a geriatric population. Other studies generated conflicting results. Van den Noortgate et al. found similar results to the present study in a comparable patient population.(14) Burkhardt et al. concluded that both CG and MDRD underestimated GFR by 20 and 40 ml/min, respectively.(12) However, in their study, only patients without signs of reduced renal function were included. Péquignot et al. stated that CG performed superior compared to the MDRD, as MDRD strongly overestimated the GFR.(15) Though, in their study only hospitalised patients with an indwelling urinary catheter were included, which may imply a more frail population in unstable medical condition. The finding that CG performs less in patients at the extremes of BMI is in concordance with the results from previous studies.(25,26) The results of the present study also confirm that MDRD and CKD-EPI perform similarly in individuals, although MDRD tends to slightly overestimate GFR compared to CKD-EPI, resulting in more misclassifications than CKD-EPI.(27) Thus, a well funded advice on which formula to use to estimate renal function in the geriatric population cannot yet be offered, although CKD-EPI classified renal impairment category best with the smallest mean absolute difference. Possibly the reliability of the different formulas is influenced by more variables than age and gender, such as the medical condition of the patient.

Furthermore, a significant part of the participants had to be excluded. These exclusions were related to the chosen method for measuring the sinistrin clearance, the Inutest single shot method. The advantage of the single shot method is that only one bolus infusion of sinistrin is necessary and that additional urinary collections are not obliged. The normal Inutest single shot measurements take four hours. Since in this population reduced renal function was expected, we prolonged these measurements to eight hours. Unfortunately, in four cases this prolongation turned out to be insufficient and reliable GFR-measurements could not be made. Furthermore, we suffered more than expected from interference with the natural fructose content of serum, which hindered accurate serum sinistrin measurements that could insufficiently be solved by subtracting the serum blank concentration from the sinistrin measurements. In two cases, we detected an improbable high sinistrin concentration at 10 and 20 min, respectively. Whether these measured concentrations were caused by a flaw in the analysis procedure, or due to insufficient flushing after the sinistrin infusion is unknown. For future research it will be of great importance to collect all variables that might influence the reliability of the formulas and may explain the large interindividual variability found in this and previous studies.

Conclusion

The results of the present study indicate that the CG, MDRD, and CKD-EPI estimate the GFR at mean rather well in a geriatric population. However, in individual cases all formulas may misestimate the GFR by up to 31 ml/min/1.73m^2 (103%). The formulas predict kidney disease stage correctly in 50% or more. CKD-EPI performed slightly better than the MDRD and CG. Furthermore, the Inutest single shot method should not be the preferred method to assess renal function in old patients.

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4.2

Adherence with dosing guideline in patients with impaired renal function at hospital discharge

A. Clara Drenth-van Maanen, Rob J. van Marum, Paul A.F. Jansen, Jeannette E.F. Zwart, Wouter W. van Solinge, Toine C.G. Egberts

Under review

Abstract

Objectives: To determine the prevalence, determinants, and potential clinical relevance of adherence with the Dutch dosing guideline in patients with impaired renal function at hospital discharge.
Design: Retrospective cohort study between January 2007 and July 2011.
Setting: Academic teaching hospital in the Netherlands.
Subjects: Patients with an estimated glomerular filtration rate (eGFR) between 10-50 ml/min/1.73m^2 at discharge and prescribed one or more medicines of which the dose is renal function dependent.
Main outcome measures: The prevalence of adherence with the Dutch renal dosing guideline was investigated, and the influence of possible determinants, such as reporting the eGFR and severity of renal impairment (severe: eGFR<30 and moderate: eGFR 30-50 ml/min/1.73m^2). Furthermore, the potential clinical relevance of non-adherence was assessed.
Results: 1327 patients were included, mean age 67 years, mean eGFR 38 ml/min/1.73m^2. Adherence with the guideline was present in 53.9% (n=715) of patients. Reporting the eGFR, which was incorporated since April 2009, resulted in more adherence with the guideline: 50.7% vs. 57.0%, RR 1.12 (95% CI 1.02-1.25). Adherence was less in patients with severe renal impairment (46.0%), compared to patients with moderate renal impairment (58.1%, RR 0.79; 95% CI 0.70-0.89). 71.4% of the cases of non-adherence had the potential to cause harm.
Conclusion: Drug dosages are often not adapted to renal function at hospital discharge, especially patients with severe renal impairment are at increased risk of inappropriate dosage prescribing. This may cause harm to the majority of patients. Reporting the eGFR slightly improves adherence with the dosing guideline.

Introduction

A reduction in glomerular filtration rate (GFR) decreases the elimination rate of medications or their metabolites that are primarily excreted by the kidneys. In that case, these medications can accumulate, which may lead to exaggerated pharmacologic effects or adverse drug reactions. As such, dose reduction is required in patients with impaired renal function.

Several studies demonstrated that during hospital stay drug prescriptions are not adapted to renal function in 25-77% of cases.(1-5) At discharge, inappropriate prescribing occurs in 25-88% of prescriptions.(1,3,4,6-10)

The abovementioned studies focused on one specific medication group, such as antibiotics, or one specific patient population. Also, the influence of reporting the eGFR in addition to the serum creatinine levels by clinical laboratories was not assessed.

Reporting the eGFR may improve acknowledgement of impaired renal function. In 42-57% of patients impaired renal function is not mentioned in the medical chart.(7,11,12) Furthermore, if only serum creatinine levels are used to estimate renal function, particularly older patients are susceptible for insufficient acknowledgement, since serum creatinine is an inaccurate measure of GFR, especially in frail and/or malnourished older people.(13) Equations to estimate GFR, such as the Modification of Diet in Renal Disease (MDRD), and Cockcroft-Gault (CG) predict GFR better than serum creatinine levels.(14-16) The CG is used to estimate creatinine clearance (CLcr) from serum/plasma creatinine (Scr). CG equation requires patient age, total body weight and gender (results in mL/min). Also based on Scr, the MDRD estimates GFR (eGFR).(17) Importantly, it does not require patient body weight, a practical advantage in a hospital setting (results in mL/min/1.73 m^2 of body surface area—BSA).

The aim of the current investigation was to analyse the prevalence and determinants of adherence with the Dutch renal dosing guideline at hospital discharge, thereby including multiple medication groups, and the influence of multiple possible determinants of non-adherence with the dosing guideline, such as different patient populations (based on age, gender, admitting medical specialty, and severity of renal impairment), reporting the eGFR, the course of renal impairment during hospital admission, and length of hospital admission. In addition, the potential clinical relevance of non-adherence was assessed.

Methods

Design and setting

A retrospective cohort study was conducted at the University Medical Center Utrecht (UMCU), a 1042-bed academic teaching hospital in the Netherlands. In the UMCU, all medications for hospitalised patients are prescribed using a computerised physician order entry (CPOE) system. All prescriptions are routinely exported to the Utrecht Patient Oriented Database (UPOD). UPOD is an infrastructure of relational databases comprising data on patient demographics, hospital discharge diagnoses, medical procedures, medication orders and laboratory tests for all patients treated at the UMCU since 2004, and has been described in detail elsewhere.(18)

Study population

All patients, aged ≥ 18 years, with an estimated (e)GFR between 10-50 ml/min/1.73m^2, based on the last measured serum creatinine level during hospital admission, discharged between January 2007 and July 2011, and using at least one of the defined set of 41 medications (see Outcome) were eligible for inclusion. Exclusion criteria were unknown renal function, patients undergoing dialysis, death during hospitalisation, no medications at discharge, and discharge within 24 hours after admission. Patients with an eGFR below 10 ml/min/1.73m^2 were not included, since they usually are on dialysis and dosing guidelines generally do not offer standard dosage advice in these cases. Only the first admission of patients during the study period was included.

GFR was estimated by the abbreviated version of the MDRD-formula:(17,19)

eGFR (ml/min./1.73m2) = 175 x (serum creatinine (μmol/l)/88.4) $^{-1.154}$ x (age in years) $^{-0.203}$ (x 0.742 if female).

Outcome

The primary outcome was the prevalence of adherence with the Dutch dosing guideline, the G-standard, in the last 24 hours before discharge.

The Dutch dosing guideline is an evidence based and professional guideline for drug dosing in renal failure, developed and maintained by the Scientific Institute for Dutch Pharmacists. For the period 2007-2009 the guideline 2007 was applied,(20) for the period 2009-2011 the guideline 2009 was applied.(21) The guideline offers dosing advices according to renal impairment category. Renal impairment is categorised according to the European Medicines Agency (EMA) guideline: moderate: eGFR 30-50 ml/min/1.73m^2 and severe: eGFR 10-29 ml/min/1.73m^2 renal impairment.(22)

When the guideline offered multiple dosage advices, e.g. in case of multiple possible indications, the highest dosage advice was applied to prevent underestimation of

adherence, as drug indication could not be retrieved from the database. Medications that did not require dosage adjustment for one of the indications were not evaluated, since in that case adherence with the guideline could not be assessed. Furthermore, medications requiring dosage adjustments based on plasma levels, body surface/weight, and monitoring of therapeutic effect were not evaluated, since this information could not be retrieved from the UPOD database.
This left 41 medications for which the prescribed dosage could be compared to the advised maximum daily dose in the Dutch dosing guideline. These medications are listed and categorised according to the Anatomical Therapeutic Chemical (ATC) Classification System classes in Appendix 1.

Determinants

The influence of the following potential determinants on adherence with the dosing guideline were studied:

- age (18-49, 50-64, 65-79, 80+ years)
- gender
- reporting of serum creatinine levels only vs. additional reporting of eGFR (in the UMCU the eGFR is reported in the electronic patient file along with the serum creatinine value in the laboratory results since April 2009)
- renal impairment category (last measured eGFR before discharge, severe: 10-29 ml/min/1.73m^2, moderate: 30-50 ml/min/1.73m^2)
- change in renal impairment category during hospital admission (stable, i.e. no change in renal impairment category, declining, i.e. decrease in renal function by one or more renal impairment categories, or improving, i.e. increase in renal function by one or more renal impairment categories)
- length of hospital stay in days (≤ 7 days, 8-30 days, or > 30 days)
- admitting medical specialty (surgical vs. non-surgical)

The secondary outcome measure was the potential clinical relevance of non-adherence with the dosing guideline. This was in consensus determined by two clinical geriatricians-clinical pharmacologists (RM and PJ) according to the classification system as described by Cornish et al.(23) This system consists of three classes, class 1 (unlikely to cause harm, such as blushing, headache); class 2 (potential to cause moderate discomfort or clinical deterioration, such as diarrhoea); and class 3 (potential to cause severe discomfort or clinical deterioration, such as central nervous system depression or irreversible peripheral polyneuropathy). For each case, the potential clinical relevance was determined based on the prescribed daily dose and the potential clinical consequences as described in the dosing guideline (Appendix 1).

Data analysis

Descriptive statistics were used to describe the following characteristics: age, gender, renal impairment category, length of hospital stay, admitting medical specialty, and number of prescriptions per patients that required dosage adjustment.
The prevalence of adherence per renal impairment category (moderate and severe) was calculated by dividing the number of adjusted dose prescriptions by the total number of prescriptions that required dosage adjustment. Also, the prevalence rates of adherence with the Dutch professional guideline were calculated per evaluated medication in the two renal impairment categories.
The prevalence of patients with adjusted dosage prescriptions was determined by dividing the number of patients with all prescriptions adapted to renal function by the total number of included patients. In addition, these results were stratified to age (18-49, 50-64, 66-80, and >80 years), gender, reporting of eGFR (yes or no), renal impairment category (moderate or severe), change in renal impairment category (stable, declining, or improving), length of hospital stay (≤ 7 days, 8-30 days, or > 30 days), and admitting medical specialty (surgical or non-surgical). The results of stratification were expressed as relative risks (RR) with 95% confidence intervals.

