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THE EVOLVING ROLE OF THE COMMUNITY PHARMACIST: FOCUS ON MEDICATION SCREENING IN OLDER PATIENTS WITH POLYPHARMACY AND MEDICATION COUNSELLING FOR PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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PREFACE

Five years ago I embarked on this project. A project that would enrich me as a researcher but also as a community pharmacist. After this project, I am convinced – even more than I ever was – that community pharmacists play an essential role in the current healthcare system. The wide-spread presence of community pharmacists in Belgium should be seen as an enormous strength that we should exploit to make healthcare even more accessible and effective.

At first instance, I hope this thesis will give a boost to community pharmacists, so they would take up their role in patient counselling with more persuasion and courage. On the other hand, I wish to convince other healthcare workers and policy makers that community pharmacists are an essential link in the healthcare system. It is therefore with great joy that I introduce my doctoral thesis, a plea for community pharmacists and their value in the current healthcare setting.

Eline Tommelein, Ghent, April 3rd 2016

VOORWOORD

Vijf jaar geleden ging ik van start met dit project. Een project dat me zoveel zou verrijken, zowel als onderzoeker maar ook als apotheker. Nu ben ik er meer dan ooit van overtuigd dat officina-apothekers een essentiële rol spelen in de hedendaagse gezondheidszorg. De wijdverspreidheid van apotheken in België moet gezien worden als een sterkte en moeten aangewend worden om de gezondheidszorg nog toegankelijker en effectiever te maken dan ze momenteel is.

Ik hoop in eerste instantie dat deze thesis officina-apothekers een duwtje in de rug geeft, opdat ze met meer overtuiging en durf hun rol in de patiëntbegeleiding zouden opnemen. Daarnaast hoop ik andere zorgberoepen en beleidsmakers te laten inzien dat de officina-apotheker een onmisbare schakel is in de gezondheidszorg. Het is dan ook met veel plezier dat ik mijn doctoraatsthesis voorstel. Een pleidooi voor de officina-apotheker en zijn waarde in de gezondheidszorg van vandaag.

Eline Tommelein, Gent, 3 April 2016

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List of Abbreviations

LIST OF ABBREVIATIONS

ACE-I	*Angiotensin Converting Enzyme Inhibitor*
ADE	*Adverse Drug Event*
ADL	*Activities of Daily LIving*
ADR	*Adverse Drug Reaction*
aMAI	*adapted Medication Appropriateness Index*
APB	*Belgian Pharmacists Association*
ASA	*Acetyl Salicylic Acid*
ATC	*Anatomical Therapeutic Chemical*
AIIA	*Angiotensin II Antagonist*
BMI	*Body Mass Index*
BPCS	*Behavioural Pharmaceutical Care Scale*
BPH	*Benign Prostatic Hyperplasia*
Ca	*Calcium*
CAT	*COPD Assessment Test*
CCB	*Calcium Channel Blocker*
CD	*Considering Diagnosis; refers to the second part of the Beers list*
CDSS	*Computerized Decision Support System*
CI	*Confidence Interval*
COMP	*Compilation*
CONSORT	*Consolidated Standards of Reporting Trials*
COPD	*Chronic Obstructive Pulmonary Disease*
CV	*Cardio Vascular*
DALY	*Disability Adjusted Life-Years*
DB	*Database*
DDI	*Drug-Drug Interaction*
DDisI	*Drug-Disease Interaction*
DM	*Diabetes Mellitus*
DPI	*Dry Powder Inhaler*
DRP	*Drug-Related Problem*
EDQM	*European Directorate for the Quality of Medicines & HealthCare*
EQ-5D	*EuroQol five-dimension Questionairre*
FEV_1	*Forced Expiratory Volume in 1 second*
FTF	*Face-To-Face*
FVC	*Forced Vital Capacity*

GheOP³S	*Ghent Older People's Prescriptions community Pharmacy Screening*
GI	*Gastro-Intestinal*
GOLD	*Global Initiative for Chronic Obstructive Lung Disease*
GP	*General Practitioner*
ICS	*Inhaled CorticoSteroid*
ID	*Independent of Diagnosis; refers to the first part of the Beers list*
INR	*International Normalized Ratio*
INS	*Institutionalized*
IPET	*Improving Prescribing in the Elderly Tool*
IPSA	*Instituut voor Permanente Studie voor Apothekers*
IQR	*Interquartile Range*
KNMP	*Koninklijke Nederlandse Maatschappij ter bevordering der Pharmacie*
LAAC	*Long-Acting AntiCholinergic*
LABA	*Long-Acting Beta$_2$-Agonist*
MARS-5	*Medication Adherence Report Scale*
MAI	*Medication Appropriateness Index*
MDI	*Metered Dose Inhaler*
mMRC	*modified Medical Research Council*
MMSE	*Mini-Mental State Examination*
MRA	*Medication Refill Adherence*
NIHDI	*National Institute for Health and Disability Insurance*
NORGEP	*Norwegian General Practice*
NSAID	*Non-Steroidal Anti Inflammatory Drug*
OTC	*Over-The-Counter*
PHARMACOP	*Pharmaceutical Care in COPD*
PIP	*Potentially Inappropriate Prescribing*
pMDI	*pressurized Metered Dose Inhaler*
PPI	*Proton Pump Inhibitor*
PPO	*Potential Prescribing Omission*
PPV	*Positive Predictive Value*
PRISMA	*Preferred Reporting Items for Systematic Reviews and Meta-Analyses*
PY	*Patient Years*
RAAS	*Renin-Angiotensin-Aldosteron System*
RAND/UCLA	*Research and Development/University of California, Los Angeles*
RCT	*Randomized Controlled Trial*

ROC	*Receiver Operating Characteristic*
SAAC	*Short-Acting AntiCholinergic*
SABA	*Short-Acting Beta$_2$-Agonist*
SD	*Standard Deviation*
SNRI	*Serotonin and Noradrenalin Reuptake Inhibitor*
SQI	*Swedish Quality Indicators*
SRHQ	*Self-Rated Health Quality*
SSPF	*Société Scientifique des Pharmaciens Francophones*
SSRI	*Selective Serotonin Reuptake Inhibitor*
START	*Screening Tool to Alert doctors to Right Treatment*
STOPP	*Screening Tool of Older Persons' potentially inappropriate Prescriptions*
STROBE	*STrengthening the Reporting of OBservational studies in Epidemiology*
SUS	*System Usability Scale*
TMP/SMX	*Trimetoprim/Sulfamethoxazol*
USA	*United States of America*
VAS	*Visual Analogue Scale*
Vit D	*Vitamine D*
VKA	*Vitamine K Antagonist*
WHO	*World Health Organization*

Chapter 1

General introduction

1. THE EVOLVING ROLE OF THE COMMUNITY PHARMACIST

1.1. Professional activities of the community pharmacist

In 1994, the World Health Organization (WHO) presented a position paper[1] about the role of the pharmacist in the healthcare system. Until then, the professional activities of the community pharmacist had mainly been limited to the oversight of the supply of medicines, both prescription and non-prescription. In addition, community pharmacists manufactured medicines on a small-scale, often through extemporaneous preparations.

The complexity of medication use, as well as the risk for Drug Related Problems (DRP), has however increased during the last decades. Accordingly, the role of the community pharmacist has become broader, resulting in more care-related activities. For example, the community pharmacist's role now often includes counselling of patients at the time of dispensing prescription and non-prescription medication, next to the provision of drug-related information to patients, the general public or other healthcare professionals. Additionally, the community pharmacist carries out a range of other professional activities (Table 1.1).

Table 1.1: Current main professional activities of the community pharmacist (adopted and adapted from [1])

Essential activities of the community pharmacist	
Processing of prescription	The pharmacist verifies the legality, safety and appropriateness of the prescription order, checks the patient medication record, ensures that the quantities of medication are accurate and decides whether the medication should be handed to the patient, with appropriate counselling.
Care of patients or clinical pharmacy	The pharmacist collects and integrates information about the patient's drug history, clarifies the patient's understanding of the intended dosage regimen and method of administration and advises the patient of drug-related precautions. Additionally, the pharmacist monitors and evaluates the therapeutic response.
Monitoring of drug utilization	The pharmacist participates in monitoring drugs utilizations, through for example, research projects and the tracking of adverse drug reactions.
Responding to symptoms of minor ailments	Pharmacists respond to requests from patients for advice on a variety of symptoms and, when appropriate, refers the inquiries to a medical practitioner. If the symptoms relate to a self-limiting minor ailment, the pharmacist can supply a non-prescription medicine, together with advice. Alternatively, the pharmacist may give advice without supplying medicines.
Health promotion	The pharmacist takes part in health promotion campaigns, both locally and nationally, on a wide range of health-related topics and particularly, on drug-related topics.
Extemporaneous preparation and small-scale manufacture of medicines	Pharmacists prepare medicines, enabling them to adapt the formulation of a medicine to the needs of an individual patient.
Optional activities of the community pharmacist	
Traditional and alternative medicines	Pharmacists can be authorized to dispense traditional medicines as well as homeopathic prescriptions.
Domiciliary services	The pharmacist can provide both an advisory and a supply service to residential homes for older patients and other long-term patients.
Informing healthcare professionals and the public	The pharmacist can compile and maintain information on all medicines, and – particularly on newly-introduced medicines – provide this information as necessary to other healthcare professionals and to patients. They also can provide consulting services regarding the rational use of drugs, to physicians and members of the public.
Agricultural and veterinary practice	Pharmacists can supply animal medicines and medicated animal feeds

1.2. Pharmaceutical care

In the early nineties of the 20th century, a large part of the pharmacists' professional tasks, besides the mere administrative ones, were merged under the term "pharmaceutical care"[2]. Later, in 2012 the European Directorate for the Quality of Medicines & HealthCare (EDQM) published a document "Pharmaceutical Care – Policies and Practices for a Safer, More Responsible and cost-effective Health System"[3], outlining a European definition for pharmaceutical care:

> *"Pharmaceutical care involves the process through which a pharmacist co-operates with a patient and other professionals in designing, implementing and monitoring a therapeutic plan that will produce specific therapeutic outcomes for the patient.[3]"*

The delivery of pharmaceutical care therefore includes the identification, resolving and prevention of both potential and actual DRPs. DRPs include all events or circumstances that interfere with the patient experiencing the optimal outcome of medical care[2]. For example, a DRP might include inappropriate prescribing of medication (e.g. inappropriate dosing), but might also include inappropriate delivery (e.g. dispensing errors) or inappropriate patient behaviour (e.g. nonadherence) (Table 1.2). In summary, providing pharmaceutical care contributes to the optimisation of outcomes from medicines and to the prevention of harm from their inappropriate use[3].

Table 1.2: Overview of different types of drug related problems (Based on [4 5])

Inappropriate prescribing
Overuse
Therapy for an indication which is no (longer) present
Combination therapy where monotherapy is sufficient
Pharmacotherapy for treatment of side effects of other drugs ('prescribing cascade')
Underuse
Not treating present medical condition
Omission of prophylactic therapy
Misuse
Wrong choice of drug (formulation)
- *Drug with better effectiveness or with lower risk available*
- *Functional capacity of the patient does not allow use of the drug*
- *Suboptimal formulation*
Dosing problem
- *Dose too high or too low*
- *Suboptimal dosing scheme*
Presence of or higher risk for adverse drug events
- *Adverse drug events (type 1 or 2)*
- *Contra-indicated drug ('Drug-Disease Interaction' (DDisI))*
- *Interaction with other drug ('Drug-Drug Interaction' (DDI))*
- *Interaction with food*
Inappropriate dispensing
Wrong drug dispensed
Insufficient or inadequate information provided during drug dispensing
Overlooking of practical problems (opening package, swallowing problems, etc.)
Inappropriate patient behaviour
Not following user instructions
Medication nonadherence
Inappropriate monitoring and reporting
Insufficient or no follow-up of medication adherence
Insufficient or no follow-up of lab values or clinical effect after start of some drugs
Not discussing or reporting side-effect with/to the treating physician.

1.3. Pharmaceutical care in Belgium

In 2009, the Belgian government voted a new Royal Decree, which legally outlines sound pharmaceutical practices for Belgian community pharmacists[6]. Pharmaceutical care became a major topic in the task description of the community pharmacist and was subdivided into '*basic* pharmaceutical care' and '*advanced* pharmaceutical care'[6].

Basic pharmaceutical care starts with the validation of each patient question. This includes ensuring sufficient information is obtained to assess a health-related problem. Consequently, a product is dispensed, advice is given or the dispensing of a product is refused. In any case, the community pharmacist stays within the boundaries of the profession and refers to a physician when needed. Second, the community pharmacist provides oral or written information and advice, appropriate to the patient's need. The information can be self-contained, e.g. self-management strategies, or linked to the dispensing of a product, e.g. dosing regimen. The goal is to increase the quality of life of the patient and to provide him or her with sufficient material to make an informed decision. Third, a patient record is set up at the pharmacy. At a minimum, this record contains contact data of the patient and his or her general practitioner, supplemented with all dispensing data. Optionally, details about delivered pharmaceutical care or personal data can be registered, as long as such details are useful in the light of the pharmacist's job function. Finally, the community pharmacist provides a general medication counselling, or when appropriate, he or she may propose advanced pharmaceutical care.

According to the Royal Decree, counselling in *basic* pharmaceutical care is therefore more general and medication-centred. A*dvanced* pharmaceutical care counselling on the other hand, is individually-adapted and patient-centred. It is meant for patients with special pathologies, multi-morbidity or poor medication adherence. The reason to proceed to advanced pharmaceutical care should be well-motivated and thoroughly documented in the patient's record. Additionally, the patient has to give his consent to this level of counselling. This is needed as advanced pharmaceutical care includes a significant role for the patient, requiring frequent visits to the pharmacy for the purpose of monitoring his or her expectations as well as participation in the development of a feasible treatment plan. When necessary, advanced pharmaceutical care can be expanded with robotic unit dose-dispensing based on a weekly validated medication chart. Advanced pharmaceutical care services are often referred to as *cognitive pharmacy services.*

For both basic and advanced pharmaceutical care, but especially for the latter, there are two essential requirements: (1) co-operation with the patient and (2) co-operation with other healthcare professions. The first emphasizes the importance of involving the patient in his therapy – currently referred to as 'patient-centred care' – and the second, underlining the role of multidisciplinary healthcare teams.

1.4. Patient-centred care

Putting the patient in the centre of his or her health care management, is what *patient-centred care* is all about[7 8]. In practice, this concept seeks to focus all medical attention on the individual patient's needs and concerns, rather than on the aspects related to the healthcare provider or the diagnosis. Patient-centred care requires that all healthcare providers enhance the patient's participation and cooperation to ensure the best possible outcomes[3].

Another catchall term for treatment plans that encompass patient-level characteristics, is *personalized medicine*[9]. This holistic approach has often been applied on an ad-hoc basis. More recently, however, algorithmic approaches are being developed. Such approaches are called *adaptive treatment strategies* or *dynamic treatment regimens*[9] and denote that the treatment is adapted to evolving patient characteristics.

With respect to the community pharmacist as a healthcare provider, a fundamental prerequisite for effective delivery of pharmaceutical care in this patient-centred context must be the pharmacist's mutually-beneficial relationship with the patient. In such a relationship, the patient grants authority to the community pharmacist, who in turn provides professional competences and commitment[1]. The community pharmacist can consequently actively involve the patient in his or her pharmacotherapy. This involvement could positively impact the patient's motivation, his or her medication adherence, and thus, the long-term effectiveness of his or her pharmacotherapy[10].

1.5. The community pharmacist as part of a multidisciplinary healthcare team

With the patient at the centre of his or her care, all involved healthcare providers should ideally co-operate as a multidisciplinary team to provide the safest and most effective pharmacotherapy for the patient. A number of different professions may participate in such a healthcare team, e.g. pharmacists, physicians, physiologists, dieticians, nurses, etc. It is essential that all these healthcare professions meet as equals to bring different knowledge, needs and concerns together, while none asserting a position of superiority[7]. In this way, healthcare teams can establish common approaches to the choice of treatment plan and increase the quality of the delivered healthcare[7 11 12].

Any healthcare team must be concerned with the use of medicines, and thus should include a pharmacist[1]. A community pharmacist is ideally placed to take part in the primary healthcare team, as he sees the patients on a regular basis and maintains communication with various healthcare workers. The community pharmacist can be consulted for typical, more practical medication-related questions, such as drug modalities and dosing regimens, as well as pharmacotherapeutic issues.

1.6. The community pharmacist makes a difference

During the last decades, the community pharmacy field has initiated extensive research on a wide range of subjects. This research shows that the involvement of a community pharmacist in patient care can make a difference. Considering cognitive pharmacy services in general, multiple programs can be identified across Canada, the United States, Europe and Australia[13]. Such programs range in complexity from emergency contraception counselling and vaccination programmes to minor ailment schemes and full clinical medication review[13 14].

A determination of the effectiveness and cost-effectiveness of advanced pharmaceutical care is challenging because of variations in healthcare settings, the populations studied and the outcome data measured[15-17]. Furthermore, performed interventions are often inadequately described or vary widely. Nevertheless, there is some consistency in concluding that falls and hospitalizations might be reduced with modest cost savings[15 18 19]. Also, significant results favouring pharmacist interventions were found for specific health outcomes such as blood pressure, blood glucose control, etc[19]. No studies reported a benefit in terms of mortality, mental capacity or activities of daily living[15 18].

It can be concluded that cognitive pharmacy services are probably of value and may be cost-effective, with estimated returns on investment ranging from $1.30 to $26 per dollar spent[13 16 20].

2. OPTIMIZATION OF PHARMACEUTICAL CARE FOR SPECIFIC PATIENT POPULATIONS AS THE MAIN GOAL OF THIS THESIS

Optimizing pharmaceutical care, especially for chronic care patients and patients with difficult medication schemata, has a great potential to improve their treatments and overall cost savings. These groups consume a disproportionate share of health care expenditures, including pharmaceuticals. Their pharmacological needs require access to a broad range of medications and an individualized approach to care. The ultimate goal is to ensure that these people derive maximum benefits from their drug therapy[21].

As the number of chronic care patients and patients with difficult medication schemata is increasing, it would be unfortunate that the added value of a community pharmacist's clinical input is not maximally utilized. These patients require surely a patient-centred and multidisciplinary care approach. Therefore, in this thesis we report on the possibilities for and effectiveness of community pharmacist interventions for two specific patient groups; (1) older patients with polypharmacy and (2) patients with Chronic Obstructive Pulmonary Disease (COPD) as an example of chronic disease. The choice for both groups was deliberate as they are both increasingly present in the ambulatory setting and place a significant burden on the healthcare system. Additionally, this way, we can validate these new role of the community pharmacist.

2.1. Medication review for older patients with polypharmacy

2.1.1. The population

Over the past years, the proportion of the European and Belgian population aged 65 years and over has been increasing[22]. Recent numbers of the European Commission Eurostat group show that almost 20% of the total population is 65 years or older[22], representing about 2,200,000 people in Belgium. When prescribing medication for older patients, we have to take into account age-related changes in pharmacokinetics and pharmacodynamics. Additionally, because of co-morbidities they are often prescribed multiple drugs (with polypharmacy defined as 5 or more different drugs). Both older age and polypharmacy increase the risk for Adverse Drug Events[1] (ADEs) significantly[23]. On its turn, this leads to increased morbidity and mortality, hereby putting a high (financial) burden on the healthcare system[23-26].

A recent systematic review reported an ADE prevalence up to 23% with preventability rates up to 53% for older adults in ambulatory care[23]. Many factors contribute to the presence of ADEs, such as number of drugs and impaired renal function[27]. As well, Potentially Inappropriate Prescribing (PIP) has shown to be a main contributor[28], and is thus a potential, though indirect, cause for increased social and economic burden[29 30].

[1] An ADE is defined by the World Health Organization as a *"medical occurrence, temporally associated with the use of a medicinal product, but not necessarily causally related"*

In 2012 Opondo et al. published a systematic review on PIP in the primary care setting[31]. An overall median PIP rate of 19.1% (range: 2.9% – 38.5%), i.e. the percentage of older patients with at least one PIP, was described. This high prevalence represents an important opportunity to improve the prescribing quality in the primary care setting. The community pharmacist is ideally placed to engage in this process because of his medication-specific knowledge and because of the availability of an electronic dispensing record in the pharmacy, including dispensed over-the-counter (OTC) medication.

The complexity of the matter however, makes it unlikely that a single intervention at one point in the medication management process will be sufficient to tackle this issue. Literature showed that multidisciplinary interventions including education and based on a systematic screening method are the most efficient for resolving and preventing all types of PIP[32-34].

2.1.2. Medication Review

Reviewing a patient's medication use can reveal potential DRPs (Table 1.2). These can be rather practical (e.g. difficulties with splitting tablets), or mainly therapeutic (e.g. dosing error). Medication reviews can be performed by any healthcare worker sufficiently trained in pharmacotherapy; however, most often, they are initiated by a (community) pharmacist. The pharmacist can review the medication use during the time of dispensing or on a regular basis, irrespective of the drug dispensing[4 31].

2.1.2.1. Medication review during dispensing

Reviewing a patient's medication at the time of dispensing has the advantage that it is quick and performed together with every medication dispensing or medication change. The limited amount of time available on the other hand implies that the review is restricted to a number of (automatized) checks, such as for interactions and contra-indications. These automatized checks are placed under the term Computerized Decision Support Systems (CDSS). CDSS appears to reduce a range of medication errors, most of them safety-related[35 36].

A systematic review evaluating the impact of pharmacy CDSS on prescribing, clinical and patient outcomes concluded that two-thirds of included Randomized Controlled Trials (RCT) showed statistically significant results in favour of CDSS on the majority of outcomes[36]. This systematic review included both RCTs that evaluated the quality of the medicines use (e.g. checking secondary prevention medication) and RCTs that evaluated drug safety and monitoring (e.g. interactions).

More recently, the PINCER-trial showed that a pharmacist-led information technology intervention, composed of feedback and educational outreach, decreased the number of patients that had at least one prescription problem or at least one monitoring problem, both after 6 and 12 months of follow-up[35]. Another RCT, recently performed in general practitioners' offices, additionally showed that CDSS led to significant improvement in appropriate medication adjustments for patients with impaired renal function, a pharmacovigilance task as well perfectly suitable for the community pharmacist[37].

2.1.2.2. Medication review on a regular basis, irrespective of dispensing

Another possibility for the community pharmacist is to screen a patient's medication on a regular basis, irrespective of dispensing. The main goal of this process is to detect DRPs, mainly focusing on PIP, including overuse, underuse and misuse of medicines (see above, Table 1.2). Detection of PIP can be very specific, for example focused on the discontinuation of benzodiazepines[38], or be very general, incorporating all aspects of PIP[39]. Three types of medication review exist: simple, intermediate or advanced (Table 1.3)[40].

Table 1.3: Types of Medication Review[40]

	Type 1: Simple	Type 2a: Intermediate	Type 2b: Intermediate	Type 3: Advanced
Data collection				
Medication history	V	V	V	V
Patient	-	V	-	V
Patient's medical records	-	-	V	V
The review				
Drug-Drug Interactions	V	V	V	V
Duplication	V	V	V	V
Drug-Disease interactions	Partly	Partly	V	V
Dosage Check	Partly	Partly	V	V
Adherence evaluation	Partly	V	Partly	V
Type of screening tool that can be used to support the medication review				
Explicit screening tool	V	V	V	V
Implicit screening tool	-	Partly	Partly	V

To support the medication review, two types of screening tools can be used: implicit or explicit tools. Implicit tools such as the (adapted) Medication Appropriateness Index (MAI – Appendix 1.1) judge the appropriateness of therapy using clinical information of an individual patient and patient preferences [39 41]. They have the advantage to be holistic, taking all patient factors into account. On the other hand, they are very time-consuming and require the availability of all clinical patient data. Explicit tools, such as the STOPP/START-criteria[21] (Appendix 1.2) or the Beers-criteria[22] (Appendix 1.3), involve lists of drugs to be avoided or describe appropriate prescribing indicators. These instruments are most often used by general practitioners, specialists or hospital pharmacists. They are straightforward, quick to apply and can be fully automatized. On the other hand, they do not take into account all patient factors in evaluating the pharmacotherapy, e.g. diagnoses, patient preferences or earlier attempts to tackle PIP. An overview of existing explicit, implicit and combined methods is given in Appendix 1.4.

