Master thesis

Polypharmacy

Effects of medication reviews on medication prescription policy in polypharmacy patients in the Netherlands

Health Sciences – Health Service and Management

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Preface

For the master Health Sciences at the University of Twente I have ended the specialization track Health Service and Management with a graduation thesis I have conducted from February till August. In this thesis, I have focused on the effect of performing a medication review on the medication list of polypharmacy patients, in terms of number of drugs, appropriateness of drugs, frequently added and stopped drugs, and dose modifications. Additionally, by means of short online questionnaires, the experiences with performing medication reviews of general practitioners and pharmacists are identified. This master thesis is written as a concept journal article.

I would like to thank a number of people for the creation of this thesis for their time and contribution. I could always contact them when I needed help. First, I would like to thank my supervisors Jeannette van Manen and Sarah Janus for their assistance and support from the University. Second, I would like to thank Kim Dorsman and Suzan van Vlieten, general practitioners, for their assistance in the practice. Finally, I would like to thank all the involved pharmacists and general practitioners for providing me the required data for performing my research. Without them, I would not have been able to conduct this master thesis at all.

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Abstract

Background: Polypharmacy, the use of five or more drugs chronically for different therapeutic (sub)groups, is a frequent phenomenon in elderly. It is associated with negative consequences; the risk of having drug-related problems increases with the increase of number of drugs. To reduce this risk, medication reviews have to be performed according to the Dutch guideline '*Polyfarmacie bij ouderen*'. In the Netherlands, little is known about the effect of performing a medication review on the Dutch prescription policy in the Netherlands. This study will focus particularly on this effect.

Methods: Two study designs are used in this study. A prospective longitudinal intervention study with a pre-test/post-test without control group, and a cross-sectional explorative cohort study have been conducted. The study population consisted of a convenience sample of patients, and their general practitioners and pharmacists in five community pharmacies in Twente with polypharmacy, of which the medication has been reviewed. Data of this population is collected through pharmacists' database and online questionnaires for general practitioners and pharmacists. The collected data has been analysed with the following statistics: descriptive statistics; paired t-test; and Pearson's correlation coefficient, and analysed through text analyses.

Results: The main finding was that medication reviews have a positive influence ($p < 0.05$) on the average decrease in number of drugs, and in number of potentially inappropriate drugs that patients use. The average number of drugs a patient used one day before the review was 8.7 (sd = 2.9), which decreased to 8.3 (sd = 2.7) drugs one week after the review, and to 8.4 (sd = 2.6) drugs three months after the review. The average number of potentially inappropriate drugs was first 0.6 (sd = 0.8) drugs per patient. Both one week and three months after the review it was 0.4 (sd = 0.6) drugs per patient. Additionally, there is positive correlation ($p < 0.01$) between number of drugs before review and (1) difference in number of drugs before review and one week after review ($r = 0.324$); (2) difference in number of drugs before review and three months after review ($r = 0.321$); and (3) number of potential inappropriate drugs before review ($r = 0.389$). Furthermore, according to general practitioners and pharmacists, medication reviews offer added value to lowering the chance of adverse events, and the contact between them and the patients becomes better. However, performing these reviews is very time-consuming and stressful.

Conclusion: This study shows that performing medication reviews in polypharmacy patients is useful to continue. In the short-term and long-term, medication reviews have a positive influence on the prescription policy in the Netherlands.

Keywords: polypharmacy, medication review, effectiveness, experiences, the Netherlands

Introduction

With aging, the risk of developing chronic diseases increases. This is often accompanied by the use of multiple drugs, (Dijk, Verheij & Schellevis, 2009) which can be referred to as polypharmacy. According to the guideline '*Polyfarmacie bij ouderen*', polypharmacy implies using five or more drugs chronically for different therapeutic groups or subgroups. (Nederlands Huisartsen Genootschap [NHG], 2012) Especially in elderly (people aging 65

years and older) polypharmacy is a frequent phenomenon. In 2007, almost 45% of the elderly used five or more different drugs. Looking at elderly above 74 years old, even more than half of the population (51%) deals with polypharmacy. (Dijk et al., 2009) It is expected that the amount of elderly with multi-morbidity will continue to increase, which makes polypharmacy an expanding societal issue. (Hurkens et al., 2012)

Drugs are prescribed to patients to treat diseases, relieve symptoms, and prevent complications. However, the use of drugs can also lead to adverse effects, drug-related problems (DRPs). Especially elderly are sensitive to DRPs, due to a high prevalence of polypharmacy, pharmacokinetic and –dynamic changes, and improper medication use because of cognitive or physical limitations. (Drenth-van Maanen, Leendertse, Marum, Egberts & Jansen, 2012) In particular, the use of corticosteroids, anticoagulants, diuretics, RAAS antagonists, NSAIDs, antidiabetic drugs, drugs with an effect on the central nervous system, and opioids is associated with DRPs. (Bemt et al., 2006; Berdot et al., 2009; Bruijne et al., 2014; Leon et al., 2010; Roughead & Semple, 2009)

The more drugs a patient uses, the higher the risk of DRPs for that patient. DRPs include the result of over- and under-treatment, inaccurate dosing, suboptimal choice of drug, incorrect/impractical mode of administration, double medication, drug interactions, an excessive or insufficient effect, side-effects, and the dealing of the patient with the medication. (Bruijne et al., 2014; Dijk et al., 2009; Passarelli, Jacob-Filho & Figueras, 2005; Rijksinstituut voor Volksgezondheid en Milieu [RIVM], 2013; Rogers et al., 2009) Not only a large number of medication thus leads to DRPs, but, especially in frail elderly, inadequate or inappropriate medication can lead to some serious general health problems, like deterioration of cognitive abilities, incontinence, immobility, and increasing fall risk. (Berdot et al., 2009; Bruijne et al., 2014; Leon et al., 2010; Roughead & Semple, 2009)

Polypharmacy in older patients is also an important risk factor for preventable hospital admissions. (Bemt, Egberts & Leendertse, 2006; Bruijne et al., 2014; RIVM, 2013) The study of Leendertse, Egberts, Stoker & Van den Bemt (2008) showed that in Dutch hospitals 5.6% of the unplanned admissions were related to medication. Of those medication-related admissions 46.5% were potentially preventable. The costs that are associated with avoidable admissions are estimated for the Netherlands at over 85 million euros. (Bemt et al., 2006)

The most important risk factors that increase the chance of unintentional injury due to inappropriate pharmacotherapy for the patient are (Bruijne et al., 2014):

- errors in prescribing;
- insufficient involvement of patient in the pharmacotherapeutic care process;
- insufficient documentation of prescribed drugs and patient history;
- multiple prescribers and pharmacists for one patient;

- inadequate transfer, in particular, the transition from the first to the second line, and vice versa; and
- insufficient directive function, cooperation, and division of responsibilities in cooperation.

To reduce the preventable admissions and the related costs, it is important that medication safety increases. In 2012, the multidisciplinary guideline '*Polyfarmacie bij ouderen*' was set up, with the goal to optimise the use of drugs by elderly, and to reduce drug-related problems and undesired hospitalizations. (Lambregtse, 2014) Adhering to the guideline will lead to safe and effective pharmacotherapeutic care by a multidisciplinary coordinated treatment and support of elderly with polypharmacy. The guideline is applicable for elderly aged 65 years and older with polypharmacy and with one or more of the following risk factors (NHG, 2012):

- impaired renal function (eGFR < 50 ml/min/1,73 m2);
- impaired cognition (dementia or indications of memory disorders and other cognitive disorders);
- increased risk of falling (patient fell at least one time in the preceding twelve months);
- signals of poor compliance; or
- not living independently (living in care or nursing home).

In this guideline, medication review is the key focus point. Medication review is a systematic assessment of the medication usage of an individual patient, done by a physician, pharmacists, and patient (and/or informal caregiver or other caretakers) according to a periodic structured, critical evaluation of the medical, pharmaceutical, and user information. Goal of the medication review is a coordinated pharmacotherapeutic treatment which is established by mutual cooperation between physicians, pharmacists and nurses, and is geared to needs (or experiences) and wishes of the patient (and informal caregivers). (NHG, 2012)

The medication review is carried out according to the Systematic Tool to Reduce Inappropriate Prescribing (STRIP) method. The STRIP method is established by Leendertse, Drenth-van Maanen, Verduijn, Jansen & van Marum (2012) according to two other medication review methods, namely '*Gebruik Indicatie Veiligheid Effectiviteit*' (GIVE) and '*Polyfarmacie Optimalisatie Methode*' (POM). STRIP consists of various steps (see *Appendix 1* for a detailed overview in Dutch):

0. Preparation:
    a. selection of patients; and
    b. collection of data.
1. Pharmacotherapeutic anamnesis: gathering information about the actual use, experiences and perception of the drugs by the patient.
2. Pharmacotherapeutic analysis: identification of (potential) pharmacotherapeutic-related problems.
3. Set up of pharmacotherapeutic treatment plan: physician and pharmacist agree on treatment goals and how these goals can be achieved.

4. Establishing the pharmacotherapeutic treatment plan: the patient participates in his or her pharmacotherapy and (s)he understands the interventions written in the plan. The participation is tailored to the capabilities of the patient.
5. Follow-up and monitoring: executing and evaluating the intended interventions.

In step 2 (pharmacotherapeutic analysis) the potential problems have to be identified using the established questions and attention areas given in *Appendix 1*, and the START and STOPP criteria. The START/STOPP is a screening list developed by Irish clinical geriatricians. START stands for *Screening Tool to Alert doctors to Right (i.e. appropriate, indicated) Treatment* and is a list of 36 evidence based prescribing indicators in frequent diseases/disorders in elderly. STOPP stands for *Screening Tool of Older Peoples' Prescriptions* and is a list of 72 clinical significant criteria for potential inappropriate medication in elderly. The START/STOPP is a validated, reliable and practicable screening tool which seems to be the most appropriate in support of choosing the best treatment in elderly patients with multi-morbidity. However, this tool cannot be directly applicable in the Dutch situation. In *Appendix 2*, an adjusted version is displayed that can be used in the Netherlands. (NHG, 2012)

In the end, it is essential that the result of a medication review will be discussed with the patient, transferred to other involved health care providers, and that a monitoring and evaluation plan will be established to ensure the continuity of the therapeutic care. (Drenth-van Maanen et al., 2012) Follow-up assessments of outpatient patients have to be carried out minimal once per year. (NHG, 2012)

Looking at the steps of performing a medication review, it can be concluded that this is a considerable workload and therefore hard to carry out for the entire group of patients at once. (Lambregtse, 2014) However, it is very important to adhere to the guideline, because with optimal medication safety, approximately 16,000 acute hospital admissions can be avoided each year. (Inspectie voor de Gezondheidszorg [IGZ], 2010)

Various studies showed that after a medication review is performed, measures are taken to optimise the drug use. An Australian study included 17 elderly with polypharmacy. The medication list of those elderly were assessed, and based on the STOPP-criteria, potentially inappropriate drugs were measured. At the beginning, the total number of potentially inappropriate drugs were 38. After optimising the medication lists, the total number declined to 14. The drugs that were frequently deprescribed were diuretics, opioids, benzodiazepines, and tricyclic antidepressants. (Mudge et al., 2016) Two Dutch studies also looked at how many times the medication list was adapted due to a medication review. The first study consists of 3807 medication reviews performed by community pharmacists. Of all suggestions that are done to optimise the drug use, 19.6% of the suggestions was to stop a drug and 14.0% was to add a drug. Other examples of suggestions that are done were provide

monitoring, adjust dose, and provide education. (Chau et al., 2016) The other study includes 58 medication reviews performed by pharmacists and general practitioners (GPs) together. In 54 patients, one or more suggestions for drug adaption is given. On average, there were 2.3 drug adaptions per patient. The most frequent suggestions were quitting (33.8%) and starting a drug (24.8%), and the most common reasons for drug changes were undertreatment (37.7%) and overtreatment (35.6%). Cardiovascular drugs, vitamin D, and proton pump inhibitors were the most frequent drugs that were added, stopped or had a dose modification. (Balen, Damen-van Beek, Nelissen-Vrancken & Verduijn, 2013)

Several studies have been performed regarding to the effectivity of a medication review. In overall, most of the studies showed that the number of drugs per patient, DRPs, emergency department contacts, and inappropriate drugs decreased, (Christensen & Lundh, 2013; Jódar-Sánchez et al., 2015; Lenaghan, Holland & Brooks, 2007; Mudge et al., 2016; Roth et al., 2013; Vinks, Egberts, Lange & Koning, 2009) and little or no effect is shown regarding to the quality of life, mortality, patients' functioning, (re)admissions, and adverse drug events. (Christensen & Lundh, 2013; Cooper et al., 2015; Frank & Weir, 2014; Geurts, Stewart, Brouwers, Graeff & Gier, 2015; Leendertse et al., 2013; Lenaghan et al., 2007)

However, for three of those types of effects of medication reviews also contradictory literature is found. First, regarding to the number of drugs per patient, three studies are found that showed a statistically significant reduction in the number of drugs after a medication review, (Lenaghan et al., 2007; Jódar-Sánchez et al., 2015; Mudge et al., 2016) but only one of them had an obvious reduction that could be regarded relevant. (Mudge et al., 2016) The other two studies, one from the United Kingdom and one from Spain, only showed an average reduction of less than 1 drug per patient. (Lenaghan et al., 2007; Jódar-Sánchez et al., 2015) In addition, two Dutch studies did not show a reduction in the number of drugs per patient at all. (Balen et al., 2013; Vinks et al., 2009) The reason for these differences is that the study of Mudge et al. (2016) included only patients with frequent hospital admissions. Those patients have already problems, so the chance of using inappropriate drugs is higher in this population.