Results

During the study period 57,264 patients ≥ 18 years were discharged from the UMCU. In 33,963 (59.3%) patients a serum creatinine level was measured during hospital admission. Of those patients, 4798 (14.1%) had an eGFR between 10 and 50 ml/min/1.73m^2. Eventually, 1327 patients met all inclusion criteria and their data were used for further analysis (Figure 1).
Mean age of the included patients was 67 years (range 18-99), 50.2% was male, and mean length of hospital stay was 12 days (Table 1). Severe renal impairment (eGFR 10-29 ml/min/1.73m^2) was present in 35.5% of these patients.

Prevalence of adherence with the Dutch dosing guideline

The 1327 patients received 1722 prescriptions in which dosage adjustment to renal function was required. Adherence with the Dutch dosing guideline was present in 53.9% (n=715) of the patients and in 59.9% (n=1032) of the prescriptions. 26.8% (n=185) of the unadjusted prescriptions concerned medications that were actually contra-indicated. The median prescribed dose was twice the recommended dose, range 1.25-8.

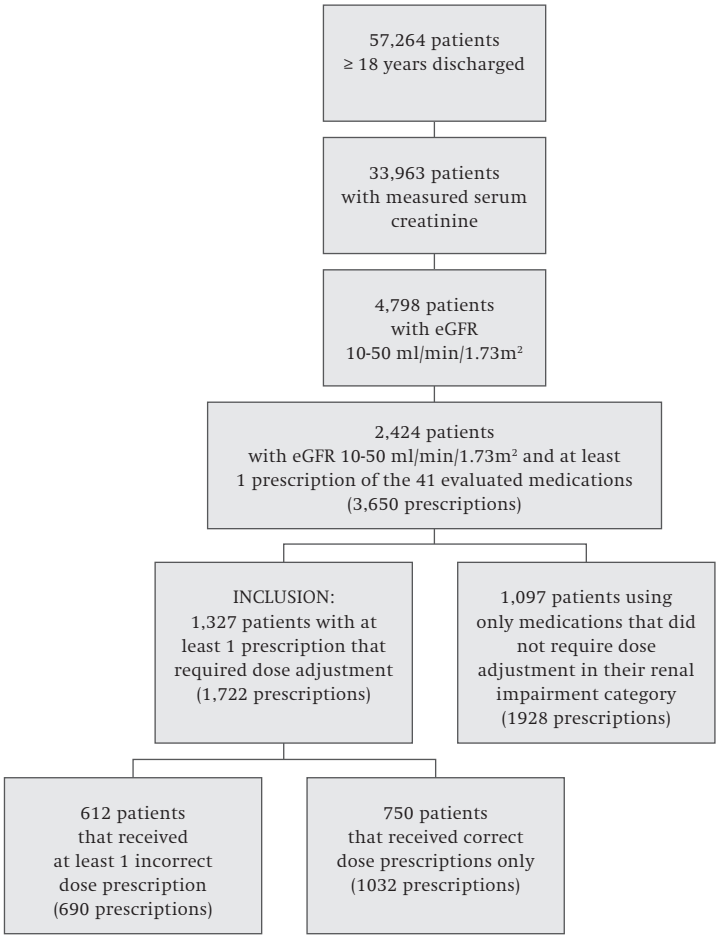

Figure 1 Flowchart of inclusion

Five of the investigated medications were in all cases prescribed according to maximum advised daily dose: acipimox, bisoprolol, cimetidine, clarithromycin, and hydroxyzine.

Cardiovascular medications were most frequently prescribed (Table 2): 27.9% (n=481), followed by medications from the ATC-classes musculoskeletal system and alimentary tract and metabolism (21.8%, n=376, and 18.6%, n=320, of the prescriptions, respectively). Within the cardiovascular group, dosages were adjusted in 67.2% (n=323) of the prescriptions, cases of non-adherence mostly concerned eplerenone (n=54). In the musculoskeletal system and alimentary tract and metabolism groups,

Table 1 Baseline characteristics

Characteristics	n = 1327
Age in years, mean (range)	67 (18-99)
Male gender, n (%)	668 (50.3)
Median length of hospital admission in days, n (range)	7 (1-261)
Admitted to surgical medical specialty, n (%)	443 (33.4)
MDRD at discharge 10-29 ml/min/1.73m^2, n (%)	461 (34.7)
MDRD at discharge 30-50 ml/min/1.73m^2, n (%)	866 (65.3)
Median number of prescriptions requiring dosage adjustment per patient, n (range)	1 (1-4)

Table 2 Adherence with the Dutch dosing guideline

	MDRD 30-50 ml/min/1.73m^2			MDRD 10-29 ml/min/1.73m^2		
Medication	**Prescriptions (n)**	**adherent (n)**	**%**	**Prescriptions (n)**	**adherent (n)**	**%**
Cardiovascular system	*323*	*249*	*77.1*	*158*	*74*	*46.8*
eplerenone**	48	0	0	6	0	0
sotalol	156	136	87.2	26	12	46.2
hydrochlorothiazide*	———	———	——	34	0	0
atenolol	———	———	——	38	26	68.4
rosuvastatin	102	102	100	14	12	85.7
bisoprolol	———	———	——	24	24	100
other	17	11	64.7	16	0	0
Musculo-skeletal system	*234*	*145*	*62.0*	*142*	*75*	*52.8*
colchicine	91	38	41.8	47	26	55.3
allopurinol	138	104	75.4	65	49	75.4
alendroninic acid*	———	———	——	14	0	0
benzbromarone*	———	———	——	15	0	0
other	5	3	60.0	1	0	0
Al. tract and metabol.	*228*	*120*	*52.6*	*92*	*33*	*35.9*
metoclopramide	228	120	52.6	51	32	62.7
metformine*	———	———	——	28	0	0
ranitidine	———	———	——	11	9	80.9
other	———	———	——	2	1	50

Table 2 Continued

Medication	MDRD 30-50 ml/min/1.73m²			MDRD 10-29 ml/min/1.73m²		
	Prescriptions (n)	**adherent (n)**	**%**	**Prescriptions (n)**	**adherent (n)**	**%**
Nervous system	*165*	*147*	*89.1*	*134*	*123*	*91.8*
tramadol	———	———	——	91	86	94.5
gabapentin	36	31	86.1	9	7	77.8
pregabalin	55	51	92.7	14	12	85.7
levetiracetam	36	31	86.1	9	7	77.8
hydroxyzine	34	34	100	11	11	100
other	4	0	0	0	n.a.	n.a.
Antiinf. for syst. use	*70*	*26*	*37.1*	*85*	*35*	*41.2*
clavulanic acid	———	———	——	44	10	22.7
valganciclovir	48	24	50.0	36	23	63.9
nitrofurantoin**	19	0	0	2	0	0
other	3	2	66.7	3	2	66.7
Respiratory system	*57*	*1*	*1.8*	*25*	*1*	*4.0*
levocetirizine	40	0	0	13	0	0
cetirizine	17	1	5.9	12	1	8.3
Genito urinary system	———	———	——	*9*	*3*	*33.3*
solifenacin	———	———	——	6	3	50.0
tolterodine	———	———	——	3	0	0
Total	**1077**	**688**	**63.9**	**645**	**344**	**53.3**

---- = no dosage adjustment required
*= contra-indicated drug in case of MDRD < 30 ml/min/1.73m²
**= contra-indicated drug in case of MDRD ≤ 50 ml/min/1.73m²
Al. tract and metabol. = alimentary tract and metabolism
Antiinf. for syst. use = antiinfectives for systemic use

dosages were adjusted in 58.5% en 47.8% of the prescriptions, respectively, cases of non-adherence mainly concerned colchicine, allopurinol, and metoclopramide. Relatively least adherence with the dosing guideline was found in medications acting on the respiratory system (2.4%: levocetirizine and cetirizine), genito urinary system (33.3%: tolterodine and solifenacin), and anti-infectives for systematic use (39.4%: clavulanic acid, valganciclovir, nitrofurantoin, norfloxacin, clarithromycin, levofloxacin, and aciclovir).

Determinants of adherence with the dosing guideline

Adherence with the Dutch dosing guideline was not influenced by age, gender, or length of hospital stay (Table 3). Reporting the eGFR in the laboratory values in addition to serum creatinine levels only, was associated with more adherence with the dosing guideline: 50.7% adherence if only creatinine levels were reported vs. 57.0% if also eGFR was reported, RR 1.12 (95% CI 1.02-1.25). Adherence with the dosing guideline was less prevalent in patients with severe renal impairment (46.0%), compared to patients with moderate renal impairment (58.1%): RR 0.79

Table 3 Determinants of adherence with dosing guideline

Characteristic	N (patients)	N patients with all dosages adjusted according to the guideline	RR (95% CI)
Total	1327	715 (53.9%)	
Age, y			
18-64	513	264 (51.5%)	ref
65-79	572	324 (56.6%)	1.10 (0.98-1.23)
≥80	242	127 (52.5%)	1.02 (0.87-1.18)
Gender			
Male	668	372 (55.7%)	ref
Female	659	343 (52.0%)	0.94 (0.84-1.04)
Reporting the eGFR			
No	655	332 (50.7%)	ref
Yes	*672*	*383 (57.0%)*	*1.12 (1.02-1.25)*
MDRD, ml/min/1.73m²			
30-50	866	503 (58.1%)	ref
10-29	*461*	*212 (46.0%)*	*0.79 (0.70-0.89)*
Change in renal impairment during hospital admission			
Stable	893	465 (52.1%)	ref
Declining 1 or more categories	234	105 (44.9%)	0.86 (0.73-1.01)
Improving 1 or more categories	*200*	*145 (72.5%)*	*1.39 (1.24-1.54)*
Duration of stay, days			
≤ 7 days	585	308 (52.6%)	0.95 (0.85-1.06)
8-30 days	653	362 (55.4%)	ref
≥ 31 days	89	45 (50.6%)	0.91 (0.71-1.12)
Prescriber			
Nonsurgical	884	454 (51.4%)	ref
Surgical	*443*	*261 (58.9%)*	*1.15 (1.03-1.27)*

(95% CI 0.70-0.89). Also, an improve in renal function during hospital admission was associated with greater adherence with the dosing guideline (72.5%), relative to stable renal function; a decline in renal function was associated with less adherence (44.9%) [RR 1.39 (95% CI 1.24-1.54) and RR 0.86 (95% CI 0.73-1.01), respectively]. Furthermore, adherence was better in patients discharged from a surgical department (58.9%), compared with patients discharged from a non-surgical department (51.4%): RR 1.15 (95% CI 1.03-1.27).

Potential clinical relevance of non adherence with the dosing guideline

All cases of non-adherence had the potential to cause harm, of which 71.4% had the potential to cause moderate to severe harm, such as the prescription of eplerenone, which is contra-indicated in cases of moderate to severe renal impairment due to the risk of increased serum potassium values, which may cause arrhythmia.

Discussion

The results of the present study indicate that adherence to the Dutch dosing guideline at hospital discharge in patients with renal impairment is 53.9%.

In this study, adherence with the dosing guideline was investigated in multiple medication groups in a large study population. Furthermore, multiple potential determinants were assessed on their influence on the prevalence of non-adherence with the dosing guideline. Another important aspect of this study was that the potential clinical relevance of non-adherence was determined. In the majority of cases, they had the potential to cause moderate to severe discomfort or clinical deterioration, which may lead to (extension of) hospital stay. This is in accordance with a previous study, that reported a clinical relevance rate of 63%.(6)

In this study population, serum creatinine values were measured in only 59% of patients. We did not find any literature in the hospital setting to compare with and to determine whether this rate is abnormal. However, in primary care, Raebel et al. have reported that in 32% of dispensings where a serum creatinine was indicated, it was not evaluated (range 12-61%).(24) So, perhaps in secondary care serum creatinine values are also insufficiently evaluated.