Two recent systematic reviews evaluated the effectiveness of pharmacist-led medication reviews[19] [33]. The first, by Meid et al[33], showed that medication review can significantly reduce the number of omitted drugs per patient. Another meta-analysis on medication review performed by pharmacists[19] showed that clinical medication review positively influenced clinical outcomes (e.g. blood pressure) and additionally significantly reduced hospitalization.

2.2. Counselling chronic diseases in the community pharmacy, an example for COPD

2.2.1. The Population

As with older patients, the proportion of patients with COPD is increasing. In Belgium and in the Netherlands, the prevalence of COPD is currently estimated to be about 2 to 3%, which increased since the early nineties[42] [43]. A systematic review published in 2012, reported that the prevalence of COPD ranged from 0.2%–37%, but prevalence varied widely across countries, populations, COPD diagnosis and classification methods[44]. Equal to the prevalence, the incidence of COPD is dependent on age and gender. Based on data of the Rotterdam Study[45], the incidence of COPD is estimated to be about 9.2/1000 person-years (PY), with a higher incidence for men (14/1000 PY) compared to women (6/1000 PY) in a cohort of patients ≥55 year.

COPD is a disease with high mortality rates. Chapman and colleagues[46] projected that from 1990 to 2020, COPD would move from the sixth- to the third-most-common cause of death worldwide, with a mortality rate from 3–111 deaths per 100,000 population[44], confirmed by WHO data of 2012[47]. Additionally, they projected a rise from fourth to third place in terms of morbidity[46].

Although COPD can be managed well with both non-pharmacological and pharmacological options[48], adherence to therapy is often suboptimal[49]. Adherence rates reported in asthma and COPD studies vary largely with rates between 22% and 78%, depending on the population assessed and the methods of measure[50]. Considering solely COPD, adherence rates are mainly estimated to be about 50%[49]. An observational study performed in Belgian community pharmacies detected underadherence in 48% of patients and overadherence in 5% of patients[51]. Suboptimal adherence has been associated with higher morbidity and healthcare use (i.e., general practitioner (GP) visits, emergency room visits and hospitalizations) due to more frequent episodes of worsening of symptoms – exacerbations – in nonadherent patients[52-54]. Similarly, an association with increased mortality has been reported[52] [54]. Consequently, treatment of COPD and its exacerbations contribute substantially to overall healthcare costs. In the European Union the costs approximately count for 6% of the total European healthcare budget[48].

Additionally, as COPD is a respiratory disease, a great deal of the medication is administered locally, through inhalation therapy. This specific administration route leads to other, more practical issues. The correct handling of inhalation devices seems to be problematic for many patients with COPD. Mehuys et al reported that 21% of patients with COPD made major inhalation errors, such as failing to remove the inhaler cap and/or failing to shake the inhaler[51]. However, research showed that inhaler mishandling remains common and is associated with reduced disease control[55]. Studies, researching the optimization of inhalation technique suggest that repeated training is necessary as positive effects disappear over time[56]. This would require long-term and continuous monitoring of patients with COPD.

Community pharmacists are well-placed to engage in COPD monitoring programs due to their frequent patient contacts upon prescription refill, and their specific medication-related expertise. Furthermore, research showed that mere self-management programs are insufficient to reduce severe exacerbations[57]. Consequently, monitoring and optimizing COPD maintenance therapy in the community pharmacy setting could be a good balance between unsupervised self-management and extensive hospital monitoring [58 59].

2.2.2. Chronic Disease Counselling

Medication or disease counselling can ensure that people derive maximum benefits from drug therapy by individualizing care plans, optimizing the communication between professionals, disease knowledge and self-care[21]. This counselling can take place, either at the time of diagnosis and start-up of chronic therapy or, later on, evaluating the effectiveness of and adherence to the chronic therapy.

2.2.2.1. Counselling start-up of chronic therapy

Starting new medication is a particularly vulnerable moment for patients who are faced with a possible new diagnosis, a new treatment plan, potential side effects, and the need to incorporate the dosing schedule into their daily routine. A study, initiated in pharmacies, showed that face-to-face counselling at start of statin therapy lead to greater medication adherence and persistence than in a comparison group (Figure 1.1)[60]. Another study, evaluating a pharmacy service consisting of a 15-min face-to-face interview and a 10-min telephone follow-up interview for patients that are initiating any type of chronic therapy, showed that patients were satisfied with the pharmacy service and reported that it helped them getting a good start with the new medication[61]. Finally, a large RCT, performed in the United Kingdom, showed that 10 weeks after receiving a new medicine counselling from the community pharmacists, patients were more likely to be taking their medicine, compared with those who received the normal service from their pharmacist[62].

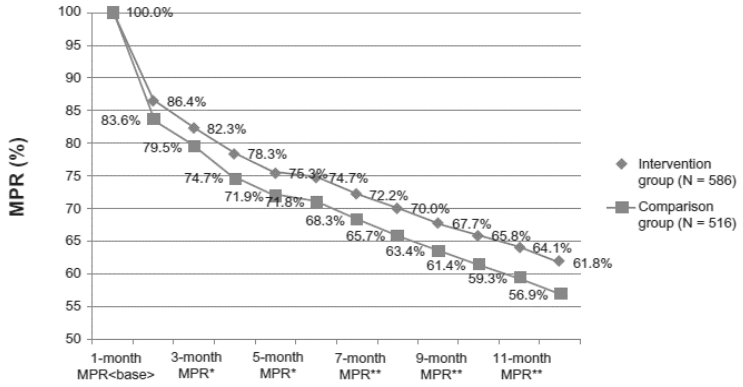

***Figure 1.1**: Adherence to statin therapy, from initiation to 12-month follow-up (Adopted from Taitel et al[60])*
***MPR**: Medication Possession Ratio*

2.2.2.2. Long-term counselling of chronic therapy

After starting new medication, long-term counselling of the patient is necessary. Not only to optimize adherence (see Figure 1.1), but also to detect ADEs (e.g. falls or dizziness), to assess risk factors (e.g. functional status) or evaluate risk/benefit ratios (e.g. potassium sparing diuretic in heart failure).

This counselling can partially be executed by a community pharmacist. Several trials have evaluated the effectiveness of community pharmacists' interventions for chronic diseases. For example, an RCT by Wu et al[63] showed that in patients receiving polypharmacy, periodic telephone counselling by a pharmacist improved adherence and reduced mortality[63]. This conversation included the pharmacist asking about the patient's treatment regimens, clarified any misconceptions, explained the nature of any side effects, reminded patients of their next clinic appointment, and reinforced the importance of compliance with treatment and relevant aspects of self-care, such as diet, exercise, and self-monitoring[63]. A systematic review specifically researching community pharmacists' interventions on adherence to chronic medication concluded more ambivalently[17]. Despite the fact that the majority of the included studies showed significant adherence improvement at one or more time points[17], there was still a need for well-designed and well-conducted studies on the topic.

REFERENCES

1. *World Health Organization. The role of the pharmacist in the health care system, 1994.*
2. *Hepler CD, Strand LM. Opportunities and responsibilities in pharmaceutical care. Am J Hosp Pharm 1990;**47**(3):533-43.*
3. *European Directorate for the Quality of Medicines & HealthCare. Pharmaceutical Care - Policies and practices for a safer, more responsible and cost-effective health system, 2012.*
4. *Spinewine A, Schmader KE, Barber N, et al. Appropriate prescribing in elderly people: how well can it be measured and optimised? Lancet 2007;**370**(9582):173-84.*
5. *Mallet L, Spinewine A, Huang A. The challenge of managing drug interactions in elderly people. The Lancet;**370**(9582):185-91.*
6. *Royal Decree. Belgisch Staatsblad, 21st January 2009.*
7. *Bardes CL. Defining "patient-centered medicine". The New England journal of medicine 2012;**366**(9):782-3.*
8. *Richards T, Coulter A, Wicks P. Time to deliver patient centred care. BMJ (Clinical research ed) 2015;**350**:h530.*
9. *Wallace MP, Moodie EE. Personalizing medicine: a review of adaptive treatment strategies. Pharmacoepidemiol Drug Saf 2014;**23**(6):580-5.*
10. *Willeboordse F, Hugtenburg JG, Schellevis FG, et al. Patient participation in medication reviews is desirable but not evidence-based: a systematic literature review. Br J Clin Pharmacol 2014;**78**(6):1201-16.*
11. *Hartgerink J, Cramm J, Bakker T, et al. The importance of multidisciplinary teamwork and team climate for relational coordination among teams delivering care to older patients. Journal of Advanced Nursing 2014;**70**(4):791-9.*
12. *Kwint HF, Bermingham L, Faber A, et al. The relationship between the extent of collaboration of general practitioners and pharmacists and the implementation of recommendations arising from medication review: a systematic review. Drugs Aging 2013;**30**(2):91-102.*
13. *Houle SKD, Grindrod KA, Chatterley T, et al. Paying pharmacists for patient care: A systematic review of remunerated pharmacy clinical care services. Canadian pharmacists journal : CPJ = Revue des pharmaciens du Canada : RPC 2014;**147**(4):209-32.*
14. *Puspitasari HP, Aslani P, Krass I. A review of counseling practices on prescription medicines in community pharmacies. Research in social & administrative pharmacy : RSAP 2009;**5**(3):197-210.*
15. *Zermansky AG, Silcock J. Is medication review by primary-care pharmacists for older people cost effective?: a narrative review of the literature, focusing on costs and benefits. PharmacoEconomics 2009;**27**(1):11-24.*
16. *Touchette DR, Doloresco F, Suda KJ, et al. Economic evaluations of clinical pharmacy services: 2006-2010. Pharmacotherapy 2014;**34**(8):771-93.*
17. *Van Wijk BL, Klungel OH, Heerdink ER, et al. Effectiveness of interventions by community pharmacists to improve patient adherence to chronic medication: a systematic review. The Annals of pharmacotherapy 2005;**39**(2):319-28.*
18. *Chinthammit C, Armstrong EP, Boesen K, et al. Cost-effectiveness of comprehensive medication reviews versus noncomprehensive medication review interventions and subsequent successful medication changes in a Medicare Part D population. Journal of managed care & specialty pharmacy 2015;**21**(5):381-9.*
19. *Hatah E, Braund R, Tordoff J, et al. A systematic review and meta-analysis of pharmacist-led fee-for-services medication review. Br J Clin Pharmacol 2014;**77**(1):102-15.*
20. *Perez A, Doloresco F, Hoffman JM, et al. ACCP: economic evaluations of clinical pharmacy services: 2001-2005. Pharmacotherapy 2009;**29**(1):128.*
21. *Okumura LM, Rotta I, Correr CJ. Assessment of pharmacist-led patient counseling in randomized controlled trials: a systematic review. International journal of clinical pharmacy 2014;**36**(5):882-91.*
22. *Statistical Office of the European Communities. EUROSTAT: Population data - Proportion of population aged 65 and over. Secondary EUROSTAT: Population data - Proportion of population aged 65 and over. http://ec.europa.eu/eurostat/tgm/table.do?tab=table&init=1&language=en&pcode=tps00028&plugin=1.*
23. *Tache SV, Soennichsen A, Ashcroft DM. Prevalence of Adverse Drug Events in Ambulatory Care: A Systematic Review. Annals of Pharmacotherapy 2011;**45**(7-8):977-89.*
24. *Sikdar KC, Dowden J, Alaghehbandan R, et al. Adverse Drug Reactions in Elderly Hospitalized Patients: A 12-Year Population-Based Retrospective Cohort Study. Annals of Pharmacotherapy 2012;**46**(7-8):960-71.*
25. *Gallagher P, Barry P, O'Mahony D. Inappropriate prescribing in the elderly. J Clin Pharm Ther 2007;**32**(2):113-21.*
26. *Al Hamid A, Ghaleb M, Aljadhey H, et al. A systematic review of hospitalization resulting from medicine-related problems in adult patients. Br J Clin Pharmacol 2014;**78**(2):202-17.*
27. *Saedder EA, Lisby M, Nielsen LP, et al. Number of drugs most frequently found to be independent risk factors for serious adverse reactions: a systematic literature review. Br J Clin Pharmacol 2015;**80**(4):808-17.*
28. *Passarelli MCG, Jacob W, Figueras A. Adverse drug reactions in an elderly hospitalised population - Inappropriate prescription is a leading cause. Drugs & Aging 2005;**22**(9):767-77.*
29. *Pammolli F, Riccaboni M, Magazzini L. The sustainability of European health care systems: beyond income and aging. Eur J Health Econ 2012;**13**(5):623-34.*
30. *Fu AZ, Jiang JZ, Reeves JH, et al. Potentially inappropriate medication use and healthcare expenditures in the US community-dwelling elderly. Med Care 2007;**45**(5):472-76.*
31. *Opondo D, Eslami S, Visscher S, et al. Inappropriateness of Medication Prescriptions to Elderly Patients in the Primary Care Setting: A Systematic Review. PloS one 2012;**7**(8).*
32. *Kaur S, Mitchell G, Vitetta L, et al. Interventions that can Reduce Inappropriate Prescribing in the Elderly A Systematic Review. Drugs & aging 2009;**26**(12):1013-28.*
33. *Meid AD, Lampert A, Burnett A, et al. The impact of pharmaceutical care interventions for medication underuse in older people: a systematic review and meta-analysis. Br J Clin Pharmacol 2015.*
34. *Cullinan S, Fleming A, O'Mahony D, et al. Doctors' perspectives on the barriers to appropriate prescribing in older hospitalized patients: a qualitative study. Br J Clin Pharmacol 2015;**79**(5):860-9.*
35. *Avery AJ, Rodgers S, Cantrill JA, et al. A pharmacist-led information technology intervention for medication errors (PINCER): a multicentre, cluster randomised, controlled trial and cost-effectiveness analysis. Lancet 2012;**379**(9823):1310-9.*
36. *Robertson J, Walkom E, Pearson SA, et al. The impact of pharmacy computerised clinical decision support on prescribing, clinical and patient outcomes: a systematic review of the literature. The International journal of pharmacy practice 2010;**18**(2):69-87.*

37. *Awdishu L, Coates CR, Lyddane A, et al. The impact of real-time alerting on appropriate prescribing in kidney disease: a cluster randomized controlled trial. Journal of the American Medical Informatics Association : JAMIA 2015.*
38. *Tannenbaum C, Martin P, Tamblyn R, et al. Reduction of inappropriate benzodiazepine prescriptions among older adults through direct patient education: the EMPOWER cluster randomized trial. JAMA internal medicine 2014;**174**(6):890-8.*
39. *Somers A, Mallet L, van der Cammen T, et al. Applicability of an adapted medication appropriateness index for detection of drug-related problems in geriatric inpatients. The American journal of geriatric pharmacotherapy 2012;**10**(2):101-9.*
40. *Pharmaceutical Care Network Europe. Report of the 2012 Medication Review Symposium 2012.*
41. *Hanlon JT, Schmader KE, Samsa GP, et al. A method for assessing drug therapy appropriateness. J Clin Epidemiol 1992;**45**(10):1045-51.*
42. *Nationaal Kompas Volksgezondheid. Hoe vaak komt COPD voor en hoeveel mensen sterven eraan? The Netherlands, 2011.*
43. *Agentschap Zorg & Gezondheid. Chronische aandoeningen: incidentie en prevalentie, 2014.*
44. *Rycroft CE, Heyes A, Lanza L, et al. Epidemiology of chronic obstructive pulmonary disease: a literature review. International journal of chronic obstructive pulmonary disease 2012;**7**:457-94.*
45. *van Durme YM, Verhamme KM, Stijnen T, et al. Prevalence, incidence, and lifetime risk for the development of COPD in the elderly: the Rotterdam study. Chest 2009;**135**(2):368-77.*
46. *Chapman KR, Mannino DM, Soriano JB, et al. Epidemiology and costs of chronic obstructive pulmonary disease. The European respiratory journal 2006;**27**(1):188-207.*
47. *World Health Organization. Fact sheet N°310 - The top 10 causes of death, 2014.*
48. *Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: Available at: http://www.goldcopd.org/, Global Initiative for chronic Obstructive Lung Disease 2011.*
49. *Bourbeau J, Bartlett SJ. Patient adherence in COPD. Thorax 2008;**63**(9):831-8.*
50. *Makela MJ, Backer V, Hedegaard M, et al. Adherence to inhaled therapies, health outcomes and costs in patients with asthma and COPD. Respir Med 2013;**107**(10):1481-90.*
51. *Mehuys E, Boussery K, Adriaens E, et al. COPD management in primary care: an observational, community pharmacy-based study. The Annals of pharmacotherapy 2010;**44**(2):257-66.*
52. *Vestbo J, Anderson JA, Calverley PMA, et al. Adherence to inhaled therapy, mortality and hospital admission in COPD. Thorax 2009;**64**(11):939-43.*
53. *Toy EL, Beaulieu NU, McHale JM, et al. Treatment of COPD: Relationships between daily dosing frequency, adherence, resource use, and costs. Respir Med 2011;**105**(3):435-41.*
54. *Butler RJ, Davis TK, Johnson WG, et al. Effects of Nonadherence With Prescription Drugs Among Older Adults. Am J Manag Care 2011;**17**(2):153-60.*
55. *Melani AS, Bonavia M, Cilenti V, et al. Inhaler mishandling remains common in real life and is associated with reduced disease control. Respir Med 2011;**105**(6):930-8.*
56. *Basheti IA, Qunaibi EA, Hamadi SA, et al. Inhaler technique training and health-care professionals: effective long-term solution for a current problem. Respiratory care 2014;**59**(11):1716-25.*
57. *Fan VS, Gaziano JM, Lew R, et al. A Comprehensive Care Management Program to Prevent Chronic Obstructive Pulmonary Disease Hospitalizations A Randomized, Controlled Trial. Ann Intern Med 2012;**156**(10):673-U46.*
58. *Brown P, Bluml BM, Kritzler R, et al. White paper on expanding the role of pharmacists in chronic obstructive pulmonary disease. J Am Pharm Assoc 2011;**51**(2):203-11.*
59. *Weinberger M, Murray MD, Marrero DG, et al. Effectiveness of pharmacist care for patients with reactive airways disease - A randomized controlled trial. JAMA-J Am Med Assoc 2002;**288**(13):1594-602.*
60. *Taitel M, Jiang J, Rudkin K, et al. The impact of pharmacist face-to-face counseling to improve medication adherence among patients initiating statin therapy. Patient preference and adherence 2012;**6**:323-9.*
61. *Kaae S, Dam P, Rossing C. Evaluation of a pharmacy service helping patients to get a good start in taking their new medications for chronic diseases. Research in social & administrative pharmacy : RSAP 2015.*
62. *Boyd M, Waring J, Barber N, et al. Protocol for the New Medicine Service Study: a randomized controlled trial and economic evaluation with qualitative appraisal comparing the effectiveness and cost effectiveness of the New Medicine Service in community pharmacies in England. Trials 2013;**14**:411.*
63. *Wu JYF, Leung WYS, Chang S, et al. Effectiveness of telephone counselling by a pharmacist in reducing mortality in patients receiving polypharmacy: randomised controlled trial. BMJ (Clinical research ed) 2006;**333**(7567):522.*

APPENDIX 1.1: THE MEDICATION APPROPRIATENESS INDEX

Table 1. Medication Appropriateness Index*

To assess the appropriateness of the drug, please answer the following questions and circle the applicable score:				
1. Is there an indication for the drug? Comments:	1 Indicated	2	3 Not Indicated	9 DK†
2. Is the medication effective for the condition? Comments:	1 Effective	2	3 Ineffective	9 DK
3. Is the dosage correct? Comments:	1 Correct	2	3 Incorrect	9 DK
4. Are the directions correct? Comments:	1 Correct	2	3 Incorrect	9 DK
5. Are the directions practical? Comments:	1 Practical	2	3 Impractical	9 DK
6. Are there clinically significant drug–drug interactions? Comments:	1 Insignificant	2	3 Significant	9 DK
7. Are there clinically significant drug–disease/condition interactions? Comments:	1 Insignificant	2	3 Significant	9 DK
8. Is there unnecessary duplication with other drug(s)? Comments:	1 Necessary	2	3 Unnecessary	9 DK
9. Is the duration of therapy acceptable? Comments:	1 Acceptable	2	3 Unacceptable	9 DK
10. Is this drug the least expensive alternative compared to others of equal utility? Comments:	1 Least expensive	2	3 Most expensive	9 DK

*Complete instructions in the use of the scale are available upon request.
†Don't know.

APPENDIX 1.2: THE STOPP AND START-CRITERIA

SCREENING TOOL OF OLDER PERSONS' PRESCRIPTIONS (STOPP) VERSION 2.

Section A: Indication of medication

1. Any drug prescribed without an evidence-based clinical indication.
2. Any drug prescribed beyond the recommended duration, where treatment duration is well defined.
3. Any duplicate drug class prescription e.g. two concurrent NSAIDs, SSRIs, loop diuretics, ACE inhibitors, anticoagulants (optimisation of monotherapy within a single drug class should be observed prior to considering a new agent).