Second, three contradictory studies are found that discussed the number of potential DRPs before and after a medication review. Two of them, one American and one Dutch study, showed a significant reduction of the average DRPs per patient. (Roth et al., 2013; Vinks et al., 2009) In the other study, a systematic review of Cooper et al. (2015), is concluded that it is still unclear whether medication reviews, or other interventions that aim to improve the appropriate use of drugs in patients with polypharmacy, result in clinically significant improvements in terms of DRPs, but also in terms of the quality of life of patients. The difference between those three studies was that they all used a different definition for polypharmacy. The American study included patients that use at least five drugs (Roth et al.,

2013), the Dutch study included patients that use at least six drugs (Vinks et al., 2009), and the review included patients that use at least four drugs. (Cooper et al., 2015)

Third, five studies show contradictory evidence whether the quality of life of patients improves. The review of Cooper et al. (2015), and two Dutch studies concluded that it is not proven that medication reviews are effective in improving the quality of life. (Frank & Weir, 2014; Geurts et al., 2015; Leendertse et al., 2013) The other two studies, one from Spain and one from Sweden, concluded the opposite, because due to medication reviews, more proper drugs will be prescribed. (Jódar-Sánchez et al., 2015; Olsson, Runnamo & Engfeldt, 2011) It is hard to conclude why those studies show contradictory results; all studies used a control group and included a large group of patients. Only the Swedish study used a different population, namely patients that were discharged from the hospital (Olsson et al., 2011)

Besides patient effects, there are also important physician effects, namely the investment time of GPs and pharmacists. Only one study is found that looked at the average time of performing a medication review for GPs and pharmacists. In this study, it appeared that pharmacists invested on average 90 minutes per patient, but the researchers could not conclude how much time GPs invested per patient, due to incomplete registrations. (Balen et al., 2013)

Because of contradictory evidence about the decrease in number of drugs, DRPs, and quality of life, this thesis will focus on the effect of performing a medication review by GPs and pharmacists on the Dutch prescription policy. It is important that more study will be done in the Netherlands, because studies from other countries cannot be extrapolated directly to GP practices in the Netherlands. The reason therefore is that, in the Netherlands, the GPs have a gatekeeping role, causing restrictive guidelines regarding to drug prescription, additional investment, and referral criteria, (Burgers, 2004) which can probably influence the type of medications in the medication lists of patients. Therefore, the following research question will be tackled in this study: '*What are the short-term and long-term effects of performing a medication review by general practitioners and pharmacists on the prescription policy in patients aging 65 years and older that use five or more different types of drugs in the Netherlands?'*

The sub-questions that help to answer the research question are:

1. Which short-term and long-term effect does a medication review have on the medication list of patients, in terms of number of drugs, appropriateness of drugs, frequently added and stopped drugs, and dose modifications?
2. What are the experiences of general practitioners and pharmacists with medication reviews in polypharmacy patients and ideas for possible improvements for performing medication reviews?

Method

Study design

To answer the research question, quantitative evaluative and qualitative explorative study was needed. The study design that fit best with the first sub-question was a prospective longitudinal intervention study with a pre-test/post-test. First of all, it was a prospective longitudinal study, because the measurements were not done at the beginning of this study and those measurements were done at multiple moments in time. At three points in time measurements are taken: one day before the medication review, one week after the medication review, and three months after the medication review. This is also why this study consisted of a pre-test/post-test. All measurements are done in the same group of patients. Furthermore, this was an intervention study, because the effect of an intervention, namely medication review, has been studied. (Bouter, Dongen & Zielhuis, 2010)

The study design that fit best with the second sub-question was a cross-sectional explorative cohort study. It was an explorative cohort study, because a group of individuals was observed without any intervention. (Twisk, 2014) In this group, each individual was measured once, but these measurements did not have to be at the same moment in time, which made it a cross-sectional study. (Bouter et al., 2010)

Study population

The study population consisted of elderly with polypharmacy that got a medication review in the time period from 2015 until April 2016. The inclusion criteria used in this study are the same as the criteria used by GPs and pharmacists (NHG, 2012):

- elderly aged 65 years and older that use five or more types of drugs and with one or more of the following risk factors:
    - impaired renal function (eGFR < 50 ml/min/1,73 m2);
    - impaired cognition (dementia or indications of memory disorders and other cognitive disorders);
    - increased risk of falling (patient fell at least one time in the preceding twelve months);
    - signals of poor compliance; or
    - not living independently (living in care or nursing home).

A sample size calculation was performed, which showed that 156 patients are needed ($\alpha = 0.05$; $\beta = 0.20$), based on the primary outcome, mean difference in number of drugs, of this study. The mean difference in number of drugs (0.28) and related standard deviation (1.25) were found in literature. (Jódar-Sánchez et al., 2015) To include this many polypharmacy patients that underwent a medication review, a convenience sample is used of five community pharmacies in Twente.

Data collection

To find out whether there was a change in the number and type of drugs, and which drugs are frequently being added, stopped or had a dose modification, their medication passports, medication profiles (a timeline of which drugs are used during which period during one year), and the pharmacist's notes are used. A form,

shown in *Appendix 3*, is made which has been filled in for each patient to get the needed patient demographics and medical information. The Anatomical Therapeutical Chemical (ATC) codes of the medications are used to have an uniform international naming. (World Health Organization [WHO] Collaborating Centre for Drug Statistics Methodology, 2009)

The appropriateness of the drugs are checked with a validated screening tool, the STOPP criteria (shown in *Appendix 2*). The STOPP criteria are laid down next to the medications that the patients used, so that potential inappropriate drugs (PIDs) could be found. To examine the appropriateness of the medications, a couple of diagnostics were needed: blood pressure, renal function, potassium level, sodium level, non-protein bounded calcium, beats per minute, HAS-BLED score, and respiratory failure (ρ_{O2}- and ρ_{CO2}-level). These diagnostics were mostly obtained in the pharmacies. Only when the pharmacies did not have this information, the GPs were asked. The diagnostics non-protein bounded calcium and respiratory failure are not included in this study, because these three were not available. This made it impossible to examine STOPP criteria C2 and G4, and partly STOPP criterion B8.

Through short online questionnaires, the GPs and pharmacists are asked whether they think that medication reviews have an added value on reduction of health care costs, reduction in number of drugs, reduction of adverse events, and increase in knowledge of drugs for GPs. They are also asked how much time they spend to perform one medication review and whether they think that this time put an extra burden on their workload. Furthermore, the GPs and pharmacists are also asked in this questionnaire why sometimes a drug had not been stopped, while the guidelines indicate that the drug has to be stopped, and whether there are any suggestions for improvements. In *Appendix 4*, an example of the questionnaire is given.

The data collection for the purpose of the analyses in this study took place from 13 April 2016 until 17 June 2016.

Data analysis

Statistical analyses (through SPSS version 23) and text analysis were performed. For answering the first sub-question, paired samples t-tests (with 95% confidence intervals) were performed on the continuous variables ‘number of drugs’ and ‘number of inappropriate drugs’. To test whether there is a correlation between the difference in number of drugs and number of drugs before the medication review; between the number of PIDs before review and number of drugs before the review; and between the difference in number of PIDs and number of drugs before the medication review, the Pearson’s correlation coefficient has been used, because all these variables are continuous. (Baarda, Dijkum & Goede, 2014) Furthermore, descriptive statistics were used to evaluate how many times a type of drug was added, stopped or had a dose modification. Finally, the notes of GPs and pharmacists that are used in the first sub-question, are analysed through the following steps:

1. Coding: the answers are given different colours to the different topics.

2. Thematise: the texts with the same colour is put together.
3. Interpret: the themed text is interpreted and understood.
4. Describe: the results are described and reported.

The completed questionnaires for sub-question two are analysed through descriptive statistics and text analyses. The closed-ended questions are analysed with means and percentages, and the open-ended questions are analysed through the same steps as the notes of GPs/pharmacists.

Ethical consideration

A study belongs to the Law Medical Research when there is a medical scientific study, and when persons are subject to actions or when behavioural rules are imposed on them in the study. (*Wet Medisch-wetenschappelijk Onderzoek*). (Centrale Commissie Mensgebonden Onderzoek [CCMO], z.d.) In this study, only patient data from the pharmacies' databases are used, so there has been no insight in the full electronic patient records, and the patients did not undergo a special intervention. For these reasons, this study did not belong to the Law Medical Research and no ethical approval was needed from the Ethical Commission. The data that is used in this study is processed anonymously, so that the data could not be traced back to patients. In all five pharmacies a confidentiality agreement is signed, so that the data would not be shared with others.

Results

Patient characteristics

One hundred twenty six elderly are included in this study. The patients that still could be included after three months are 118 patients, eight patients were lost to follow up. The population consists of more women than men (58.7% vs. 41.3%) and the mean age of the population is 76 years old (see *Table 1*).

Table 1: Baseline characteristics of study population

	N	
Number of patients included in study		
1 day before review	126	
1 week after review	126	
3 months after review	118	
	N	*%*
Gender:		
Man	52	41.3
Woman	74	58.7
	M	*Sd*
Mean age at review		
Man	76	6.0
Woman	76	8.0
Total	76	7.4

Effect evaluation

One week after the medication review, the total number of drugs, the mean, and the range decreased (see *Table 2*). One day before the review, these numbers were 1100, 8.7, and 5 – 21 respectively, which decreased to 1048, 8.3, and 3 – 20 respectively. The number of PIDs, mean, range, and number of elderly with PIDs also decreased after the review: from 70, 0.6, 0

– 5, and 52 to 45, 0.4, 0 – 4, and 38 respectively. Even after three months, the numbers decreased a little bit, except for the mean number of drugs per patient. Performing medication reviews in polypharmacy patients has a significant result ($p < 0.05$) on the average decrease in number of drugs that patients use one week (from 8.7 to 8.3) and three months (from 8.7 to 8.4) after the review. Furthermore, it also has a significant result ($p < 0.05$) on the average decrease in number of PIDs one week and three months after the review (both decreased from 0.6 to 0.4).

Looking at the individual level instead of means, one can see that the difference in number of drugs between one day before review and one week after review decreased with a maximum of five drugs , and increased with a maximum of four drugs (see *Table 2)*. The difference between one day before review and three months after review has a maximum decrease, and increase of four drugs on individual level. In case of the PIDs on individual level, both one week and three months after review, the maximum decrease was two drugs, and maximum increase one drug.

One week after the review, not all 45 PIDs are new, some were not stopped during the review. *Table 3*, lists the reasons for not stopping a PID. The most frequent reasons were that the health status of a patient is so bad that the negative consequences of the drug are taken for granted, and that a patient experiences negative effects of stopping the drug, so it was better to continue the drug.

Table 2: Total number, mean number (sd), and range of drugs and PIDs, and total number and mean number (sd) of elderly (N=126 in case of 1 day before review and 1 week after review and N=118 in case of 3 months after review) with PIDs at the three measurement moments

	Total number of drugs	*Mean number (sd) drugs per patient*	*Range number of drugs*	*Range difference in drugs per individual*	*Total number of PIDs*	*Mean number (sd) PIDs per patient*	*Range number of PIDs*	*Total number of elderly with PIDs*	*Mean number (sd) of elderly with PIDs*	*Range difference in PIDs per individual*
1 day before review	1100	8.7 (2.9)	5 – 21	-	70	0.6 *(0.8)*	0 – 5	52	0.4 *(0.1)*	-
1 week after review	1048	8.3 (2.7)*	3 – 20	-5 — +4	45	0.4 *(0.6)**	0 – 4	38	0.3 *(0.1)*	-2 — +1
3 months after review	985	8.4 (2.6)*	3 – 18	-4 — +4	42	0.4 *(0.6)**	0 – 3	37	0.3 *(0.1)*	-2 — +1

** P < 0.05 (paired samples t-test, reference 1 day before review)*

Other spontaneous written notes by the GPs or pharmacists are shown in *Table 4*. The most common notes were that the patient, pharmacist, and GP agreed to change a drug, but in the end, nothing happened, and that the patient did not want to undergo any changes.