Adherence with the dosing guideline is influenced by multiple determinants, which may also mediate each other (Figure 2). Reporting the eGFR was associated with more adherence with the dosing guideline. Possibly, this effect is mediated by a consult request to a nephrologist, when the reported eGFR is low. Unfortunately, we do not have information on nephrologists consults. We would expect more adherence with the dosing guideline in cases of severe renal impairment with

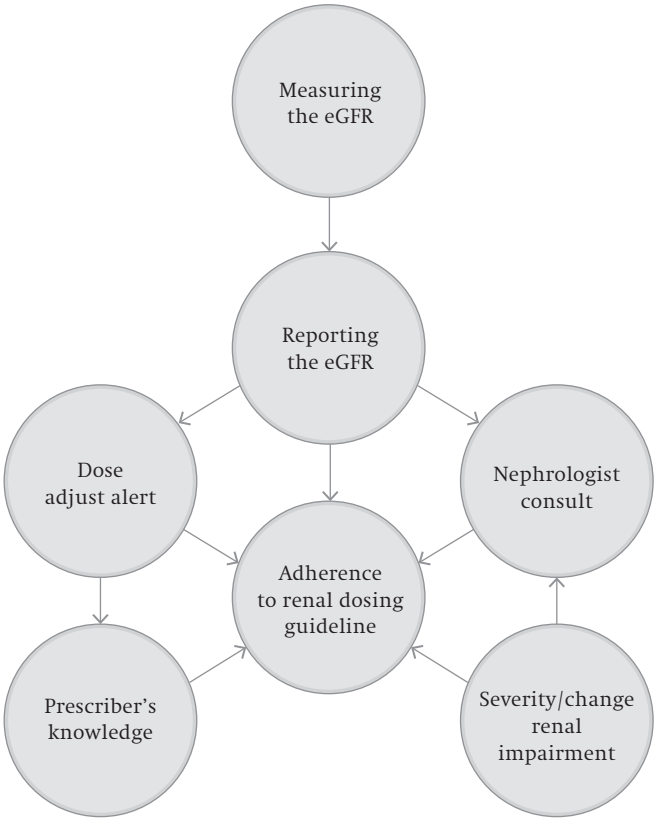

Figure 2 Possible determinants of adherence

subsequently a nephrologist consult. However, non-adherence was most frequently found in patients with severe renal impairment. On the other hand, in the UMCU surgeons routinely consult a nephrologist whenever they treat patients with impaired renal function, and we found that physicians from surgical specialties were more adherent with the dosing guideline than physicians from non surgical specialties. Most cases of non-adherence were identified in cardiovascular medications, especially eplerenone, drugs acting on the musculoskeletal system, especially allopurinol and colchicine, and drugs acting on the alimentary tract and metabolism, especially metoclopramide. Furthermore, in none of the cases the prescribers were adherent with the maximum advised daily dose for levocetirizine. The prevalence rates of adherence with the dosing guideline found in this study were comparable to prevalence rates reported in other studies.(1,9) In order to

improve adherence with dosing guidelines, physicians first need to identify patients with impaired renal function, and second to identify medication that require dosage adjustment. Reporting the eGFR helps to identify patients with impaired renal function. Previous studies have shown conflicting results for the effect of reporting the eGFR on adherence with dosing guidelines.(25,26) Although the present study showed that adherence with the dosing guideline improved significantly after introduction of reporting the eGFR, the absolute effect was relatively small. Routinely consulting a nephrologist will probably be more effective, as the results of this study showed that surgeons, who routinely consult a nephrologist, adhere better with the dosing guideline than other physicians. A recent systematic review has shown that reporting the eGFR is associated with increases in consults, referrals, or nephrology clinic attendances.(27) Increases ranged from 13%-270% of the pre–eGFR period numbers and often occurred abruptly after implementation of eGFR reporting. However, nephrologists do not have the capacity to be involved with all hospitalised patients with impaired renal function. Therefore, dose adjust alerts for drug dosage adjustment by computerised clinical decision support systems (CDSS) may be the most feasible and effective intervention. Dose adjust alerts assist physicians with identifying medications that require dosage adjustment. However, there is wide variability in the adaptation of recommendations generated by CDSS systems, with 49 to 96% of alerts being overridden or ignored.(28) A systematic review has identified a range of factors that adversely affect the utilisation of CDSS, including unsuitable content of alerts, excessive frequency of alerts, and alerts causing unwarranted disruption to the prescriber's workflow.(29) Various studies have investigated the effect of dose adjust alerts, and except for the study of Sellier et al., these studies confirmed that dose adjust alerts improve adherence with dosing guidelines.(30-33) The study of Sellier et al. had a low baseline inappropriate dosage prescribing rate of 21%, probably because of pharmacists already reviewed all prescriptions. This may implicate a ceiling effect, and therefore explain the limited impact of dose adjust alerts in this study. Consequently, hospitals with a high baseline non-adherence rate can benefit from dose adjust alerts. Also in primary care dose adjust alerts by CDSS have proven to be effective.(34,35) Reporting the eGFR, which is currently done by more than 80% of clinical laboratories in the USA, could be a simple first step to improve adherence with dosing guidelines.(36)

The present study was subject to several limitations. First, it was conducted in only one hospital, which limits the generalisability of the study results. Second, GFR was estimated by the three-variable version of the MDRD formula, which did not correct for race and body surface area. For patients at the extremes of muscle mass or those with an unusual diet or a condition associated with changes in creatinine secretion, the MDRD estimate, which is based on serum creatinine, is likely to be

inaccurate.(37) This is particularly relevant for populations who are most likely to require medications, such as the frail older patients, critically ill, or cancer patients. This limitation holds for all serum creatinine-based formulas, although the Cockcroft-Gault formula seems to perform better in those populations, as well as cystatin C based formulas.(38,39) Third, the actual discharge prescriptions could not be assessed due to limitations of the database. Therefore, the prescriptions in the last 24 hours before discharge were assessed. These could have differed from the actual discharge prescriptions. At the time of providing the discharge prescriptions, physicians may have performed a last medication check and adjust dosage prescriptions. Fourth, as we had no information on pre-admission medication use, we could not assess whether prescriptions were initiated in the hospital or before hospital admission. Fifth, since this was a large retrospective cohort study, we could not study dosages in individual cases, for example on indication. Therefore we chose to set the maximum possible dose in each medication as high as possible. This implicates that it is possible that we have made an overestimation of adherence with the dosing guideline. Sixth, intentional non-adherence with the dosing guideline could not be assessed. Finally, we relied on the Dutch dosing guideline. This guideline may vary from other internationally used dosing guidelines. Though, because the guideline is based on international research results, we do not expect that these variations have major clinical implications.

Conclusion

For patients with impaired renal function medication dosages are often not adjusted at hospital discharge. Especially for patients with severe renal impairment and/or declining renal function dosages are frequently not adjusted. Non-adherence with the dosing guideline was mainly found for eplerenone, allopurinol, colchicine, metoclopramide, and levocetirizine and was potentially harmful in the majority of cases. Although reporting the eGFR improves adherence with dosing advices, the prevalence of non-adherence remains high. Nonetheless, reporting the eGFR may be a simple first step to improve adherence with dosing guidelines.

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Appendix 1 Analysed medications, dosage advices, and potential clinical consequences

Medication	Dosage advice 30-50 ml/min/1.73m^2	Dosage advice 10-29 ml/min/1.73m^2	Potential clinical Consequences
Cardiovascular system			
acebutolol	n.a.	Dose reduction 50%	Hypotension, bradycardia
sotalol	max. 160 mg/day	max. 80 mg/day	Hypotension, ventricular tachycardia
rosuvastatin	max. 20 mg/day	max. 10 mg/day	Myopathy, rhabdomyolysis
atenolol	n.a.	Dose reduction 50%	Hypotension, bradycardia
hydrochlorothiazide	n.a.	Contra-indicated	Therapy failure
eplerenone	Contra-indicated	Contra-indicated	Life threatening hyperkalemia
bisoprolol	n.a.	max. 10 mg/day	Hypotension, bradycardia
chlorthalidone	n.a.	Contra-indicated	Therapy failure
amiloride	n.a.	Contra-indicated	Life threatening hyperkalemia
pentoxifylline	400 mg twice daily	400 mg once daily	Nausea, vomiting, headache
epitizide/ triamtereen	n.a.	Contra-indicated	Therapy failure
acipimox	250 mg once daily	250 mg every other day	Blushing, headache
indapamide	n.a.	Contra-indicated	Therapy failure
Musculo-skeletal system			
allopurinol	max. 200 mg/day	max. 100 mg/day	Severe skin reactions, trombocytopenia
colchicine	max. 0.5 mg/day	max. 0.5 mg/day	Toxicity: nausea, diarrhoea
alendroninic acid	n.a.	Contra-indicated	Diarrhoea, nausea, hypocalcemia
benzbromarone	n.a.	Contra-indicated	Uric acid nephrolithiasis/-pathy
risedronic acid	n.a.	Contra-indicated	Diarrhoea, nausea, hypocalcemia
clodronic acid	Dose reduction 25%	Dose reduction 50%	Nausea, diarrhoea, stomach ache
etidronic acid	n.a.	Contra-indicated	Diarrhoea, nausea, hypocalcemia

Appendix 1 Continued

Medication	Dosage advice 30-50 ml/min/1.73m²	Dosage advice 10-29 ml/min/1.73m²	Potential clinical Consequences
Musculo-skeletal system			
sodium-aurothiomalate	Contra-indicated	Contra-indicated	Haematuria, proteinuria, fever
Al. tract and metabol.			
metoclopramide	Dose reduction 50%	Dose reduction 50%	Extrapyramidal symptoms
cimetidine	n.a.	Dose reduction 50%	Psychic and psychomotor symptoms
ranitidine	n.a.	Dose reduction 50%	Psychic and psychomotor symptoms
metformine	n.a.	Contra-indicated	Lactate acidosis
famotidine	n.a.	Dose reduction 50%	Psychic and psychomotor symptoms
Nervous system			
tramadol	n.a.	100 mg twice daily	Central nervous system depression
gabapentin	max. 1200 mg/day	max. 600 mg/day	Fever, ataxia, dizziness, fatigue
hydroxyzine	Dose reduction 50%	Dose reduction 50%	Central nervous system depression
pregabalin	Dose reduction 50%	Dose reduction 75%	Increase side effects, e.g. confusion
levetiracetam	750 mg twice daily	500 mg twice daily	Increase side effects, e.g. fatigue
chloralydrate	Contra-indicated	Contra-indicated	Respiratory depression, coma
amantadine	100 mg every other day	100 mg every 3 days	Depression, hallucinations, insomnia
Antiinf. for syst. use			
clavulanic acid	n.a.	max. twice daily	Liver damage
valganciclovir	450 mg once daily	450 mg twice a week	Myelosuppression
nitrofurantoin	n.a.	Contra-indicated	Peripheral neuropathy (irreversible)
norfloxacin	n.a.	Once daily	Peripheral neuropathy (reversible)