Section B: Cardiovascular System

1. Digoxin for heart failure with normal systolic ventricular function (no clear evidence of benefit)
2. Verapamil or diltiazem with NYHA Class III or IV heart failure (may worsen heart failure).
3. Beta-blocker in combination with verapamil or diltiazem (risk of heart block).
4. Beta blocker with bradycardia (< 50/min), type II heart block or complete heart block (risk of complete heart block, asystole).
5. Amiodarone as first-line antiarrhythmic therapy in supraventricular tachyarrhythmias (higher risk of side-effects than beta-blockers, digoxin, verapamil or diltiazem)
6. Loop diuretic as first-line treatment for hypertension (safer, more effective alternatives available).
7. Loop diuretic for dependent ankle oedema without clinical, biochemical evidence or radiological evidence of heart failure, liver failure, nephrotic syndrome or renal failure (leg elevation and /or compression hosiery usually more appropriate).
8. Thiazide diuretic with current significant hypokalaemia (i.e. serum K+ < 3.0 mmol/l), hyponatraemia (i.e. serum Na+ < 130 mmol/l) hypercalcaemia (i.e. corrected serum calcium > 2.65 mmol/l) or with a history of gout (hypokalaemia, hyponatraemia, hypercalcaemia and gout can be precipitated by thiazide diuretic)
9. Loop diuretic for treatment of hypertension with concurrent urinary incontinence (may exacerbate incontinence).
10. Centrally-acting antihypertensives (e.g. methyldopa, clonidine, moxonidine, rilmenidine, guanfacine), unless clear intolerance of, or lack of efficacy with, other classes of antihypertensives (centrally-active antihypertensives are generally less well tolerated by older people than younger people)
11. ACE inhibitors or Angiotensin Receptor Blockers in patients with hyperkalaemia.
12. Aldosterone antagonists (e.g. spironolactone, eplerenone) with concurrent potassium- conserving drugs (e.g. ACEI's, ARB's, amiloride, triamterene) without monitoring of serum potassium (risk of dangerous hyperkalaemia i.e. > 6.0 mmol/l – serum K should be monitored regularly, i.e. at least every 6 months).
13. Phosphodiesterase type-5 inhibitors (e.g. sildenafil, tadalafil, vardenafil) in severe heart failure characterised by hypotension i.e. systolic BP < 90 mmHg, or concurrent nitrate therapy for angina (risk of cardiovascular collapse)

Section C: Antiplatelet/Anticoagulant Drugs

1. Long-term aspirin at doses greater than 160mg per day (increased risk of bleeding, no evidence for increased efficacy).
2. Aspirin with a past history of peptic ulcer disease without concomitant PPI (risk of recurrent peptic ulcer).
3. Aspirin, clopidogrel, dipyridamole, vitamin K antagonists, direct thrombin inhibitors or factor Xa inhibitors with concurrent significant bleeding risk, i.e. uncontrolled severe hypertension, bleeding diathesis, recent non-trivial spontaneous bleeding) (high risk of bleeding).
4. Aspirin plus clopidogrel as secondary stroke prevention, unless the patient has a coronary stent(s) inserted in the previous 12 months or concurrent acute coronary syndrome or has a high grade symptomatic carotid arterial stenosis (no evidence of added benefit over clopidogrel monotherapy)
5. Aspirin in combination with vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors in patients with chronic atrial fibrillation (no added benefit from aspirin)
6. Antiplatelet agents with vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors in patients with stable coronary, cerebrovascular or peripheral arterial disease (No added benefit from dual therapy).
7. Ticlopidine in any circumstances (clopidogrel and prasugrel have similar efficacy, stronger evidence and fewer side-effects).
8. Vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors for first deep venous thrombosis without continuing provoking risk factors (e.g. thrombophilia) for > 6 months, (no proven added benefit).
9. Vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors for first pulmonary embolus without continuing provoking risk factors (e.g. thrombophilia) for > 12 months (no proven added benefit).
10. NSAID and vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors in combination (risk of major gastrointestinal bleeding).
11. NSAID with concurrent antiplatelet agent(s) without PPI prophylaxis (increased risk of peptic ulcer disease)

Section D: Central Nervous System and Psychotropic Drugs

1. TriCyclic Antidepressants (TCAs) with dementia, narrow angle glaucoma, cardiac conduction abnormalities, prostatism, or prior history of urinary retention (risk of worsening these conditions).
2. Initiation of TriCyclic Antidepressants (TCAs) as first-line antidepressant treatment (higher risk of adverse drug reactions with TCAs than with SSRIs or SNRIs).

3. Neuroleptics with moderate-marked antimuscarinic/anticholinergic effects (chlorpromazine, clozapine, flupenthixol, fluphenzine, pipothiazine, promazine, zuclopenthixol) with a history of prostatism or previous urinary retention (high risk of urinary retention).
4. Selective serotonin re-uptake inhibitors (SSRI's) with current or recent significant hyponatraemia i.e. serum Na+ < 130 mmol/l (risk of exacerbating or precipitating hyponatraemia).
5. Benzodiazepines for ≥ 4 weeks (no indication for longer treatment; risk of prolonged sedation, confusion, impaired balance, falls, road traffic accidents; all benzodiazepines should be withdrawn gradually if taken for more than 4 weeks as there is a risk of causing a benzodiazepine withdrawal syndrome if stopped abruptly).
6. Antipsychotics (i.e. other than quetiapine or clozapine) in those with parkinsonism or Lewy Body Disease (risk of severe extra-pyramidal symptoms)
7. Anticholinergics/antimuscarinics to treat extra-pyramidal side-effects of neuroleptic medications (risk of anticholinergic toxicity),
8. Anticholinergics/antimuscarinics in patients with delirium or dementia (risk of exacerbation of cognitive impairment).
9. Neuroleptic antipsychotic in patients with behavioural and psychological symptoms of dementia (BPSD) unless symptoms are severe and other non-pharmacological treatments have failed (increased risk of stroke).
10. Neuroleptics as hypnotics, unless sleep disorder is due to psychosis or dementia (risk of confusion, hypotension, extra-pyramidal side effects, falls).
11. Acetylcholinesterase inhibitors with a known history of persistent bradycardia (< 60 beats/min.), heart block or recurrent unexplained syncope or concurrent treatment with drugs that reduce heart rate such as beta-blockers, digoxin, diltiazem, verapamil (risk of cardiac conduction failure, syncope and injury).
12. Phenothiazines as first-line treatment, since safer and more efficacious alternatives exist (phenothiazines are sedative, have significant anti-muscarinic toxicity in older people, with the exception of prochlorperazine for nausea/vomiting/vertigo, chlorpromazine for relief of persistent hiccoughs and levomepromazine as an anti-emetic in palliative care).
13. Levodopa or dopamine agonists for benign essential tremor (no evidence of efficacy)
14. First-generation antihistamines (safer, less toxic antihistamines now widely available).

Section E: Renal System. The following drugs are potentially inappropriate in older people with acute or chronic kidney disease with renal function below particular levels of eGFR (refer to summary of product characteristics datasheets and local formulary guidelines)

1. Digoxin at a long-term dose greater than 125µg/day if eGFR < 30 ml/min/1.73m2 (risk of digoxin toxicity if plasma levels not measured).
2. Direct thrombin inhibitors (e.g. dabigatran) if eGFR < 30 ml/min/1.73m2 (risk of bleeding)
3. Factor Xa inhibitors (e.g. rivaroxaban, apixaban) if eGFR < 15 ml/min/1.73m2 (risk of bleeding)
4. NSAID's if eGFR < 50 ml/min/1.73m2 (risk of deterioration in renal function).
5. Colchicine if eGFR < 10 ml/min/1.73m2 (risk of colchicine toxicity)
6. Metformin if eGFR < 30 ml/min/1.73m2 (risk of lactic acidosis).

Section F: Gastrointestinal System

1. Prochlorperazine or metoclopramide with Parkinsonism (risk of exacerbating Parkinsonian symptoms).
2. PPI for uncomplicated peptic ulcer disease or erosive peptic oesophagitis at full therapeutic dosage for > 8 weeks (dose reduction or earlier discontinuation indicated).
3. Drugs likely to cause constipation (e.g. antimuscarinic/anticholinergic drugs, oral iron, opioids, verapamil, aluminium antacids) in patients with chronic constipation where non- constipating alternatives are available (risk of exacerbation of constipation).
4. Oral elemental iron doses greater than 200 mg daily (e.g. ferrous fumarate> 600 mg/day, ferrous sulphate > 600 mg/day, ferrous gluconate> 1800 mg/day; no evidence of enhanced iron absorption above these doses).

Section G: Respiratory System

1. Theophylline as monotherapy for COPD (safer, more effective alternative; risk of adverse effects due to narrow therapeutic index).
2. Systemic corticosteroids instead of inhaled corticosteroids for maintenance therapy in moderate-severe COPD (unnecessary exposure to long-term side-effects of systemic corticosteroids and effective inhaled therapies are available).
3. Anti-muscarinic bronchodilators (e.g. ipratropium, tiotropium) with a history of narrow angle glaucoma (may exacerbate glaucoma) or bladder outflow obstruction (may cause urinary retention).
4. Non-selective beta-blocker (whether oral or topical for glaucoma) with a history of asthma requiring treatment (risk of increased bronchospasm).
5. Benzodiazepines with acute or chronic respiratory failure i.e. $pO_2 < 8.0$ kPa ± $pCO_2 > 6.5$ kPa (risk of exacerbation of respiratory failure).

Section H: Musculoskeletal System

1. Non-steroidal anti-inflammatory drug (NSAID) other than COX-2 selective agents with history of peptic ulcer disease or gastrointestinal bleeding, unless with concurrent PPI or H2 antagonist (risk of peptic ulcer relapse).
2. NSAID with severe hypertension (risk of exacerbation of hypertension) or severe heart failure (risk of exacerbation of heart failure).

3. Long-term use of NSAID (>3 months) for symptom relief of osteoarthritis pain where paracetamol has not been tried (simple analgesics preferable and usually as effective for pain relief)
4. Long-term corticosteroids (>3 months) as monotherapy for rheumatoid arthrtitis (risk of systemic corticosteroid side-effects).
5. Corticosteroids (other than periodic intra-articular injections for mono-articular pain) for osteoarthritis (risk of systemic corticosteroid side-effects).
6. Long-term NSAID or colchicine (>3 months) for chronic treatment of gout where there is no contraindication to a xanthine-oxidase inhibitor (e.g. allopurinol, febuxostat) (xanthine- oxidase inhibitors are first choice prophylactic drugs in gout).
7. COX-2 selective NSAIDs with concurrent cardiovascular disease (increased risk of myocardial infarction and stroke)
8. NSAID with concurrent corticosteroids without PPI prophylaxis (increased risk of peptic ulcer disease)
9. Oral bisphosphonates in patients with a current or recent history of upper gastrointestinal disease i.e. dysphagia, oesophagitis, gastritis, duodenitis, or peptic ulcer disease, or upper gastrointestinal bleeding (risk of relapse/exacerbation of oesophagitis, oesophageal ulcer, oesophageal stricture)

Section I: Urogenital System

1. Antimuscarinic drugs with dementia, or chronic cognitive impairment (risk of increased confusion, agitation) or narrow-angle glaucoma (risk of acute exacerbation of glaucoma), or chronic prostatism (risk of urinary retention).
2. Selective alpha-1 selective alpha blockers in those with symptomatic orthostatic hypotension or micturition syncope (risk of precipitating recurrent syncope)

Section J. Endocrine System

1. Sulphonylureas with a long duration of action (e.g. glibenclamide, chlorpropamide, glimepiride) with type 2 diabetes mellitus (risk of prolonged hypoglycaemia).
2. Thiazolidenediones (e.g. rosiglitazone, pioglitazone) in patients with heart failure (risk of exacerbation of heart failure)
3. Beta-blockers in diabetes mellitus with frequent hypoglycaemic episodes (risk of suppressing hypoglycaemic symptoms).
4. Oestrogens with a history of breast cancer or venous thromboembolism (increased risk of recurrence).
5. Oral oestrogens without progestogen in patients with intact uterus (risk of endometrial cancer).
6. Androgens (male sex hormones) in the absence of primary or secondary hypogonadism (risk of androgen toxicity; no proven benefit outside of the hypogonadism indication).

Section K: Drugs that predictably increase the risk of falls in older people

1. Benzodiazepines (sedative, may cause reduced sensorium, impair balance).
2. Neuroleptic drugs (may cause gait dyspraxia, Parkinsonism).
3. Vasodilator drugs (e.g. alpha-1 receptor blockers, calcium channel blockers, long-acting nitrates, ACE inhibitors, angiotensin I receptor blockers,) with persistent postural hypotension i.e. recurrent drop in systolic blood pressure ≥ 20mmHg (risk of syncope, falls).
4. Hypnotic Z-drugs e.g. zopiclone, zolpidem, zaleplon (may cause protracted daytime sedation, ataxia).

Section L: Analgesic Drugs

1. Use of oral or transdermal strong opioids (morphine, oxycodone, fentanyl, buprenorphine, diamorphine, methadone, tramadol, pethidine, pentazocine) as first line therapy for mild pain (WHO analgesic ladder not observed).
2. Use of regular (as distinct from PRN) opioids without concomitant laxative (risk of severe constipation).
3. Long-acting opioids without short-acting opioids for break-through pain (risk of persistence of severe pain)

Section N: Antimuscarinic/Anticholinergic Drug Burden

1. Concomitant use of two or more drugs with antimuscarinic/anticholinergic properties (e.g. bladder antispasmodics, intestinal antispasmodics, tricyclic antidepressants, first generation antihistamines) (risk of increased antimuscarinic/anticholinergic toxicity)

SCREENING TOOL TO ALERT TO RIGHT TREATMENT (START), VERSION 2.

Section A: Cardiovascular System

1. Vitamin K antagonists or direct thrombin inhibitors or factor Xa inhibitors in the presence of chronic atrial fibrillation.
2. Aspirin (75 mg – 160 mg once daily) in the presence of chronic atrial fibrillation, where Vitamin K antagonists or direct thrombin inhibitors or factor Xa inhibitors are contraindicated.
3. Antiplatelet therapy (aspirin or clopidogrel or prasugrel or ticagrelor) with a documented history of coronary, cerebral or peripheral vascular disease.
4. Antihypertensive therapy where systolic blood pressure consistently > 160 mmHg and/or diastolic blood pressure consistently >90 mmHg; if systolic blood pressure > 140 mmHg and/or diastolic blood pressure > 90 mmHg, if diabetic.
5. Statin therapy with a documented history of coronary, cerebral or peripheral vascular disease, unless the patient's status is end-of-life or age is > 85 years.

6. Angiotensin Converting Enzyme (ACE) inhibitor with systolic heart failure and/or documented coronary artery disease.
7. Beta-blocker with ischaemic heart disease.
8. Appropriate beta-blocker (bisoprolol, nebivolol, metoprolol or carvedilol) with stable systolic heart failure.

Section B: Respiratory System

1. Regular inhaled 2 agonist or antimuscarinic bronchodilator (e.g. ipratropium, tiotropium) for mild to moderate asthma or COPD.
2. Regular inhaled corticosteroid for moderate-severe asthma or COPD, where FEV1 <50% of predicted value and repeated exacerbations requiring treatment with oral corticosteroids.
3. Home continuous oxygen with documented chronic hypoxaemia (i.e. pO2 < 8.0 kPa or 60 mmHg or SaO2 < 89%)

Section C: Central Nervous System& Eyes

1. L-DOPA or a dopamine agonist in idiopathic Parkinson's disease with functional impairment and resultant disability.
2. Non-TCA antidepressant drug in the presence of persistent major depressive symptoms.
3. Acetylcholinesterase inhibitor (e.g. donepezil, rivastigmine, galantamine) for mild- moderate Alzheimer's dementia or Lewy Body dementia (rivastigmine).
4. Topical prostaglandin, prostamide or beta-blocker for primary open-angle glaucoma.
5. Selective serotonin reuptake inhibitor (or SNRI or pregabalin if SSRI contraindicated) for persistent severe anxiety that interferes with independent functioning.
6. Dopamine agonist (ropinirole or pramipexole or rotigotine) for Restless Legs Syndrome, once iron deficiency and severe renal failure have been excluded.

Section D: Gastrointestinal System

1. Proton Pump Inhibitor with severe gastro-oesophageal reflux disease or peptic stricture requiring dilatation.
2. Fibre supplements (e.g. bran, ispaghula, methylcellulose, sterculia) for diverticulosis with a history of constipation.

Section E: Musculoskeletal System

1. Disease-modifying anti-rheumatic drug (DMARD) with active, disabling rheumatoid disease.
2. Bisphosphonates and vitamin D and calcium in patients taking long-term systemic corticosteroid therapy.
3. Vitamin D and calcium supplement in patients with known osteoporosis and/or previous fragility fracture(s) and/or (Bone Mineral Density T-scores more than -2.5 in multiple sites).
4. Bone anti-resorptive or anabolic therapy (e.g. bisphosphonate, strontium ranelate, teriparatide, denosumab) in patients with documented osteoporosis, where no pharmacological or clinical status contraindication exists (Bone Mineral Density T-scores -> 2.5 in multiple sites) and/or previous history of fragility fracture(s).
5. Vitamin D supplement in older people who are housebound or experiencing falls or with osteopenia (Bone Mineral Density T-score is > -1.0 but < -2.5 in multiple sites).
6. Xanthine-oxidase inhibitors (e.g. allopurinol, febuxostat) with a history of recurrent episodes of gout.
7. Folic acid supplement in patients taking methotexate.

Section F: Endocrine System

1. ACE inhibitor or Angiotensin Receptor Blocker (if intolerant of ACE inhibitor) in diabetes with evidence of renal disease i.e. dipstick proteinuria or microalbuminuria (>30mg/24 hours) with or without serum biochemical renal impairment.

Section G: Urogenital System

1. Alpha-1 receptor blocker with symptomatic prostatism, where prostatectomy is not considered necessary.
2. 5-alpha reductase inhibitor with symptomatic prostatism, where prostatectomy is not considered necessary.
3. Topical vaginal oestrogen or vaginal oestrogen pessary for symptomatic atrophic vaginitis.

Section H: Analgesics

1. High-potency opioids in moderate-severe pain, where paracetamol, NSAIDs or low- potency opioids are not appropriate to the pain severity or have been ineffective.
2. Laxatives in patients receiving opioids regularly.

Section I: Vaccines

1. Seasonal trivalent influenza vaccine annually
2. Pneumococcal vaccine at least once after age 65 according to national guidelines

AGS BEERS CRITERIA
FOR POTENTIALLY INAPPROPRIATE MEDICATION USE IN OLDER ADULTS

FROM THE AMERICAN GERIATRICS SOCIETY

This clinical tool, based on The *AGS 2012 Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults (AGS 2012 Beers Criteria)*, has been developed to assist healthcare providers in improving medication safety in older adults. Our purpose is to inform clinical decision-making concerning the prescribing of medications for older adults in order to improve safety and quality of care.

Originally conceived of in 1991 by the late Mark Beers, MD, a geriatrician, the *Beers Criteria* catalogues medications that cause adverse drug events in older adults due to their pharmacologic properties and the physiologic changes of aging. In 2011, the AGS undertook an update of the criteria, assembling a team of experts and funding the development of the AGS 2012 *Beers Criteria* using an enhanced, evidence-based methodology. Each criterion is rated (quality of evidence and strength of evidence) using the American College of Physicians' Guideline Grading System, which is based on the GRADE schema developed by Guyatt et al.

The full document together with accompanying resources can be viewed online at www.americangeriatrics.org.

INTENDED USE

The goal of this clinical tool is to improve care of older adults by reducing their exposure to Potentially Inappropriate Medications (PIMs).

- This should be viewed as a guide for identifying medications for which the risks of use in older adults outweigh the benefits.
- These criteria are not meant to be applied in a punitive manner.
- This list is not meant to supersede clinical judgment or an individual patient's values and needs. Prescribing and managing disease conditions should be individualized and involve shared decision-making.
- These criteria also underscore the importance of using a team approach to prescribing and the use of non-pharmacological approaches and of having economic and organizational incentives for this type of model.
- Implicit criteria such as the STOPP/START criteria and Medication Appropriateness Index should be used in a complementary manner with the 2012 AGS *Beers Criteria* to guide clinicians in making decisions about safe medication use in older adults.

The criteria are not applicable in all circumstances (eg, patient's receiving palliative and hospice care). If a clinician is not able to find an alternative and chooses to continue to use a drug on this list in an individual patient, designation of the medication as potentially inappropriate can serve as a reminder for close monitoring so that the potential for an adverse drug effect can be incorporated into the medical record and prevented or detected early.

TABLE 1: 2012 AGS Beers Criteria for Potentially Inappropriate Medication Use in Older Adults

Organ System/ Therapeutic Category/Drug(s)	Recommendation, Rationale, *Quality of Evidence (QE) & Strength of Recommendation (SR)*
Anticholinergics (excludes TCAs)	
First-generation antihistamines (as single agent or as part of combination products) ■ Brompheniramine ■ Carbinoxamine ■ Chlorpheniramine ■ Clemastine ■ Cyproheptadine ■ Dexbrompheniramine ■ Dexchlorpheniramine ■ Diphenhydramine (oral) ■ Doxylamine ■ Hydroxyzine ■ Promethazine ■ Triprolidine	**Avoid.** Highly anticholinergic; clearance reduced with advanced age, and tolerance develops when used as hypnotic; increased risk of confusion, dry mouth, constipation, and other anticholinergic effects/ toxicity. Use of diphenhydramine in special situations such as acute treatment of severe allergic reaction may be appropriate. *QE = High (Hydroxyzine and Promethazine), Moderate (All others); SR = Strong*
Antiparkinson agents ■ Benztropine (oral) ■ Trihexyphenidyl	**Avoid.** Not recommended for prevention of extrapyramidal symptoms with antipsychotics; more effective agents available for treatment of Parkinson disease. *QE = Moderate; SR = Strong*

Table 1 (continued from page 1)

TABLE 1: 2012 AGS Beers Criteria for Potentially Inappropriate Medication Use in Older Adults

Organ System/ Therapeutic Category/Drug(s)	Recommendation, Rationale, *Quality of Evidence (QE) & Strength of Recommendation (SR)*
Antispasmodics ■ Belladonna alkaloids ■ Clidinium-chlordiazepoxide ■ Dicyclomine ■ Hyoscyamine ■ Propantheline ■ Scopolamine	**Avoid except in short-term palliative care to decrease oral secretions.** Highly anticholinergic, uncertain effectiveness. *QE = Moderate; SR = Strong*
Antithrombotics	
Dipyridamole, oral short-acting* *(does not apply to the extended-release combination with aspirin)*	**Avoid.** May cause orthostatic hypotension; more effective alternatives available; IV form acceptable for use in cardiac stress testing. *QE = Moderate; SR = Strong*
Ticlopidine*	**Avoid.** Safer, effective alternatives available. *QE = Moderate; SR = Strong*
Anti-Infective	
Nitrofurantoin	**Avoid for long-term suppression; avoid in patients with CrCl <60 mL/min.** Potential for pulmonary toxicity; safer alternatives available; lack of efficacy in patients with CrCl <60 mL/min due to inadequate drug concentration in the urine. *QE = Moderate; SR = Strong*
Cardiovascular	
Alpha, blockers ■ Doxazosin ■ Prazosin ■ Terazosin	**Avoid use as an antihypertensive.** High risk of orthostatic hypotension; not recommended as routine treatment for hypertension; alternative agents have superior risk/ benefit profile. *QE = Moderate; SR = Strong*
Alpha agonists ■ Clonidine ■ Guanabenz* ■ Guanfacine* ■ Methyldopa* ■ Reserpine (>0.1 mg/day)*	**Avoid clonidine as a first-line antihypertensive. Avoid others as listed.** High risk of adverse CNS effects; may cause bradycardia and orthostatic hypotension; not recommended as routine treatment for hypertension. *QE = Low; SR = Strong*
Antiarrhythmic drugs (Class Ia, Ic, III) ■ Amiodarone ■ Dofetilide ■ Dronedarone ■ Flecainide ■ Ibutilide ■ Procainamide ■ Propafenone ■ Quinidine ■ Sotalol	**Avoid antiarrhythmic drugs as first-line treatment of atrial fibrillation.** Data suggest that rate control yields better balance of benefits and harms than rhythm control for most older adults. Amiodarone is associated with multiple toxicities, including thyroid disease, pulmonary disorders, and QT interval prolongation. *QE = High; SR = Strong*
Disopyramide*	**Avoid.** Disopyramide is a potent negative inotrope and therefore may induce heart failure in older adults; strongly anticholinergic; other antiarrhythmic drugs preferred. *QE = Low; SR = Strong*
Dronedarone	**Avoid in patients with permanent atrial fibrillation or heart failure.** Worse outcomes have been reported in patients taking dronedarone who have permanent atrial fibrillation or heart failure. In general, rate control is preferred over rhythm control for atrial fibrillation. *QE = Moderate; SR = Strong*
Digoxin >0.125 mg/day	**Avoid.** In heart failure, higher dosages associated with no additional benefit and may increase risk of toxicity; decreased renal clearance may increase risk of toxicity. *QE = Moderate; SR = Strong*