Table 3: Registered reasons why some PIDs are not stopped

*Registered reason for continuing the drug**	*Times of occurrence*	*ATC code*	*STOPP criterion*
The health status of patient is that bad that the negative consequences of the drug are taken for granted	3	STOPP A2	Any drug that is prescribed longer than the well-defined recommended duration
		STOPP B8	Thiazide diuretic with a current hypokalemia (serum concentration of potassium < 3.0 mmol/L), hyponatremia (serum concentration of sodium < 130 mmol/L), hypercalcemia (corrected serum concentration of non-protein-bounded calcium > 2.65 mmol/L) or with a history of gout with simultaneous use of thiazide diuretic
		STOPP K3	Vasodilators (e.g. α1-receptor blockers, calcium channel blockers, long-acting nitrates, ACE inhibitors, angiotensin II-antagonists) with orthostatic hypotension
Patient experiences negative effects of stopping the drug	3	STOPP B7	Loop diuretic for the treatment of ankle oedema without clinical, biochemical or radiological evidence of heart failure, liver failure, nephrotic syndrome or renal failure
		STOPP D5	Benzodiazepines lasting ≥ 4 weeks
		STOPP H6	COX-2 selective NSAIDs and diclofenac with cardiovascular diseases
The potassium level will be under surveillance by the GP, when the potassium level rises, the drug will be stopped	2	STOPP B11 (2 times)	Aldosterone antagonists (e.g. spironolactone, eplerenone) simultaneous with potassium-sparing drugs (such as ACE inhibitors, angiotensin II-antagonists, amiloride or triamterene) without regular monitoring of potassium
Patient does not experience any adverse events of this drug	1	STOPP B6	Loop diuretic for the treatment of hypertension
The drug has been stopped partially, now it is being used on an as needed base	1	STOPP D5	Benzodiazepines lasting ≥ 4 weeks

The drug has not been stopped directly, but the patient has a scheme to reduce the drug in steps	1	STOPP H3	Long-term use of glucocorticoids (> 3 months) as monotherapy for rheumatoid arthritis
Indication to stop the drug does not apply in this case, because the patient only has a little superficially ulcer in the duodenum	1	STOPP H7	Oral bisphosphonates in patients with a history or current upper gastrointestinal disorders (dysphagia, esophagitis, gastritis, duodenitis, gastric ulcer or upper gastrointestinal bleeding) or in bedridden patients
Instead of stopping the drug, the dose is lowered	1	STOPP J1	Sulphonylureas with a longer duration and active metabolites, such as glibenclamide and glimepiride, in patients with diabetes mellitus type 2
There is no better alternative	1	STOPP J1	Sulphonylureas with a longer duration and active metabolites, such as glibenclamide and glimepiride, in patients with diabetes mellitus type 2

** See Appendix 5 for the literal reasons*

Table 4: Spontaneous written notes by general practitioner or pharmacist

*General spontaneous written notes by general practitioner or pharmacist**	*Times of occurrence*
Patient, pharmacist, and GP agreed to change a drug, but in the end, nothing happened	12
Patient did not want to undergo any changes	9
Patient asked the pharmacist for a medication review (patient's own initiative)	2
Better to keep the medication list the same, because of the situation of patient	2
Pharmacist did not get any reaction from the GP	1
Health status of patient was very bad, patient was dying	1

** See Appendix 6 for the literal notes*

Like shown in *Table 5*, the number of drugs one day before the review correlates reasonably with (1) the difference in number of drugs before the review and one week after the review ($r = 0.324$; $p < 0.01$); (2) the difference in number of drugs before the review and three months after the review ($r = 0.321$; $p < 0.01$); and (3) with the number of PIDs one day before the review ($r = 0.389$; $p < 0.01$). So, the more drugs a patient uses before the review, the higher the reduction in number of drugs, both one week and three months after the review, and the higher the number of PIDs that (s)he has prescribed.

Table 5: Pearson's correlation coefficients

		Amount of drugs before review minus amount of drugs one week after the review	*Amount of drugs before review minus amount of drugs three months after the review*	*Amount of PIDs before review*	*Amount of PIDs before review minus amount of PIDs one week after the review*	*Amount of PIDs before review minus amount of PIDs three months after the review*
Amount of drugs before review	*N*	126	118	126	126	118
	r	0.324**	0.321**	0.389**	0.112	0.082

*** Correlation is significant at the 0.01 level (2-tailed)*

One week after the medication review, 241 changes are made (see *Table 6*). In 48.5% of the modifications a drug is stopped, in 27% of the modifications a drug is added, and the remaining 24.5% were dose modifications. After three months, changes were still made (see *Table 6*); sometimes new changes and sometimes the elderly changed back to the initial drug. Three months after the medication review, 314 changes are made in total. Of which 44.6% were stopped drugs, 32.5% were added drugs, and 22.9% were dose modifications. In these percentages also the turning back to the old situations are included, so the stopped drugs after being added by the review, the added drugs after being stopped by the review, and the drugs that returned to their initial dose. In both cases, one week and three months after, the number of elderly that quit a drug is highest.

The most frequently drugs that are added, stopped, and that had a dose modification are from the groups 'alimentary tract and metabolism' and 'cardiovascular system' (see *Table 7, 8,* and *9*). Mostly vitamins and minerals of the group 'alimentary tract and metabolism' were added, and diuretics, agents acting on the renin-angiotensin system and lipid modifying agents of the other group. For stopped drugs it mostly concerns the same drugs in the 'cardiovascular system' group, and drugs for constipation and diabetes in the group 'alimentary tract and metabolism'. Another group in which relatively many drugs are stopped is the 'nervous system'. Here, it mostly concerns the analgesics.

Mostly drugs used for diabetes, minerals, cardiac therapy, and agents acting on the renin-angiotensin system underwent a dose modification. 52.5% of the dose modifications after one week, and 53,8% of the dose modification after three months led to a dose reduction, shown in *Table 9*. So, the medication reviews led in most drugs to a reduction in dose compared with increase in dose, however, the difference between a reduction and an increase is very small.

Table 6: Amount, mean and range of the interventions, and amount and mean of elderly (1 week after review the total N=126, and three months after review the N=118) that underwent the interventions

		Number of drugs	*Mean number (sd) of drugs*	*Range of drugs*	*Number of elderly*	*Mean number (sd) of elderly*
Modification of dose compared to initial dose	1 week after review	59	0.5 *(0.7)*	0 – 3	48	0.4 *(0.1)*
	3 months after review	70	0.6 *(0.8)*	0 – 3	51	0.4 *(0.1)*
Added drug	1 week after review	65	0.5 *(0.8)*	0 – 4	48	0.4 *(0.1)*
	3 months after review	95	0.8 *(1.1)*	0 – 6	56	0.4 *(0.0)*
Stopped drug	1 week after review	117	0.9 *(1.2)*	0 – 6	70	0.6 *(0.0)*
	3 months after review	127	1.0 *(1.2)*	0 – 6	72	0.6 *(0.0)*
Drug that first had a dose modification and after 3 months returned to its initial dose	3 months after review	2	0.0 *(0.1)*	0 – 1	2	0.0 *(0.1)*
*Added drug after being stopped**	3 months after review	7	0.1 *(0.3)*	0 – 3	5	0.0 *(0.1)*
*Stopped drug after being added**	3 months after review	13	0.1 *(0.4)*	0 – 2	10	0.1 *(0.1)*

** The number of drugs that belong to those is not included in the number of added drugs and number of stopped drugs*

Table 7: Drugs that are added one week after review and three months after medication review

Drugs	**1 week after review (N=65)**		**3 months after review (new added drugs) (N=30)**		**3 months after review (added drugs after being stopped) (N=7)**	
	N	*%*	*N*	*%*	*N*	*%*
Alimentary tract and metabolism	30	46.2	8	26.7	2	28.6

Drugs for acid related disorders	5	7.7	4	13.3	1	14.3
Drugs for functional gastro-intestinal disorders	1	1.5	-	-	-	-
Drugs for constipation	3	4.6	-	-	1	14.3
Drugs used in diabetes	2	3.1	3	10	-	-
Vitamins	12	18.5	1	3.3	-	-
Mineral supplements	7	10.8	-	-	-	-
Blood and blood forming organs	5	7.7	8	26.7	0	0
Anti-thrombotic agents	3	4.6	8	26.7	-	-
Antianemic preparations	2	3.1	-	-	-	-
Cardiovascular system	14	21.5	10	33.3	4	57.1
Diuretics	5	7.7	1	3.3	-	-
Beta blocking agents	-	-	1	3.3	1	14.3
Calcium channel blockers	-	-	2	6.7	-	-
Agents acting on the renin-angiotensin system	5	7.7	4	13.3	1	14.3
Lipid modifying agents	4	6.2	2	6.7	2	28.6
Genito urinary system and sex hormones	3	4.6	0	0	0	0
Urologicals	3	4.6	-	-	-	-
Systemic hormonal preparations, excl. sex hormones and insulins	1	1.5	0	0	0	0
Corticosteroids for systemic use	1	1.5	-	-	-	-
Musculo-skeletal system	0	0	1	3.3	0	0
Anti-inflammatory and antirheumatic products	-	-	1	3.3	-	-
Nervous system	7	10.8	3	10	1	14.3
Analgesics	3	4.6	1	3.3	-	-
Antieleptics	-	-	1	3.3	-	-
Psycholeptics	2	3.1	-	-	1	14.3
Psychoanaleptics	1	1.5	1	3.3	-	-

Other nervous system drugs	1	1.5	-	-	-	-
Respiratory system	2	3.1	0	0	0	0
Drugs for obstructive airway diseases	1	1.5	-	-	-	-
Cough and cold preparations	1	1.5	-	-	-	-
Sensory organs	3	4.6	0	0	0	0
Opthalmologicals	3	4.6	-	-	-	-

Table 8: Drugs that are stopped one week after and three months after medication review

Drugs	**1 week after review (N=117)**		**3 months after review (new stopped drugs) (N=10)**		**3 months after review (stopped drugs after being added) (N=13)**	
	N	*%*	*N*	*%*	*N*	*%*
Alimentary tract and metabolism	21	17.9	3	30	4	30.8
Drugs for acid related disorders	4	3.4	2	20	-	-
Drugs for functional gastro-intestinal disorders	-	-	-	-	1	7.7
Drugs for constipation	5	4.3	-	-	3	23.1
Antidiarrheals, intestinal anti-inflammatory/anti-infective agents	1	0.9	-	-	-	-
Drugs used in diabetes	6	5.1	1	10	-	-
Vitamins	3	2.6	-	-	-	-
Mineral supplements	2	1.7	-	-	-	-
Blood and blood forming organs	11	9.4	1	10	1	7.7
Anti-thrombotic agents	9	7.7	1	10	1	7.7
Antianemic preparations	2	1.7	-	-	-	-
Cardiovascular system	34	29.1	6	60	3	23.1
Cardiac therapy	5	4.3	-	-	-	-
Antihypertensives	1	0.9	-	-	-	-
Diuretics	7	6.0	2	20	2	15.4
Beta blocking agents	1	0.9	-	-	-	-

Calcium channel blockers	4	3.4	-	-	-	-
Agents acting on the renin-angiotensin system	7	6.0	2	20	1	7.7
Lipid modifying agents	9	7.7	2	20	-	-
Dermatologicals	2	1.7	0	0	0	0
Emollients and protectives	1	0.9	-	-	-	-
Corticosteroids, dermatological preparations	1	0.9	-	-	-	-
Genito urinary system and sex hormones	8	6.8	0	0	1	7.7
Sex hormones and modulators of the genital system	2	1.7	-	-	-	-
Urologicals	6	5.1	-	-	1	7.7
Systemic hormonal preparations, excl. sex hormones and insulins	1	0.9	0	0	0	0
Corticosteroids for systemic use	1	0.9	-	-	-	-
Antiinfectives for systemic use	1	0.9	0	0	0	0
Antibacterials for systemic use	1	0.9	-	-	-	-
Antineoplastic and immuno-modulating agents	1	0.9	0	0	0	0
Immunosuppressants	1	0.9	-	-	-	-
Musculo-skeletal system	6	5.1	0	0	0	0
Anti-inflammatory and antirheumatic products	4	3.4	-	-	-	-
Antigout preparations	2	1.7	-	-	-	-
Drugs for treatment of bone diseases	4	3.4	-	-	-	-
Nervous system	19	16.2	0	0	4	30.8
Analgesics	9	7.7	-	-	1	7.7
Psycholeptics	5	4.3	-	-	2	15.4
Psychoanaleptics	5	4.3	-	-	-	-
Other nervous system drugs	-	-	-	-	1	7.7

Respiratory system	3	2.6	0	0	0	0
Drugs for obstructive airway diseases	2	1.7	-	-	-	-
Antihistamines for systemic use	1	0.9	-	-	-	-
Sensory organs	6	5.1	0	0	0	0
Opthalmologicals	6	5.1	-	-	-	-

Table 9: Drugs that had a dose modification one week after and three months after medication review

Drugs	**1 week after review (N=59)**			**3 months after review (new dose modifications) (N=13)**		
	-/+	*N*	*%*	*+/-*	*N*	*%*
Alimentary tract and metabolism	9-, 9+	18	30.5	4-, 4+	8	61.5
Drugs for acid related disorders	2-, 1+	3	5.1	0-, 2+	2	15.4
Drugs for constipation	3-, 1+	4	6.8	1-, 0+	1	7.7
Digestives, incl. enzymes				1-, 0+	1	7.7
Drugs used in diabetes	3-, 2+	5	8.5	0-, 2+	2	15.4
Vitamins	0-, 1+	1	1.7	1-, 0+	1	7.7
Mineral supplements	1-, 4	5	8.5	1-, 0+	1	7.7
Cardiovascular system	9-, 11+	20	33.9	1-, 1+	2	15.4
Cardiac therapy	3-, 3+	6	10.2			
Diuretics	2-, 2+	4	6.8			
Beta blocking agents	0-, 3+	3	5.1	1-, 0+	1	7.7
Calcium channel blockers	1-, 0+	1	1.7			
Agents acting on the renin-angiotensin system	3-, 1+	4	6.8	0-, 1+	1	7.7
Lipid modifying agents	0-, 2+	2	3.4			
Systemic hormonal preparations, excl. sex hormones and insulins	1-, 0+	1	1.7		0	0
Corticosteroids for systemic use	1-, 0+	1	1.7			
Antiinfectives for systemic use	1-, 0+	1	1.7		0	0
Antibacterials for systemic use	1-, 0+	1	1.7			

Antineoplastic and immuno-modulating agents	1-, 0+	1	1.7		0	0
Immunosuppressants	1-, 0+	1	1.7			
Musculo-skeletal system	1-, 1+	2	3.4		0	0
Anti-inflammatory and antirheumatic products	1-, 0+	1	1.7			
Antigout preparations	0-, 1+	1	1.7			
Nervous system	1-, 4+	5	8.5	2-, 1+	3	23.1
Analgesics	0-, 2+	2	3.4	1-, 0+	1	7.7
Psycholeptics	1-, 2+	3	5.1	1-, 0+	1	7.7
Psychoanaleptics				0-, 1+	1	7.7
Respiratory system	6-, 2+	8	13.6		0	0
Nasal preparations	2-, 0+	2	3.4			
Drugs for obstructive airway diseases	4-, 2+	6	10.2			
Sensory organs	2-, 1+	3	5.1		0	0
Opthalmologicals	2-, 1+	3	5.1			

Experiences of general practitioners and pharmacists

The questionnaire for GPs and pharmacists has been filled in by 5 GPs and 4 pharmacists, with a mean age of 40 years old (see *Table 10*).