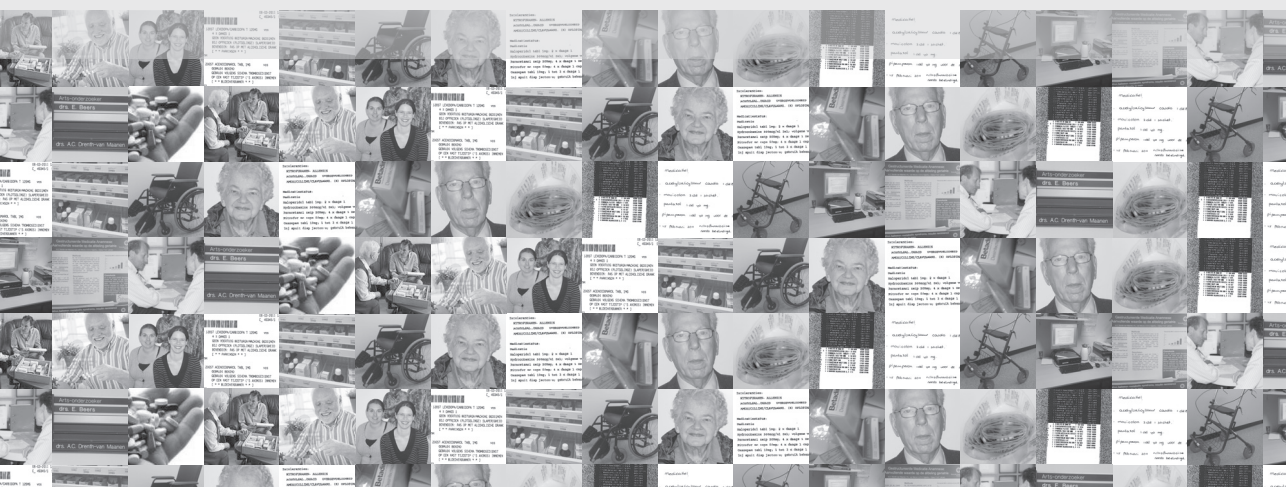
Appendix 1 Continued

Medication	Dosage advice 30-50 ml/ min/1.73m^2	Dosage advice 10-29 ml/ min/1.73m^2	Potential clinical Consequences
Antiinf. for syst. use			
clarithromycin	n.a.	Dose reduction 50%	Stomach disorders, pancreatitis
levofloxacin	Dose reduction 50%	Dose reduction 75%	Peripheral neuropathy (reversible)
aciclovir	n.a.	max. 2400 mg/day	Convulsions, coma, renal failure
Respiratory system			
levocetirizine	Dose reduction 50%	Dose reduction 50%	Central nervous system depression
cetirizine	Dose reduction 50%	Dose reduction 50%	Central nervous system depression
Genito urinary system			
solifenacin	n.a.	max. 5 mg/day	Constipation, urinary retention
tolterodine	n.a.	max. 2 mg/day	Constipation, urinary retention

n.a. = not applicable

5

General Discussion



Appropriate prescribing for older people is a challenging task. Inappropriate prescribing, which frequentlyoccurs in this population, can be defined as the prescribing of medicationsleading to unwanted outcomes outweighing the benefits, or the omission of medications that are indicated for that patient given the patient's pathophysiology or risk profile.[1, 2] Unwanted outcomes of prescribingare for example adverse drug reactions which may lead to increased morbidity, hospitalisation and mortality.[3-8] Older patients often have multiple risk factors for such outcomes of prescribing, such as polypharmacy, polymorbidity, impaired renal function, and frequent transfers between health care settings.[9]

The objective of this thesis was to describe the frequency and nature of such risk factors forinappropriate prescribing for older people, with a focus on polypharmacy, transitional care and impaired renal function, and to develop and investigate interventions to improve appropriate prescribing. In this chapter, the studies in this thesis will be discussed in a broader perspective. First, prescribing tools are discussed as a tool to detect potentially inappropriate prescribing and improve appropriate prescribing. The domains addressed by the different indicators are discussed, including the Prescribing Optimization Method (POM), presented in this thesis. Furthermore, specific attention is paid to the validity of these indicators and the implementation in daily practice. Second,the effectiveness of interventions to improve transitional pharmaceutical care will be examined, as well as issues that hinder implementation of these interventions. Third, impaired renal function as a risk factor for inappropriate prescribing will be discussed. Finally, the implications of this thesis and further research questions will be addressed.

Prescribing tools

Since it can only be determined afterwards whether prescribing has been appropriate or not, the detection of potentially inappropriate medications (PIMs) can be difficult. For instance, in the example used in the general introduction the physician prescribed an NSAID for gout in the toe. The prescription was in accordance with the current guidelines, however, it turned out to be inappropriate, since the patient developed a gastro-intestinal bleeding. This case of inappropriate prescribing was not necessarily preventable. However, in some cases one can expect an increased risk of negative outcomes of a prescription. If, for example, the patient was a man of 85 years old who also used 80 mg of acetylic salicylic acid per day, the physician could have expected an increased risk of gastro-intestinal bleeding. In that case, the prescription of a proton pomp inhibitor along with the NSAID may have prevented the gastro-intestinal bleeding. Consequently, the prescription of an NSAID without a proton pomp inhibitor would have been irrational and potentially inappropriate.

In the general introduction, six steps were identified to achieve appropriate prescribing: (1) definition of the patient's problem; (2) specification of the therapeutic aims; (3) suitability of the selected intervention(s); (4) writing prescriptions and updating medication list; (5) informing the patient; and (6) monitoring the treatment outcome. To aid physicians with the detection of PIMs in the third step of this cycle, several prescribing tools have been developed. Prescribing tools are screening tools for the detection of potentially inappropriate prescribing. These indicators can be divided into explicit (criterion-based) or implicit (judgement-based) prescribing tools, which are summarised in Table 1.

Explicit prescribing tools

Explicit prescribing tools are usually developed based upon literature reviews, expert opinion and consensus techniques. They mostlyinclude lists of drugs or drug classes to be avoided in older people, which are known to have an increased risk of negative outcomes in this population. For example, older people usually respond more strongly to the negative effect of anticholinergic medications on cognitive function. Explicit prescribing toolsdo not specifically require clinical expertise, which makes them easily accessible for less experienced physicians. However, they usually do not address specific patient-related risk factors frequently found in older people, such as co-morbidity, nor do they take into account patient preference or previously unsuccessful treatment approaches.

The Beers' criteria are the first and most widely known explicit prescribing indicator, which have been created in 1991through a consensus panel of experts in the United States of America.[10] These criteria initially consisted of two lists of medications to be avoided in older people, one independent of diagnosis, and one based on drug-disease interactions. The Beers' criteria have been revised in 1997,[11] 2003,[12] and 2012.[13] In the latest revision a third list of medications to be used with caution in older people was added.

The European counterparts of the Beers' criteria are the STOPP (Screening Tool of Older People' potentially inappropriate Prescriptions) criteria, developed in Ireland.[14] Like the Beers criteria they address contra-indications and interactions, but they also refer to drug class duplication, and drug-drug interactions. Alongside with the STOPP criteria, the same group developed the START (Screening Tool to Alert physicians to the Right Treatment) criteria.[15] These criteria address omission of clinically indicated, evidence-based medications, an often unmentioned and frequent problem in older patients. (ziepublicatiepaul en mij→welke?)

In 1997 a Canadian consensus-based list of inappropriate practices in prescribing for older peoplewas developed.[16] This list is subdivided into four topics: cardio-vascular drugs, psychotropic drugs, analgesic drugs, and miscellaneous drugs. The list addresses mainly contra-indications and interactions, in one case also drug

duplication. Additionally this list offers options for alternative therapy. The list contains however also obsolete criteria, such as the contra-indication of β-adrenergic blocking agents for patients with a history of asthma, COPD, or heart failure.
Also in Canada, Rancourt et al. composed in 2004 a large set of criteria for potentially inappropriate prescribing which were categorised as potentially inappropriate medication (contra-indication), potentially inappropriate dosage, potentially inappropriate drug-drug interactions, and additionally potentially inappropriate duration.[17]
The Norwegian General Practice (NORGEP) explicit criteria have been developed in 2009 and comprise mainly medications that are contra-indicated in older people and drug-drug interactions. In two cases also dosage control is included.[18]
Explicit criteria have the disadvantage that they have limited transferability between countries due to variations in regional prescribing patterns and drug availability. Explicit criteria also require regular updates in line with evolving clinical evidence.

Implicit prescribing tools

Implicit criteria refer to quality indicators of prescribing that a clinician or pharmacist can apply to any prescription, using expert professional judgment. Implicit criteria are not drug or disease specific and consequently rely on a clinician's medical knowledge.
The Medication Appropriateness Index (MAI) is an implicit tool, developed in the United States of America in 1992, which measures prescribing appropriateness according to ten criteria, including whether there is an indication for the drug, the medication is effective for the condition, the dosage is correct, the directions are correct, the directions are practical, there are clinical significant drug-drug interactions, there are clinical significant drug-disease interactions, there is unnecessary duplication with other drug(s), the duration of the therapy is acceptable, and whether the drug is the least expensive alternative compared to others of equal utility.[19] It does not address under-prescribing. Clinical expertise is required to apply some of the criteria, resulting in variable interrater reliability. Furthermore, it is not suitable for clinical practice due to its time-consuming nature. Consequently, the MAI is mainly used as a research tool.
In 2009, the TIMER (Tool to Improve Medications in the Elderly via Review) has been developed in the United States of America.[20] It makes use of the Beers criteria, and additionally highlights cost-effectiveness, adherence, and attaining therapeutic goals. It provides specific advices on the most common medication issues that affect older patients.
The Dutch Prescribing Optimization Method (POM) aims to the address the most frequently occurring prescribing errors, as described in existing literature.[21] In six

Table 1 Prescribing tools

Explicit prescribing tools	**Domains addressed**				
	Actual medication use/ adherence	Practical intake problems	Under prescribing	Over prescribing/ drug duplication	Contra indications
Beer's criteria	–	–	–	–	√
STOPP and START	–	–	√	√	√
Rancourt	–	–	–	√	√
Canadian	–	–	–	√	√
APIT	–	–	√	√	√
NORGEP	–	–	–	–	√
Implicit prescribing tools	**Domains addressed**				
	Actual medication use/ adherence	Practical intake problems	Under prescribing	Over prescribing /drug duplication	Contra indications
MAI	√	√	–	√	√
TIMER	√	–	√	√	√
POM	√	√	√	√	√
PHARM	√	√	√	√	√
STRIP	√	√	√	√	√

STOPP: Screening Tool of Older People' Prescriptions
START: Screening Tool to Alert physicians to the Right Treatment
APIT: Australian Prescribing tools Tool
NORGEP: Norwegian General Practice criteria
MAI: Medication Appropriateness Index
TIMER: Tool to Improve Medications in the Elderly via Review
POM: Prescribing Optimization Method
PHARM: Preventing hospital admissions by reviewing medication
STRIP: Systematic Tool to Reduce Inappropriate Prescribing

steps it checks for adherence, under-prescribing, over-prescribing, adverse effects, interactions, and dosage and dose frequency control. Chapter 2 showed that POM is an effective indicator for improving appropriate prescribing by general practitioners. When applied to case histories, theproportion of correct decisions increased from 34.7% without the POM to48.1% with the POM ($p < 0.01$), and the number of potentially harmfuldecisions decreased from 3.3 without the POM to2.4 with the POM ($p < 0.01$). As both the TIMER and the POM only provide specific advices on the most common medication issues that affect older patients, their

Interactions	Dosage/ formulation control	Dose frequency control	Costs	Alternative therapy	Shared decision making	Monitor
√	–	–	–	–	–	–
√	–	–	–	–	–	√
√	√	–	–	–	–	√
√	–	–	–	√	–	–
√	√	–	–	–	–	√
√	√	–	–	–	–	–

Interactions	Dosage/ formulation control	Dose frequency control	Costs	Alternative therapy	Shared decision making	Monitor
√	√	√	√	–	–	√
√	–	–	√	–	–	–
√	√	√	–	√	√	–
√	√	√	–	–	√	√
√	√	√	–	√	√	√

lists of medications to be initiated or discontinued is less extended than the Beers criteria and the START en STOPP criteria. However, these criteria address less aspects of appropriate prescribing than the TIMER and the POM.

PHARM (Preventing Hospital Admissions by Reviewing Medication) is also developed in the Netherlands and designed to support the total pharmaceutical care process.[22] It does not make use of explicit prescribing tools.

In 2012, the developers of POM and PHARM combined these two methods into the STRIP (Systematic Tool to Reduce Inappropriate Prescribing), so all pharmacists and general practitioners in the Netherlands would use the same method, which promotes cooperation. [23]The STRIP consists of five steps: pharmaceutical anamnesis, pharmacotherapy review, pharmaceutical care plan, shared decision making with patient, monitoring and follow-up. The STOPP and START criteria are used as explicit prescribing indicator within the STRIP.

The limitations of implicit criteria aretheir time-consuming nature and dependence on clinical expertise, which can partly be solved by implementing explicit criteria

into the implicit criteria. Their main advantage is that they focus on the patient and decisions with regard to prescribing appropriateness are made at an individual level.