Appendix Table 1.4.3: Overview of explicit screening tools

Tool name	Author	Country	Year of publication	Overuse	Misuse							Underuse	Alternative	Applied to	Number of criteria
					PIM	Dose	Duration	DDI	DDisI	Duplication	Route of administration				
ACOVE[84, 85, 86, 58]		USA	1999 2001 2007	X	X	-	X	X	X	-	X	X	X	Vulnerable older patients =75 year Community-dwelling patients =65 year	236 392
Austrian criteria[37]	Mann	Austria	2012	-	X	-	-	-	-	-	-	-	X	=65 year	73
Beers criteria ([37, 38, 30, 23, 87, 67])	Beers Fick AGS	USA	1991 1997 2003 2012 2015	-	X	X	X	-	X	-	X	-	-	Institutionalized patients =65 year Community-dwelling patients	30 43 68 53
Beers liste[39]	Schwalbe	Germany	2007	-	X	X	X	-	X	-	-	-	X	=65 year	47
Campbell's Prescribing Indicators[72]	Campbell	UK	2000	-	X	X	-	-	-	-	-	-	-	Community setting	12
FORTA criteria[88, 64]	Wehling	Germany	2008 2013 update	X	X	X	-	-	-	-	-	X	-	Community-dwelling patients	190 206
HEDIS[46, 89, 65]	NCQA	USA	2006	-	X	-	-	-	X	-	-	-	-	Community-dwelling patients =65 year	42
Hospital prescribing indicators of potential harms[74]	Thomas	UK	2013	-	X	X	X	X	X	X	X	X	-	Hospitalized patients	80
IPET[31, 30]	Naugler	Canada	2000	-	X	-	-/X	-	X	-	-	-	-	=70 year	14
KPC criteria[41]	KPC	USA	2007	-	x	-	-	-	-	-	X	-	X	Community-dwelling patients =65 year	11
Laroche criteria[37, 42]	Laroche	France	2007	-	X	X	-	X	X	X	-	-	X	=75 year	34
Lechevallier criteria[23]	Lechevallier	France	2004-2005	-	X	-	-	-	-	X	-	-	-	Community-dwelling patients =65 year	24
Lindblad[43]	Lindblad	USA	2006	-	-	-	-	-	X	-	-	-	-	Community-dwelling patients =65 year	28
List of unnecessary Medications Used in Residents of Long-term Care Facilities[90]	CMS	USA	2006	-	X	X	X	X	X	-	X	-	-	Chronic care patients	27
Maio Criteria[44]	Maio	Italy	2010	-	X	X	X	-	-	-	X	-	-	Community-dwelling patients =65 year	23
Malones list of drug-drug interactions[91]	Malone	USA	2004	-	X	-	-	X	-	-	-	-	-	Community setting	25
Matsumura Alert System for inappropriate Prescriptions[92]	Matsumura	Japan	2009	-	X	X	-	-	X	-	-	-	-	Community setting	3

Appendix Table 1.4.3: Overview of explicit screening tools (Continued)

Tool name	Author	Country	Year of publication	Overuse	Misuse							Underuse	Alternative	Applied to	Number of criteria
					PIM	Dose	Duration	DDI	DDisI	Duplication	Route of administration				
McLeod criteria [37, 45]	McLeod	Canada	1997	-	X	-	X	X	X	-	-	-	X	Older patients	38
New mexico criteria [47]	NMPIC	USA	2009	-	X	X	-	-	-	-	-	-	X	Older patients	72
NORGEP [48]	Rognstad	Norway	2009	-	X	X	-	X	-	X	-	-	-	Community-dwelling patients =70 year	36
Rancourt criteria [50]	Rancourt	Canada	2004	-	X	X	X	X	-	X	-	-	-	Chronic care patients =65 year	111
Scottish Criteria [75]	Dreischulte	Scotland	2012	X	X	X	X	X	X	-	-	X	-	Community-dwelling patients	176 38
Sloane list of inappropriate prescribed medicines [51]	Sloane	USA	2002	-	X	-	-	-	-	-	-	-	X	Patients in service flats =65 year	20
START [92, 93]	Barry	Ireland	2007	-	-	-	-	-	-	-	-	X	-	=65 year	22
STOPP [37, 67, 36, 93]	Gallagher	Ireland	2008	-	X	X	X	X	X	X	-	-	-	=65 year	65
Terrell computerised decision support system to reduce potentially inappropriate prescribing [52]	Terrell	USA	2009	-	X	-	-	-	-	-	-	-	X	=65 year at hospital discharge	9
The PRISCUS list [37, 49]	Holt	Germany	2010	-	X	X	-	-	X	-	-	-	X	=65 year	83
Top 10 particulary dangerous drug-interactions [94]	AMDA	USA	2011	-	-	-	-	X	-	-	-	-	X	Institutionalized patients and patients in chronic care	10
Unangemessene arzeistoffe für geriatrische patienten [40]	Kölzsch	Germany	2010	-	X	X	-	-	X	X	-	-	-	Institutionalized patients =65 year	26
Winit-Watjana criteria [35]	Winit-Watjana	Thailand	2007	-	X	-	-	X	X	-	-	-	-	Older patients	77
Zhan criteria [53]	Zhan	USA	2001	-	X	-	-	-	-	-	-	-	-	Community-dwelling patients =65 year	33

***ACOVE**: Assessing Care of Vulnerable Elders Quality Indicators, **AMDA**: American Medical Directors Association, **CC**: Conference Call, **CMS:** Centre of Medicare and Medicaid Services, **DDI:** Drug-Drug Interaction, **DDisI:** Drug-Disease Interaction, **FORTA**: Fit For The Age Criteria, **HEDIS**: Health Care Effectiveness Data Information Set, **IPET**: Improving Prescribing in the Elderly Tool, KPC: Kaiser Permanente Colorado Criteria, **NCQA**: National Committee for Quality Assurance, **NMPIC**: The New Mexico Prescription Improvement Coalition, **NORGEP**: Norwegian General Practice Criteria, **NV:** niet vermeld, **NVT:** niet van toepassin, **PDRM**: Preventable Drug Related Morbidity, **PSI**: Prescribing Safety Indicators, **QI**: Quality indicator, **RAND/UCLA**: RAND Appropriate Method/ University of California at Los Angeles , **START**: Screening Tool to Alert doctors to the Right Treatment, **STOPP**: Screening Tool of Older Person's Prescriptions*

Appendix Table 1.4.2: Overview of implicit screening tools

Tool name	Author	Country	Year of publication	Overuse	Misuse								Underuse	Alternative	Allergies	Adherence	Cost-effectiveness	Applied to	Number of criteria
					PIM	Dose	Duration	Frequence	DDI	DDisI	Duplication	Route of administration							
***Barenholtz Levy self-administered Medication-Risk Questionnaire*[57]**	Barenholtz	USA	2003	-	X	-	-	X	-	-	-	-	-	-	-	X	-	Community-dwelling older patients	10
***Cantrill indicator of Appropriateness of long term prescribing*[56]**	Cantrill	UK	1998	X	X	X	X	X	X	-	-	-	-	-	-	-	X	Community-dwelling patients in chronic care	9
***Hamdy criteria for medication Profile Review in Extended Care*[95]**	Hamdy	USA	1995	X	X	X	-	X	X	X	X	X	-	-	-	-	-	Community-dwelling patients in chronic care with extra focus on those with ≥10 drugs	5
***Lipton's Tool to assess the Appropriateness of Physicians' Geriatric Drug Prescribing*[16, 13]**	Lipton	USA	1992	X	X	X	-	X	X	-	X	-	X	-	X	-	-	Older patients with ≥3 drugs	7
***MAI*[6,13]**	Hanlon	USA	1992	X	X	X	X	-	X	X	X	X	-	-	-	-	X	None specified	10
***Owens Steps to Achieve optimal Pharmacotherapy*[a, b, 69]**	Owens	USA	1994	X	X	X	X	-	-	X	-	-	-	-	-	-	-	Older patients	5
***PMDRP*[13, 68a]**	Universiteit van Toronto	Canada	1997	X	X	X	-	-	X	X	-	-	X	-	-	X	-	None specified	9
***Robertson's Flow Chart*[c, 96]**	Robertson	USA	1996	X	X	X	-	-	X	X	-	X	X	-	X	X	X	Hospitalized patients	10

DDI: *Drug-Drug Interaction,* ***DDisI:*** *Drug-Disease Interaction,,* ***KPM:*** *Kaiser Permanente Model,* ***MAI:*** *Medication Appropriateness Index,* ***PIM:*** *Potentially Inappropriate Medication,* ***PMDRP:*** *The Pharmacist's Management of Drug-Related Problems,* ***UK:*** *United Kingdom,* ***USA:*** *United States of America*

Appendix Table 1.4.3: Overview of combined (partly explicit and partly implicit) screening tools

Tool name	Author	Country	Year of publication	Overuse	Misuse								Underuse	Alternative	Allergies	Adherence	Cost-effectiveness	Applied to	Number of criteria
					PIM	Dose	Duration	Frequency	DDI	DDisI	Duplication	Route of administration							
ARMOR[97]	Haque	USA	2009	X	X	X	-	-	X	X	X	-	-	-	-	X	-	Older patients	5
Australian Prescribing Indicators[55, 4]	Basger	Australia	2008 2012 update	X	X	X	X	-	X	X	-	-	X	-	-	-	-	=65 year =65 year - =85 year	48 41
Home Health criteria[98, 71]	Brown	USA	1998	-	X	X	-	-	X	X	X	-	-	X	-	-	-	Community-dwelling, older patients	15
IQUM[99]	NSW	Australia	2007	-	X	X	X	-	X	X	X	-	X	-	-	-	-	Hospitalized patients	30
Kaiser Permanente Model[100]	KPMCP	USA	1995	-	X	X	-	-	X	X	X	X	-	-	-	X	-	All patients	14
Medication Management Outcomes Monitor[101]	Bergman-Evans	USA	2006	X	X	X	-	X	-	-	X	X	-	-	-	X	X	=65 year	4
Oborne's Prescribing Indicators[102]	Oborne	USA	1997 2003	X	X	X	-	-	X	X	X	-	X	-	X	-	X	Hospitalized patients =65 year Institutionalized patients	14 13
POM[9]	Drenth-van Maanen DGM	The Netherlands	2009	X	X	X	-	X	X	X	-	X	X	X	-	X	-	Community-dwelling, older patients	6
The geriatric medication algorithm[70]	Newton	USA	1994	X	X	X	-	-/X	X	X	-	-/X	-	-	-	X	-	Community-dwelling, older patients	4
TIMER[103]	Snyder Lee	USA	2009	-	X	-	-	-	X	X	X	-	X	X	X	X	X	Older patients	4

ARMOR: *A Tool to Evaluate Polypharmacy in Elderly Persons,* ***Brown:*** *Brown Model for Improving Medication Use in Home Health Care Patients,* ***DDI:*** *Drug-Drug Interaction,* ***DDisI:*** *Drug-Disease Interaction,* ***DGM:*** *department geriatric medicine the Netherlands,* ***IQUM:*** *Indicators for Quality Use of Medicines,* ***KPMCP:*** *Kaiser permanente Medical Core Programme,* ***NSW:*** *the New South Wales Therapeutic Advisory Group,* ***POM:*** *Prescribing Optimisation Method for Improving Prescribing in Elderly Patients,* ***QI:*** *kwaliteitsindicatoren,* ***TIMER:*** *Tool to Improve Medications in the Elderly via Review,* ***USA:*** *United States of America*

Outline and aims of the thesis

The main goal of this thesis is to develop, optimize and evaluate advanced pharmaceutical care interventions in chronic care. We focused on older patients with polypharmacy and on patients with COPD as an example of chronic disease. The choice for both groups is deliberate as they are both increasingly present and are burdensome for both the patient and the healthcare system.

In **Chapter 2** we developed and validated a strategy to optimize pharmaceutical care for older patients with polypharmacy. This strategy included the development and validation of a new screening tool to perform a medication review originating from the community pharmacy. This way, community pharmacists can initiate this process and use the outcomes to improve interdisciplinary communication. Additionally, we assessed the prevalence of Potentially Inappropriate Prescribing (PIP) according to this screening tool in the ambulatory and nursing home setting and evaluated usability and feasibility. The specific aims are as follows:

Aim 1: To get an insight in the overall prevalence of PIP in Europe, the drugs and drug groups that are mainly involved in PIP and the most important risk factors associated with PIP.

To this end, we performed a systematic literature review of 52 observational studies on PIP in community-dwelling older patients in Europe, described in **Part 1**.

Aim 2: To develop an explicit screening tool to detect PIP with high clinical relevance, usable in a typical community pharmacy practice and specifically adapted to the European market

In **Part 2**, the developmental process of a new screening tool is elaborately described. The process was completed using the RAND/UCLA method. An additional round on feasibility for the contemporary community pharmacy setting resulted in the Ghent Older People's Prescriptions community Pharmacy Screening (GheOP^{3}S-)tool, a list of 83 PIP-items.

Aim 3: To validate the newly developed GheOP^{3}S-tool

In **Part 3** we describe the validation of the GheOP^{3}S-tool, using the results of an observational study, performed on acutely hospitalized older patients with polypharmacy. For each PIP-item detected with the GheOP^{3}S-tool, the clinical relevance, the relevance of the proposed alternative treatment plan and the subsequent acceptance by the geriatrician was evaluated. Additionally, we assessed the contribution to the admission and preventability. Lastly, we evaluated the completeness of a PIP-screening with the GheOP^{3}S-tool through comparison with the adapted Medication Appropriateness Index (aMAI).

Aim 4: To determine the prevalence of PIP in Belgian older adults with polypharmacy

To this end, two observational studies, using the GheOP³S-tool to determine PIP-prevalence, were performed. The first was executed in 204 Belgian community pharmacies and included 1016 ambulatory older patients (≥ 70 years) with polypharmacy (≥ 5 drugs) (see **Part 4**). Analogously, a second observational study, was performed in 10 nursing homes in Flanders, all supplied by one community pharmacy chain. From each nursing home, 40 residents aged 70 years or older and using 5 or more chronic drugs were included (**Part 5**). Besides determining PIP-prevalence, the feasibility of applying the GheOP³S-tool in daily community pharmacy practice was as well evaluated (**Part 4**).

Consequently, in **Chapter 3,** we shifted our focus to patients with COPD as an example of chronic disease. To document the extent of the issues experienced by patients with COPD, we elaborately introduce COPD by reviewing the pathology, pathophysiology, epidemiology and burden of disease in **Part 1**. Additionally, we elaborate on pharmacotherapeutical optimisation possibilities, with regard to inhalation technique and medication adherence. Subsequently, from Part 2 on, we evaluated a counselling strategy, provided by the community pharmacist in the management of the disease. The specific aims are as follows:

Aim 1: To evaluate the effectiveness of a pharmaceutical care intervention, focusing on inhalation technique and medication adherence, executed in the community pharmacy.

Part 2, describes the results of the PHARMAceutical care in COPD-trial (PHARMACOP-trial). This was a single-blind 3-month randomized controlled trial, conducted in 170 community pharmacies in Belgium, including 734 patients. Patients were allocated to the intervention group, receiving protocol-defined pharmacist care, or control group, receiving usual pharmacist care. The primary outcomes were inhalation technique and medication adherence, however, also secondary outcomes such as exacerbation rate were evaluated.

Aim 2: To assess the current implementation level of the items included in the PHARMACOP-protocol in Flemish community pharmacies and perspectives on future implementation.

To this end, **Part 3** describes the results of a cross-sectional study, conducted in randomly selected community pharmacies in Flanders. Pharmacists were questioned using structured interviews.

Aim 3: To assess the accuracy of a self-report measure of adherence for identifying nonadherent users of inhalation medication among patients with COPD

As medication adherence seemed to be problematic in patients with COPD, the availability of an accurate method to measure adherence appeared to be essential. Therefore, in **Part 4,** we used the results of the PHARMACOP-trial to determine the accuracy of the Medication Adherence Report Scale (MARS-5) to identify nonadherent users of inhalation medication among patients with COPD. This was accomplished through comparison with the medication refill adherence (MRA) as a reference.

Chapter 2

Medication screening for older patients with polypharmacy in the community pharmacy setting

PART 2.1:

POTENTIALLY INAPPROPRIATE PRESCRIBING IN COMMUNITY DWELLING OLDER PEOPLE ACROSS EUROPE: A SYSTEMATIC LITERATURE REVIEW

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ABSTRACT

Background. Potentially Inappropriate Prescribing (PIP) is one of the main risk factors for adverse drug events (ADEs) in older people.

***Purpose*.** This systematic literature review aims to determine prevalence and type of PIP in community dwelling older people across Europe, as well as identifying risk factors for PIP.

Methods. The PubMed and Web of Science database were searched systematically for relevant manuscripts (January 1, 2000 - December 31, 2014). Manuscripts were included if the study design was observational, the study participants were community-dwelling older patients in Europe, and if a published screening method for PIP was used. Studies that focused on specific pathologies or that focused on merely one inappropriate prescribing issue were excluded. Data analysis was performed using R statistics.

Results. Fifty-two manuscripts were included, describing 82 different sample screenings with an estimated overall PIP prevalence of 22.6% (CI: 19.2– 26.7%; Range: 0.0 – 98.0%). Ten of the sample screenings were based on the Beers 1997 criteria, 19 on the Beers 2003 criteria, 14 on STOPP-criteria (2008 version), 8 on START-criteria (2008 version) and 7 on the PRISCUS-list. The 24 remaining sample screenings were carried out using compilations of screening methods or used country specific lists such as the Laroche-criteria. It appears that only PIP prevalence calculated from insurance data significantly differs from the other data collection method categories. Furthermore, risk factors most often positively associated with PIP prevalence were polypharmacy, poor functional status and depression. Drug groups most often involved in PIP were anxiolytics (ATC-code: N05B), antidepressants (N06A) and non-steroidal anti-inflammatory and anti-rheumatic products (M01A).

Conclusion. PIP prevalence in European community-dwelling older adults is high and depends partially on the data collection method used. Polypharmacy, poor functional status and depression were identified as most common risk factors for PIP.

INTRODUCTION

Over the past years, the proportion of the European population aged 65 years and over has been increasing[1]. Aging is often associated with a growing number of chronic diseases and hence polypharmacy, which increases the risk for adverse drug events (ADEs)[2 3], drug-related hospitalizations and related costs[2 4]. A recent systematic review reported an ADE prevalence up to 23% for older adults in ambulatory care with preventability rates up to 53%[3].

Previous studies have identified Potentially Inappropriate Prescribing (PIP) as one of the main risk factors for ADEs in older adults[5-9]. PIP is defined as the prescribing of medication that could introduce a significant risk of an ADE, in particular when there is an equally or more effective alternative with lower risk available[10 11]. PIP encompasses three main categories: over-, under- and misprescribing (e.g. inappropriate dose or duration)[12]. Both explicit (criteria-based) and implicit (judgement-based) screening methods were developed and used to detect PIP[13-16]. Studies using these tools clearly demonstrated that PIP prevalence is high and that an early detection may indeed prevent hospitalizations and improve health outcomes[10 17-19]. Research to detect and reduce PIP was initially mainly situated in hospital and nursing home settings as one of the strategies to prevent and lower the prevalence of ADEs[20-22]. Over the past decade however, PIP-screening in primary care received increasing attention among health care workers because detecting and tackling PIP at that point in the health care system could be more (cost-)effective[10 19].

In 2012 Opondo et al. published the first systematic review on PIP in the primary care setting[10]. Eight of the 19 included studies were carried out in Europe, describing an overall median PIP rate of 19.1% (range: 2.9% – 38.5%). However, this review only included studies that reported on 'unconditionally inappropriate medication prescriptions'. Studies investigating drug-drug interactions drug-disease interactions, or other types of PIP were excluded. In addition, risk factors for PIP have not yet been reviewed. This information is however needed to enable the design of well-defined targeted interventions to improve the quality of prescribing for older adults. Furthermore, since the publication of the systematic review of Opondo et al.[10], several new studies in the European ambulatory setting have emerged, which have contributed to a better characterization of the contemporary field[23-26].

In order to improve quality of care for community-dwelling older adults, it is necessary to determine the magnitude, nature and relevance of PIP in Europe. Only then, straightforward and targeted management plans for patient groups at risk can be developed to tackle the most problematic PIPs in primary care. The aim of this systematic review is (1) to synthesize observational research on PIP prevalence in community-dwelling older adults in Europe, (2) to present an overview of the risk factors mostly described in association with PIP and (3) to summarize the drugs or drug groups most often involved in PIP.

METHODS

Searches

We searched the PubMed and Thomson Reuters Web of Science™ database for relevant manuscripts from January 1, 2000 to December 31, 2014. The search strategy contained terms and combinations related to older patients, medications, (in)appropriateness, ambulatory care, outpatient care or community-dwelling patients, including the MeSH terms "Aged" and "Inappropriate prescribing" as shown in Appendix 2.1.1. The final literature search was performed on the 31st December 2014. The database search was completed with a manual search of the reference lists of included articles (i.e. "snowballing"). The quality of the systematic review was supported by the use of the PRISMA guidelines[27] .

Eligibility criteria

Manuscripts were eligible for inclusion if they met the following criteria: (1) study design was observational, (2) study participants were community-dwelling older patients (65 years and older) in Europe and (3) a published screening method, either implicit or explicit for PIP was used. Manuscripts could be published in English, French, Dutch, German or Spanish. Studies that focused on specific pathologies (e.g. patients with dementia) or that focused on merely one inappropriate prescribing issue (e.g. benzodiazepine use) were excluded in addition to manuscripts that not specifically mentioned a focus on the primary care setting or the older age group.

Study selection

Duplicate manuscripts were removed after exporting search results to Endnote (Thomson Reuters, Times Square, New York, NY, USA). Subsequently, two reviewers (ET & EM) independently screened the title, abstract and full-text of the retrieved manuscripts for eligibility. Each manuscript showing uncertainty regarding inclusion criteria was discussed until consensus about inclusion in the following selection round was reached.

Data collection, synthesis & analysis

Data concerning country, study period, inclusion criteria, used data collection method and used screening method were collected from the selected manuscripts. Additional extracted data included sample size, mean (SD) age of the screened population, mean (SD) or median (IQR) number of drugs taken (as presented in the original manuscript and therefore sometimes including OTC-drugs), and PIP prevalence (reported as the percentage of patients or prescriptions with at least one PIP). When repeated measurements were reported, we included only the most recent rate of PIP.

When data could not be retrieved from the published manuscript, we contacted the corresponding author to request for additional information. If the corresponding author did not reply, a reminder e-mail was sent one month later. The study quality ("risk of bias") of the included studies was evaluated by using a slightly adapted quality assessment scale from the Cochrane Collaboration group, including the following domains: study participation, data collection, screening method used, outcome measurement and statistical analysis. All studies were judged having a low or moderate risk of bias.

We estimated an overall prevalence with its 95% confidence interval (CI), using a random effects model with random intercepts. Prevalence data were modelled on a logit scale using sample size as a weighting factor. Likewise, a conditional prevalence with its 95% CI was estimated for the most used PIP screening methods (Beers, STOPP, START and PRISCUS), each method of data collection ((1) face-to-face interview, (2) prescribing, dispensing or primary health database, (3) insurance data, (4) questionnaire, (5) medical record or (6) combinations) and their interactions, using a (saturated) random effects model with fixed effects. For this analysis, all Beers analyses and combinations of data collection methods were collapsed into single categories. Analyses were carried out using R® (R Foundation for Statistical Computing, Vienna, Austria).

Subsequently, we selected those manuscripts that assessed risk factors associated with PIP and extracted the results as mentioned in the original manuscript. For the factor 'polypharmacy', different groups used other definitions (varying from the use of ≥4 up to ≥7 drugs), which were merged for reasons of comparability. Finally, we selected those manuscripts that provided detailed information about PIP prevalence for specific drugs or drug groups and summarized the information. The 10 drugs or drug groups most frequently associated with PIP were extracted as originally mentioned in the included manuscript and classified according to the Anatomical Therapeutic Chemical (ATC) classification system (3rd level) (e.g. 'M01AB05 - diclofenac' was classified as 'M01A – anti-inflammatory and antirheumatic products, non-steroids', or 'B01AC - platelet aggregation inhibitors' as 'B01A – antithrombotic agents')[28]. Due to the heterogeneity of the methodologies applied in the included studies, the overview of risk factors and drugs or drug groups most frequently associated with PIP are merely reported in a descriptive way.