Table 10: Characteristics of questionnaire population

	N	*%*
Gender:		
Man	2	22.2
Woman	7	77.8
Profession:		
GP	5	55.6
Pharmacist	4	44.4
	M (sd)	*Range*
Age:	40 *(10.8)*	25 – 54

The opinions about whether medication reviews offer added value to the following topics: ‘reduction in costs’, ‘reduction in number of drugs’, and ‘extra knowledge of drugs for GPs’ differ greatly (see *Table 11*). In general, the GPs and pharmacists think that performing medication reviews offers added value to less adverse events, both mild and serious. Two respondents are neutral towards ‘mild adverse events’, and one respondent is neutral towards ‘serious adverse events’, but no one disagrees.

The mean time that GPs invest in performing one medication review, shown in *Table 12*, is 21 minutes. Pharmacists invest a lot more time, namely a mean of 105 minutes per medication review. GPs and pharmacists both think that the

investment time causes a burden when looking at their workload. Pharmacists think that the investment time takes a little bit more effort than GPs, namely a mean of 4.8 and 4.0 respectively, with 0.0 as lowest rate, and 5.0 as highest rate (see *Table 12*).

Table 11: Added value of medication reviews to different topics

	Total	**Fully disagree**	**Disagree**	**Neutral**	**Agree**	**Fully agree**
Added value	*N*	*N*	*N*	*N*	*N*	*N*
Reduction in costs	9	0	2	4	2	1
Reduction in number of drugs	9	1	4	2	2	0
Mild adverse events	9	0	0	2	7	0
Serious adverse events (death, hospital admission)	9	0	0	1	7	1
Knowledge of drugs*	5	0	1	1	3	0

** Only GPs filled in this sub-question*

Table 12: Investment time and workload of medication reviews (mean, sd, and range)

	N	*M*	*Sd*	*Range*
Investment time (in minutes)				
General practitioner	5	21.0	8.9	10 – 30
Pharmacist	4	105.0	17.3	90 – 120
Workload (range: 1 totally no burden – 5 causes a burden)				
General practitioner	5	4.0	0.0	4 – 4
Pharmacist	4	4.8	0.5	4 – 5

Sometimes according to a guideline, a patient has to quit or start a drug to improve his/her health status, but that change has not being implemented. The most indicated reason for not adhering to the guidelines, according to GPs and pharmacists (shown in *Table 13*) is that a patient wants to stick to his/her drugs and does not want to undergo a change. The majority of the respondents that indicated this reason, indicates an occurrence rate above 0%, but less than 50% (see *Table 13*). One respondent said that due to medical exceptions, guidelines sometimes are being ignored. The medical exception that is given is that a lot of 'old' patients become quickly disorganized by changes. The respondents also had an option to give other reasons that are not mentioned, which is done by five respondents. Two of them said that

sometimes a patient receives treatment by a specialist and according to the prescription of the specialist the change has not to be implemented. Two other respondents said that sometimes a patient does not fit to the guideline, due to age and comorbidity, causing to choose for something different than the guideline. The remained respondent said that sometimes the GP does not want to change.

The GPs and pharmacists had the space to give other, not mentioned, pros and cons of medication reviews, and to give suggestions for improving the STRIP method. Seven out of nine respondents gave one or more pro, con or both, and three respondents gave suggestions, shown in *Table 14*. The most important advantages of performing medication review are that (1) they have *"better contact with the patients"*, they get to know each other better; (2) patients comply better with the prescriptions, *"they are dealing their drugs more consciously"*, because they know that their GP and pharmacist are actively looking at their medication list and health status; and (3) patients are more satisfied with the care they receive and with the collaboration between their GP and pharmacist, this collaboration also gets better due to the medication reviews. Examples of mentioned disadvantages of medication reviews are (1) the STRIP method is time-consuming, when the STRIP method becomes less comprehensive and simpler the time-burden reduces; (2) the GP and pharmacist have to *"constantly make considerations between adhering to the guideline or not because of the age/comorbidities of the patient, there are regularly different particularities"*; and (3) there are more complaints with generic or cheaper drugs, which causes extra work for the patient and GP, and makes the patients more restless. So, it is better to not switch always to those generic or cheaper drugs.

Table 13: Reasons and their occurrence rates for not adhering to the guidelines according to GPs and pharmacists

	True or not true		**If true, what is the occurrence**		
	True	*Not true*	*Sometimes (1 – 49%)*	*Often (50 – 80%)*	*Very often (> 80%)*
	N	*N*	*N*	*N*	*N*
Patient does not want to change	8	1	6	2	0
GP thinks that patient does not want to change	3	6	2	1	0
Previous experience with the change, without good outcomes	3	6	2	0	1
Medical exceptions	1	8	0	0	1
Other reasons	5	4	-	-	-

Table 14: Pros and cons of medication reviews, and suggestions for improving the STRIP method

Pros medication reviews	*N*	*Cons medication reviews*	*N*	*Suggestions STRIP method*	*N*
Better contact with patients	2	Time-consuming	1	Simplification of STRIP method, so that it becomes less comprehensive and time-consuming	1
Better compliance	2	Constant considerations between guidelines and age/comorbidity	1	Permission for performing medication review between patient and pharmacist is lacking in STRIP method	1
Patients more satisfied with care delivery and collaboration GP-pharmacist	2	More complaints with generics or cheaper drugs	1	Do not switch a lot to generics or other cheaper drugs, because mostly it gives complaints and it generates extra work	1
Better collaboration between GP-pharmacist	1	Some GPs are conservative towards medication reviews	1		
Better insight into the contra-indication 'renal impairment'	1	Insufficient reimbursement	1		

Discussion

Interpretation of striking results

This effect-analysis aimed to assess the effects of medication reviews on the prescription policy in polypharmacy patients. The overall findings suggest that medication reviews have a positive influence on the decrease in number of drugs, and in number of potentially inappropriate drugs that patients use. The drug groups 'alimentary tract and metabolism' and 'cardiovascular system' consist of the leading types of drugs that undergo changes due to the medication reviews. In overall, there were more elderly that stopped one or more drugs than elderly that were prescribed one or more additional drugs.

Furthermore, according to GPs and pharmacists, performing medication reviews offers added value to lowering the chance of adverse events. Other benefits of medication reviews are better contact with patients, better compliance to drugs, and more satisfied patients about care delivery and collaboration between GP and pharmacist. On the other hand, medication reviews are very time-consuming. GPs and pharmacists both consider the

investment time too much, taking in consideration the workload they already have.

Although there were more drugs stopped than added, which is confirmed by two other Dutch studies (Chau et al., 2016; Balen et al., 2013), the average decrease between before and after the review was still very small. Lenaghan et al. (2007) and Jódar-Sánchez et al. (2015) also showed an average reduction of less than one drug per patient, which confirms this result. There is a chance that the chosen pharmacies and the corresponding general practices already pay much attention to the medication of the patients, because a convenience sample is used, and not a random sample of the Netherlands. Which results in a small difference between before and after the review. However, the ultimate goal of medication reviews is not to reduce the number of drugs, but to improve the medication lists when needed, so that the drug use will be safer, i.e. less PIDs are prescribed. We observed a significant decrease in PIDs from 0.6 per patient to 0.4 per patient, both one week and three months after the medication review. Although this is on average a small difference, it is meaningful on the individual level. The number of PIDs decreased in some patients with two drugs, which can make a huge difference in the health status of a patient.

Possible explanations for the small decreases in means are that in some cases drugs were not stopped, while the guideline indicate stopping. It seems as if the STOPP criteria are not used well, or the GPs and pharmacists do not adhere to those criteria. However, for some specific patients there are other reasons why it is better to keep using a drug, and to ignore the guidelines, and some patients refused to stop a drug. Chau et al. (2016) gave reasons for this phenomenon. The most frequent reasons were: the specialist rejected the intervention; the patient did not want to stop the drug; and sometimes is decided to monitor the use of the drug by the patient and to intervene when really needed. All those reasons are found in this study as well. Besides those reasons, we also found two other reasons that occurred relatively frequent: the health status of patients is too bad to stop the drug, so the negative consequences of continuing the drug are taken for granted; and patients tried to stop a drug before and experienced negative effects of stopping the drug, so they keep using it.

Striking in this study were the types of drugs that were stopped most frequently. Most stopped drugs belonged to the groups ‘alimentary tract and metabolism’, ‘cardiovascular system’, and ‘nervous system’. The types of the most frequently stopped drugs in these groups were drugs for constipation, drugs used in diabetes, diuretics, agents acting on the renin-angiotensin system, lipid modifying agents, and analgesics. Looking at existing literature, Mudge et al. (2016) concluded that diuretics and analgesics were the most common deprescribed drugs. However, they also concluded that antieleptics and psychoanaleptics were common deprescribed drugs, which is not concluded in this study. In this study there were more cardiovascular drugs that were stopped frequently, which is being confirmed by a Dutch study, in which

cardiovascular drugs were the most deprescribed drugs. (Balen et al., 2013) Possible explanations for these differences are first, antieleptics are typically being prescribed to patients with epilepsy. When this is the case, the drug will not be stopped frequently. Second, when antieleptics are being prescribed as painkillers, the chance of stopping this drug is higher, however, this is still a very small group of patients in the Netherlands. Third, psychoanaleptics are not frequently being prescribed for elderly in the Netherlands. There is only a very small group of elderly that uses psychoanaleptics.

Finally, looking at the effect of medication reviews on the dose modifications, it can be concluded that there were more dose reductions compared with dose increases. However, the difference was very small. One week after the medication reviews, 52.5% of the dose modifications were reductions, and three months after the reviews, 53.8% were reductions. So, the number of dose reductions and the number of dose increases are almost equal. Balen et al. (2013) also showed an almost equal number between dose reductions and dose increases. In their study, 57.7% of the dose modifications were reductions, which confirms the result found in this study.

Study limitations

This study presents some limitations. First, the underlying limitation that come with a pre-test/post-test study design is that there is no control group. A disadvantage of this absence is that the natural course of the patients' situation is unknown. For example, sometimes a drug is added, because the patient has other complaints that were not present when the medication review is executed. It is not completely sure whether this is only due to the medication review. Especially in case of three months after the review, the researcher can never be sure whether the health of the patient has deteriorated or whether something is neglected during the medication review. However, it is assumed that this will not have a strong influence on the outcomes of three months after the review, because the differences between one week and three months after the review are very small.

Second, it is not always written down and known for the researcher when a patient does not want to undergo any changes. When the pharmacist or GP wrote this on paper of in the patient's file, it is known. But otherwise, qualitative research is needed with interviews to figure this out per patient. So, a limitation of this study is that a special case (i.e. a patient does not want to undergo any changes) is only known when the GP or pharmacist registered this.

Third, the GPs' and pharmacists' notes that are used in this study for identifying reasons why some PIDs were not stopped during the medication review, are not the only possible reasons. These are the only known reasons, because they are registered. Besides this, the occurrence rate of all those given reasons could be higher than shown in the results, but only these rates are known.

Fourth, according to the power calculation, 156 patients were needed to find a significant effect,

but only 126 patients are included in this study. However, those 126 patients already showed a significant effect. So, probably it would not have made a difference in the effects if there were 30 more patients included.