Prescribing tools can be used when prescribing new medications, but are mostly appliedfor medication reviews, which can be performed at several levels: (1) prescription level, (2) concordance and compliance level, and (3) clinical medication review level.[8] The primary purpose of a prescription review is to address practical medicines management issues that can improve the clinical and cost-effectiveness of medicines and patient safety. A prescription review can take place without the patient present and can serve the purpose of improving patient safety through case finding. For example by considering the results of renal function testing for patients taking medications for which the dosage depends on renal function. A concordance and compliance review takes place in partnership with the patient and/or caregiver, and enables patients and practitioners to explore the patient's medicine taking, including the patient's actual pattern of medicine taking and the patient's beliefs about medicines. A concordance and compliance review may be appropriate when a patient is admitted to or discharged from the hospital. A clinical medication review is a structured, critical examination of a patient's medicines with the objective of reaching an agreement with the patient about treatment, optimising the impact of medicines, minimising the number of medication-related problems and reducing waste.[24, 25] For a clinical medication review the patient's presence is required, as well as full access to the patient file and all prescription and non-prescription medicines. The best level for medication reviews is the clinical medication review. It is, however, also the most time-consuming one.

Validity of prescribing tools

The aim of prescribing tools and medication reviews is to reduce inappropriate prescribing. It is however difficult to determine the validity of prescribing tools and medication reviews in terms of morbidity and mortality, since they do not directly influence morbidity and mortality. Studies aimed at investigating the effect of medication reviews on clinical endpoints, such as hospital admissions, mortality, and quality of life, were not able to show an effect on these endpoints;[26-29] although medication reviews during hospital admission may reduce hospital readmissions.[30] Most studies use surrogate endpoints, such as potentially inappropriate medications (PIMs) or falls.[17, 31-41] These studies find that PIMs occur in over 10% of community living older people, and in up to 60% of nursing home residents and that prescribing tools are effective in reducing PIMs. Also in our study the reduction in PIMs was used as a surrogate endpoint to determine the validity of the POM.

Although the effect of prescribing tools on 'hard' clinical outcomes, such as hospital admissions and mortality still has to be determined, their use fits very well into good clinical practice and therefore implementation of prescribing tools should not be postponed awaiting the results of large randomised trials.

Implementation of prescribing tools

In 2012 the Dutch multidisciplinary guideline 'Polypharmacy in older people' is published, which provides guidance on how to perform a medication review.[23] As the combined approach by general practitioners and community pharmacists seems to be most effective,[42] they are the first ones indicated to perform medication reviews. Medication reviews are probably most effective in patients with an increased risk of medication related adverse events. Leendertse et al. identified the following risk factors for medication related hospital admissions: impaired cognition, polymorbidity, impaired renal function, dependent living situation, polypharmacy, and nonadherence to the medication regimen.[9]

Consequently, patients with one or more of these risk factors may be the first to select for a medication review. As falls are frequently used as a surrogate endpoint to measure the effect of medication reviews,[43] one could also select patients with a known risk of falls.

Figure 1 illustrates the necessary steps to adequately perform a clinical medication review. Step 1 comprises the medication history taking of a patient in a structured manner with use of multiple sources of information, such as medication overviews from the community pharmacy and medication vials of the patient. In chapter 3.1 and 3.2 it was shown that structured history taking of medication use (SHIM) is an effective tool for medication history taking. When SHIM is applied, the medication history will not only provide information on the actual medication use of the patient, but also on experienced adverse effects and other concerns of the patient with taking the medication. Also, additional information on clinical parameters that affect medication prescribing has to be gathered, such as blood pressure, HbA1c in case of diabetes, and renal function. Step 2 comprises the medication analysis, for which explicit prescribing tools can be used. Step 3 is the communication with the patient and/or caregiver and all other involved health care providers, as well as the monitoring for the outcomes of prescribing.

At present, medication reviews are time-consuming. In the guideline 'Polypharmacy in older people' the total time invested to perform a medication review is estimated at 120 to 150 minutes.[23] The use of supporting personnel, such as pharmacy technicians, may reduce the invested time for a community pharmacist to 45 minutes and for a general practitioner to 25 minutes. Further time savingscan be reached by more efficient application of information technology support. Currently general practitioners and community pharmacists perform medication

reviews mainly without the support of information technology applications. When prescribing tools are available as clinical decision support systems, adherence with the indicators may be improved and the time required to perform medication reviews can be reduced as manual searches in the prescribing tools will no longer be necessary. Linking of patient files between general practitioner and community pharmacy information systems may further reduce the time invested for data entry and administration.

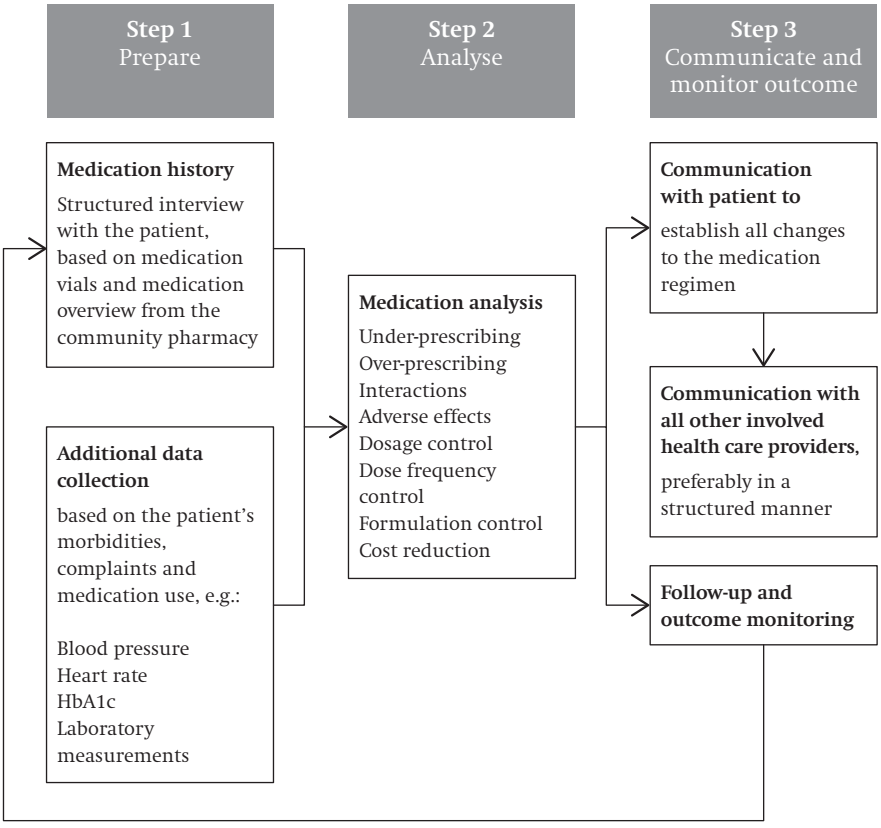


Figure 1 Steps to adequately perform a medication review

In the end, the results of a medication review will be based on shared decision-making by the patient, the physician, and the pharmacist. Through shared decision making the communication between health care providers and patients

is supported. Patients are encouraged to deliberate about the possible attributes and consequences of pharmacotherapeutic options andto discuss their preferences. Furthermore shared decision making respects patient autonomy and improves patient involvement with the pharmacotherapeutic regimen.
To maximise the effect of medication reviews, the results should be adequately documented in order for them to be readily available for future treatment decisions. Adequate documentation is also indispensable for communication with other involved health care providers, especially at times of transfer between health care settings.

Transitional pharmaceutical care

Patient transfer between health care settings is a well-known risk factor for medication errors and negative outcomes. Adequate communication between health care providers and patients at times of transitions between health care settings is important in order to prevent these medication errors. At least four people are involved with transitional pharmaceutical care: the patient, the referent physician, the physician the patient is referred to, and the (community and/or hospital) pharmacist. In olderpatients caregivers and home care nurses are also often involved.

Accountability

Accountability for accurate transfer of information on the medication regimen is an important issue in transitional pharmaceutical care, since there are so many people involved. In theory, the patient always knows which medications are on his/her medication regimen, because the patient is the one who actually uses the medication and only the patient is always present when changes are made to themedication regimen.However, in practice patients often do not remember which medications they have been prescribed and what changes are made to the medication regimen, or changes to the medication regimen are not at all or insufficiently communicated to the patient. Community pharmacists are very well capable of composing and maintaining a medication overview. However, since they are not the ones who make changesto the medication regimen, they are dependent on the information provided by physicians. Consequently, transitional pharmaceutical care is a shared responsibility of the patient, the pharmacist, and the physician. Unfortunately, shared responsibility facilitates the shirking of responsibility. It is therefore essential to define the different tasks in transitional care and to determine which of these tasks should be made accountable and subsequently to whom. Table 2 summarises the different tasks in transitional pharmaceutical care and how accountability for these tasks could be assigned.

Table 2 Shared responsibility transitional pharmaceutical care

Person	Accountability
Patient	• Bring medication overview or medication vials at each visit to the physician • Inform physician and/or pharmacist when non-prescription medications are used • Inform physician and/or pharmacist when medication is not used as prescribed • Inform physician and/or pharmacist on experienced side effects or other concerns about medication use
Physicians	• Discusseach change to the medication regimen with the patient • Communicate all (reasons for) medication changes to other involved health care providers (including pharmacist), including reasons for discontinuing medication meant for chronic use • Communicate monitoring advices to other involved health care providers (including pharmacist), such as renal function in case of impaired renal function, or adverse drug effects
Pharmacist	• Compose and maintain an overview of actual medication use • Document all changes to the medication regimen • Monitor for contra-indications, adverse effects, interactions and communicate this with physicians • Communication between community- and hospital pharmacy

Communication

Transitional pharmaceutical care consists on the one hand of sending information, and on the other hand of receiving information. Only if both sending and receiving of information is flawless, communication can be effective. In the Netherlands a guideline for transferring information on the medication regimen has been developed, which offers guidance on which information about the medication regimen should be send at times of transfer between health care settings. When information is send in a structured manner, ambiguity is reduced, and consequently efficiency is increased. Subsequently, the receiver should process the information in a structured manner. In chapter 3.4 it was shown that although information on the discharge medication regimen was send in a structured manner according to the guideline, the implementation of this information did not improve. Thus, improving the quality of information transfer as a single intervention is insufficient. Probable causes of the insufficient implementation-were that the information could not be processed adequately and in a structured manner into the information systems of the next health care providers. Enhancement in information technology applications may therefore significantly improve the processing of information and consequently contribute to patient safety.

Information technology applications

Information technology applications can aid transitional pharmaceutical care in three ways. First, relevant data can be automatically retracted from the electronic patient files, such as information on prescribed medications, and experienced adverse drug events. Second, these applications can offer a single and structured format for sending information on the medication regimen to the next health care provider. Third, when electronic patient records can be linked, information on changes to the medication regimen can be automatically processed into other health care providers patient files, which minimizes the risk on processing errors. Ideally all health care providers work with a single patient record to make transitional pharmaceutical care more safe and efficient. Plans for a national Electronic Health record in the Netherlands are still in a developing phase. They have been delayed many times, mainly due to confidentiality and security issues. If appropriate solutions can be found for these issues, a national Electronic Health record can improve patient safety issues significantly. For medication safety this means that each patient has one single electronic medication file. This medication file should primarily contain the current medication use by the patient, and second the documentation of all changes made to the medication regimen (including rationale and start/stop dates), contra-indications, known allergies/ intolerances for medications including the symptoms of intolerance with advice for future use (e.g. do not prescribe at all, or monitor intensively for adverse effects), and if applicable specific patient concerns/wishes. Many changes to the medication regimen should be documented automatically in the medication file (e.g. when a physician prescribes a new medication, the electronic medication file should automatically document the name, dosage, dosage frequency, and administration route of the prescribed medication, as well as the name and function of the physician and the date of the first prescription. Furthermore, an electronic medication file should stimulate physicians to document reasons for medication changes. Currently, physicians insufficiently document medication changes, even if the reason of discontinuation is an adverse drug event.[44] It is shown that pop-up windows in an electronic decision support system, which force physicians to document reasons for medication discontinuation is effective in improving documentation of medication changes and is also considered user-friendly.[45] Thus, a national electronic medication file with an electronic decision support system can minimize medication errors at times of transitional care, and aid physicians with complete and accurate documentation of medication changes.