RESULTS

We identified 1375 manuscripts and screened 1138 titles and 154 abstracts for eligibility after duplicate removal. We screened the full text of 62 manuscripts and excluded 23. Thirteen manuscripts were added via manual search of the references. Our final sample comprised 52 manuscripts reporting on 82 sample screenings of PIP in community-dwelling older adults in Europe (Figure 2.1.1). These studies were performed in 23 different European countries. The eventual list of included manuscripts is presented in Table 2.1.1, arranged by country and year of publication.

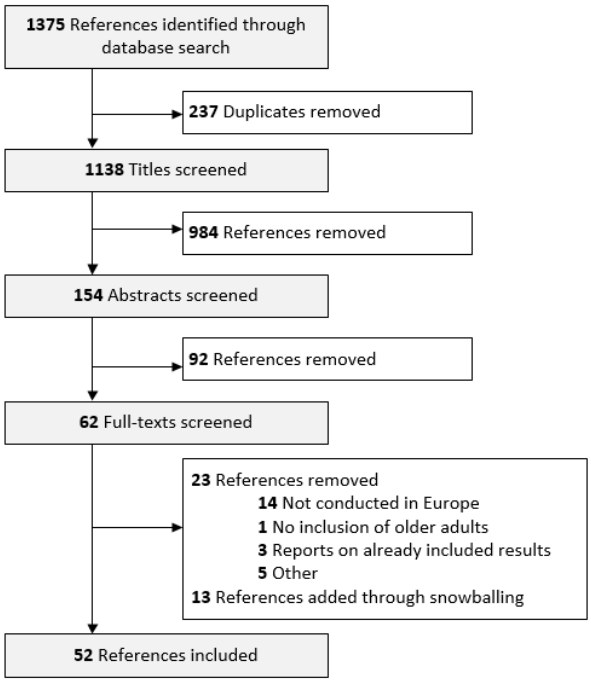

***Figure 2.1.1**: Flowchart of the literature search*

Table 2.1.1: Summary of the manuscripts included in the systematic review

Country *Author (year published)*	Period studied	Inclusion criteria	Sample size (patients / *prescriptions*)	Age (year); Mean (SD)	Number of drugs per patient / *prescription;* Mean (SD)	Data Collection Method	Screening Method based on (only referenced on first mentioning)	Adaptation of original screening method	Prevalence (patients or *prescriptions* with ≥1 PIP; no. (%))
Austria									
Koper et al. (2013)[a, 29]	2011*	≥65 years ≥5 drugs	158	76.4 (8.5)[a]	9.1 (3.0)[a]	GP Questionnaire	PRISCUS[16]	82/82 items included*	59 (37.3%)
Croatia									
Vlahović-Palčevski et al. (2004)[30]	2002	≥70 years	1/ *78091* 2/ 2114	1/ - [$] 2/ - [$]	1/ *7.5* (- [$]) 2/ - [$]	Dispensing DB	1/ Beers 1997[31] 2/ Set of 8 DDIs	1/ Only ID list used (7/28 criteria) 2/ Nothing mentioned	1/ *1677 (2.2%)* 2/ 40 (1.9%)
Popović et al. (2014)[32]	- [$]	≥65 years ≥5 drugs	29418	77 (- [$])	- [$]	Insurance data	Matanovic 2012[33]	Excluding 'Part 2: Drugs with questionable efficacy' Part 3: 7136 PIPs (CD) detected Part 4: 33231 PIPs (DDIs) detected	Part 1: 18358 (62.4%)
Denmark									
Bregnøj et al. (2007)[34]	- [$]	≥65 years ≥5 drugs	212	76.6 (7.3)	7.6 (2.9)	Prescribing DB + GP Questionnaire	MAI[35]	The item concerning the price of the medication was excluded	178 (84.0%)
Finland									
Pitkala et al. (2002)[36]	1998-1999	≥75 years	2511	- [$]	- [$]	Patient Questionnaire	Beers 1997	Both ID- (21/28 items) and CD-list (23/35 items) used	134 (12.5%) (only ID)
Leikola et al. (2011)[37]	2007	≥65 years	841509	- [£]	- [£]	Insurance data	Beers 2003[11]	Only ID list used (37/76 drugs)	123545 (14.7%)
Bell et al. (2013)[38]	2004	≥75 years	781[b]	81.7 (5.0)	- [$]	Patient interview	ABCD-categorization[39]	Only Category D Drugs were used	234 (30%)
France									
Lechevallier-Michel et al. (2005)[40]	1999-2001	≥65 years	9294	74.4 (5.6)	4.4 (2.9)	Patient interview	Beers 1997	Only ID list used (23/28 criteria included and 3 criteria added)	3597 (38.7%)
Berdot et al. (2009)[c, 41]	1999-2000	≥65 years	6343	73.7 (5.3)	- [$] (2172 ≥5)	Patient interview	COMP: Beers 1997, Beers 2003 & Laroche[42]	29 items used	2004 (31.6%)
Bongue et al. (2009)[c, 43]	1995 - 2004	≥65 years	30683	70.1 (4.3)	3.3 (2.6)	Patient interview	1/ Beers 1997 2/ Adapted Beers 1997	1/ Only ID list used (20/28 criteria) 2/ Only ID list used (23/28 criteria included and 3 criteria added)	1/ 3097 (10.1%) 2/ 7802 (25.4%)
Bongue et al. (2011)[44]	2007-2008	≥75 years	35259	81.5 (5.3)	- [$] (31847 ≥7)	Insurance Data	Laroche	20/34 criteria used, 1 criterion added	18864 (53.5%)
Jardin et al. (2012)[45]	2009	≥70 years	500904	78.8 (6.2)*	- [£]	Insurance Data	Laroche	4/34 criteria used, 6 criteria added	242438 (48.4%)*
Germany									
Fiss et al. (2011)[46]	2006-2008	≥65 years ≥1 drug	744	80.5 (6.7)	8.2 (4.0)	Patient interview	Beers 2003	Both ID- (21/48 criteria) and CD-list (6/20 criteria) used (27/68 criteria)	134 (18.0%)
Amann et al. (2012)[47]	2007	≥65 years	804400	71.6 (6.1)	5.9 (4.8)	Insurance Data	PRISCUS	Nothing mentioned [$]	201472 (25.0%)
Goltz et al. (2012)[c, 48]	2004	≥65 years ≥1 drug	542426	- [$]	*18.7 (14.3)*	Insurance Data	Beers 2003	Only ID list used (35/76 drugs)	98465 (18.2%)
Schubert et al. (2013)[49]	2010	≥65 years	16535	- [$] (57.5% ≥75y)	- [$]	Insurance Data	PRISCUS	73/82 items included	3638 (22.0%)
Zimmermann et al. (2013)[c, 50]	2009	≥75 years ≥ 1 drug	1855	84.4 (3.3)	4.7 (2.6)	Patient interview	1/ Beers 2003 2/ PRISCUS	1/ ID: 48/48 criteria; CD: 20/20 criteria* 2/ 82/82 criteria*	1/ 317 (17.1%) 2/ 464 (25.0%)
Linder et al. (2014)[c, 51]	2012	≥65 years	1077978	73.0 (5.9)*	1.2 (0.5)*	Insurance Data	PRISCUS	80/82 items included	203738 (18.9%)

Table 2.1.1 (Continued): Summary of the manuscripts included in the systematic review

Country *Author (year published)*	Period studied	Inclusion criteria	Sample size (patients / *prescriptions*)	Age (year); Mean (SD)	No. of drugs per patient / *prescription;* Mean (SD)	Data Collection Method	Screening Method based on (only referenced on first mentioning)	Adaptation of original screening method	Prevalence (patients or *prescriptions* with ≥1 PIP; no. (%))
Ireland									
Ryan et al. (2009)[52]	2006	≥65 years ≥1 drug	500	74.7 (6.2)	4.5 (2.6)	Medical record	1/ Beers 2003 2/ IPET[53]	1/ - [$] 2/ - [$]	1/ 65 (13.0%) 3/ 52 (10.4%)
Ryan et al. (2009)[54]	2007-2008	≥65 years ≥1 drug	1329	74.9 (6.4)	Median (IQR): 5 (3-7)	Medical record	1/ Beers 2003 2/ STOPP 2008[55] 3/ START 2008[55]	1/ 19/68 criteria used (ID + CD) 2/ 28/65 criteria used 3/ 15/22 criteria used	1/ 243 (18.3%) 2/ 284 (21.4%) 3/ 302 (22.7%)
Cahir et al. (2010)[56]	2007	≥70 years	338801	- [$] (62% ≥75y)	- [$]	Dispensing DB	STOPP 2008	30/65 criteria used	121454 (35.8%)
Cahir et al. (2014)[57]	2010	≥70 years	931	78 (5.4)	- [$]	Dispensing DB + Medical record	STOPP 2008	50/65 criteria used	377 (40.5%)
Galvin et al. (2014)[23]	2009-2011	≥65 years	3507	73.3 (6.4)*	3.6 (2.9)*	Patient Questionnaire	1/ STOPP 2008 2/ START 2008	1/ 26/65 criteria used 2/ 10/22 criteria used	1/504 (14.6%) 2/ 1035 (29.5%)
Italy									
Maio et al. (2006) [58]	2001	≥65 years ≥1 drug	849425	75.6 (7.5)	- [$] (344711≥7)	Prescribing DB	Beers 2003	Only ID list used (19/48 criteria)	152641 (18.0%)
Landi et al. (2007)[59]	2003-2004	≥65 years	364	85.8 (4.8)	2.9 (1.3)	Patient interview	Beers 2003	Only ID list used (27/48 criteria)	94 (25.8%)
Lapi et al. (2009)[c] [60]	1999	≥65 years	568	76.7 (0.2)	2.9 (0.1)	Patient interview	Beers 1991[20]	Only ID list used (13/30 criteria)	26 (5.1%)
Maio et al. (2010)[61]	2006	≥65 years ≥1 drug	91741	75.7 (7.7)	- [$] (46444 ≥7)	Prescribing DB	Beers 2003	Only ID list used (22/48 criteria, 1 criterion added)	23662 (25.8%)
Northern Ireland									
Bradley et al. (2012)[62]	2009-2010	≥70 years	166108	- [£] (63.3% ≥75y)	- [£]	Prescribing DB + Dispensing DB	STOPP 2008	28/65 criteria used	53423 (32.2%)
Norway									
Nyborg et al. (2012)[63]	2008	≥70 years ≥1 drug	445900	- [$] (69.4% ≥75y)	Median (IQR): 7 (4-10)	Dispensing DB	NORGEP-criteria[64]	36/36 criteria used	155341 (34.8%)
Poland									
Rajska-Neumann et al. (2007)[d, 65]	- [$]	≥65 years	1000	72.6 (6.5)[d]	6.9 (3.2)[d]	Patient Questionnaire	Beers 1997	Only ID list used (17/28 criteria)	285 (28.5%)
Portugal									
De Oliveira-Martins (2006)[66]	2002-2003	≥60 years ≥2 drugs	213	75.0 (- [$])	7.2 (- [$])	Patient interview	1/ Beers 1997 2/ Beers 2003	1/ Only ID list used (12/28 criteria) 2/ Only ID list used (17/48 criteria)	1/ 59 (27.7%) 2/ 82 (38.5%)
Romania									
Primejdie et al. (2012) [25]	2009-2010	≥65 years	*857*	75.7 (6.9)*	4.1 (2.3)*	Insurance data	1/ Beers 2003 2/ STOPP 2008 3/ START 2008	1/ Only ID list used (36/76 drugs) 2/ 19/65 criteria used 3/ 13/22 criteria used	*1/ 73 (8.5%)** *2/ 50 (5.8%)** *3/ 68 (7.9%)**
Scotland									
Barnett et al. (2011)[67]	2005-2006	66-99 years	65742	75.2 (6.8)	8.8 (2.6)	Dispensing DB + Prescribing DB + Medical record	Beers 2003	1/ Only ID list used (14/48 criteria)*	20304 (30.9%)
Serbia									
Kovačevíc et al. (2014)[24]	2012	≥65 years ≥1 drug	509	74.8 (6.5)	5.1 (2.2)	Patient interview	1/ STOPP 2008 2/ START 2008	1/ 17/65 criteria used 2/ 15/22 criteria used	1/ 139 (27.3%) 2/ 257 (50.5%)

Table 2.1.1 (Continued): Summary of the manuscripts included in the systematic review

Country *Author (year published)*	Period studied	Inclusion criteria	Sample size (patients / *prescriptions*)	Age (year); Mean (SD)	No. of drugs per patient / *prescription;* Mean (SD)	Data Collection Method	Screening Method based on (only referenced on first mentioning)	Adaptation of original screening method	Prevalence (patients or *prescriptions* with ≥1 PIP; no. (%))
Spain									
Gavilán Moral et al. (2006)[68]	- [$]	≥65 years	143	81.3 (7.9)	6.8 (3.4)	Patient interview	Beers 1997	Only ID list used (NM)	50 (35.0%)
Conejos Miquel et al. (2010)[69]	- [$]	≥70 years	50	78.8 (5.3)	- [$]	Dispensing DB + Medical record	1/ Beers 2003 2/ STOPP 2008 3/ START 2008	1/ Both ID- and CD-list used (68/68 criteria) 2/ 65/65 criteria used 3/ 22/22 criteria used	1/ 12 (24.0%) 2/ 18 (36.0%) 3/ 14 (28.0%)
Mera et al. (2011)[70]	2009	=85 years	78	85 (0)	6.1 (3.3)	Patient interview + Medical record	COMP: Beers 91 & STOPP 2008	Beers 91: 23/30 criteria used STOPP: 33/65 criteria used Total: 39 criteria used	54 (69.2%)
Lesende et al. (2013)[71]	- [$]	≥65 years ≥4 drugs	100	77.2 (5.7)	12.3 (3.6)	Medical record	1/ STOPP 2008 2/ START 2008	1/ 65/65 criteria used 2/ 22/22 criteria used	1/ 42 (42.0%) 2/ 31 (31.0%)
Blanco-Reina et al. (2014)[26]	2005-2008	≥65 years	407	79.3 (8.0)	4.5 (2.9)	Patient interview	1/ Beers 2003 2/ Beers 2012[14] 3/ STOPP 2008	1/ Both ID- and CD-list used (21/68 criteria) 2/ Both ID- and CD-list used (18/53 criteria) 3/ 25/65 criteria used	1/ 99 (24.3%) 2/ 179 (44.0%) 3/ 144 (35.4%)
Parodi López et al. (2014)[72]	2011	≥65 years	247	77 (7.0)	Median (IQR) 5 (3-8)	Medical record	1/ STOPP 2008 2/ START 2008	1/ 65/65 criteria used 2/ 22/22 criteria used	1/ 81 (32.8%) 2/ 73 (29.6%)
Sweden									
Klarin et al. (2005)[e, 73]	1995-1998	≥75 years	657	82.2 (- [$])[e]	4.4 (3.3)[e]	Patient interview	COMP: Beers 1997, McLeod & Robertson[74]	23 criteria used	102 (15.5%)
Johnell et al. (2007)[75]	2005	≥75 years	732228	82 (- [£])	5.4 (- [£])	Dispensing DB	SQIs[76]	4/4 criteria used	132153 (16.5%)
Switzerland									
Blozik et al. (2013)[77]	2008-2010	≥65 years	220453	- [$]	- [$] (41.2% ≥5)	Insurance Data	1/ Beers 2003 2/ PRISCUS	1/ Only ID list used (40/76 drugs)* 2/ 53/82 criteria used	1/ 22708 (10.3%) 2/ 35272 (16.0%)
Reich et al. (2014)[78]	2008-2012	≥65 years	49668	74.6 (6.5)	10.1 (7.7)	Insurance Data	1/ Beers 2003 2/ PRISCUS 3/ Beers 2012	1/ Only ID list used (40/76 drugs)* 2/ 53/82 criteria used* 3/ - [£]	1/ 4669 (9.4%)* 2/ 7252 (14.6%)* 3/ 8146 (16.4%)*
The Netherlands									
Van der Hooft et al. (2005)[c, 79]	1997-2001	≥65 years	25258	74.9 (- [$])	- [$]	Primary Care DB	1/ Beers 1997 2/ Beers 2003	1/ Both ID- (21/28 criteria) and CD-list (11/15 criteria) used (32/43 criteria) 2/ Both ID- (30/48 criteria) and CD-list (12/20 criteria) used (43/68 criteria)	1/4673 (18.5%) 2/ 5052 (20.0%)
Denneboom et al. (2006)[80]	2001-2002	≥75 years ≥4 drugs	107	81 (- [$])	6.8 (- [$])	Dispensing DB	MAI (Adapted)	10/10 QI criteria used	105 (98%)
Turkey									
Ay et al. (2005)[f, 81]	2000	≥70 years	1019	74.6 (5.1)	2.9 (2.0)	Patient interview	Beers 1997	Only ID list used (11/28 criteria)	100 (9.8%)
Yayla et al. (2013)[82]	2012*	≥65 years	325	73.2 (6.4)	2.2 (1.0)	Patient interview	1/ STOPP 2008 2/ START 2008	1/ 65/65 criteria used* 2/ 22/22 criteria used*	1/ 48 (14.8%) 2/ 0 (0%)

Table 2.1.1 (Continued): Summary of the manuscripts included in the systematic review

Country *Author (year published)*	Period studied	Inclusion criteria	Sample size (patients / *prescriptions*)	Age (year); Mean (SD)	No. of drugs per patient / *prescription;* Mean (SD)	Data Collection Method	Screening Method based on (only referenced on first mentioning)	Adaptation of original screening method	Prevalence (patients or *prescriptions* with ≥1 PIP; no. (%))
United Kingdom									
De Wilde et al. (2007)[c, 83]	2003	≥65 years	171690	- [$]	- [$]	Primary Care DB	Beers 2003	Both ID- (60/76 drugs, 10 criteria added) and CD-list (20/20 criteria) used.	55325 (32.2%)
Carey et al. (2008)[c, 84]	2005	≥65 years	218567	- [$] (13% ≥85y)	7.4 (- [$])	Primary Care DB	Beers 2003	Both ID- (60/76 drugs, 10 criteria added) and CD-list (20/20 criteria) used.	61958 (28.3%)
Bradley et al. (2014)[85]	2007	≥70 years	1019491	- [£] (78.5% ≥75y)	- [£]	Prescribing DB + Medical Record	1/ STOPP 2008 2/ STOPP 2008	1/ 28/65 criteria used 2/ 52/65 criteria used	1/ 151598 (14.9%) 2/ 295653 (29.0%)
Multiple Countries									
Fialová et al. (2005)[a, 86]	2000-2003	≥65 years	1/ 428 2/ 400 3/ 187 4/ 405 5/ 412 6/ 198 7/ 388 8/ 289 9/ 2707	9/ 82.2 (7.2)	9/ - [$] (51.0%≥6)	Patient interview	COMP: Beers 1997, Beers 2003 and mcLeod 1997	Beers 97: 8/28 criteria used Beers 03: 17/48 criteria used McLeod 97: 6/38 criteria used Total: 28 different criteria	1/ 176 (41.1%) 2/ 23 (5.8%) 3/ 39 (20.9%) 4/ 61 (15.1%) 5/ 109 (26.5%) 6/ 26 (13.1%) 7/ 60 (15.5%) 8/ 41 (14.2%) 9/ 1381 (19.8%)
1/ Czech Republic									
2/ Denmark									
3/ Finland									
4/ Iceland									
5/ Italy									
6/ The Netherlands									
7/ Norway									
8/ United Kingdom									
9/ Overall									

CD: *refers to the second part of the Beers list, items considering confirmed underlying diagnosis;* ***COMP:*** *Compilation;* ***DB****: Database;* ***DDIs:*** *Drug-Drug Interactions****;*** ***FTF:*** *Face-to-face;* ***ID:*** *refers to the first part of the Beers list, items independent of underlying diagnosis****;*** ***SQI:*** *(Swedish) Quality Indicators;* ***SD:*** *standard deviation;* ***START****: Screening Tool to Alert doctors to Right Treatment;* ***STOPP****: Screening Tool of Older Person's Prescriptions*

***** *E-mail confirmation of the data, included in the table.*
[£] *E-mail confirmation that source data are no longer available or calculations cannot be made from available data.*
[$] *E-mail with request for additional data to corresponding author was not answered.*

[a] *A total of 169 patients were included in this study. 158 (93%) were ≥65y. Mean age (SD) and mean (SD) number of drugs of the complete sample is given (i.e. for 169 patients). % of PIPs is given for subsample of 158 patients.*
[b] *700/781 patients are community-dwelling*
[c] *This study reports on multiple measurements. Only the most recent data are presented in the table. Berdot et al only mentioned PIP at study-entry.*
[d] *Only the mean age (SD) and the mean number of drugs (SD) for the largest included subgroup (Poznan area)are reported in the summary (680/1000). No overall value is given in the original manuscript.*
[e] *657/785 patients are community-dwelling (83.7%). Mean age (SD) and mean (SD) number of drugs of the complete sample is given (i.e. for 785 patients). % of PIPs is given for subsample of 657 patients*
[f] *Only the mean age (SD) and the mean number of drugs (SD) for the largest included subgroup (females) are reported in the summary (624//1019). No overall value is given in the original manuscript.*

PIP Prevalence

The overall estimated weighted PIP prevalence was 22.6% (CI: 19.5-26.7%). PIP prevalence ranged from 0.0 % to 98.0%, with sample sizes varying from 50 to 1,019,491 patients. A large heterogeneity and inconsistency in study design (data collection methods) and outcome measures (screening methods used) was however observed.

Eighteen of the 52 included manuscripts used more than one screening method to assess PIP prevalence, resulting in 82 different sample screenings. Nineteen of the sample screenings were based on Beers 2003 criteria[11], 10 on the Beers 1997 criteria[31], 14 on STOPP-criteria (2008 version) [55], 8 on START-criteria (2008 version)[55] and 7 on the PRISCUS-list[16]. Twenty-two sample screenings were carried out using compilations of the previously mentioned lists or used country specific lists such as the Laroche-criteria[42], the improving prescribing in the elderly tool (IPET)[53] or NORGEP-criteria[64]. Only two sample screenings used the Medication Appropriateness Index (MAI) but accounted however for the two highest mentioned prevalence rates (84% and 98%)[34 80]. In only 14 of the 82 sample screenings (17%) the complete original screening method was maintained. In all other sample screenings (n = 68), the screening method was adapted.

Accordingly, large differences were seen in the method of data collection. Of the 52 included manuscripts, 16 collected data via patient interviews (30 sample screenings). Eleven studies used insurance data (16 sample screenings) while 11 manuscripts used another specific type of database (dispensing, prescribing or primary care database – 13 sample screenings). Four studies used medical records (9 sample screenings), 4 used a questionnaire, either filled in by a general practitioner or patient (5 sample screenings) and 6 used a combination of data sources (9 sample screenings).

To estimate an overall conditional prevalence for different methods of data collection, different screening methods and possible interactions, fifty-nine sample screenings were included in the random effects model (parameter estimates from the model are presented in Appendix 2.1.2). Only the data collection method proved to be a significant predictor in the model and in addition, it appears that only PIP prevalence calculated from insurance data significantly differs from the other data collection method categories ($p<.05$).