Finally, for identifying the experiences about performing medication reviews and wishes for improvements of the performance, short online questionnaires are used. The limitation with questionnaires is that the researcher cannot respond to the given answers. There is no depth like someone can create during an interview. Sometimes it is better when the respondent can clarify his/her answer, so that the meaning of the answer is known better. Which could be helpful in this study. Especially, because the workload of the respondents is already high, they maybe do not want to spend much time on giving comprehensive answers. For example, the open question in the questionnaire where is being asked what the pros and cons are of medication reviews according to them, is answered with short answers. When there is an interview, the interviewer can create depth by asking what the respondent means with that answer, so that more interpretable results can be found. However, we still decided to use online questionnaire because of limited time and hopefully getting a higher response rate, because the questionnaires could be filled whenever they wanted without making an appointment.

Study strength

Despite these limitations, this study is still very important. It adds to the limited and contradictory international literature. For the Netherlands there was little evidence about the effect of the medication review, this study contributes to more evidence. It is the first Dutch study that looked at the effects of medication review in terms of difference in number of drugs, difference in number of PIDs, number of medication adaptations, most frequently added/stopped drugs, most frequently drugs with dose modifications, and opinions of GPs and pharmacists about medication reviews.

Conclusion

It can be concluded that performing medication reviews in polypharmacy patients is sometimes, despite the enormous workload they bring with it, useful to continue. In the short-term, and also in the long-term, medication reviews have a positive influence on the prescription policy. One shortcoming of the way the medication reviews are being performed now, is that sometimes, after the medication list of the patient has been assessed, that patient does not want to undergo changes. It will be better if the pharmacists tell the patients precisely what the intention of performing a medication review is, and ask whether they are open minded for changes. When patients do not want to have any changes, it is only a waste of time to review their medication list. When only the medication lists of patients that are open for changes are being reviewed, the medication review will have more effect.

Furthermore, it is still not clear whether the quality of life of patients increases after a medication review has been done. This subject was not included in this study, because it was

out of this scope. Therefore, further study is needed in which the quality of life of patients before and after the review will be assessed.

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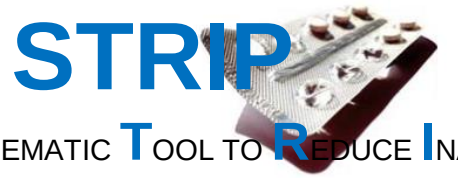
Appendix 1: STRIP method

dr A.J. Leendertse, A.C. Drenth-van Maanen, M.M. Verduijn, dr P.A.F. Jansen en dr R.J. van Marum



SYSTEMATIC **T**OOL TO **R**EDUCE **I**NAPPROPRIATE **P**RESCRIBING

Voorbereiding:

1. selectie patiënten door arts en apotheker
2. verzamelen gegevens:
   - medicatieoverzicht van apotheek, inclusief allergieën, overgevoeligheden en reden van start/stop
   - medische voorgeschiedenis/episode of probleemlijst
   - gegevens uit lichamelijk onderzoek (bloeddruk, pols, gewicht)
   - meetwaarden van het laboratorium over de afgelopen 12 maanden (nierfunctie, leverfunctie, evt. HbA1c, cholesterol, serumconcentraties etc)

Stap 1: Farmacotherapeutische Anamnese

Doelen: verzamelen van informatie over daadwerkelijk gebruik, ervaringen en beleving van de medicatie door de patiënt en het betrekken van de patiënt bij zijn farmacotherapie.

De farmacotherapeutische anamnese wordt afgenomen bij de patiënt. Als de patiënt zijn medicatie niet (volledig) in eigen beheer heeft, participeert idealiter ook degene die de patiënt hierbij helpt (de verzorgende of mantelzorger) in het gesprek. Het medicatieoverzicht en de medicijndoosjes van de patiënt vormen de basis voor de farmacotherapeutische anamnese. Gebruik bij voorkeur een gestructureerde vragenlijst.

Bespreek in ieder geval:

- wat verwacht de patiënt van zijn medicatie, wat vindt de patiënt van zijn farmacotherapie?
- wat zijn de ervaringen van de patiënt met de huidige medicatie en de eerder gebruikte medicatie?
- heeft de patiënt klachten, is de farmacotherapeutische behandeling effectief?
- ervaart de patiënt bijwerkingen?
- wat gebruikt de patiënt daadwerkelijk aan medicatie?
- gebruikt de patiënt zelfzorg- of kruidengeneesmiddelen?
- hoe volgt de patiënt de gebruiksadviezen op?
- ervaart de patiënt praktische problemen bij het gebruik van zijn medicatie?
- om welke redenen wijkt de patiënt af van het geadviseerde gebruik?

Stap 2: Farmacotherapeutische Analyse
Doel: identificatie van (potentiële) FTP's (farmacotherapie gerelateerde problemen).

De analyse begint met het ordenen van de gegevens uit de voorbereiding en de farmacotherapeutische anamnese. De actuele aandoeningen en problemen worden gekoppeld aan de voorgeschreven actuele medicatie en indien mogelijk aan meetwaarden. Bij deze aandoeningen en problemen worden behandeldoelen geformuleerd. Deze behandeldoelen kunnen symptomatisch, curatief of palliatief zijn en worden in stap 3 met de betrokken behandelaren en in stap 4 met de patiënt vastgesteld.

Controleer met deze geordende informatie op mogelijke FTP's zoals:
- onderbehandeling
- niet-effectieve behandeling
- overbehandeling
- (potentiële) bijwerking
- klinisch relevante contra-indicatie en interactie
- onjuiste dosering
- probleem bij gebruik

Identificeer de problemen met behulp van onderstaande vragen en aandachtspunten, de tabel Startcriteria en de tabel Stopcriteria (zie Bijlage 2):
- **onderbehandeling:**
  - worden alle aandoeningen of klachten behandeld?
  - worden alle aandoeningen of klachten op een doelmatige manier behandeld (volgens de geldende richtlijnen)?
  - controleer met behulp van tabel Start-criteria.
- **niet effectieve behandeling**
  - hebben alle geneesmiddelen het beoogde effect (worden behandeldoelen gehaald?
  - zijn er aandoeningen of klachten die onvoldoende effectief behandeld zijn?
  - controleer of de voorgeschreven dosering effectief is (sterkte, frequentie, duur, lab) Gebruik voor de effectiviteitsbeoordeling de gegevens uit de algemene voorbereiding (metingen, lab) en de farmacotherapeutische anamnese.
- **overbehandeling**
  - zijn er geneesmiddelen waarvoor geen indicatie (meer) is?
- **(potentiële) bijwerking**
  - controleer of er sprake is van een (potentiële) bijwerking van een geneesmiddel.
  - controleer met behulp van tabel Stop-criteria (zie *Bijlage 2*).
  - controleer bij een potentiële bijwerking:
    B of dit een **B**ekende bijwerking is,
    A welke **A**lternatieve verklaringen er zijn voor de klacht(en), en
    T hoe de **T**ijdsrelatie is (is de bijwerking opgetreden na start van het verdachte geneesmiddel).

    Meld afwijkende bijwerkingen bij Lareb.
    - controleer of er bij risico op een bijwerking de benodigde monitoring wordt uitgevoerd (bijvoorbeeld laboratoriummetingen zoals nierfunctie of bloedbeeld, bloeddruk, evaluatie klachten met patiënt).

- **klinisch relevante contra-indicatie en interactie**
  - controleer of er sprake is van geneesmiddeleninteractie of van contra-indicaties (CI) voor een geneesmiddel. Bepaal vervolgens of de interactie of CI voor deze patiënt relevant is en of deze invloed heeft op de behandeling omdat deze mogelijk minder effectief of minder veilig is of dat de patiënt hier een bijwerking van ervaart. Denk hierbij ook aan interacties met voeding, grapefruitsap, kruiden of zelfzorgmiddelen.
  - controleer of er geneesmiddelen gecontra-indiceerd zijn gezien de nierfunctie van de patiënt.
  - controleer of bij geneesmiddelinteractie of bij een gecontra-indiceerd geneesmiddel de benodigde monitoring wordt uitgevoerd.
- **onjuiste dosering**
  - controleer of de voorgeschreven dosering past bij de indicatie
  - controleer of de voorgeschreven dosering veilig is (sterkte, frequentie, duur, lab)
  - controleer of de voorgeschreven dosering past bij de nierfunctie en leeftijd van de patiënt
- **probleem bij gebruik**
  - gebruikt de patiënt zijn geneesmiddelen volgens voorschrift?
  - is de patiënt gemotiveerd om zijn geneesmiddelen te gebruiken?
  - is de toedieningsweg het meest gemakkelijk en meest effectief voor de patiënt?
  - is de toedieningsvorm het meest gemakkelijk en meest effectief voor de patiënt?
  - kan het geneesmiddelgebruik gemakkelijker voor de patiënt: - kan de doseerfrequentie
  - omlaag?
  - kan de patiënt baat hebben bij een andere formulering?
  - zijn er hulpmiddelen waardoor het gebruik gemakkelijker wordt voor deze patiënt?

Stap 3 Overleg arts en apotheker: Opstellen Farmacotherapeutisch Behandel Plan (FBP)
Doelen: arts en apotheker bereiken overeenstemming over de behandeldoelen en hoe deze doelen voor de patiënt bereikt kunnen worden.

De arts en apotheker bespreken en stellen vast:
- de behandeldoelen voor de patiënt
- de relevante FTP's uit stap 1 en 2
- prioritering van de FTP's
- interventies door de verantwoordelijke zorgverlener
- hoe, wanneer en door wie deze geëvalueerd worden

Bespreek de gesignaleerde problemen uit stap 1 en 2. Prioriteer de verschillende interventies en verdeel de verantwoordelijkheid tussen arts en apotheker voor de verschillende acties (zoals overleg met de oorspronkelijke voorschrijver bij voorgestelde medicatiewijzigingen, recepten schrijven, gesprek met patiënt, aanpassen Actueel Medicatieoverzicht). Overweeg bij een potentiële bijwerking het geneesmiddel te stoppen en te herstarten. Doe dit alleen in overleg met de patiënt en als de patiënt hier open voor staat. Stel vast of een gesignaleerde interactie of contra-indicatie ook klinisch relevant is bij deze patiënt.

Neem bij dit behandelplan de wensen van de patiënt naast specifieke patiëntkenmerken en ervaringen en levensverwachting (‘time until benefit’) mee. Streef naar zo weinig mogelijk innamemomenten per dag, schrijf zo weinig mogelijk voor, schrijf alleen hele tabletten voor en houd het aantal wijzigingen per keer beperkt. Denk aan de mogelijkheid van weekdoseersystemen zoals ‘medicatie op rol’.

Stap 4 Overleg patiënt: Vaststellen Farmacotherapeutisch Behandel Plan (FBP)
Doelen: de patiënt participeert in zijn of haar farmacotherapie en hij begrijpt de interventies in het FBP. De participatie is afgestemd op de mogelijkheden van de patiënt.

Bespreek met de patiënt (en/of diens verzorgende) de voorgestelde wijzigingen en neem op grond daarvan de definitieve beslissing welke wijzingen worden doorgevoerd. Maak daarbij een tijdpad voor elke verandering. Geef de wijzigingen op schrift mee zodat de patiënt dit desgewenst kan nalezen of kan bespreken met de mantelzorger.

Geef iedere wijziging ook aan op het Actueel Medicatieoverzicht en communiceer dit met de andere behandelaren.

Stap 5: Follow-up en monitoring
Doelen: uitvoeren en evalueren van de voorgenomen interventies.

Documenteer in het FBP welke controles uitgevoerd dienen te worden en op welke termijn. Bespreek met de patiënt hoe hij het geneesmiddelengebruik zelf kan evalueren en wanneer het goed is om contact op te nemen met de behandelend arts of apotheker. Documenteer tevens welke evaluatieafspraken er gemaakt zijn met de patiënt.

Leg vast op welke termijn de medicatielijst opnieuw gereviseerd zal worden.

Vervolgbeoordelingen
Een vervolgbeoordeling dient minimaal 1x per jaar plaats te vinden. Dit is niet relevant voor patiënten die voor een opname in het ziekenhuis zijn, maar wel voor patiënten die in een ambulante setting worden behandeld.

Samenwerking
Spreek de organisatie van het doorlopen van de STRIP-methode lokaal af en besluit als arts en apotheker samen wie wat doet. Het opstellen en evalueren van het behandelplan gebeurt onder gezamenlijke verantwoordelijkheid van de arts en de apotheker. Praktijkondersteuners, verpleegkundigen, farmaceutische consulenten, doktersassistenten, apothekersassistenten en andere hulpverleners kunnen bij de uitvoering behulpzaam zijn.

Bij het opstellen van deze STRIP zijn de voorheen in Nederland gebruikte instrumenten POM en GIVE in elkaar geschoven.