Impaired renal function

Renal function assessment is necessary to prevent inappropriately high dosage prescribing for patients with impaired renal function. Accurate renal function

assessment is difficult in frail, geriatric patients. In chapter 4.1 no best method to estimate renal function in geriatric patients could be indicated, although the CKD-EPI (Chronic Kidney Disease – Epidemiology) formula performed slightly better than the Cockcroft-Gault and MDRD (Modification of Diet in Renal Disease) formulas. These formulasare based on serum creatinine values. Especially in frail, geriatric patient, serum creatinine levels are unreliable to use for renal function assessment, since creatinine is a waste product of muscle mass, which is significantly declined in geriatric patients compared to younger adults. Furthermore, due to variability in serum creatinine measurements multiple (at least two) creatinine measurements are necessary to reliably measure creatinine levels, especially in patients who are not in a stable clinical situation.[46, 47] So, when physicians face prescribing issues with old, frail patients, they may not settle with an estimated glomerular filtration rate (eGFR) by a serum creatinine based formula, especially when misestimating GFR may have serious consequences. Chapter 4.2 showed that there is much room for improvement concerning adherence with dosing guidelines in patients with known impaired renal function at hospital discharge, especially in patients with severe renal impairment. This chapter also illustrated that adherence was better when estimated values of glomerular filtration rate were automatically provided whenever a serum creatinine level was requested. This confirms that physicians first need to identify patients with impaired renal function. Unfortunately, appropriate documentation of impaired renal function in patient files lacks in more than 20% of patients with impaired renal function.[48] So, the first step to improve adherence with dosing guidelines should be to adequately assess and document renal function in patient files. The next step to improve adherence with dosing guidelines would be to make dosing guidelines more readily available to physicians, preferably through a decision support system. In the Netherlands, the dosing guideline impaired renal function is available for pharmacists, but not for physicians. When physicians do not have access to the guideline, they cannotbe expected to adhere with the guideline. And because impaired renal function is insufficiently documented in patient files and communicated to the pharmacists, they cannot check for inappropriate dosage prescribing. This vicious circle inhibits appropriate prescribing for patients with impaired renal function and can be broken by appropriate renal function documentation and implementation of dosing guidelines into clinical decision support systems. However, the advices offered in the Dutch dosing guideline are limited by the information available per medication on dosage prescribing for case of renal function. The advices in the guideline are based on literature, registration files, and expert opinion. As the amount and quality of available information varies per medicine, the advices may consequently vary from primarily evidence based to primarily expert consensus based. Thus, physicians may explicitly choose

not to adhere with the guideline, depending on the extent to which the guideline advice is based on evidence based medicine, the expected potential adverse effects, the expected benefit for the patient, prior experience (e.g. in case of chronic use with an established clinical effect the physician may choose not to change the treatment), and the setting (e.g. in a clinical setting adverse effects can be monitored for more easily than in an outpatient setting).

Implications for practice and future research

Implications for practice

Improving appropriate prescribing for older people is essential in order to improve the pharmacotherapeutic care for this population and subsequently to reduce medication related adverse events. Medication reviews reduce PIMs and can potentially reduce medication related adverse events, such as falls, hospital (re) admissions and mortality. However, medication reviews are time-consuming and consequently expensive and are therefore difficult to implement in daily practice. Thus, in order to effectively implement medication reviews in daily practice, resources to facilitate medication reviews are indispensable. One option is to deploy lower educated personnel for aspects of the medication reviews that do not specifically require the expertise of a physician or a pharmacist, such as the medication history taking. Another important condition for effective implementation of medication reviews is information technology assistance. Electronic available prescribing tools may significantly reduce the time invested to perform medication reviews. The current fragmentation of the patient's medical information over various patient records from general practitioners, community pharmacists, hospitals, etc. is a major factor comprising patient and medication safety. The absence of a national electronic health record results in inefficiency and preventable (medication) errors. In a national electronic health record all the patient's medical information is stored and documented at one single place. Consequently, all health care providers work in the same health record, which prevents information from being lost. Consequently, the introduction of a national electronic health record can significantly reduce the time invested in gaining the medication history and communicating the medication regimen at times of transfer between health care settings. A national electronic health recordcan also reduce medication errors due to incorrect or insufficient processing of information on the medication regimen and confusion due to multiple different medication overviews from different prescribers and the community pharmacist.[49] However, a national electronic health record depends for its success on the accurateness and completeness of information documented into this health record by health care

providers.Therefore, physicians should be educated and stimulated to accurately document all relevant information in this record, for example by pop-up windows forcing physicians to document reasons for changes to the medication regimen.
Awaiting the implementation of a national electronic health record, the cooperation between primary and secondary care health care providers must be intensified, as well as the cooperation between general practitioners and community pharmacists. As medication safety is a core business of pharmacists, they must more explicitly come to the fore and realise agreements with both primary and secondary care physicians to improve pharmaceutical care and make it more efficient, as well as inform and stimulate patients (or caregivers) to be involved with their medication regimen as much as possible.

Implications for future research

Future research may focus on electronic available prescribing tools, such as the STRIP. A large, prospective study is required to investigate primarily the effect of electronic prescribing tools on morbidity, falls, quality of life, mortality and hospital (re)admissions, and secondary time-reduction, patient satisfaction, and cost-effectiveness of electronic prescribing tools. A stepped wedge design can be an appropriate design for such a study, as in this design all participating general practitioner practices and pharmacies serve as their own control, which minimises selection bias.
Furthermore, more research is required on renal function assessment in older people. Possibly more variables than age, gender, serum creatinine, weight and race influence the reliability of frequently used formulas to estimate the glomerular filtration rate (GFR). One could think of comorbidities, medication use, or medical condition (stable or acutely ill). So a larger prospective study than conducted for this thesis, with measurement of all variables that could possibly influence the reliability of GFR assessment formulas, may provide insight into the factors that are important for GFR determination. A first step to identify potential variables could be an individual patient data (IPD) meta analysis on renal function assessment in older patients.

Conclusion

The research presented in this thesis demonstrates that much can and needs to be done to improve appropriate prescribing for older people. Medication reviews, with accurate identification of patients with impaired renal function, and transitional pharmaceutical care programs are important factors that can improve appropriate prescribing.

Medication reviews are effective in reducing potentially inappropriate medications and falls. They have not yet shown to be effective in reducing mortality and hospital admissions, although they have been shown to reduce potentially inappropriate prescribing. As medication reviews are time-consuming, steps need to be taken to improve the efficiency of medication reviews, for example by utilising information technology applications to make prescribing tools more readily available and by deploying lower educated personnel.

Transitions between health care settings induce an increased risk of prescribing errors. Information on the medication regimen at times of transfer between health care settings requires improvement by both sending more complete and structured information, and by receiving and processing this information in a structured manner.

To actually improve appropriate prescribing for older people the cooperation and communication between health care providers and patients needs to be intensified. Appropriate prescribing is a continuing process that can only be successful if patients, physicians, pharmacists and other involved parties document, communicate, cooperate in shared decision making and all take responsibility for their part of the process.

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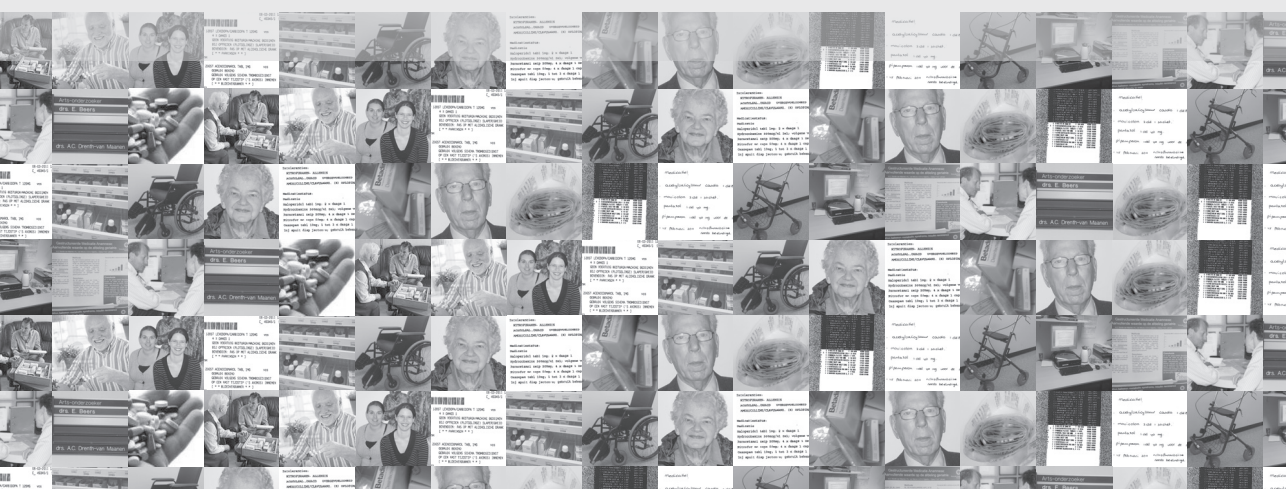

Summary

Appropriate prescribing is the result of pharmacotherapeutic decision-making to maximise the net health benefit of treatment, given the resources available. The risk of inappropriate prescribing increases with age, which means that older people are at increased risk of the adverse effects of inappropriate medications, leading to adverse outcomes such as admission to hospital.

Chapter 1 described the scope, objectives, and outline of this thesis. Several risk factors for inappropriate prescribing in older people have been identified, such as polypharmacy, altered pharmacokinetics and pharmacodynamics (due to impaired renal function, ageing, polymorbidity, etc.), and frequent transfers between healthcare settings. This makes prescribing appropriately for older people a challenge. On the basis of treatment aims, comorbidities, and contraindications (such as previously experienced adverse effects), physicians have to decide which medications are to be preferred and in what dosages they can best be prescribed. The objectives of the studies described in this thesis were to describe the frequency and nature of risk factors for inappropriate prescribing in older people, with a focus on polypharmacy, transitional care, and impaired renal function, and to develop and investigate interventions to improve appropriate prescribing.

Chapter 2 focused on polypharmacy. **Chapter 2.1** described a study in which general practitioners (GPs) applied the Prescribing Optimization Method (POM) to the case histories of patients on polypharmacy. The POM is an implicit prescribing indicator to optimize polypharmacy and consists of six questions plus checklists. The questions ask about adherence, undertreatment, overtreatment, adverse effects, interactions, and adjustment of dose, dose frequency, and/or formulation. In this study, 45 GPs first reviewed the medication lists of a patient without using the POM or another prescribing indicator. Then, the GPs received a 2-hour lecture about the POM and subsequently used it to optimise the medication of a second patient. The medications recommended by the GPs were then compared with those advised by an expert panel of four geriatricians specialised in clinical pharmacology. Inappropriate prescribing occurred significantly less often when GPs used the POM: the proportion of correct treatment decisions increased by 13.4%, while the number of potentially harmful decisions decreased by almost 1 per patient.