Factors associated with PIP

Twenty-seven of the 52 included manuscripts evaluated factors associated with overuse and misuse without taking underuse into consideration. Seventeen used multivariate logistic regression analyses, 8 a bivariate logistic regression and 2 a univariate logistic regression. The studies evaluated a total of 24 different risk factors. All risk factors, evaluated in at least 3 studies, are presented in Table 2.1.2. Polypharmacy, advanced age and female gender were most often taken into account, however only polypharmacy showed a consistent positive association with PIP. Factors that were less often taken into account but showed a repeated positive association in multiple studies with PIP were presence of depression, moderate self-rated health quality, a low functional status or a poor economic status.

Only 2 manuscripts reviewed factors associated with underuse of medication, taking into account polypharmacy, advanced age and female gender in the analyses. One study found a positive association between underuse of medication and polypharmacy and the other between underuse and advanced age. One study found a negative association between underuse of medication and female gender[23 24].

Table 2.1.2: Summary of factors associated with PIP (overuse and misuse) (n = 27)

Risk factor	No. of studies evaluating this risk factor (%)	No. of studies detecting positive association with PIP (%)	No. of studies detecting negative association with PIP (%)	No. of studies detecting no association with PIP (%)
Polypharmacy	27	27 (100)	0 (0)	0 (0)
Advanced age	25	12 (48)	2 (8)	11 (44)
Female gender	25	10 (40)	2 (8)	13 (52)
Comorbidity score / presence of comorbidities	10	6 (60)	1 (10)	3 (30)
Depressive feelings / depression	7	5 (71)	0 (0)	2 (29)
Reduced cognition	7	4 (57)	0 (0)	3 (43)
Advanced education	7	1 (14)	0 (0)	6 (86)
Moderate SRHQ	6	4 (67)	0 (0)	2 (33)
Poor economic situation / low household income	6	4 (67)	0 (0)	2 (33)
Living alone	6	3 (50)	0 (0)	3 (50)
Low functional status (using ADL-score)	3	3 (100)	0 (0)	0 (0)
Increasing BMI	3	1 (33)	0 (0)	2 (67)
Recent hospital stay	3	1 (33)	0 (0)	2 (67)

ADL: *Activities of Daily Living;* ***BMI:*** *Body Mass Index;* ***SRHQ:*** *Self-Rated Health Quality*

Drugs most frequently involved in PIP

Forty of the 52 included manuscripts mentioned detailed drug information on 53 sample screenings (Appendix 2.1.3).

Forty-seven of those 53 sample screenings used a screening method to detect overuse or misuse. The most frequently overused or misused drugs were: (1) anxiolytics (N05B), (2) antidepressants (N06A) and (3) non-steroidal anti-inflammatory and anti-rheumatic products (M01A). PIP dependent on an underlying diagnosis is part of misuse of drug. However, only 15 of the 47 sample screenings used a screening method that – additional to PIPs independent of underlying diagnosis – also included PIP dependent on confirmed diagnosis (e.g. different STOPP criteria, the second part of the Beers list). Therefore, no PIPs dependent on underlying diagnoses are mentioned in Appendix 2.1.3. We believe however that this information is of importance and therefore, we performed a subanalysis to detect these PIPs and reported them separately in a subsection of Appendix 2.1.3. Eleven of the 15 sample screenings taking into account underlying diagnoses used the STOPP-criteria and 4 the second part of the Beers list. Most frequent were (1) the long-term use of NSAIDs (>3 months) in mild osteoarthritis, (2) the use of calcium channel blockers in chronic constipation and (3) the use of noncardioselective β-blockers in patients with COPD.

The 6 remaining sample screenings used a tool to detect underuse of medication, and all made use of START-criteria. When considering the 10 most prevalent items of each screening, a total of 17 different START-criteria were detected. The START-criterion most often mentioned by the included sample screenings was the omission of antiplatelet therapy in diabetes mellitus with co-existing major cardiovascular risk factors. This criterion was detected in all of the 6 sample screenings. An overview of the other most prevalent underused drugs detected by START-criteria is given in Appendix 2.1.3.

DISCUSSION

In this systematic literature review, we evaluated the prevalence of PIP in community-dwelling older adults across Europe. Our review included studies evaluating all types of PIP (overuse, misuse and underuse) and included all studies irrespective of the fact that they presented detailed information on the specific PIP-items, or used a specific type of data collection. Fifty-two manuscripts were selected, describing 82 different sample screenings with an estimated weighted overall PIP prevalence of 22.6% (CI: 19.5-26.7%).

PIP prevalence

Consistent with the reviews performed by Aparasu et al.[21] and Opondo et al.[10] (both mainly USA based), our review found that about one in five older patients in Europe is exposed to PIP. This suggests that the possible inappropriateness of prescribing in Europe and the USA is comparable. To obtain a contemporary image of the problem, we only included manuscripts published after 2000. It seems though that the overall PIP rate hasn't substantially decreased since the previous reviews despite considerable attention in the scientific literature and increasing research on this topic (22 manuscripts published between 2000 and 2009 compared to 30 between 2010 and 2014). Three other reviews, by Shade et al.[18], Hill-Taylor et al.[17] and Guaraldo et al[87] didn't calculate an overall PIP prevalence. Our estimated mean falls however within the ranges observed in these studies (22.7-74%[17], 21.4-79%[17] and 11.5-62.5%[87]).

The wide range in observed PIP prevalence probably relates to the wide diversity of screening methods used and the sometimes extensive adaptations to these screening methods. In 83% of the sample screenings the original screening method was adapted; either because it was not compatible with the applied data collection method (e.g. STOPP/START on insurance data with no clinical data detected significantly lower prevalence of 6% compared to 30% when used on medical record – Appendix 2.1.2) or because it didn't fully match the European setting (e.g. Beers criteria). Using such adapted screening methods seems contra-intuitive, hampers interpretation of the data, and probably leads to an underestimation of the true PIP prevalence. If limited clinical data are available, the use of the GheOP³S-tool[88] or the Matanovic criteria[33] may offer a better approach, since they both present a comprehensive protocol that screens for overuse, misuse and underuse, are adapted to the European setting and do not require clinical data or confirmed diagnoses.

Moreover, as underuse, overuse and misuse are all types of PIP[12], it is surprising that in multiple research, PIP prevalence is separately given for START and STOPP criteria[23 69 72]. Presenting the prevalence as the proportion of patients with at least one START or STOPP criterion might represent a more accurate image of PIP. Additionally, different data collection methods, differences in quality of prescribing across geographical regions or the status of medication review practices in the European countries could furthermore also have contributed to the reported wide range[89 90].

Despite the impossibility of comparing the individual sample screenings, the information presented in the sample screenings did give an interesting insight in the way data collection methods or used screening methods influence PIP prevalence (see Appendix 2.1.2). Although not significant, there is a trend that the combination of data collection methods leads to higher prevalence. As well, the two screenings that used an implicit screening method – the MAI –, showed the highest PIP prevalence. It will be interesting to see whether the new version of STOPP/START[91], where some implicit criteria were added, will follow this trend and lead to higher prevalence rates.

Factors associated with PIP

Many research showed that advanced age and polypharmacy are important and independent risk factors for the presence of PIPs and ADEs[17 87]. It was however unclear whether other factors are also of significance and could help to further target patient groups at risk for PIPs and ADEs. The present evaluation of risk factors showed that polypharmacy, a low functional status, depression, a moderate self-rated health quality, poor economic situation, a high comorbidity score and reduced cognition are most often positively associated with a higher risk for PIP. It was however remarkable that from those studies that evaluated the association between PIP and advanced age, only in about half a positive association was found[17 87].

Drugs most frequently involved in PIP

In concordance with previous findings[10], we observed that the use of anxiolytics, hypnotics and sedatives are most often involved in PIP. In addition, antidepressants (such as amitriptyline and doxepin), NSAIDs and antithrombotic agents (such as ticlopidine and dipyridamole) are also often involved in PIP. One drug group that was not mentioned in previous systematic research as substantially associated with PIP but highly present in this review, is the “antihistamines for systemic use”-group.

In our review, we additionally focused on PIPs depending on a confirmed diagnosis and underuse because until now, only little systematic research on these types of PIP has been performed. It appears that NSAIDs are most often interfering with underlying diseases such as peptic ulcer and moderate or severe hypertension. In contrast to other research[92-94], interactions with chronic heart failure, dementia and renal impairment are not often detected in our review. This discrepancy could be explained by the fact that many of the research included in the current review used data collection methods without confirmed diagnoses as 3 were solely dispensing databases, 5 were based on patient interviews and 7 (partially) on medical records.

Considering underuse, the results of our review are in line with a previous review performed by Hill-Taylor et al., reviewing studies that used START-criteria[17]. Besides the underuse of calcium/vitamin D supplements and statin therapy, we observed that antiplatelet therapy and metformin are often omitted in diabetes mellitus as well as β-blockers in chronic stable angina.

Strengths and limitations

In order to obtain as much available research as possible, more than one electronic database was used and literature was supplemented by manually checking reference lists of all included manuscripts. Compared to previously published reviews[10 87], this systematic review gives a larger overview of PIP, including underuse, drug-disease interactions and drug groups most often associated with PIP. In addition, the review specifically focuses on the European setting which was not the focus of any other previous research[10 17 18 21 87]. Furthermore, this is the first review summarizing all research regarding risk factors for PIP. By limiting the time period and including all European studies, we attempted to provide a contemporary and country-specific overview of PIP, offering a point of reference for countries in which PIP is still poorly characterized. Nevertheless, several limitations remain when interpreting the findings of this systematic review. Comparing results from the included manuscripts was difficult due to use of different inclusion criteria, different screening methods and inconsistent adaptations of these tools. Additionally, differences in health-care settings and countries may also have impacted PIP prevalence.

Conclusion

This systematic review shows that PIP prevalence in community-dwelling older adults in Europe remains high and depends partially on the screening method used. Additionally, the review gives an insight in the risk factors most commonly associated with PIP and the drug groups most commonly involved in PIP. The results can contribute to outlining cross-border and country-specific action plans to reduce PIP in primary care as they represent an important opportunity to improve the prescribing quality in the primary care setting. There is a need for randomized controlled trials evaluating interventions that resolve PIP in the most cost-effective way to improve patient related outcomes such as quality of life and to prevent drug related problems leading to hospitalizations. A formal and straightforward screening method can be a great support in the evaluation of the patient's pharmacotherapy, but should always be embedded in a global patient assessment by a multidisciplinary care team. Only then, positive effects on patients' health outcomes can be shown[95]. Moreover, the complexity of the matter makes it unlikely that a single intervention at one point in the medication management process will be sufficient to tackle PIP. It had been demonstrated that multidisciplinary interventions including education and a systematic screening method are the most efficient for resolving and preventing all types of PIP[96-98].

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AUTHOR CONTRIBUTIONS

Tommelein had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Conception and design: Tommelein, Boussery
Analysis of the data: Tommelein, Colin
Interpretation of the data: Tommelein, Colin
Drafting of the article: Tommelein
Critical revision and final approval of the article: Tommelein, Mehuys, Petrovic, Somers, Colin, Boussery
Study supervision: Boussery

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All authors completed the ICMJE-form. No competing interests were declared.

REFERENCES

1. *Statistical Office of the European Communities. EUROSTAT: Population data - Proportion of population aged 65 and over. Secondary EUROSTAT: Population data - Proportion of population aged 65 and over. http://ec.europa.eu/eurostat/tgm/table.do?tab=table&init=1&language=en&pcode=tps00028&plugin=1.*
2. *Al Hamid A, Ghaleb M, Aljadhey H, et al. A systematic review of hospitalization resulting from medicine-related problems in adult patients. British journal of clinical pharmacology 2014;**78**(2):202-17.*
3. *Tache SV, Soennichsen A, Ashcroft DM. Prevalence of Adverse Drug Events in Ambulatory Care: A Systematic Review. Annals of Pharmacotherapy 2011;**45**(7-8):977-89.*
4. *Thomsen LA, Winterstein AG, Sondergaard B, et al. Systematic review of the incidence and characteristics of preventable adverse drug events in ambulatory care. The Annals of pharmacotherapy 2007;**41**(9):1411-26.*
5. *Lund BC, Carnahan RM, Egge JA, et al. Inappropriate Prescribing Predicts Adverse Drug Events in Older Adults. Annals of Pharmacotherapy 2010;**44**(6):957-63.*
6. *Hamilton H, Gallagher P, Ryan C, et al. Potentially inappropriate medications defined by STOPP criteria and the risk of adverse drug events in older hospitalized patients. Archives of internal medicine 2011;**171**(11):1013-9.*
7. *Price SD, Holman CD, Sanfilippo FM, et al. Association between potentially inappropriate medications from the Beers criteria and the risk of unplanned hospitalization in elderly patients. The Annals of pharmacotherapy 2014;**48**(1):6-16.*
8. *Pasina L, Djade CD, Tettamanti M, et al. Prevalence of potentially inappropriate medications and risk of adverse clinical outcome in a cohort of hospitalized elderly patients: results from the REPOSI Study. Journal of clinical pharmacy and therapeutics 2014;**39**(5):511-5.*
9. *Laroche ML, Charmes JP, Nouaille Y, et al. Is inappropriate medication use a major cause of adverse drug reactions in the elderly? British journal of clinical pharmacology 2007;**63**(2):177-86.*
10. *Opondo D, Eslami S, Visscher S, et al. Inappropriateness of Medication Prescriptions to Elderly Patients in the Primary Care Setting: A Systematic Review. PloS one 2012;**7**(8).*
11. *Fick DM, Cooper JW, Wade WE, et al. Updating the beers criteria for potentially inappropriate medication use in older adults - Results of a US consensus panel of experts. Archives of internal medicine 2003;**163**(22):2716-24.*
12. *Spinewine A, Schmader KE, Barber N, et al. Appropriate prescribing in elderly people: how well can it be measured and optimised? Lancet 2007;**370**(9582):173-84.*
13. *Hanlon JT, Schmader KE. The Medication Appropriateness Index at 20: Where It Started, Where It Has Been, and Where It May Be Going. Drugs & aging 2013;**30**(11):893-900.*
14. *American Geriatrics Society updated Beers Criteria for potentially inappropriate medication use in older adults. Journal of the American Geriatrics Society 2012;**60**(4):616-31.*
15. *O'Mahony D, O'Sullivan D, Byrne S, et al. STOPP/START criteria for potentially inappropriate prescribing in older people: version 2. Age and ageing 2014.*
16. *Holt S, Schmiedl S, Thurmann PA. Potentially inappropriate medications in the elderly: the PRISCUS list. Deutsches Arzteblatt international 2010;**107**(31-32):543-51.*
17. *Hill-Taylor B, Sketris I, Hayden J, et al. Application of the STOPP/START criteria: a systematic review of the prevalence of potentially inappropriate prescribing in older adults, and evidence of clinical, humanistic and economic impact. Journal of clinical pharmacy and therapeutics 2013;**38**(5):360-72.*
18. *Shade MY, Berger AM, Chaperon C. Potentially inappropriate medications in community-dwelling older adults. Research in gerontological nursing 2014;**7**(4):178-92.*
19. *Gallagher PF, O'Connor MN, O'Mahony D. Prevention of Potentially Inappropriate Prescribing for Elderly Patients: A Randomized Controlled Trial Using STOPP/START Criteria. Clinical Pharmacology & Therapeutics 2011;**89**(6):845-54.*
20. *Beers MH, Ouslander JG, Rollingher I, et al. Explicit criteria for determining inappropriate medication use in nursing home residents. UCLA Division of Geriatric Medicine. Archives of internal medicine 1991;**151**(9):1825-32.*
21. *Aparasu RR, Mort JR. Inappropriate prescribing for the elderly: beers criteria-based review. The Annals of pharmacotherapy 2000;**34**(3):338-46.*
22. *Gallagher P, Barry P, O'Mahony D. Inappropriate prescribing in the elderly. Journal of clinical pharmacy and therapeutics 2007;**32**(2):113-21.*
23. *Galvin R, Moriarty F, Cousins G, et al. Prevalence of potentially inappropriate prescribing and prescribing omissions in older Irish adults: findings from The Irish LongituDinal Study on Ageing study (TILDA). European journal of clinical pharmacology 2014;**70**(5):599-606.*
24. *Kovacevic SV, Simisic M, Rudinski SS, et al. Potentially Inappropriate Prescribing in Older Primary Care Patients. PloS one 2014;**9**(4).*
25. *Primejdie D, Bojita M, Popa A. POTENTIAL INAPPROPRIATE MEDICATION USE IN COMMUNITY - DWELLING ELDERLY PATIENTS. A QUALITATIVE STUDY. Farmacia 2012;**60**(3):366-78.*
26. *Blanco-Reina E, Ariza-Zafra G, Ocana-Riola R, et al. 2012 American Geriatrics Society Beers Criteria: Enhanced Applicability for Detecting Potentially Inappropriate Medications in European Older Adults? A Comparison with the Screening Tool of Older Person's Potentially Inappropriate Prescriptions. Journal of the American Geriatrics Society 2014;**62**(7):1217-23.*
27. *Shamseer L, Moher D, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ (Clinical research ed) 2015;**349**:g7647.*
28. *WHO Collaborating Centre for Drug Statistics Methodology. ATC/DDD Index 2015.*
29. *Koper D, Kamenski G, Flamm M, et al. Frequency of medication errors in primary care patients with polypharmacy. Family practice 2013;**30**(3):313-19.*
30. *Vlahovic-Palcevski V, Bergman U. Quality of prescribing for the elderly in Croatia-computerized pharmacy data can be used to screen for potentially inappropriate prescribing. European journal of clinical pharmacology 2004;**60**(3):217-20.*
31. *Beers MH. Explicit criteria for determining potentially inappropriate medication use by the elderly. An update. Archives of internal medicine 1997;**157**(14):1531-6.*
32. *Popovic B, Quadranti NR, Matanovic SM, et al. Potentially inappropriate prescribing in elderly outpatients in Croatia. European journal of clinical pharmacology 2014;**70**(6):737-44.*
33. *Mimica Matanovic S, Vlahovic-Palcevski V. Potentially inappropriate medications in the elderly: a comprehensive protocol. European journal of clinical pharmacology 2012;**68**(8):1123-38.*

34. *Bregnhoj L, Thirstrup S, Kristensen MB, et al. Prevalence of inappropriate prescribing in primary care. Pharmacy World & Science 2007;**29**(3):109-15.*
35. *Hanlon JT, Schmader KE, Samsa GP, et al. A method for assessing drug therapy appropriateness. Journal of clinical epidemiology 1992;**45**(10):1045-51.*
36. *Pitkala KH, Strandberg TE, Tilvis RS. Inappropriate drug prescribing in home-dwelling, elderly patients: a population-based survey. Archives of internal medicine 2002;**162**(15):1707-12.*
37. *Leikola S, Dimitrow M, Lyles A, et al. Potentially Inappropriate Medication Use Among Finnish Non-Institutionalized People Aged >= 65 Years A Register-Based, Cross-Sectional, National Study. Drugs & aging 2011;**28**(3):227-36.*
38. *Bell JS, Ahonen J, Lavikainen P, et al. Potentially inappropriate drug use among older persons in Finland: application of a new national categorization. European journal of clinical pharmacology 2013;**69**(3):657-64.*
39. *Finnish Medicines Agency. Database of medication for the elderly. Secondary Database of medication for the elderly 2010. http://www.fimea.fi/development/medicines_information/database_of_medication_for_the_elderly.*
40. *Lechevallier-Michel N, Gautier-Bertrand M, Alperovitch A, et al. Frequency and risk factors of potentially inappropriate medication use in a community-dwelling elderly population: results from the 3C Study. European journal of clinical pharmacology 2005;**60**(11):813-9.*
41. *Berdot S, Bertrand M, Dartigues JF, et al. Inappropriate medication use and risk of falls--a prospective study in a large community-dwelling elderly cohort. BMC geriatrics 2009;**9**:30.*
42. *Laroche ML, Charmes JP, Merle L. Potentially inappropriate medications in the elderly: a French consensus panel list. European journal of clinical pharmacology 2007;**63**(8):725-31.*
43. *Bongue B, Naudin F, Laroche ML, et al. Trends of the potentially inappropriate medication consumption over 10 years in older adults in the East of France. Pharmacoepidemiology and drug safety 2009;**18**(12):1125-33.*
44. *Bongue B, Laroche ML, Gutton S, et al. Potentially inappropriate drug prescription in the elderly in France: a population-based study from the French National Insurance Healthcare system. European journal of clinical pharmacology 2011;**67**(12):1291-9.*
45. *Jardin M, Bocquier A, Cortaredona S, et al. [Potentially inappropriate prescriptions for the elderly: a study of health insurance reimbursements in Southeastern France]. Revue d'epidemiologie et de sante publique 2012;**60**(2):121-30.*
46. *Fiss T, Dreier A, Meinke C, et al. Frequency of inappropriate drugs in primary care: analysis of a sample of immobile patients who received periodic home visits. Age and ageing 2011;**40**(1):66-73.*
47. *Amann U, Schmedt N, Garbe E. Prescribing of potentially inappropriate medications for the elderly: an analysis based on the PRISCUS list. Deutsches Arzteblatt international 2012;**109**(5):69-75.*
48. *Goltz L, Kullak-Ublick GA, Kirch W. Potentially inappropriate prescribing for elderly outpatients in Germany: a retrospective claims data analysis. International journal of clinical pharmacology and therapeutics 2012;**50**(3):185-94.*
49. *Schubert I, Kupper-Nybelen J, Ihle P, et al. Prescribing potentially inappropriate medication (PIM) in Germany's elderly as indicated by the PRISCUS list. An analysis based on regional claims data. Pharmacoepidemiology and drug safety 2013;**22**(7):719-27.*
50. *Zimmermann T, Kaduszkiewicz H, van den Bussche H, et al. Potentially inappropriate medication in elderly primary care patients. A retrospective, longitudinal analysis. Bundesgesundheitsblatt-Gesundheitsforschung-Gesundheitsschutz 2013;**56**(7):941-49.*
51. *Linder R, Schneider U, Kothemann M, et al. [Physicians' prescription behavior of potentially inappropriate medications for elderly people: an analysis using the PRISCUS list based on TK routine data]. Deutsche medizinische Wochenschrift (1946) 2014;**139**(19):983-9.*
52. *Ryan C, O'Mahony D, Kennedy J, et al. Appropriate prescribing in the elderly: an investigation of two screening tools, Beers criteria considering diagnosis and independent of diagnosis and improved prescribing in the elderly tool to identify inappropriate use of medicines in the elderly in primary care in Ireland. Journal of clinical pharmacy and therapeutics 2009;**34**(4):369-76.*
53. *McLeod PJ, Huang AR, Tamblyn RM, et al. Defining inappropriate practices in prescribing for elderly people: a national consensus panel. CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne 1997;**156**(3):385-91.*
54. *Ryan C, O'Mahony D, Kennedy J, et al. Potentially inappropriate prescribing in an Irish elderly population in primary care. British journal of clinical pharmacology 2009;**68**(6):936-47.*
55. *Ryan C, O'Mahony D, Kennedy J, et al. Screening tools for elderly patients in primary care: STOPP (Screening Tool of Older Persons' potentially inappropriate Prescriptions) and START (Screening Tool to Alert doctors to Right i.e. appropriate, indicated Treatment). Pharmacoepidemiology and drug safety 2008;**17**(7):746-47.*
56. *Cahir C, Fahey T, Teeling M, et al. Potentially inappropriate prescribing and cost outcomes for older people: a national population study. British journal of clinical pharmacology 2010;**69**(5):543-52.*
57. *Cahir C, Bennett K, Teljeur C, et al. Potentially inappropriate prescribing and adverse health outcomes in community dwelling older patients. British journal of clinical pharmacology 2014;**77**(1):201-10.*
58. *Maio V, Yuen EJ, Novielli K, et al. Potentially inappropriate medication prescribing for elderly outpatients in Emilia Romagna, Italy: a population-based cohort study. Drugs & aging 2006;**23**(11):915-24.*
59. *Landi F, Russo A, Liperoti R, et al. Impact of inappropriate drug use on physical performance among a frail elderly population living in the community. European journal of clinical pharmacology 2007;**63**(8):791-9.*
60. *Lapi F, Pozzi C, Mazzaglia G, et al. Epidemiology of Suboptimal Prescribing in Older, Community Dwellers A Two-Wave, Population-Based Survey in Dicomano, Italy. Drugs & aging 2009;**26**(12):1029-38.*
61. *Maio V, Del Canale S, Abouzaid S. Using explicit criteria to evaluate the quality of prescribing in elderly Italian outpatients: a cohort study. Journal of clinical pharmacy and therapeutics 2010;**35**(2):219-29.*
62. *Bradley MC, Fahey T, Cahir C, et al. Potentially inappropriate prescribing and cost outcomes for older people: a cross-sectional study using the Northern Ireland Enhanced Prescribing Database. European journal of clinical pharmacology 2012;**68**(10):1425-33.*
63. *Nyborg G, Straand J, Brekke M. Inappropriate prescribing for the elderly-a modern epidemic? European journal of clinical pharmacology 2012;**68**(7):1085-94.*
64. *Rognstad S, Brekke M, Fetveit A, et al. The Norwegian General Practice (NORGEP) criteria for assessing potentially inappropriate prescriptions to elderly patients. Scandinavian journal of primary health care 2009;**27**(3):153-59.*
65. *Rajska-Neumann A, Wieczorowska-Tobis K. Polypharmacy and potential inappropriateness of pharmaco-logical treatment among community-dwelling elderly patients. Archives of gerontology and geriatrics 2007;**44 Suppl 1**:303-9.*
66. *de Oliveira Martins S, Soares MA, Foppe van Mil JW, et al. Inappropriate drug use by Portuguese elderly outpatients--effect of the Beers criteria update. Pharmacy world & science : PWS 2006;**28**(5):296-301.*
67. *Barnett K, McCowan C, Evans JMM, et al. Prevalence and outcomes of use of potentially inappropriate medicines in older people: cohort study stratified by residence in nursing home or in the community. Bmj Quality & Safety 2011;**20**(3):275-81.*