Appendix 2: START/STOPP criteria

Tabel 1 STOPP-criteria van potentieel ongeschikte medicijnen voor oudere patiënten

geneesmiddelgroep en criteriumnummer	**geneesmiddel**	**argument**
algemeen		
STOPP A1	elk medicijn zonder een op bewijs gebaseerde klinische indicatie	
STOPP A2	elk medicijn dat langer dan de goed gedefinieerde aanbevolen duur wordt voorgeschreven	
STOPP A3	dubbelmedicatie (verschillende medicijnen uit dezelfde geneesmiddelgroep), bijvoorbeeld 2 vergelijkbare NSAID's, SSRI's, lisdiuretica, ACE-remmers of orale anticoagulantia	
cardiovasculair		
STOPP B1	digoxine bij hartfalen met normale systolische ventrikelfunctie	niet bewezen effectief en risico op verslechtering bij diastolisch hartfalen
STOPP B2	verapamil of diltiazem bij hartfalen NYHA klasse III of IV	kan hartfalen verergeren
STOPP B3	bètablokker in combinatie met verapamil of diltiazem	risico op een hartblok
STOPP B4	bètablokker bij bradycardie (< 50/min), een 2e-graads AV-blok of compleet AV-blok N.B. dosis verlagen of stoppen	risico op compleet hartblok, asystolie
STOPP B5	amiodaron als eerstelijns anti-aritmicum	hoog risico op bijwerkingen
STOPP B6	lisdiureticum als behandeling van hypertensie	niet geregistreerd voor deze indicatie; veiliger en doeltreffender alternatieven beschikbaar
STOPP B7	lisdiureticum bij enkeloedeem zonder klinisch, biochemisch of radiologisch bewijs van hartfalen, leverfalen, nefrotisch syndroom of nierinsufficiëntie	indien mogelijk elastische kousen en bewegen of been in hoogstand
STOPP B8	thiazidediureticum bij een actuele hypokaliëmie (serumconcentratie kalium < 3,0 mmol/l), hyponatriëmie (serumconcentratie natrium < 130 mmol/l), hypercalciëmie (gecorrigeerd serumconcentratie niet-eiwitgebonden calcium > 2,65 mmol/l) of met een voorgeschiedenis van jicht bij gelijktijdig gebruik van thiazidediureticum	hypokaliëmie, hyponatriëmie, hypercalciëmie en jicht kunnen uitgelokt worden door thiazidediureticum
STOPP B9	centraal werkende antihypertensiva, zoals methyldopa, clonidine, moxonidine	centraal aangrijpende antihypertensiva worden slechter verdragen door ouderen
STOPP B10	ACE-remmers of angiotensine II-antagonisten bij patiënten met hyperkaliëmie (serumconcentratie kalium ≥ 5,5 mmol/l)	verergering hyperkaliëmie
STOPP B11	aldosteron-antagonisten (bijvoorbeeld spironolacton, eplerenon) gelijktijdig met kaliumsparende geneesmiddelen (zoals ACE-remmers, angiotensine II-antagonisten, amiloride of triamtereen) zonder regelmatige controle van de kaliumconcentratie	risico op hyperkaliëmie – tenminste halfjaarlijkse controle van de kaliumconcentratie in serum
STOPP B12	fosfodiësterase-type 5-remmers zoals sildenafil, tadalafil of vardenafil) bij ernstig hartfalen gekenmerkt door hypotensie (systolische bloeddruk < 90 mmHg) of in combinatie met nitraatgebruik voor angina pectoris	risico op cardiovasculaire collaps
trombocytenaggregatieremmers/antistolling		
STOPP C1	trombocytenaggregatieremmers (acetylsalicylzuur, carbasalaatcalcium) in een dosis hoger dan	een verhoogd risico op bloeding; niet bewezen effectief

geneesmiddelgroep en criteriumnummer	geneesmiddel	argument
	respectievelijk 80 of 100 mg per dag, met uitzondering van oplaaddosis	
STOPP C2	trombocytenaggregatieremmers, clopidogrel en andere middelen uit deze groep, dipryidamol, vitamine K-antagonisten, directe orale anticoagulantia bij verhoogd risico op bloeding (dat wil zeggen: ongecontroleerde hypertensie), versterkte bloedingsneiging of een recente relevante spontane bloeding. N.B. gebruik de HASBLED-score†; een score ≥ 3 betekent verhoogd bloedingsrisico	verhoogd risico op bloeding
STOPP C3	trombocytenaggregatieremmer in combinatie met clopidogrel – of andere middelen uit deze groep – als secundaire preventie van een beroerte, tenzij een coronaire stent is ingebracht in de voorafgaande 12 maanden of bij gelijktijdig acuut coronair syndroom of een hooggradige symptomatische carotisstenose	er is geen bewijs voor voordeel boven monotherapie met clopidogrel
STOPP C4	trombocytenaggregatieremmer in combinatie met vitamine K-antagonisten of directe orale anticoagulantia bij patiënten met chronisch atriumfibrilleren	geen extra voordeel van salicylaten
STOPP C5	trombocytenaggregatieremmers met vitamine K-antagonisten of directe orale anticoagulantia bij patiënten met een stabiele coronaire, cerebrovasculaire of perifere arteriële symptomen	geen bewijs voor extra voordeel van combinatie therapie
STOPP C6	vitamine K-antagonisten of directe orale anticoagulantia langer dan 6 maanden bij een eerste, ongecompliceerde diepveneuze trombose	geen bewijs voor aanvullende effectiviteit
STOPP C7	vitamine K-antagonisten of directe orale anticoagulantia langer dan 12 maanden bij een eerste ongecompliceerde longembolie	geen bewijs voor aanvullende effectiviteit
STOPP C8	NSAID's in combinatie met vitamine K-antagonisten of directe orale anticoagulantia	verhoogd risico op ernstige maagbloeding
centraal zenuwstelsel en psychofarmaca		
STOPP D1	tricyclische antidepressiva – anticholinerge effecten zijn het sterkst bij amitriptyline en het minst sterk bij nortriptyline – bij dementie, onbehandelde nauwe-kamerhoekglaucoom, cardiale geleidingsstoornissen, prostatisme, ziekte van Sjögren, of een voorgeschiedenis van urineretentie	risico op verergering van deze aandoeningen
STOPP D2	tricyclische antidepressiva als eerstelijns behandeling van depressie	hoger risico op bijwerkingen
STOPP D3	antipsychotica met matige anticholinerge effecten (chloorpromazine, clozapine, flupentixol, flufenazine, zuclopentixol) bij prostatisme of voorgeschiedenis van urineretentie	hoog risico op urineretentie
STOPP D4	SSRI's bij niet-iatrogene hyponatriëmie (serumconcentratie natrium < 130 mmol/l) in de laatste 2 maanden	risico op het verergering of recidief hyponatriëmie
STOPP D5	benzodiazepinen gedurende ≥ 4 weken. N.B. geleidelijke afbouw van alle benzodiazepinen bij gebruik langer dan 4 weken vanwege risico op ontwenningssymptomen	geen indicatie voor een langere behandeling; risico op verlengde sedatie, verwardheid, slechtere balans, vallen, verkeersongevallen
STOPP D6	antipsychotica (met uitzondering van clozapine en quetiapine) bij patiënten met parkinsonisme	risico op ernstige extrapiramidale bijwerkingen
STOPP D7	anticholinergica, zoals biperideen of trihexyfenidyl, bij behandeling van extrapiramidale bijwerkingen van antipsychotica	verhoogd risico op anticholinerge toxiciteit
STOPP D8	middelen met anticholinerge bijwerkingen bij patiënten met delirium of dementie, bijvoorbeeld oxybutynine,	verhoogd risico op verergering van cognitieve stoornissen

geneesmiddelgroep en criteriumnummer	geneesmiddel	argument
	tolterodine, promethazine, hydroxyzine, clemastine, alimemazine en amitriptyline; deze lijst is niet limitatief§	
STOPP D9	antipsychotica bij patiënten met probleemgedrag bij dementie, tenzij symptomen zeer ernstig zijn en niet-medicamenteuze maatregelen geen effect hebben	beperkte effectiviteit, verhoogd risico
STOPP D10	antipsychotica als slaapmiddelen	risico op verwardheid, hypotensie, extrapiramidale bijwerkingen, vallen
STOPP D11	acetylcholinesteraseremmers bij bradycardie (< 60 slagen/min), hartblok of recidiverende, onverklaarde syncope	risico op manifeste hartgeleidingsstoornissen, syncope en verwonding
STOPP D12	fenothiazine-antipsychotica, met uitzondering van chloorpromazine tegen de hik en levopromazine in palliatieve zorg	er zijn alternatieven die veiliger en effectiever zijn
STOPP D13	levodopa of dopamine-agonisten voor benigne essentiële tremor	niet bewezen effectief
STOPP D14	antihistaminica met sterk sederende werking	veiliger en minder toxische antihistaminica beschikbaar
potentieel ongeschikte medicatie bij verminderde nierfunctie‡		
STOPP E1	digoxine in een dosis > 0,125 mg/dag bij eGFR < 30 ml/min/1,73 m^2	verhoogd risico op toxiciteit
STOPP E2	directe trombineremmers zoals dabigatran bij eGFR < 30 ml/min/1,73 m^2	verhoogd risico op bloeding
STOPP E3	factor Xa-remmers zoals rivaroxaban bij eGFR < 15 ml/min/1,73 m^2	verhoogd risico op bloeding
STOPP E4	NSAID's bij eGFR < 30 ml/min/1,73 m^2	risico op verslechtering van de nierfunctie
STOPP E5	metformine bij eGFR < 30 ml/min/1,73 m^2	risico op lactaatacidose
STOPP E6*	bisfosfonaten:‡ clodroninezuur en ibandroninezuur: bij eGFR < 50 ml/min/1,73 m^2 dosis aanpassen alendroninezuur, etidroninezuur en risedroninezuur: bij eGFR < 30 ml/min/1,73 m^2 toediening staken	risico op toxiciteit van bisfosfonaten
gastro-intestinaal		
STOPP F1	metoclopramide bij parkinsonisme	verhoogd risico op verergering van parkinsonisme door centrale dopamineblokkade; domperidon is een alternatief
STOPP F2	protonpompremmer in maximale therapeutische dosis > 8 weken bij peptische ulcera of oesofagitis, met uitzondering van een Barrett-slokdarm	geen bewijs voor extra effectiviteit
STOPP F3	geneesmiddelen die obstipatie kunnen veroorzaken of verergeren (bijvoorbeeld anticholinerge medicatie, oraal ijzer, opiaten, verapamil, aluminiumhoudende antacida) bij patiënten met chronische obstipatie	risico op verergering van obstipatie
STOPP F4	ijzerpreparaten met een gereguleerde afgifte (ferrosulfaat mga/Ferogradumet) of oraal elementair ijzer in een dosis hoger dan 200 mg per dag, bijvoorbeeld ferrofumaraat > 600 mg/dag of ferrogluconaat > 1800 mg/dag	geen bewijs voor meer opname van ijzer boven deze dosis
respiratoir		
STOPP G1	theofylline als monotherapie bij COPD	er zijn veiligere en effectievere alternatieven beschikbaar; risico op bijwerkingen als gevolg van nauwe therapeutische breedte

geneesmiddelgroep en criteriumnummer	geneesmiddel	argument
STOPP G2	systemische glucocorticosteroïden in plaats van inhalatiecorticosteroïden als onderhoudsbehandeling bij matig tot ernstige COPD of astma	onnodige blootstelling aan langetermijnbijwerkingen van systemische glucocorticosteroïden
STOPP G3	inhalatie-parasympaticolytica, zoals ipratropium en tiotropium, bij onbehandelde nauwe-kamerhoekglaucoom of blaasledigingsproblemen	kan glaucoom verergeren en urineretentie geven
STOPP G4	benzodiazepinen bij acute of chronische respiratoire insufficiëntie (Po_2 < 8,0 kPa/60 mmHg en/of Pco_2 > 6,5 kPa/50 mmHg	verhoogd risico op verergering van respiratoire insufficiëntie
bewegingsapparaat		
STOPP H1	NSAID's bij matige tot ernstige hypertensie of bij hartfalen	kan verergering hypertensie en hartfalen geven
STOPP H2	langdurig gebruik van NSAID's (> 3 maanden) voor pijnverlichting bij artrose zonder dat paracetamol in adequate dosering geprobeerd is	eenvoudige pijnstillers zijn veiliger en meestal even effectief in pijnbestrijding
STOPP H3	langdurig gebruik van glucocorticosteroïden (> 3 maanden) als monotherapie voor reumatoïde artritis	verhoogd risico op systemische bijwerkingen van glucocorticosteroïden
STOPP H4	gebruik van glucocorticosteroïden – anders dan periodieke intra-articulaire injecties voor mono-articulaire pijn – bij artrose	risico op systemische bijwerkingen van glucocorticosteroïden
STOPP H5	langdurig NSAID's of colchicine bij chronische behandeling van jicht zonder contra-indicatie voor xanthine-oxidaseremmers, bijvoorbeeld allopurinol	xanthine-oxidaseremmers zijn profylactische geneesmiddelen van eerste keus bij jicht
STOPP H6	COX-2-selectieve NSAID's en diclofenac bij hart- en vaatziekten	verhoogd risico op hartinfarct en beroerte
STOPP H7	orale bisfosfonaten bij patiënten met in voorgeschiedenis of actuele bovenste gastrointestinale aandoeningen (dysfagie, oesofagitis, gastritis, duodenitis, maagulcus of bovenste gastro-intestinale bloeding) of bij bedlegerige patiënten	verhoogd risico op recidief of verergering van aandoening
urogenitaal		
STOPP I1	urogenitale anticholinergica (oxybutynine, solifenicine, tolterodine, darifenacine, fesoterodine) bij dementie of cognitieve stoornis, bij onbehandeld nauwe-kamerhoekglaucoom of bij chronisch prostatisme	risico op toename van verwardheid, agitatie; risico op acute verergering; risico op urineretentie
STOPP I2	selectieve alfa-1-blokkers bij dagelijkse incontinentie of symptomatische orthostase of mictie-syncope of bij urinecatheter in situ > 2 mnd	kan toename urinefrequentie en incontinentie geven; risico op verergering symptomen; niet bewezen effectief
endocrien		
STOPP J1	sulfonylureumderivaten met een langere werkingsduur en actieve metabolieten, zoals glibenclamide en glimepiride, bij diabetes mellitus type 2	kan de duur van de hypoglykemie verlengen
STOPP J2	thiazolidinedionen, bijvoorbeeld pioglitazon, bij patiënten met gedocumenteerd hartfalen	kan verergering van hartfalen geven
STOPP J3	bètablokkers bij patiënten met diabetes mellitus die frequent hypoglykemie hebben	kan hypoglykemie maskeren
STOPP J4	oestrogenen bij patiënten met een borstkanker of veneuze trombo-embolie in voorgeschiedenis	verhoogd risico op recidief
STOPP J5	orale oestrogenen zonder progestagenen bij patiënten met een intacte uterus	verhoogd risico op endometriumcarcinoom
STOPP J6	androgenen zonder dat er sprake is van primair of secundair hypogonadisme	