Chapter 3 focused on transitional pharmaceutical care. When patients are transferred from one healthcare setting to another, their medication regimens should be passed on in an accurate and timely manner to the next healthcare

provider. The study described in **Chapter 3.1** investigated the accuracy of the medication history taken when patients were admitted to hospital. The number of discrepancies found when the medication history was taken in the usual fashion and when it was taken using a structured history of medication use (SHIM) checklist was assessed in 100 patients. Discrepancies were found in 92% of patients, with a median of three discrepancies per patient. Almost 75% of these discrepancies were potentially clinically relevant, and more than one in five patients experienced adverse consequences as a result of these discrepancies, such as recurrence of hallucinations after the omission of quetiapine, an increase in blood pressure after the omission of nifedipine, and chest pain after the omission of isosorbide mononitrate. In a subsequent study (**Chapter 3.2**), the SHIM was investigated in another setting: an old age psychiatry clinic with 50 patients older than 55 years. The results of this study confirmed that the SHIM improved medication history taking. Discrepancies were found in 78% of patients, with a median of two per patient; 82% of the discrepancies were potentially clinically relevant and 14% had clinical consequences, such as the recurrence of pain after omission of fentanyl.
The study described in **Chapter 3.3** investigated the effect of a discharge medication intervention on the incidence and nature of post-discharge medication discrepancies (i.e., differences between the medications and dosages prescribed at discharge and those used by patients at home). Forty-one patients were included in the control group and 44 patients in the intervention group. The intervention, consisting of patient counselling and a structured medication overview for the patient, GP, and community pharmacist, did not affect the number of post-discharge medication discrepancies. The overall incidence of medication discrepancies was 13.5% in the control group and 10.9% in the intervention group (HR 0.82, 95% CI 0.52–1.93). After further analysis, it transpired that the number of discrepancies due to patient-related factors, such as unintentional continuation of discontinued medications, decreased significantly after the intervention (2.4% vs. 0.8%; HR 0.34, 95% CI 0.21-0.94). However, the intervention had no influence on discrepancies due to system-related factors, such as dispensing errors or administration errors by homecare nurses. A subsequent study (**Chapter 3.4)** investigated whether changes to patients' medication regimens at discharge were entered in the patient files held by GPs and community pharmacists (CPs). GPs and CPs were asked to provide a medication overview from their patient files, from the time their patient were discharged from hospital. CPs changed patients' medication files to incorporate information about medications prescribed at discharge in 84.0% of cases in the control group compared with 84.1% in the intervention group (HR 1.00, CI 95% 0.83–1.21). GPs incorporated changes in 64.6% of cases in the control group and in 67.5% of cases in the intervention group (HR 1.05, 95% CI 0.84–1.30). The results showed that a structured review of medication use at hospital discharge did not

improve the implementation of changes to the medication regimen into CPs' and GPs' patient files.

Chapter 4 focused on the prescribing consequences of renal impairment. It is important to identify patients with impaired renal function, as these patients are less able to excrete medications or their metabolites that depend on renal excretion. Medications, or their active components, may accumulate, potentially to toxic levels, in these patients, and for this reason the dosage of many medications should be adjusted if renal function is impaired. The study reported in **Chapter 4.1** investigated the best method for estimating renal function in older patients. The glomerular filtration rate (GFR), which is often used to express renal function, can be accurately measured by administering an exogenous marker that is completely filtered by the glomeruli and not reabsorbed or actively secreted by the kidney. Inulin is such a marker. However, this standard method is cumbersome, expensive, and unpleasant for patients, and for this reason in daily practice physicians use formulae to estimate GFR (or creatinine clearance), based on plasma creatinine levels, age, sex, and other variables. The most widely used formulae are the Cockcroft-Gault (CG) formula, the Modification of Diet in Renal Disease (MDRD) formula, and the Chronic Kidney Disease-Epidemiology (CKD-EPI) formula. Unfortunately, these formulae are mainly based on data for younger adults, and for this reason a study (**Chapter 4.1**) was performed to estimate GFR in geriatric patients, using these formulae. To this end, the clearance of sinistrin, an analogue of inulin, was measured in 16 patients with a mean age of 82 years. On average, all formulae slightly overestimated GFR: CG +0.05 (95% CI -28 to +28) ml/min/1.73 m^2; MDRD +9 (95% CI -16 to +34) ml/min /1.73 m^2; and CKD-EPI +5 (95% CI -20 to +29) ml/min/1.73 m^2. These results indicate that in general the formulae estimate GFR rather well in geriatric patients. However, the formulae considerably overestimated or underestimated the GFR in individual cases. Overall, the CKD-EPI performed slightly better than the CG and MDRD. The study reported in **Chapter 4.2** investigated prescriber adherence to the Dutch dosing guideline for patients with renal impairment. To this end, the medication prescribed to 1327 patients in the last 24 hours before discharge was assessed for adherence to the dosing guideline. Only 54% of patients were prescribed medications in compliance with the guideline. Adherence to guideline recommendations improved when information about the eGFR became routinely available (in April 2009), namely, 50.7% versus 57.0% (RR 1.12, 95% CI 1.02–1.25). Prescriber adherence to guideline recommendations was worse in patients with severe renal impairment (46.0%) than in patients with moderate renal impairment (58.1%; RR 0.79, 95% CI 0.70–0.89); in 71.4% of the cases, non-adherence had the potential to cause moderate to severe harm. Non-adherence mainly concerned frequently prescribed medications, such as metoclopramide and colchicine.

The main results of the above-mentioned studies were discussed in **Chapter 5**. Appropriate prescribing for older people depends on cooperation, documentation of medication changes and clinical parameters that affect prescribing, such as impaired renal function, and communication between patients and/or caregivers, physicians, pharmacists, and any other involved healthcare providers. But it also depends on prescribers having sufficient knowledge of pharmacotherapy for elderly patients, and this may be facilitated by the use of prescribing tools, which can be divided into explicit (criterion-based) or implicit (judgement-based) prescribing tools. Explicit prescribing tools mostly include lists of drugs or drug classes to be avoided because they are known to carry an increased risk of negative outcomes in elderly individuals. Implicit prescribing tools are prescribing quality indicators that a clinician or pharmacist can apply to any prescription, using expert professional judgement. Implicit criteria are not drug or disease specific and consequently rely on a clinician's medical knowledge.

The Expertise Centre Pharmacotherapy in Old Persons (Ephor) provides healthcare providers with tools to facilitate appropriate prescribing, such as the POM, an implicit prescribing tool with additional explicit checklists. In the future, an electronic version of the Systematic Tool to Reduce Inappropriate Prescribing (STRIP), an improved version of the POM, will be available to physicians and pharmacists. Preferably, the STRIP will be supported by clinical decision support systems with dose adjust alerts for medications that require dose adaptation to renal function. Initiatives are also being taken to improve pharmacotherapy education and training for medical students. It is to be hoped that a national electronic health record will become available in the future, so that prescribers can optimally benefit from information technology support.

Samenvatting

Het optimaal voorschrijven van geneesmiddelen is het maken van medicatiekeuzes die leiden tot een maximale gezondheidswinst voor de patiënt, binnen de mogelijkheden van de maatschappij. Oudere mensen hebben een verhoogd risico om medicatie voorgeschreven te krijgen die ongeschikt voor ze is. Dit kan leiden tot ongewenste uitkomsten, zoals bijwerkingen en mogelijk zelfs medicatiegerelateerde ziekenhuisopnames.

In **Hoofdstuk 1**, de algemene introductie, worden de aanleiding, doelstelling en opzet van dit proefschrift beschreven. Deze algemene introductie beschrijft dat er bij ouderen meerdere factoren zijn die bijdragen aan het verhoogde risico op ongeschikte medicatie. Zo worden polyfarmacie, een veranderde farmacokinetiek en –dynamiek (bijvoorbeeld door een verminderde nierfunctie, veroudering, polymorbiditeit), en momenten van medicatieoverdracht geïdentificeerd als risicofactoren. Dit maakt optimaal voorschrijven voor ouderen lastig. Voor elke patiënt moet een arts beslissen welke geneesmiddelen in welke doseringen het meest optimaal zijn, op basis van het behandeldoel, comorbiditeit en contra-indicaties (zoals bekende allergieën).
De studies in dit proefschrift hadden als doel de frequentie en de aard van risicofactoren voor ongeschikt voorschrijven aan ouderen te onderzoeken, waarbij de focus op polyfarmacie, medicatieoverdracht en verminderde nierfunctie lag. Interventies ter verbetering hiervan werden ontwikkeld en onderzocht op effectiviteit.

Hoofdstuk 2 van dit proefschrift legt de focus op polyfarmacie. In **Hoofdstuk 2.1** worden de resultaten beschreven van een onderzoek waarbij huisartsen de Polyfarmacie Optimalisatie Methode (POM) toepassen op casuïstiek. De POM is een impliciete voorschrijfmethode, die bestaat uit zes open vragen, met additionele controlelijsten die gebruikt kunnen worden om polyfarmacie te optimaliseren. De vragen richten zich op therapietrouw, onderbehandeling, overbehandeling, bijwerkingen, interacties, en tenslotte de dosering, doseerfrequentie en toedieningsvorm van medicatie. Vijfenveertig huisartsen optimaliseerden eerst de medicatielijst van een casus zonder gebruik van de POM. Vervolgens kregen ze gedurende twee uur onderwijs over de POM, waarna ze met behulp van de POM de medicatielijst van een tweede casus optimaliseerden. De medicatiewijzigingen, gemaakt door de huisartsen, werden vergeleken met de adviezen van een expert panel, bestaande uit vier klinisch geriaters-klinisch farmacologen. Keuzes voor ongeschikte medicatie(doseringen) werden significant minder gemaakt door het gebruik van de POM: het percentage correcte beslissingen door huisartsen steeg met 13,4%,

terwijl het aantal potentieel schadelijke beslissingen daalde met bijna één per patiënt.

Hoofdstuk 3 heeft als onderwerp medicatieoverdracht. Wanneer de zorg voor een patiënt wordt overgedragen van de ene naar de andere zorgverlener, dan is het belangrijk dat er een complete, heldere en snelle medicatieoverdracht plaats vindt. **Hoofdstuk 3.1** richt zich op de medicatieanamnese bij opname in het ziekenhuis. Het aantal verschillen (discrepanties) tussen de reguliere medicatieanamnese en een gestructureerde medicatie anamnese (GMA) is onderzocht onder 100 patiënten die opgenomen werden op de afdeling geriatrie van het UMC Utrecht. Discrepanties werden gevonden bij 92% van de patiënten, met een mediaan van drie per patiënt. Bijna driekwart van deze discrepanties zijn potentieel klinisch relevant. Meer dan één op de vijf patiënten ontwikkelde ook daadwerkelijk klachten aan de discrepantie gerelateerde klachten, zoals het heroptreden van hallucinaties nadat het gebruik van quetiapine ten onrechte niet uit de reguliere medicatie anamnese naar voren was gekomen, of zoals het stijgen van de bloeddruk doordat nifedipine ontbrak in de reguliere medicatieanamnese. In **Hoofdstuk 3.2** is de GMA in een andere setting onderzocht: de ouderenpsychiatrie. Voor deze studie zijn 50 patiënten ouder dan 55 jaar geïncludeerd. De resultaten van dit onderzoek bevestigen dat de GMA een betere methode is voor het afnemen van de medicatieanamnese dan de reguliere medicatieanamnese. Discrepanties werden gevonden bij 78% van de patiënten, met een mediaan van twee per patiënt: 82% van de discrepanties waren potentieel klinisch relevant. Dit leidde in 14% van de discrepanties tot daadwerkelijke klinische gevolgen voor de patiënt, zoals het heroptreden van pijn na het ontbreken van fentanyl in de reguliere medicatie anamnese. In **Hoofdstuk 3.3** is het effect van een uitgebreide medicatieoverdracht bij ontslag op de incidentie en aard van discrepanties tussen de ontslagmedicatie en het daadwerkelijk medicatiegebruik in de thuissituatie onderzocht. Bij 41 patiënten in de controlegroep verliep de medicatieoverdracht bij ontslag via reguliere zorg: er werd een lijst opgesteld van de ontslagmedicatie, die zowel werd verzonden naar de apotheek en huisarts, alsook werd meegegeven aan de patiënt. Vervolgens werd bij 44 andere patiënten geïncludeerd de interventie toegepast: een uitgebreide medicatieoverdracht, bestaande uit een medicatie-ontslaggesprek met de patiënt en/of mantelzorger en een gestructureerde schriftelijke medicatieoverdracht voor zowel patiënt, huisarts, als apotheker, waarin per geneesmiddel werd aangegeven of het geneesmiddel nieuw, gewijzigd, ongewijzigd of gestopt was, en de reden hiervoor. Deze interventie bleek geen significante invloed te hebben op het aantal medicatiediscrepanties direct na ontslag uit het ziekenhuis. De incidentie van discrepanties was 13,5% in de controlegroep versus 10,9% in de interventiegroep. Uit nadere analyse bleek dat er een significante reductie was in

discrepanties veroorzaakt door patiëntgerelateerde factoren, zoals het onbedoeld doorgebruiken van gestopte geneesmiddelen, van 2,4% naar 0,8%. Er was echter geen afname in discrepanties veroorzaakt door systeemgerelateerde factoren, zoals afleverfouten van de apotheek of toedieningsfouten door de thuiszorg. Vervolgens is in **Hoofdstuk 3.4** onderzocht in hoeverre medicatieveranderingen tijdens ziekenhuisopname ingevoerd werden in de patiëntendossiers van huisartsen en openbare apothekers. Bij huisartsen en apothekers werd van patiënten die geparticipeerd hadden in de studie beschreven in Hoofdstuk 3.3, een medicatieoverzicht vanaf het moment van ontslag uit het ziekenhuis opgevraagd. Apothekers voerden wijzigingen in het medicatiebeleid door in 84,0% van de gevallen in de controlegroep. In de interventiegroep voerden zij 84,1% van de wijzigingen door. Dit was een niet-significant verschil. Huisartsen voerden wijzigingen in het medicatiebeleid door in 64,4% van de gevallen in de controlegroep, ten opzichte van 67,5% in de interventiegroep, eveneens niet significant. Uit dit onderzoek blijkt dat een uitgebreide en gestructureerde medicatieoverdracht bij ontslag niet leidt tot een betere verwerking van de medicatieoverdracht in de eerste lijn.