68. Gavilan Moral E, Morales Suarez-Varela MT, Hoyos Esteban JA, et al. [Inappropriate multiple medication and prescribing of drugs immobile elderly patients living in the community]. Atencion primaria / Sociedad Espanola de Medicina de Familia y Comunitaria 2006;**38**(9):476-80.
69. Conejos Miguel MD, Sanchez Cuervo M, Delgado Silveira E, et al. Potentially inappropriate drug prescription in older subjects across health care settings. European Geriatric Medicine 2010;**1**(1):9-14.
70. Mera F, Mestre D, Almeda J, et al. [Inappropriate prescription in the community elderly, are we aware of?]. Revista espanola de geriatria y gerontologia 2011;**46**(3):125-30.
71. Lesende IM, Crespo IM, Lopez GM, et al. Potentiality of STOPP/START criteria used in primary care to effectively change inappropriate prescribing in elderly patients. European Geriatric Medicine 2013;**4**(5):293-98.
72. Parodi Lopez N, Villan Villan YF, Granados Menendez MI, et al. Potentially inappropriate prescribing in patients over 65 years-old in a primary care health centre. Atencion Primaria 2014;**46**(6):290-97.
73. Klarin I, Wimo A, Fastbom J. The association of inappropriate drug use with hospitalisation and mortality: a population-based study of the very old. Drugs & aging 2005;**22**(1):69-82.
74. Robertson HA, MacKinnon NJ. Development of a list of consensus-approved clinical indicators of preventable drug-related morbidity in older adults. Clinical therapeutics 2002;**24**(10):1595-613.
75. Johnell K, Fastbom J, Rosen M, et al. Inappropriate drug use in the elderly: a nationwide register-based study. The Annals of pharmacotherapy 2007;**41**(7):1243-8.
76. National Board of Health and Welfare (Socialstyrelsen). Indikatorer för god läkemedelsterapi hos äldre Secondary Indikatorer för god läkemedelsterapi hos äldre 2003. http://www.socialstyrelsen.se/publikationer2010/2010-6-29.
77. Blozik E, Rapold R, von Overbeck J, et al. Polypharmacy and potentially inappropriate medication in the adult, community-dwelling population in Switzerland. Drugs & aging 2013;**30**(7):561-8.
78. Reich O, Rosemann T, Rapold R, et al. Potentially inappropriate medication use in older patients in Swiss managed care plans: prevalence, determinants and association with hospitalization. PloS one 2014;**9**(8):e105425.
79. van der Hooft CS, t Jong GW, Dieleman JP, et al. Inappropriate drug prescribing in older adults: the updated 2002 Beers criteria - a population-based cohort study. British journal of clinical pharmacology 2005;**60**(2):137-44.
80. Denneboom W, Dautzenberg MGH, Grol R, et al. Analysis of polypharmacy in older patients in primary care using a multidisciplinary expert panel. British Journal of General Practice 2006;**56**(528):504-10.
81. Ay P, Akici A, Harmanc H. Drug utilization and potentially inappropriate drug use in elderly residents of a community in Istanbul, Turkey. International journal of clinical pharmacology and therapeutics 2005;**43**(4):195-202.
82. Yayla ME, Bilge U, Binen E, et al. The Use of START/STOPP Criteria for Elderly Patients in Primary Care. Scientific World Journal 2013.
83. De Wilde S, Carey IM, Harris T, et al. Trends in potentially inappropriate prescribing amongst older UK primary care patients. Pharmacoepidemiology and drug safety 2007;**16**(6):658-67.
84. Carey IM, De Wilde S, Harris T, et al. What factors predict potentially inappropriate primary care prescribing in older people? Analysis of UK primary care patient record database. Drugs & aging 2008;**25**(8):693-706.
85. Bradley MC, Motterlini N, Padmanabhan S, et al. Potentially inappropriate prescribing among older people in the United Kingdom. BMC geriatrics 2014;**14**.
86. Fialova D, Onder G. Medication errors in elderly people: contributing factors and future perspectives. British journal of clinical pharmacology 2009;**67**(6):641-45.
87. Guaraldo L, Cano FG, Damasceno GS, et al. Inappropriate medication use among the elderly: a systematic review of administrative databases. BMC geriatrics 2011;**11**:79.
88. Tommelein E, Petrovic M, Somers A, et al. Older patients' prescriptions screening in the community pharmacy: development of the Ghent Older People's Prescriptions community Pharmacy Screening (GheOP(3)S) tool. J Public Health (Oxf) 2015.
89. Bulajeva A, Labberton L, Leikola S, et al. Medication review practices in European countries. Research in social & administrative pharmacy : RSAP 2014;**10**(5):731-40.
90. Zhang Y, Baicker K, Newhouse JP. Geographic variation in the quality of prescribing. N Engl J Med 2010;**363**(21):1985-8.
91. O'Mahony D, O'Sullivan D, Byrne S, et al. STOPP/START criteria for potentially inappropriate prescribing in older people: version 2. Age and ageing 2015;**44**(2):213-8.
92. Lindblad CI, Hanlon JT, Gross CR, et al. Clinically important drug-disease interactions and their prevalence in older adults. Clinical therapeutics 2006;**28**(8):1133-43.
93. Pugh MJV, Starner CI, Amuan ME, et al. Exposure to Potentially Harmful Drug-Disease Interactions in Older Community-Dwelling Veterans Based on the Healthcare Effectiveness Data and Information Set Quality Measure: Who Is at Risk? Journal of the American Geriatrics Society 2011;**59**(9):1673-78.
94. Aspinall SL, Zhao X, Semla TP, et al. Epidemiology of drug-disease interactions in older veteran nursing home residents. Journal of the American Geriatrics Society 2015;**63**(1):77-84.
95. Onder G, van der Cammen TJ, Petrovic M, et al. Strategies to reduce the risk of iatrogenic illness in complex older adults. Age and ageing 2013;**42**(3):284-91.
96. Kaur S, Mitchell G, Vitetta L, et al. Interventions that can Reduce Inappropriate Prescribing in the Elderly A Systematic Review. Drugs & aging 2009;**26**(12):1013-28.
97. Meid AD, Lampert A, Burnett A, et al. The impact of pharmaceutical care interventions for medication underuse in older people: a systematic review and meta-analysis. British journal of clinical pharmacology 2015.
98. Cullinan S, Fleming A, O'Mahony D, et al. Doctors' perspectives on the barriers to appropriate prescribing in older hospitalized patients: a qualitative study. British journal of clinical pharmacology 2015;**79**(5):860-9.

APPENDIX 2.1.1: DETAILED SEARCH STRATEGY OF THE SYSTEMATIC REVIEW

A. Define text words & synonyms for the text words

1. (elder* or senior* or geriatr* or (old* and adult*)).af.
2. (medication and error*).af.
3. (prescr* and error*).af.
4. (medication and safety).af.
5. (prescr* and safety).af.
6. (inappropriate* and prescr*).af.
7. (inappropriate* and medication).af.
8. 2 or 3 or 4 or 5 or 6 or 7
9. ((primary and care) or (office and practice) or (ambulat* and care) or (general and practice) or (outpatient* and care)).af

B. Perform test searches – I

10. 1 AND 8 AND 9
11. Limit to following languages: German, Dutch, English, French & Spanish
12. 10 AND 11 AND 2000/01/01 to present.date

C. Identify "controlled vocabulary" (keywords) used for the indexing of databases (MeSH)

12. Inappropriate prescribing (Mesh)
13. Aged (Mesh)

D. Perform test searches – II

14. 12 AND 13
15. Limit to following languages: German, Dutch, English, French & Spanish
16. 14 AND 15 AND 2000/01/01 to present.date

E. Remove duplicates

APPENDIX 2.1.2: PREVALENCE OF PIP BASED ON THE MAIN DIFFERENT SCREENING METHODS AND METHODS OF DATA COLLECTION

Appendix Table 2.1.2: Prevalence of PIP based on the main different screening methods and methods of data collection

→ Screening method used ↓Method of Data collection		**Beers**	**PRISCUS**	**START**	**STOPP**
n = 59 – 21.06% [18.2 – 24.2]		18.6% [15.1 – 22.7; 30]	21.9% [13.7 – 33.1; 7]	23.6% [14.8 – 35.4; 8]	25.2% [17.8 – 34.4; 14]
Insurance Data	13.6% [9.9 – 18.2; 13]	12.5% [7.8 – 19.3; 6]	19.0% [11.8 – 29.2; 5]	7.9% [2.3 – 23.8; 1]	5.8% [1.7 - 18.5; 1]
Prescribing, Dispensing or Primary health Database	20.4% [12.9 – 30.7; 9]	17.4% [11.5 – 25.3; 7]	-	-	34.7% [17.4 – 55.7; 2]
FTF interview	23.7% [16.2 – 33.4; 17]	22.9% [16.8 – 30.4; 11]	25.0% [8.6 – 54.2; 1]	27.9% [10.7 – 55.7; 2]	24.9% [13.6 – 41.0; 3]
Questionnaire	23.0% [13.2 – 36.8; 5]	19.3 % [8.9 – 36.9; 2]	37.3% [13.9 – 68.7; 1]	25.9% [10.6 – 59.7; 1]	14.6% [4.6 – 37.8; 1]
Medical Record	25.2% [15.9 – 37.4; 8]	15.5% [6.9 – 31.2; 2]	-	27.5% [15.2 – 44.5; 3]	31.1% [17.6 – 48.8; 3]
Combination methods	28.3% [17.6 – 42.0; 7]	27.7% [13.0 – 49.6; 2]	-	28.0% [8.7 – 61.3; 1]	28.6% [17.3 – 43.3; 4]

All data are presented as: estimated prevalence (%) [confidence interval; number of studies used for the estimation]

APPENDIX 2.1.3: SUMMARY OF THE MOST PREVALENT PIPS

Appendix Table 2.1.3: Summary of the most prevalent PIPs

1. Overuse or misuse of drugs for older patients (47 sample screenings)			
Mentioned drug or drug group	**ATC-category**	**No. of screenings having this drug or drug group in top 10 of most prevalent PIPs (n=47)**	**% of studies reporting this item in their top ten**
Anxiolytics	N05B	38	81
Benzodiazepine derivatives	*N05BA*	*26*	
Diazepam	*N05BA01*	*15*	
Antidepressants	N06A	29	62
Amitriptyline	*N06AA09*	*25*	
Doxepin	*N06AA12*	*8*	
Anti-inflammatory and anti-rheumatic products, non-steroids	M01A	21	45
Indomethacin	*M01AB01*	*14*	
Hypnotics and sedatives	N05C	20	43
Benzodiazepine derivatives	*N05CD*	*16*	
Antithrombotic agents	B01A	20	43
Ticlopidine	*B01AC05*	*9*	
Dipyridamole	*B01AC07*	*9*	
Antihistamines for systemic use	R06A	20	43
Antiadrenergic agents, peripherally acting	C02C	14	30
Doxazosin	*C02CA04*	*11*	
Cardiac glycosides	C01A	13	28
Digoxin	*C01AA05*	*8*	
Antiarrhythmics, class I and III	C01B	13	28
Amiodarone	*C01BC01*	*10*	
1bis. Subanalysis: PIPs for older adults, dependent on an underlying diagnosis (15 of 47 sample screenings)			
Mentioned Drug Disease Interaction	**Diagnosis**	**No. of screenings having this item in top 10 of most prevalent PIPs (n=15)**	**%**
Long-term use of NSAIDs (>3 months)	Mild osteoarthritis	7	47
Calcium Channel Blocker	Chronic constipation	7	47
Noncardioselective β-blocker	COPD	5	33
NSAID	Peptic Ulcer	4	27
Thiazide diuretic	Gout	4	27
NSAID	Moderate-severe hypertension	4	27
Benzodiazepines	Fallers	4	27
2. Underuse of drugs, indicated for older patients (6 sample screenings)			
START-criterion		**No. of screenings having this START-criterion in top 10 of most prevalent PIPs (n=6)**	**%**
Antiplatelet therapy in DM with co-existing major cardiovascular risk factors		6	100
Ca and VitD supplement in patients with known osteoporosis		5	83
Statin therapy in DM if coexisting major cardiovascular risk factors present		5	83
Metformin with DMII ± metabolic syndrome		5	83
Statin therapy with a documented history of coronary, cerebral or peripheral vascular disease, where the patient's functional status remains independent for activities of daily living and life expectancy is >5years		5	83
β-blockers with chronic stable angina		5	83
ACE inhibitor with chronic heart failure		4	67
Aspirin or clopidogrel with a documented history of atherosclerotic coronary, cerebral or peripheral vascular disease in patients with sinus rhythm		4	67
ACE inhibitor or AIIA in diabetes with nephropathy, i.e. overt urinalysis proteinuria or microalbuminuria (>30mg/24h) ± serum biochemical renal impairment		3	50
ACE inhibitor following acute myocardial infarction		3	50
Regular inhaled β_2 agonist or anticholinergic agent for mild to moderate asthma or COPD		3	50

***ACE**: Angiotensin Converting Enzyme; **AIIA**: Angiotensin II antagonist; **Ca**: Calcium; **COPD**: Chronic Obstructive Pulmonary Disease; **DM**: Diabetes Mellitus; **NSAID**: Non Steroidal Anti Inflammatory Drugs; **VitD**: Vitamine D*

PART 2.2:

OLDER PATIENTS' PRESCRIPTIONS SCREENING IN THE COMMUNITY PHARMACY: DEVELOPMENT OF THE GHENT OLDER PEOPLE'S PRESCRIPTIONS COMMUNITY PHARMACY SCREENING (GHEOP³S) TOOL

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ABSTRACT

Background. Aging of the population often leads to polypharmacy. Consequently, Potentially Inappropriate Prescribing (PIP) becomes more frequent. Systematic screening for PIP in older patients in primary care could yield a large improvement in health outcomes, possibly an important task for community pharmacists. In this manuscript, we develop an explicit screening tool to detect relevant PIP that can be used in the typical community pharmacy practice, adapted to the European market.

Methods. Eleven panellists participated in a two-round RAND/UCLA (Research and Development/ University of California, Los Angeles) process, including a round zero meeting, a literature review, a first written evaluation round, a second face-to-face evaluation round, and finally, a selection of those items that are applicable in the contemporary community pharmacy.

Results. Eighteen published lists of PIP for older patients were retrieved from the literature, mentioning 398 different items. After the two-round RAND/UCLA process, 99 clinically relevant items were considered suitable to screen for in a community pharmacy practice. A panel of seven community pharmacists selected 83 items, feasible in the contemporary community pharmacy practice, defining the final GheOP³S-tool.

Conclusion. A novel explicit screening tool (GheOP³S) was developed to be used for PIP-screening in the typical community pharmacy practice.

INTRODUCTION

The population of older patients is increasing in most European countries[1]. Because of co-morbidities and polypharmacy, in addition to age-related changes in pharmacokinetics and pharmacodynamics, older patients are more at risk for adverse drug events (ADEs), leading to increased morbidity, mortality and financial costs[2 3]. ADE prevalence has been shown to be associated with Potentially Inappropriate Prescribing (PIP)[4]. PIP comprises overuse, underuse and misuse of drugs[5] and is thus a potential, though indirect, cause for increased social and economic burden[1 6]. Despite increasing awareness of PIP in older patients and its consequences, PIP prevalence remains high[7 8].

Several interventions aiming to reduce PIP in older patients have been proposed and evaluated[9]. Most of these interventions apply an approach that involves a (clinical) pharmacist who initiates a screening process using a specifically developed screening tool[9]. However, most of these screening tools have been designed and validated solely in hospitals or nursing home settings[10-23], and often require clinical and laboratory information, usually unavailable to the community pharmacist. Therefore, studies that investigate PIP in primary care need to either modify or can only use portions of existing screening criteria[24-27]. Furthermore, some screening tools lack scientific evidence, are not yet validated in clinical practice, do not offer alternative therapeutic options or are not adapted to the European market[10-12 22]. Yet, it seems reasonable that systematic screening for PIP in older patients in primary care could yield a large improvement in health outcomes[28].

The community pharmacist may be ideally placed to engage in this process because of his medication-specific knowledge and because of the availability of an electronic dispensing record in the pharmacy. However, this engagement would require an evidence-based and feasible screening tool specifically suitable for use in the typical community pharmacy practice. Such a tool, to the best of our knowledge, has not yet been developed. In this manuscript, we therefore present the development of the GheOP³S-tool: the Ghent Older People's Prescriptions community Pharmacy Screening tool.

METHODS

Design summary

The GheOP³S-tool was developed in five steps, based on the RAND/UCLA (Research and Development/University of California Los Angeles) method[29]. It included (i) a round zero meeting, (ii) a literature review, (iii) a first written Delphi round, (iv) a second face-to-face Delphi round based on the first round evaluation, and (v) finally, a selection of those items considered applicable in the contemporary community pharmacy practice.

Round zero meeting

In the round zero meeting the research team (ET, MP, AS, EM, KB) reached consensus on the working procedures, and on a 5-part structure for the GheOP³S-tool: Part 1: Potentially inappropriate drugs, independent of diagnosis, Part 2: Potentially inappropriate drugs, dependent on diagnosis, Part 3: Potential Prescribing Omissions (PPOs), Part 4: Drug-Drug Interactions (DDIs) of specific relevance and Part 5: General care-related items to be addressed in the community pharmacy (Table 2.2.1). This structure was deliberately chosen to make community pharmacists familiar with the existence of different types of PIP (underuse, overuse and misuse). Furthermore, this structure offers the opportunity of a stepwise implementation of the tool.

Literature review

To identify previously developed screening tools for the detection of PIP in older adults, a literature search was performed within the PubMed database, using following terms and/or combinations: “elderly”, “older age”, “Aged”, “inappropriate prescribing”, “inappropriate medication”, “protocol”, ”criteria” and “screening tool”. All articles published between January 1990 and December 2012 were eligible if they contained explicit criteria addressing inappropriate prescribing in older patients. For lists that were updated (such as Beers List), only the most recent version was included. References of included articles were manually searched for completeness.

A total of 18 explicit lists were retrieved [10-23] [30-33] and summarized. All mentioned items were classified into the 5-part-structure of the GheOP³S-tool. Criteria to withhold items for evaluation by the Delphi-panel were determined for each part of the tool (See Appendix 2.2.1). This way, a literature-based list of potential items for the tool was created. Furthermore, the literature review was extended with an up-to-date summary of the best available scientific evidence regarding all withheld items. Where evidence from randomized controlled trials was missing, the review also included lower quality of evidence. Additionally, for each PIP item, an alternative therapeutic option was offered, relying on existing evidence.