geneesmiddelgroep en criteriumnummer	geneesmiddel	argument
verhoogd valrisico		
STOPP K1	benzodiazepinen bij voorgeschiedenis van val of valneiging	verhoogd risico op sedatie, bewustzijnsvermindering en verslechtering balans
STOPP K2	antipsychotica bij voorgeschiedenis van val of valneiging	kunnen parkinsonisme, duizeligheid en orthostatische hypotensie geven
STOPP K3	vasodilatatoren (bijvoorbeeld α1-receptorblokkers, calciumantagonisten, langwerkende nitraten, ACE-remmers, angiotensine II-antagonisten) bij orthostatische hypotensie	verhoogd risico op syncope, vallen
STOPP K4	aan benzodiazepine verwante geneesmiddelen, zopiclon en zolpidem bij voorgeschiedenis van val of valneiging	kunnen langdurige sedatie overdag en ataxie veroorzaken
pijn		
STOPP L1	sterke orale of transdermale opiaten (bijvoorbeeld morfine, oxycodon, fentanyl of buprenorfine) als eerste keus bij lichte pijn	
anticholinerge belasting		
STOPP N1	gelijktijdig gebruik van 2 of meer geneesmiddelen met anticholinerge eigenschappen, bijvoorbeeld blaasspasmolytica (oxybutinine, tolterodine, solifenacine, darifenacine, fesoterodine) of intestinale spasmolytica (scopolaminebutyl, tricyclische antidepressiva of klassieke antihistaminica)§	verhoogd risico op anticholinerge toxiciteit

STOPP = Screening tool of older person's prescriptions.
* Niet opgenomen in de internationale herziene versie.
† ESC richtlijn atriumfibrilleren en http://spoedpedia.nl/wiki/HaS-BLED_score.
ǂ De genoemde medicatie is niet compleet. Volledige geneesmiddellijst is beschikbaar op www.ephor.nl; voor doseringsadvies wordt verwezen naar het advies bij verminderde nierfunctie van de KNMP Kennisbank.
§ www.ephor.nl of tabel 1 uit J am Geriatr Soc. 2014;62(10):1916-22.

Bron: Ned Tijdschr Geneesk. 2015;159:A8904

Tabel 2 START-criteria voor het voorschrijven van medicijnen aan ouderen bij veelvoorkomende aandoeningen, ter vermijding van onderbehandeling

geneesmiddelgroep	**criterium**
cardiovasculair	
1	vitamine K-antagonist of directe orale anticoagulantia bij chronisch atriumfibrilleren; uitzondering: mannen van 65-75 jaar zonder cardiovasculaire comorbiditeit
2	acetylsalicylzuur of carbasalaatcalcium (80-100 mg 1dd) bij chronisch atriumfibrilleren, indien een vitamine K-antagonist of directe orale anticoagulantia gecontra-indiceerd zijn of door de patiënt niet gewenst worden
3	acetylsalicylzuur, carbasalaatcalcium, clopidogrel, prasugrel of ticagrelor bij een voorgeschiedenis van coronaire, cerebrale of perifere arteriële symptomen en sinusritme bij patiënten die niet reeds behandeld worden met een vitamine K-antagonist of directe orale anticoagulantia
4	antihypertensiva indien bij herhaling systolische bloeddruk > 160 mmHg en/of diastolische bloeddruk > 90 mmHg en leefstijlmaatregelen onvoldoende effect hebben. N.B. systolische bloeddruk dient niet veel verder dan tot 150 mmHg te dalen; bij patiënten met diabetes mellitus* indien systolische bloeddruk > 140 mmHg en/of diastolische bloeddruk > 90 mmHg
5	statine bij een voorgeschiedenis van coronaire, cerebrale of perifere arteriële symptomen of een verhoogd cardiovasculair risico en LDL-waarde > 2,5 mmol/l, tenzij de patiënt een levensverwachting < 3 jaar heeft
6	ACE-remmer of – bij bijwerkingen – een angiotensine II-antagonist bij systolisch hartfalen en/of een coronaire hartziekte
7	bètablokker na myocardinfarct of stabiele angina pectoris
8	cardioselectieve bètablokker (bijvoorbeeld metoprolol, bisoprolol of nebivolol) bij stabiel systolisch hartfalen
respiratoir	
1	inhalatie van bèta-2-agonist of parasympaticolyticum bij lichte tot matige astma of COPD
2	proefbehandeling met inhalatiecorticosteroïd (ICS) bij COPD in geval van frequente exacerbaties (2 of meer per jaar) ondanks behandeling met langwerkende luchtwegverwijder. N.B. Evalueer na een jaar en stop ICS als het aantal exacerbaties niet afneemt
3	continue zuurstoftherapie bij chronisch respiratoir falen (d.w.z. Po2 < 8,0 kPa of 60 mmHg of S_AO_2 < 89%)
centraal zenuwstelsel en ogen	
1	antiparkinsonmiddel (L- DOPA met decarboxylaseremmer of dopamine-agonist) bij de ziekte van Parkinson met functionele beperkingen en de daaruit voortvloeiende invaliditeit
2	antidepressivum (tricyclische antidepressiva (nortriptyline) als SSRI/SNRI onvoldoende effectief is) bij matige tot ernstige depressie (volgens DSM-V-criteria)
3	voor 2e lijn: bespreken van behandeling met acetylcholinesteraseremmer (bijvoorbeeld rivastigmine, galantamine of donepezil) bij lichte tot matige dementie op basis van de ziekte van Alzheimer of 'Lewy body'-dementie (rivastigmine) volgens een behandelprotocol
4	prostaglandine-analogen of bètablokker bij primair open-kamerhoekglaucoom
5	SSRI (of SNRI of pregabaline als SSRI gecontra-indiceerd is) voor persisterende, ernstige angst die interfereert in het dagelijks functioneren
6	dopamine-agonist (bijvoorbeeld ropinirol, pramipexol of rotigotine) bij ernstig restless-legs-syndroom met onacceptabele lijdensdruk ondanks niet-medicamenteuze behandeling, indien ijzertekort en ernstig nierfalen zijn uitgesloten
gastro-intestinaal	
1	protonpompremmer bij ernstige gastro-oesofageale refluxziekte of peptische strictuur waarvoor dilatatie nodig is
2a	protonpompremmer bij patiënten die NSAID gebruiken* en: (complicatie van) peptisch ulcus/*Helicobacter pylori* in anamnese hebben; ernstige invaliderende reumatoïde artritis, hartfalen of diabetes mellitus hebben; 70 jaar of ouder zijn; 60 tot 70 jaar oud zijn en gelijktijdig orale anticoagulantia, orale glucocorticosteroïden, SSRI, acetylsalicylzuur of carbasalaatcalcium gebruiken

geneesmiddelgroep	criterium
2b	protonpompremmer bij patiënten die lage dosering acetylsalicylzuur of carbasalaatcalcium* gebruiken en: 60 jaar of ouder zijn en een peptisch ulcus in de anamnese hebben; 70 jaar of ouder zijn en gelijktijdig orale anticoagulantia, een P2Y12-remmer (clopidogrel, prasugrel of ticagrelor), systemisch werkend glucocorticosteroïden, spironolacton, SSRI, venlafaxine, duloxetine of trazodon gebruiken; 80 jaar of ouder zijn
3	vezelsupplement bij chronische symptomatische diverticulose met obstipatie
bewegingsapparaat	
1	'disease modifying antirheumatic drugs' (DMARD) bij actieve, invaliderende reumatoïde artritis (gedurende > 4 weken)
2	bisfosfonaten en vitamine D en calcium bij onderhoudstherapie met glucocorticosteroïden > 3 maanden, als de dosis ≥ 7,5 mg prednison (of het equivalent daarvan) per dag bedraagt
3	vitamine D en calcium (tenzij voldoende inname) bij patiënten met osteoporose
4	inhibitie botafbraak en/of stimulatietherapie (bijvoorbeeld met bisfosfonaten, denosumab, teriparatide) bij gedocumenteerde osteoporose (BMD T-score < -2,5) en op voorwaarde dat er geen contra-indicaties zijn
5	vitamine D bij ouderen die aan huis gebonden zijn of vallen of die osteopenie hebben (-2,5 < BMD T-score < -1,0)
6	xanthine-oxidaseremmer (bijvoorbeeld allopurinol) bij recidiverende episoden met jicht (aanvalsfrequentie van > 3 per jaar) of bij jichttophi
7	foliumzuur bij patiënten die behandeld worden met methotrexaat
endocrien	
1	metformine* bij diabetes mellitus type 2. N.B. starten met 500 mg 2 dd indien eGFR 30-50 ml/min/1,73 m^2; niet geven bij eGFR < 30 ml/min/1,73 m^2
2	ACE-remmer of – bij bijwerkingen – angiotensine II-antagonist bij diabetes mellitus met tekenen van nierschade, dat wil zeggen: microalbuminurie (> 30 mg/24 h) eventueel gecombineerd met eGFR < 50 ml/min/1,73 m^2. N.B. pas zo nodig de dosering aan bij verminderde nierfunctie
urogenitaal	
1	α 1-receptorblokker bij symptomatisch prostatisme en wanneer prostatectomie als onnodig wordt beschouwd
2	5-α-reductaseremmer bij symptomatisch prostatisme en wanneer prostatectomie als onnodig wordt beschouwd of kan worden uitgesteld
3	vaginale oestrogenen of vaginaal oestrogeenpessarium bij symptomatische atrofische vaginitis. N.B. evaluatie en overweging tot staken tenminste elke 6 maanden
analgetica	
1	sterk werkende opioïden (met uitzondering van methadon) bij matige tot ernstige pijn, indien paracetamol, NSAID's of minder sterk werkende opioïden niet geschikt zijn gezien de ernst van de pijn of onvoldoende effectief zijn
2	kortwerkende opiaten voor doorbraakpijn bij behandeling met langwerkende opiaten
3	laxeermiddelen (bijvoorbeeld macrogol, lactulose of magnesiumoxide) bij gebruik van opiaten
vaccinaties	
1	seizoensgebonden griepvaccinatie (influenza) jaarlijks
START = 'Screening tool to alert doctors to right treatment'; S_aO_2 = arteriële zuurstofsaturatie. *Niet opgenomen in herziene internationale versie	

Bron: Ned Tijdschr Geneesk. 2015;159:A8904

Appendix 3: Form for collecting patient demographics and medical information

Form for collecting patient demographics and medical information

Date:

Patient number:

PATIENT DEMOGRAPHICS																					
Gender																					
Date of birth																					
Date of review																					
eGFR																					
Sodium level																					
Potassium level																					
Blood pressure																					
Beats per minute																					
MEDICAL INFORMATION 1 DAY BEFORE MEDICATION REVIEW																					
Which drugs			ATC-code			Start date			Episode			Dose									Potential STOPP drugs

MEDICAL INFORMATION 1 WEEK AFTER MEDICATION REVIEW							
Which drugs	ATC-code	Dose modi-fication	Actual stopped drugs	Reason for (not) stopping	Added drugs	Reason for adding	New potential STOPP drugs

MEDICAL INFORMATION THREE MONTHS AFTER MEDICATION REVIEW									
Which drugs	ATC-code	Dose modi-fication	Added drugs after being stopped	Reason for this adding	Stopped drugs after being added	Reason for this stopping	New added drugs	New stopped drugs	New potential STOPP drugs

Appendix 4: Questionnaire design

Stap 1 en 2: van onderzoeksdoel naar theoretische variabelen:

Door middel van deze vragenlijst moet duidelijk worden gemaakt wat volgens de huisartsen en apothekers de voor- en nadelen zijn van een medicatiebeoordeling; wat de redenen zijn waarom er soms niks aan de medicatielijsten verandert ondanks dat het wel zou moeten; hoeveel tijd huisartsen en apothekers investeren in het uitvoeren van een medicatiebeoordeling bij één patiënt; en of deze investeringstijd belastend is.