Hoofdstuk 4 richt zich op patiënten met een verminderde nierfunctie. Het is belangrijk om deze patiënten te herkennen, omdat zij minder goed in staat zijn om geneesmiddelen of hun actieve metabolieten die renaal geklaard worden uit te scheiden. Dientengevolge lopen deze patiënten een verhoogd risico op accumulatie tot toxische concentraties. Een dosisverlaging aan de hand van de nierfunctie kan deze problemen voorkomen. Het correct meten van de nierfunctie is echter niet eenvoudig. **Hoofdstuk 4.1** beschrijft de resultaten van een onderzoek naar de beste methode om de nierfunctie te schatten bij oudere patiënten. De glomerulaire filtratiesnelheid (GFR) van de nieren wordt vaak gebruikt om de nierfunctie mee uit te drukken. De gouden standaard voor het meten van de GFR is de intraveneuze toediening van een exogene marker, zoals inuline, die volledig gefilterd wordt door de glomeruli en niet gereabsorbeerd of actief uitgescheiden wordt. Aan de hand van plasma- en urineconcentraties over de tijd kan gemeten worden hoe snel deze stof uit het lichaam gefilterd wordt door de glomeruli. Deze meetmethode is echter omslachtig, duur en belastend voor de patiënt en is daardoor niet geschikt voor de dagelijkse praktijk. Artsen maken daarom vaker gebruik van formules om de GFR (of kreatineklaring) te schatten. Deze formules zijn gebaseerd op plasmakreatinine spiegels, leeftijd, geslacht en vaak nog aanvullende variabelen. De meest gebruikte formules zijn de Cockcroft-Gault (CG), Modification of Diet in Renal Disease (MDRD) en de Chronic Kidney Disease-Epidemiology (CKD-EPI) formule. Deze formules zijn echter ontwikkeld op basis van data van jongere volwassenen. Het is niet goed bekend of deze formules ook gebruikt kunnen worden bij oudere, geriatrische, patiënten. In **Hoofdstuk 4.1** is de sinistrineklaring

gemeten bij 16 patiënten met een gemiddelde leeftijd van 82 jaar. Sinistrine is een stof analoog aan inuline. Bij deze patiënten is ook de GFR geschat aan de hand van de CG, MDRD en CKD-EPI formules. De formules geven allen een milde overschatting van de GFR: CG + 0,05 (95% BI -28 tot +28) ml/min/1,73m^2; MDRD +9 (95% BI -16 tot +34) ml/min/1,73m^2; en CKD-EPI +5 (95% BI -20 tot +29) ml/min/1,73m^2. Deze resultaten suggereren dat gemiddeld gezien deze drie formules de GFR goed schatten bij geriatrische patiënten. In individuele gevallen kunnen zij echter alledrie de GFR zowel aanzienlijk onderschatten als overschatten. Voor het nemen van klinische beslissingen voldoet de CKD-EPI iets beter dan de CG en MDRD. In **Hoofdstuk 4.2** is onderzocht of doseringsadviezen uit de G-standaard "verminderde nierfunctie", een richtlijn ontwikkeld door de Koninklijke Nederlandse Maatschappij ter bevordering der Pharmacie (KNMP), worden opgevolgd voor de ontslagmedicatie bij patiënten met een verminderde nierfunctie. Bij 1327 patiënten zijn de voorgeschreven medicatiedoseringen tijdens de laatste 24 uur voor ontslag uit het ziekenhuis vergeleken met de doseringsadviezen volgens de G-standaard. Deze adviezen worden slechts bij 54% van de patiënten volledig opgevolgd. Bijna driekwart van de te hoog gedoseerde geneesmiddelen had de potentie om matige tot ernstige problemen te veroorzaken. De richtlijn werd voornamelijk niet opgevolgd bij geneesmiddelen die frequent voorgeschreven worden, zoals metoclopramide en colchicine. Met name bij patiënten met een ernstige nierinsufficiëntie (eGFR 10-30 ml/min/1,73m^2) werden de adviezen matig opgevolgd: in 46,0% van de gevallen ten opzichte van 58,1% bij patiënten met een matige nierinsufficiëntie (eGFR 30-50 ml/min/1,73m^2). Sinds april 2009 wordt de eGFR automatisch weergegeven in de laboratorium uitslagen en wordt de richtlijn beter opgevolgd: 50,7% versus 57,0%.

De belangrijkste resultaten van bovenvermelde studies worden bediscussieerd in **Hoofdstuk 5** van dit proefschrift. Een belangrijke voorwaarde voor optimaal voorschrijven voor ouderen is een goede samenwerking en communicatie tussen patiënt en/of mantelzorger, arts, apotheker, en alle andere betrokken zorgverleners. Een andere belangrijke voorwaarde is dat artsen voldoende kennis hebben van farmacotherapie bij de oudere patiënt om optimaal te kunnen voorschrijven. Artsen kunnen hierbij ondersteund worden door voorschrijfcriteria. Hierbij wordt onderscheid gemaakt tussen expliciete criteria en impliciete criteria. Expliciete criteria zijn lijsten met geneesmiddelen die beter niet of juist wel voorgeschreven moeten worden. Impliciete criteria verschaffen artsen een leidraad aan de hand van open vragen, waardoor meer parate kennis van artsen wordt gevergd. De methodes beschreven in dit proefschrift, zoals de GMA en de POM, kunnen artsen ondersteunen met optimaal voorschrijven. In de toekomst zal een elektronische versie van de Systematic Tool to Reduce Inappropriate Prescribing (STRIP), een

verder ontwikkelde versie van de POM, beschikbaar komen voor artsen en apothekers. Idealiter wordt de STRIP ondersteund met een elektronische doserings-controle voor patiënten met en verminderde nierfunctie. Tevens zijn er ontwikkelingen gaande om het farmacotherapie-onderwijs aan medische studenten te verbeteren. In de toekomst zal er hopelijk een nationaal Elektronisch Patiëntendossier (EPD) beschikbaar komen. Hierdoor kan er per patiënt centraal één medicatiedossier bijgehouden worden, waardoor communicatiefouten verminderd kunnen worden. Tevens kan er dan optimaal gebruik gemaakt worden van voorschrijfcriteria, die ingebouwd kunnen worden in het EPD. Zo kunnen zorgverleners optimaal profiteren van ICT-ondersteuning om optimaal voor te kunnen schrijven aan de oudere patiënt.

Dankwoord

Gedurende mijn middelbare schooltijd en studententijd was hockey mijn grote passie. Ik stond bijna dagelijks op het hockeyveld, ofwel om zelf training te geven, danwel om zelf te trainen of wedstrijden te spelen. Tijdens mijn promotietraject vond ik veel overeenkomsten met deze periode. Maar in plaats van mijn oude vertrouwde plekje als keeper, stond ik dit keer in de spits: het doel (promotie) duidelijk voor ogen, maar het overzicht volledig kwijt. Het training geven, dit keer in de vorm van onderwijs geven, wisselde zich eveneens af met zelf trainen, oftewel cursussen volgen en onderzoek doen. Net als bij het trainen had ik tijdens het onderzoek momenten dat alles op zijn plek viel, maar ook momenten dat alles leek te mislukken. De cursussen waren noodzakelijk om het onderzoek doen onder de knie te krijgen. Dit alles om toe te werken naar de wedstrijden, het schrijven en indienen van de artikelen. Bij winst (acceptatie) was er euforie, bij verlies (afwijzing) teleurstelling. Aan het eind van deze periode lijkt promotie in zicht, een uitkomst die ik tijdens mijn hockey carrière niet altijd meemaakte.

Voor mijn hockeyteam werd ik destijds geselecteerd door het begeleidingsteam, net als nu voor het promotietraject.

Paul Jansen was de scout. Hij heeft mij niet alleen voorgedragen als kandidaat voor dit promotietraject, maar heeft mij ook de opleidingen klinische geriatrie en klinische farmacologie ingeloodst. Paul, dank dat je deze deuren voor mij hebt geopend en mij hiermee de kans hebt gegeven om mij niet alleen in de breedte te ontwikkelen, maar ook in de diepte. Van jou heb ik geleerd hoe je het beste polyfarmacie kunt optimaliseren, uit mijn onderzoek is gebleken dat jouw aanpak inderdaad effectief is. Gedurende mijn hele promotietraject stond je deur altijd voor mij open en heb je mij het vertrouwen en de vrijheid gegeven om mijn dagen flexibel in te delen, wat voor mij het combineren van werk en gezin enorm vergemakkelijkt heeft.

Rob van Marum was een combinatie van een looptrainer en een tactische trainer. Rob, jij wist als geen ander altijd de vinger op de zere plek van mijn onderzoek te leggen. Waar ik zelf vaak wel aanvoelde dat het niet helemaal was zoals het moest zijn, maar er eigenlijk niet zo goed uitkwam, had jij dat altijd direct door en je kwam dan ook met een idee hoe het beter zou kunnen. Je kon ook goed relativeren en aangeven wanneer een stuk goed genoeg was. Zo zorgde je er voor dat ook de vaart er in bleef en ik niet onnodig bleef hangen in het blijven schaven aan artikelen.

En dan hebben we Toine Egberts, de hoofdcoach oftewel promotor, de Marc Lammers van het stel. Je enorme analytische capaciteiten en je vermogen om een brei aan informatie te reduceren tot een simpel overzicht waren voor mij van onschatbare waarde. Je hebt me meer dan eens geholpen om zelf beter boven de stof te komen staan en weer een stap verder te kunnen zetten in mijn onderzoek. Jouw voorstellen tot het visualiseren van gegevens in een figuur waren ontzettend leerzaam.
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About the author

Clara Drenth-van Maanen was born on April 29, 1980 in Delft, the Netherlands. In 1998, she graduated from the secondary school *'Erasmiaans Gymnasium'* in Rotterdam. She studied Business Administration at Erasmus University Rotterdam from 1998 to 2000. In 2001 she started to study pharmacy at Utrecht University. In 2004 she obtained her bachelor's degree and from 2004 to 2008 she studied medicine at the School for Utrecht Medical Masters (SUMMA).
In 2009 she worked as a geriatric resident at the University Medical Center Utrecht, where she started her PhD research in 2010. During this period she was a member of the working group clinical gerontopharmacology and a member of the public relations committee of the Dutch Geriatrics Society. She registered as a clinical pharmacologist in 2012.
Currently, she works as an internal resident at the St. Antonius Hospital Nieuwegein, where she is also a member of the medicines committee. Furthermore, she is a member of the committee '*Farmacotherapeutisch Kompas*' (the Dutch national formulary) since 2013. She aims to register as a geriatrician in 2018.
She is married to Huib Drenth, they have two children, Floris and Francien.