De onderzoeksvraag is: "*What are the experiences of general practitioners and pharmacists with medication reviews in polypharmacy patients and ideas for possible improvements for performing medication reviews?"*

Theoretische variabelen:

- Investeringstijd
- Voordelen
- Nadelen
- Ongeschikte medicijnen

Stap 3 – 5: van theoretische variabelen tot indicatoren, ruwe variabelen, en vragen:

Theoretische variabelen	**Indicatoren**	**Ruwe variabelen**	**Concept vragen**
Algemene achtergrond variabelen			
Leeftijd	Leeftijd	Leeftijd in jaren	Wat is uw leeftijd (in jaren)?
Geslacht	Geslacht	Man/vrouw	Bent u man/vrouw?
Beroep	Beroep	Huisarts/apotheker	Bent u huisarts/ apotheker?
Onderzoeksvariabelen			
Ervaringen met medicatiebeoordeling	Toegevoegde waarde	Toegevoegde waarde van medicatiebeoordeling aan zorgkosten, aantal medicijnen, bijwerkingen, kennis over medicatie bij huisartsen	In hoeverre vindt u dat het uitvoeren van medicatiebeoordelinge n toegevoegde waarde biedt aan de onderstaande factoren?
	Investeringstijd	Aantal minuten nodig voor het uitvoeren van één medicatiebeoordeling	Hoeveel minuten investeert u in het uitvoeren van één medicatiebeoordeling (inclusief voorbereiding)?
		Is de investeringstijd belastend	Wat vindt u van de tijd die u investeert in het uitvoeren van een medicatiebeoordeling naast het werk dat u verder hoort te doen?

Suggesties	Verbeteringen	Suggesties voor verbeteringen/aanpassingen	Heeft u suggesties voor verbeteringen/ aanpassingen van de STRIP methode voor het uitvoeren van een medicatiebeoordeling?
Ongeschikte medicijnen	Veranderingen in medicijnen niet doorgevoerd	Er verandert niks in de medicatie, ondanks dat dat volgens de richtlijn wel zou moeten	Soms verandert er niets in de medicatie van de patiënt, ondanks dat dat volgens de richtlijnen wel zou moeten en het de gezondheidsstatus van de patiënt zou gaan verbeteren. Wat zijn volgens u de redenen daarvoor?

Stap 6-9: formuleren van antwoordcategorieën bij gesloten vragen en afronden vragenlijst

Introductie

Zoals u misschien al weet ben ik bezig met mijn afstudeeropdracht over polyfarmacie in de eerste lijn. Naast het kijken naar welk effect een medicatiebeoordeling heeft op de medicatie van de patiënten, wil ik ook graag kijken naar hoe jullie als huisartsen en apothekers tegen de medicatiebeoordeling aankijken. Het invullen van deze vragenlijst zal ongeveer 5 minuten duren.

De gegeven antwoorden zullen vertrouwelijk worden behandeld en anoniem gerapporteerd worden.

De vragenlijst bestaat uit 10 vragen.

Marian Hurmuz – master student Health Sciences (Universiteit Twente)

Definitieve vragen

1. Wat is uw leeftijd (in jaren)?
   … jaar

2. Wat is uw geslacht?
   Vrouw/Man

3. Wat is uw beroep?
   Huisarts/apotheker

4. In hoeverre vindt u dat het uitvoeren van medicatiebeoordelingen toegevoegde waarde biedt aan de onderstaande factoren?

	Helemaal oneens	Oneens	Neutraal	Eens	Helemaal eens
Daling van zorgkosten	O	O	O	O	O
Daling aantal medicijnen in gebruik	O	O	O	O	O
Milde bijwerkingen	O	O	O	O	O
Ernstige bijwerkingen (bijv. ziekenhuisopnames, overlijden)	O	O	O	O	O
Extra kennis over medicijnen*	O	O	O	O	O

** Deze vraag wordt alleen getoond bij huisartsen*

5. Hoeveel minuten investeert u in het uitvoeren van één medicatiebeoordeling (inclusief voorbereiding)?
   … minuten per medicatiebeoordeling

6. Wat vindt u van de tijd die u investeert in het uitvoeren van een medicatiebeoordeling naast het werk dat u verder hoort te doen?
   1 → totaal niet belastend, 5 → heel erg belastend
   1 2 3 4 5

7. Soms verandert er niets in de medicatie van de patiënt, ondanks dat dat volgens de richtlijnen wel zou moeten en het de gezondheidsstatus van de patiënt zou gaan verbeteren. Wat zijn volgens u de redenen daarvoor?
   Meerdere antwoorden mogelijk
   - o Patiënt geeft aan dat hij/zij niet wil veranderen
   - o Huisarts gaat er zelf van uit dat zijn/haar patiënt niet wil veranderen
   - o Al eerder ervaring gehad met starten/stoppen van een medicijn maar hielp niet
   - o Medische bijzonderheden, zoals …….
   - o Andere: ……

8. Hoe vaak komt dit voor?

	Nooit (0%)	Af en toe (1 – 49 %)	Vaak (50 – 80%)	Heel vaak (> 80%)
Patiënt geeft aan dat hij/zij niet wil veranderen	O	O	O	O
Huisarts gaat er van uit dat zijn/haar patiënt niet wil veranderen	O	O	O	O
Al eerder ervaring gehad met starten/stoppen van een medicijn maar hielp niet	O	O	O	O
Medische bijzonderheden	O	O	O	O

9. Heeft u misschien ook nog andere niet genoemde voor- en nadelen ondervonden van het uitvoeren van medicatiebeoordelingen bij polyfarmacie patiënten?
   ……
   ……

10. Heeft u verder nog suggesties voor verbeteringen/ aanpassingen van de STRIP methode voor het uitvoeren van een medicatiebeoordeling?
    ……
    ……

Slot

Hartelijk dank dat u tijd heeft genomen om deze vragenlijst in te vullen.

Appendix 5: Literal registered reasons why some PIDs are continued

Precise registered reasons why some PIDs are not stopped

STOPP code	*STOPP criterion*	*Registered reason for continuing the drug*
STOPP A2	Any drug that is prescribed longer than the well-defined recommended duration	Alendronic acid (M05BA04) has not been stopped because the patient suffers from collapsing of the vertebrae
STOPP B6	Loop diuretic for the treatment of hypertension	Furosemide (C03CA01) has not been stopped because the patient responds well to this drug
STOPP B7	Loop diuretic for the treatment of ankle oedema without clinical, biochemical or radiological evidence of heart failure, liver failure, nephrotic syndrome or renal failure	Furosemide (C03CA01) has been stopped before, which resulted into swollen ankles. So, it is better to not stop it
STOPP B8	Thiazide diuretic with a current hypokalemia (serum concentration of potassium < 3.0 mmol/L), hyponatremia (serum concentration of sodium < 130 mmol/L), hypercalcemia (corrected serum concentration of non-protein-bounded calcium > 2.65 mmol/L) or with a history of gout with simultaneous use of thiazide diuretic	Chlortalidone (C03BA04) has not been stopped because of considerable hypertension
STOPP B11 (2 times same reason)	Aldosterone antagonists (e.g. spironolactone, eplerenone) simultaneous with potassium-sparing drugs (such as ACE inhibitors, angiotensin II-antagonists, amiloride or triamterene) without regular monitoring of potassium	Spironolactone (C03DA01) has not been stopped, but the potassium level will be under surveillance by the GP. When the potassium level rises, spironolactone will be stopped.
STOPP D5	Benzodiazepines lasting ≥ 4 weeks.	Oxazepam (N05BA04) has not been stopped completely. The patient uses it now only when it is really needed.

		Oxazepam (N05BA04) has not been stopped because the patient cannot fall asleep without this drugs. She feels too much pain.
STOPP H3	Long-term use of glucocorticoids (> 3 months) as monotherapy for rheumatoid arthritis	Prednisolone (H02AB06) has not been stopped directly. The patient has a scheme to reduce this drug in steps.
STOPP H6	COX-2 selective NSAIDs and diclofenac with cardiovascular diseases	Diclofenac (M01AB05) has been stopped before, but that did not go well.
STOPP H7	Oral bisphosphonates in patients with a history or current upper gastrointestinal disorders (dysphagia, esophagitis, gastritis, duodenitis, gastric ulcer or upper gastrointestinal bleeding) or in bedridden patients	Alendronic acid/colecalciferol (M05BB03) was not needed to be stopped, because the patient only has a little superficially ulcer in the duodenum.
STOPP J1	Sulphonylureas with a longer duration and active metabolites, such as glibenclamide and glimepiride, in patients with diabetes mellitus type 2	Glimepiride (A10BB12) has not been stopped, but the dose is lowered, so that the chance to get a hypo is reduced. Glimepiride (A10BB12) has not been stopped. The patient used before metformin (A10BA02), but this drug was not effective.
STOPP K3	Vasodilators (e.g. α1-receptor blockers, calcium channel blockers, long-acting nitrates, ACE inhibitors, angiotensin II-antagonists) with orthostatic hypotension	Amlodipine (C08CA01) has not been stopped, because the blood pressure still is high (131/79)

Appendix 6: Literal spontaneous registered notes

Literal spontaneous registered notes by the general practitioner or the pharmacist

General spontaneous written notes by general practitioner or pharmacist	*Times of occurrence*	*Literal spontaneous registered notes*
Patient, pharmacist, and GP agreed to change a drug, but in the end, nothing happened (without any reasons)	12	Vitamin D (A11CC05) had to be started, because the patient is relatively a lot of the time inside and the patient suffers from vitamin D deficiency. The patient uses tamsulosin (G04CA02) consecutively since 2008, they agreed to stop this on trial. The combination simvastatin (C10AA01) with diltiazem (C08DB01) increases the chance of myopathy and rhabdomyolysis. Advice is to reduce the dose simvastatin to a maximum of 20 mg/day and in case of complaints of muscle pain or dark urine the patient has to go to the doctor. Or simvastatin had to be exchanged to pravastatin (C10AA03), because this drug can be combined with diltiazem without any problems. The blood pressure of the patient was good, and the cholesterol was low, so it could be converted, but is not done. The patient still uses venlafaxine (N06AX16) daily, and does not notice whether it is effective or not. The drug may be stopped (right away or in steps), especially since it can create many problems for this patient. In this patient three changes were agreed on, but they all did not occur: 1. Perindopril (C09AA04) and losartan (C09CA01) are both prescribed for hypertension, but research has shown that the use of both ACE inhibitors and angiotensin II-antagonists offers no added value in case of hypertension and it increases the risk for adverse events. So, one of the two drugs can be stopped. 2. Ezetimibe (C10AX09) and fluvastatin (C10AA04) are both cholesterol lowering drugs.

		However, ezetimibe is an expensive drug which has not been proven to reduce the risk of cardiovascular diseases and fluvastatin is not first choice statin. Ezetimibe can be stopped and fluvastatin can be replaced by simvastatin (C10AA01) or atorvastatin (C10AA05). 3. Vitamin D (A11CC05) has to be started. Pantoprazole (A02BC01) could be stopped or replaced by omeprazole (A02BC01). Colchicine (M04AC01) should be stopped due to the liver values. Betahistine (N07CA01) should be stopped, because it is not rational. Temazepam (N05CD07) should be stopped. PPI should be started, because the patient sometimes suffers from gastric acid and the patient uses platelet aggregation inhibitor. Clopidogrel (B01AC04) should be discontinued after one year according to the prescription. LDL of the patient is 5.9! Statins are needed, but the patient cannot tolerate simvastatin (C10AA01) and rosuvastatin (C10AA07). Atorvastatine (C10AA05) or ezetimibe (C10AX09) are not yet tried, so those could be started.
Patient did not want to undergo any changes	9	Amitriptyline (N06AA09) could be stopped, the patient uses this drug for twelve years. But the patient is afraid to get a relapse, so the drug has not been stopped due to anxiety/depression. Patient did not want to change anything, because she becomes very restless if something changes. The changes that could be done were: 1. Omeprazole (A02BC01) dosage could be reduced due to over-treatment. 2. Metformin (A10BA02) dosage could be reduced. 3. The LDL is too high, but the patient refuses to use statins.

		Paroxetine (N06AB05) could be stopped, but the patient is afraid to get a relapse. Patient is not open minded for any changes (**3 times**) PPI should be started, because the patient uses aspirin and coumarin, and is over 70 years old, but the patient refuses. Vitamin D (A11CC05) should have been started, but the patient does not want to, because he thinks that he already uses many drugs. LDL is high, but the patient does not want to use statins.
Patient asked the pharmacist for a medication review (patient's own initiative)	2	Patient asked the pharmacist for a medication review, because the patient wanted to have less drugs. Patient asked the pharmacist for a medication review because of persistent complaint of: not feeling well/dizziness/fainting, without a visible cause.
Better to keep the medication list the same, because of the situation of patient	2	Statin may be considered to be started due to the patient's hypertension and diabetes, but it has not been started because of the patient's forgetfulness. LDL is high, but the patient cannot tolerate statins.
Pharmacist did not get any reaction from the GP	1	The pharmacist did not received a response from the GP, even though some changes could be made.
Health status of patient was very bad	1	The patient was dying, so no adjustments are made, even though there were some indications for changes.