Table 2.2.1: The GheOP³S-tool

Part 1a: Potentially inappropriate drugs, independent of diagnosis - Drug classes		
No	Item	Alternative
1	Any antidepressant ≥1year	Check if indication is still present, if not: discontinue therapy If therapy is continued: check co-medication
2	Any antipsychotic drug ≥1 month	1st Consider need for chronic use (≈ Is original indication still present?) , if not: discontinue therapy 2nd Always consider non-pharmacological approach
3	Any drug for arterial vascular disorders	Therapeutic abstention Recommend non-pharmacological approach (compression hosiery, discuss referral to surgery with GP, physiotherapy...).
4	Any intermediate acting benzodiazepine or Z-product at full dose or any dose ≥30 subsequent days	- For sleeping disorders: Startup: 1st Consider non-pharmacological approach 2nd Prefer intermediate acting benzodiazepine or Z-product at 1/2 dose of young adults >30 subsequent days: Consider non-pharmacological approach (sleep hygiene), provide GP with withdrawal plan and assure GP of support by pharmacists in withdrawal - For anxiety: consider non-pharmacological approach and switching to SSRI
5	Any short or long-acting benzodiazepine	- Startup: 1st Consider non-pharmacological approach 2nd Prefer intermediate acting benzodiazepine or Z-product at 1/2 dose of young adults <30 subsequent days - Chronic: Consider non-pharmacological approach (sleep hygiene), provide GP with withdrawal plan and assure GP of support by pharmacists in withdrawal
6	Any long-acting sulfonylurea derivative	Metformin or any short-acting sulfonylurea derivative
7	Any nasal vasoconstrictor ≥1 month	Hypertonic saline solution or referral to GP
8	Any oral NSAID	Consider need for anti-inflammatory therapy. If possible: paracetamol or stronger non-NSAID (eg. opioid) is safer choice If therapy is considered necessary, prefer low dose ibuprofen. Avoid NSAIDs with high GI-risk (piroxicam, ketorolac) Prefer ibuprofen/naproxen when CV-risk Prefer NSAIDs with short half-life (ibuprofen, diclofenac) Always add gastroprotection (most evidence for PPI in standard dose) Closely monitor renal function or blood pressure depending on present diagnoses
9	Any PPI at full dose[a] ≥8 weeks	Consider need for chronic use and reduce dose if possible
10	Any recently marketed drug (black triangles)	Consider using drug with similar indication and more evidence in older patients
11	Any sedating antihistaminic drug	1st Verify indication, if not valid: stop therapy or switch to appropriate therapy 2nd If indication is valid: switch to non-sedating antihistaminic drug

Table 2.2.1 (Continued): The GheOP³S-tool

Part 1b: Potentially inappropriate drugs, independent of diagnosis - Specific molecules		
12	Alizapride	Non pharmacological approach, if not sufficient: Reduce dose to 3 x 25 mg/day
13	Bisacodyl	Macrogol/lactulose
14	Clonidine	Consider other safer antihypertensive
15	Codeine and its derivatives for acute cough	Therapeutic abstention or safer alternative (eg., honey)
16	Dabigatran	Warfarin/Acetylsalicylic acid/Heparin, depending on indication
17	Digoxin >0,125mg/day	Digoxin ≤0,125mg/day or serum level between 0,5 and 0,8 µg/L
18	Dipyridamole monotherapy (without ASA)	Acetylsalicylic acid in low dose
19	Ginkgo biloba or Panax ginseng	Referral depending on underlying condition.
20	Liquid paraffin	Macrogol/lactulose
21	Methyldopa	Consider other safer antihypertensive
22	Metoclopramide	Non pharmacological approach, if not sufficient: Reduce dose to 3 X 5 mg/day
23	Pentazocine	Consider paracetamol/codeine combination or pure morphinomimetic agent, depending on indication
24	Phenobarbital	Verify that GP checked diagnosis with prescribing neurologist
25	Pseudoephedrine oral	Short-term intranasal therapy (nasal vasoconstrictor <7 days or hypertonic saline solution)
26	Rivaroxaban or Apixaban	Warfarin/Acetylsalicylic acid/Heparin, depending on indication
27	Senna glycosides	Macrogol/lactulose
28	Picosulfate	Macrogol/lactulose
29	Theophylline	Reconsider indication, preferably stop theophylline
30	Ticlopidine, new prescription	Verify indication, prefer safer alternative
31	Tramadol, new prescription	Check if step-up approach was used. Paracetamol/Codeine could be more appropriate
Part 2a: Potentially inappropriate drugs, dependent on diagnosis - Drug classes		
32	Any antipsychotic other than quetiapine and clozapine with Parkinson's disease	Quetiapine and clozapine are preferred: they appear to be less likely to precipitate worsening of Parkinson's disease
33	Anticholinergics (e.g. Antihistamines, Antidepressants, Antipsychotics, Antispasmodics…) (cfr Table 2.2.2) with dementia or cognitive impairment	Consider drug for same indication with less or none anticholinergic activity (cfr Table 2.2.2)
34	Anticholinergics (e.g. Antihistamines, Antidepressants, Antipsychotics, Antispasmodics…) (cfr Table 2.2.2) with constipation	Consider drug for same indication with less or none anticholinergic activity (cfr Table 2.2.2) If therapy is necessary: add osmotic laxative and apply non-pharmacological measures
35	Anticholinergics (e.g. Antihistamines, Antidepressants, Antipsychotics, Antispasmodics…) (cfr Table 2.2.2) with BPH	Consider drug for same indication with less or none anticholinergic activity (cfr Table 2.2.2) If therapy is necessary: check urinary residue shortly after start with anticholinergic drug. Recheck when suspicion of urine retention.
36	Calcium Channel Blockers with constipation	Prefer class of antihypertensive agent that hasn't constipation as side-effect If calcium channel blocker is necessary, prefer dihydropyridines (amlodipine) and/or add osmotic laxative
37	Non-selective beta-blockers with asthma or COPD	Consider cardioselective beta-blocker or other class of antihypertensive drugs
38	Oral corticosteroids >1 week with diabetes	Closely monitor glycemic control and blood pressure Shorten therapy duration as much as possible Always warn patient about possible dysregulation
39	Oral corticosteroids >1 week with hypertension	Closely monitor blood pressure and glycemic control Shorten therapy duration as much as possible Always warn patient about possible dysregulation
40	Thiazide and loop diuretics with gout	Prefer other class of antihypertensive drugs If diuretic is necessary; prefer potassium sparing (pay attention to renal impairment and probable interactions)

Table 2.2.1 (Continued): The GheOP^{3}S-tool		
Part 2b: Potentially inappropriate drugs, dependent on diagnosis - Specific molecules		
41	Alizapride with Parkinson's disease	1st Always apply non-drug and diet therapy. 2nd If anti-emetic therapy is necessary, prefer domperidone in low dose only if no cardiac risk factors are present and no other QT-prolonging drugs are used
42	Metoclopramide with Parkinson's disease	1st Always apply non-drug and diet therapy. 2nd If anti-emetic therapy is necessary, prefer domperidone in low dose only if no cardiac risk factors are present and no other QT-prolonging drugs are used
Part 3: Potential prescribing omissions		
43	The patient is taking ≥ an equivalent of 7.5 mg of oral prednisone for ≥3 months and is not prescribed Ca/VitD supplementation and bisphosphonates.	
44	The patient is taking narcotic analgesics and is not prescribed appropriate preventative bowel regimen (preferably macrogol or lactulose).	
45	The patient has an elevated risk for osteoporosis (determined via FRAX-tool[48]) and is not prescribed Calcium/Vitamin D supplementation.	
46	The patient is taking oral corticosteroids for ≥1 month and is not prescribed Ca/VitD supplementation.	
47	The patient is not reminded and proposed to undergo yearly influenza vaccination.	
48	The patient is taking methotrexate and is not prescribed folic acid supplementation.	
Part 4: Drug-Drug interactions of specific relevance		
49	VKA + oral NSAIDs	1st Consider need for NSAID. If possible: paracetamol or stronger non-NSAID (eg. opioid) is safer choice 2nd If NSAID is unavoidable, prefer low dose ibuprofen, but always add gastroprotection (most evidence for PPI in standard dose) and keep in mind to closely monitor renal function or blood pressure depending on present diagnoses
50	RAAS-inhibitor + potassium sparing diuretic/potassium supplements/potassium containing drugs[b]	1st Preferably change to non-potassium sparing diuretic/switch to non-potassium containing drug equivalent 2nd If combination is unavoidable: monitor renal function and serum potassium and always inform patient about symptoms of hyperkalaemia
51	VKA + Antiplatelet drugs (esp. ASA), unless prescribed by internist/cardiologist	1st Check if combination is appropriate (artificial valve, up to 3 months after acute coronary syndrome and for rheumatic mitral valve stenosis) 2nd When combination is not appropriate: stop ASA and monitor INR
52	VKA + TMP/SMX	1st Preferably switch to other antibiotic based on indication 2nd If combination is unavoidable: monitor INR
53	Oral NSAID + Oral Corticosteroids	1st Consider need for NSAID. If possible: paracetamol or stronger non-NSAID (eg. opioid) is safer choice 2nd If NSAID is unavoidable, prefer low dose ibuprofen, but always add gastroprotection (most evidence for PPI in standard dose) and keep in mind to closely monitor renal function or blood pressure depending on present diagnoses
54	Oral NSAID + Diuretic	1st Consider need for NSAID. If possible: paracetamol or stronger non-NSAID (eg. opioid) is safer choice 2nd If NSAID is unavoidable: monitor renal function, blood pressure and serum potassium
55	Digoxin + Macrolide antibiotics	1st Preferably switch to other antibiotic based on indication 2nd If combination is unavoidable: monitor serum digoxin levels and always inform patient about signs of digoxin toxicity
56	Digoxin + Verapamil/Diltiazem	1st Starting digoxin: use lowest possible dose 2nd Starting diltiazem: check serum digoxin levels for 1 to 2 weeks 3rd Starting verapamil: lower digoxin dose to 50-70% of usual dose + check serum digoxin levels for 1 to 2 weeks 4th Altering dose of verapamil/diltiazem: alter digoxin dose using serum digoxin levels Always inform patient about signs of digoxin toxicity
57	Lithium + RAAS-inhibitors	1st Consider need for RAAS-inhibitor 2nd If combination is unavoidable: monitor lithium levels within 3-5 days after starting RAAS-inhibitor and always inform patient about signs of lithium toxicity
58	Lithium + Oral NSAID	1st Consider need for NSAID. If possible: paracetamol or stronger non-NSAID (eg. opioid) is safer choice 2nd If combination is unavoidable: determine lithium levels before starting NSAID, give NSAID with strict schedule, check lithium levels after 3 days and modify intake dosage. Act similarly when NSAID is stopped and always inform patient about signs of lithium toxicity

Table 2.2.1 (Continued): The GheOP^{3}S-tool		
59	Lithium + Diuretics	1st Consider need for diuretic. If possible: replace with appropriate alternative. 2nd If combination is unavoidable: determine lithium levels before starting diuretic, avoid 'on demand' use of diuretic, determine lithium levels after 3 days and modify intake dosage. Act similarly when diuretic is stopped and always inform patient about signs of lithium toxicity
60	Theophylline + Quinolones/Macrolides	1st Consider switching to other antibiotic based on indication 2nd If combination is unavoidable: monitor theophylline levels and always consider stopping theophylline
61	RAAS-inhibitor + Oral NSAID	1st Consider need for NSAID. If possible: paracetamol or stronger non-NSAID (eg. opioid) is safer choice. 2nd If NSAID is unavoidable: monitor renal function, blood pressure and serum potassium
62	Oral NSAID + SSRI/SNRI	1st Consider need for NSAID. If possible: paracetamol or stronger non-NSAID (eg. opioid) is safer choice 2nd If NSAID is unavoidable, prefer low dose ibuprofen, but always add gastroprotection (most evidence for PPI in standard dose) and keep in mind to closely monitor renal function or blood pressure depending on present diagnoses
63	RAAS-inhibitor + TMP/SMX	1st Preferably switch to other antibiotic based on indication 2nd If combination is unavoidable: monitor renal function and potassium level
64	Oral antidiabetics/insulin + non-selective beta-blocker	1st Always change to cardioselective beta-blocker (also relevant for eye drops) 2nd Inform patient about possible changes in awareness of hypoglycaemia
65	Oral antidiabetics/insulin + cardioselective beta-blocker	1st Consider need for beta-blocker + check glycemic control 2nd Inform patient about possible changes in awareness of hypoglycaemia
66	Alprazolam/Midazolam/Triazolam/Zolpidem/Zopiclone + Strong CYP3A4 inhibitor	1st Preferably stop benzodiazepine use during treatment with CYP3A4 inhibitor 2nd Switch to equivalent drug with less or without CYP3A4 inhibiting activity
67	CCB + Strong CYP3A4 inhibitor	Preferably switch to equivalent drug with less or without CYP3A4 inhibiting activity
68	Oral NSAID + Antipletelet drugs	1st Consider need for NSAID. If possible: paracetamol or stronger non-NSAID (eg. opioid) is safer choice 2nd If NSAID is unavoidable, prefer low dose ibuprofen, but always add gastroprotection (most evidence for PPI in standard dose) and keep in mind to closely monitor renal function or blood pressure depending on present diagnoses
69	Phenytoin + TMP/SMX	1st Preferably switch to other antibiotic based on indication 2nd If combination is unavoidable: monitor phenytoin levels
70	First dose RAAS-inhibitor at full dosage + pre-treatment with diuretic	1st Start RAAS-inhibitor in lowest possible dose for 3 days 2nd Always give RAAS-inhibitor first 3 days at night and diuretic in the morning 3rd Always inform patient about possible orthostatic effect
71	Tamoxifen + strong CYP2D6 inhibitors	Prefer equivalent drug with less or without CYP2D6 inhibiting activity
72	Calcium + Quinolones/Tetracyclines	1st Use Calcium minimum 2 hours after quinolone/tetracycline or take quinolone/tetracycline 6 hours after intake of Calcium 2nd If not possible: Stop calcium
73	Calcium + Stontium ranelate	1st Use Calcium minimum 2 hours after strontium ranelate or take strontium ranelate 6 hours after intake of Calcium 2nd If not possible: Stop calcium
74	Calcium + Levothyroxine	1st Use Calcium minimum 2 hours after levothyroxine drug or take levothyroxine 6 hours after intake of Calcium 2nd If not possible: Stop calcium
75	Bisphosphonate + Calcium, Magnesium, Zinc, Iron or Aluminium	1st Use complexing agent minimum 2 hours after bisphosphonate 2nd If not possible: Switch to equivalent drug without complexing activity
76	VKA + Vitamin K containing drugs/supplements[c]	1st Switch to equivalent drug/supplement without Vitamin K 2nd If not possible: Monitor INR
77	Any combination of anticholinergic drug	1st Replace 1 of the drugs by an equivalent with less or without anticholinergic activity 2nd Always advise patients to report anticholinergic side-effects

Table 2.2.1 (Continued): The GheOP³S-tool	
Part 5: General care-related items to be addressed in the community pharmacy	
78	Dispensation of over-the-counter medication (NSAID, ASA…) was not added in the electronic patient record.
79	Contra-indications that can unambiguously be derived from patient's medication were not added to the electronic patient record.
80	Availability of assistance in medication/health issues (by nurse, neighbour, children etc.) was not checked nor discussed in frail older patients or older patients with reduced cognition, especially when taking drugs needing strict intake scheme.
81	The patient was not asked which aspects of pharmaceutical care could be improved for him/her (Translated into practical questions for the specific patient: e.g. correct inhaler use, splitting tablets…).
82	Adherence for all chronic medication was not checked or discussed during the past year (refill rate). Adherence for all new medication was not checked or discussed at first refill during the past year?
83	Polypharmacy patients (chronically taking ≥ 5 drugs) were not questioned about whether a clear medication scheme was available to him/her.

***ASA**: Acetylsalicylic acid; **BPH**: Benign prostatic hyperplasia; **CCB**: Calcium Channel Blocker; **COPD**: Chronic Obstructive Pulmonary Disease; **CV-risk**: Cardiovascular risk; **GI-risk**: Gastro-intestinal risk; **GP**: General Practitioner; **NSAID**: Non Steroidal Anti-Inflammatory Drug; **INR**: International Normalized Ratio; **PPI**: Proton Pump Inhibitor; **RAAS-inhibitor**: Renin-Angiotensin-Aldosteron System Inhibitors; **SNRI**: Serotonin and Noradrenalin Reuptake Inhibitor; **SSRI**: Selective Serotonin Reuptake Inhibitor; **TMP/SMX**: Trimetoprim/Sulfamethoxazol; **VKA**: Vitamin K Antagonist.*

[a] Full dose defined as: >20 mg (es)omeprazole, >20mg pantoprazole, >30mg lansoprazole, >20mg rabeprazole
[b] Some drugs contain considerable potassium amounts: Glucosamine in potassium salt (up to 300mg/tablet), oral nutritional supplements (up to 200mg/unit).... (Recommended Daily Dose: 3000mg/day for ≥60 year old patients)
[c] Some supplements such as oral nutritional supplements contain considerable Vitamin K amounts (up to 13µg/unit). (Recommended Daily Dose: 50-70µg/day for ≥60 year old patients)

Table 2.2.2: Drugs with high risk for anticholinergic (side-)effects (Adapted from Duran et al. [47])

High-potency anticholinergics		Low-potency anticholinergics		
Acepromazine	Hydroxyzine	Alimemazine	Fluoxetine	Prochlorperazine
Amitriptyline	Hyoscyamine	Amantadine	Fluvoxamine	Promazine
Atropine	Imipramine	Baclofen	Haloperidol	Quetiapine
Belladonna Alkaloids	Levomepromazine	Bromocriptine	Hydrocodone	Ranitidine
Brompheniramine	Meclozine	Carbamazepine	Ketorolac	Risperidone
Chlorphenamine	Nortriptyline	Cetirizine	Lithium	Temazepam
Chlorpromazine	Orphenadrine	Chlordiazepoxide	Loperamide	Theophylline
Clemastine	Oxybutynin	Cimetidine	Loratadine	Tramadol
Clomipramine	Procyclidine	Citalopram	Loxapine	Trazodone
Clozapine	Promethazine	Clonazepam	Meperidine (=Pethidine)	Triazolam
Cyproheptadine	Propantheline	Codeine	Methadone	
Darifenacin	Pyrilamine	Cyclobenzaprine	Methocarbamol	
Dexchlorpheniramine	Scopolamine	Diazepam	Mirtazapine	
Dicyclomine	Thioridazine	Digitoxin	Morphine	
Dimenhydrinate	Tizanidine	Disopyramide	Olanzapine	
Diphenhydramine	Tolterodine	Domperidone	Oxcarbazepine	
Doxepin	Trihexyphenidyl	Dosulepin	Oxycodone	
Flavoxate	Trimipramine	Entacapone	Paroxetine	
Fluphenazine	Tropatepine	Fentanyl	Phenelzine	
Homatropine		Fexofenadine	Pimozide	

***Remark**: Tiotropium and ipratropium not included because of low risk for systemic side-effects after inhalation.*

First Delphi round: written individual evaluation

The research team invited a 12-person multidisciplinary Delphi panel encompassing all decision-making disciplines involved in geriatric care, including 4 clinical pharmacists, 2 geriatricians, 2 general practitioners, 2 academics, one community pharmacist, and an emergency physician. Eleven panellists from various European countries agreed to participate. The main selection criteria for panellists were acknowledged leadership in the panel member's specialty, absence of conflicts of interest, geographic diversity and diversity of practice setting.

In February 2013, all participating panellists were provided with the literature review and a scoring form. For each item, panellists were asked to reply to the following questions considering scientific evidence from the literature review and using their best clinical judgement: "How do you rate the added clinical value of a check on this item for an older patient by the community pharmacist?" and "How do you rate the proposed alternative?". Prescribing and sales data of the proposed items were available to the panellists upon request. Practical aspects considering the organization of community pharmacies in the panellist's country and cost implications were on the other hand specifically instructed to be excluded in making this judgement (e.g., access to patients' clinical records at the community pharmacy had not be taken into account). All items were scored on a scale, ranging from 1 to 9, with 1 indicating that checking for this item in the community pharmacy has no added clinical value or the proposed alternative was not appropriate. A score of 9 indicated that checking for this item in the community pharmacy has a high added clinical value or that the proposed alternative is highly appropriate.

After summarizing all panellists' individual ratings, a preliminary list of clinically relevant items for the tool was created, consisting of all items with a median score in the 7-9 range and all items rated "with disagreement". To define "disagreement" we used the previously developed "D9R" definition: "considering all ratings, at least one falls in the lowest 3-point region and at least one falls in the highest". We controlled results with the IPRAS method described in the RAND/UCLA user manual, however no discrepancies were detected[29]. The panellists were also offered the possibility to add items and to suggest alternative treatments, which, to their judgement, would form a positive contribution to the screening tool. A summary of these items was made and the evidence supporting the suggested items was collected. These suggestions were also added to the preliminary list. Panellists were provided with the complete preliminary list of clinically relevant items for the tool two weeks prior to the second Delphi round. Only items scored with disagreement and suggested items or alternative treatments were to be discussed in the second Delphi round.

Second Delphi round: face-to-face meeting

During the second Delphi round in May 2013, all participating panellists were provided with their individual ratings and the ratings of the other group members. One general practitioner, one clinical pharmacist and one emergency physician could not attend, resulting in an 8-member panel. The moderator specifically focused the discussion on newly suggested items and on items for which there was "disagreement" among the panellists, as described in the RAND/UCLA manual[29]. After discussing each part of the preliminary list of clinically relevant items for the GheOP³S-tool, panellists were asked to re-rate the items. No attempt was made to force panellists to consensus.

The same summarizing method was used as in the first Delphi round, with the exception that all items rated "with disagreement" at this stage were deleted from the list. This resulted in a *final list of clinically relevant items for the tool*, which was sent out to all panellists for final approval.

Retaining items applicable in contemporary community pharmacy practice

Finally, the research team invited a panel of 7 Belgian community pharmacists to select those items that were applicable in the contemporary community pharmacy practice, using the same methodology as in steps 3 and 4: a two-round Delphi consisting of a first written round and a second verbal round. Panellists were asked the following question "How do you rate the feasibility of a check on this item in the current community pharmacy practice?" and "How do you rate the feasibility of the proposed alternative strategy?". To clarify that the goal of this developmental stadium was merely a selection of items that are presently applicable, pharmacists were instructed to consider practical aspects of pharmacy workflow and cost implications rather than assess the clinical relevance of each item.

RESULTS

Literature review

Eighteen published lists of potentially inappropriate medications for older patients were retrieved from the literature, mentioning a total of 398 different items, each of them categorized in one of the predefined parts of the GheOP³S-tool. After applying selection criteria mentioned in Appendix 2.2.1 (e.g., availability in at least 4 European countries), a total of 121 items were retained, each complemented with the best available scientific evidence considering older patients. The specific lists used for each part of the GheOP³S-tool are displayed in Table 2.2.3. The flow of the items through the development process is shown in Table 2.2.4.

Table 2.2.3: Published lists, used as basis for the GheOP³S-tool.

	Part 1	Part 2	Part 3	Part 4	Part 5
Beers-list (2012 update) [10]	X	X		X	
Austrian list[12]	X				
Australian list[11]	X	X			
Laroche-criteria[13]	X			X	
Rancourt-criteria[14]	X			X	
PRISCUS-list[15]	X				
Lindblad-list[16]		X			
NORGEP-criteria[17]	X			X	
McLeod-criteria[18]	X	X		X	
IPET[19]	X	X			
START[20]			X		
STOPP[21]	X	X		X	
Winit-Watjana-criteria[22]	X	X		X	
Zhan-criteria[23]	X				
ACOVE-criteria[30]			X		X
HARM-Wrestling report[31]		X	X	X	X
KNMP-guidelines[32]		X			
Hines et al[33]				X	

ACOVE: *Assessing Care of Vulnerable Elders;* ***HARM:*** *Hospital Admissions Related to Medication;* ***IPET:*** *improving prescribing in the elderly tool;* ***KNMP:*** *Koninklijke Nederlandse Maatschappij ter bevordering der Pharmacie* ***NORGEP:*** *Norwegian General Practice;* ***START:*** *screening tool to alert to right treatment;* ***STOPP:*** *screening tool of older people's prescriptions;*

Table 2.2.4: Flow of the items through the development process of the GheOP³S-tool.

	Part 1	Part 2	Part 3	Part 4	Part 5	Total
Number of different items retrieved in the literature	188	67	22	117	4	**398**
Number of items in literature-based list of potential items	53	33	7	24	4	**121**
Number of items added during the first Delphi round	13	1	3	5	6	**28**
Number of items in preliminary list of clinically relevant items	65	34	10	29	10	**148**
→ of which to be discussed in second Delphi round because of 'disagreement'	33	13	5	17	8	**76**
Number of items in final list of clinically relevant items	32	26	7	28	6	**99**
Number of items in the GheOP³S-tool	31	11	6	29	6	**83**

First Delphi round: written individual evaluation

In the first Delphi round, panellists reached immediate consensus on 73 of the 121 literature-based items (Part 1: 33/53; Part 2: 21/33; Part 3: 5/7; Part 4: 12/24 and Part 5: 2/4), leaving 48 items for discussion in the second Delphi round. Furthermore, an additional 28 items were proposed by the panellists. Only one item concerning loperamide was considered of no clinical relevance and was omitted from the preliminary list of items for the tool. 53 of the 121 alternative therapeutic options were rated with disagreement and were also to be discussed in the second Delphi round.

Second Delphi round: face-to-face meeting

During the second Delphi round, all items rated "with disagreement" after the first round (48 items) were discussed as well as the 28 additional panellist-proposed items. The panel decided to group some of the items together (e.g. instead of including all individually named long-acting sulfonylurea derivatives such as glibenclamide and glimepiride, a new item was created: "Any long-acting sulfonylurea derivative") (Table 2.2.1 Part 1a). After discussion, consensus was reached for all proposed alternatives. After sending out the final list of 99 clinically relevant items and their therapeutic alternatives for approval, no further changes were requested by participating panellists.

Retaining items applicable in contemporary community pharmacy practice

The panel of community pharmacists selected 83 items that they found to be applicable in the contemporary community pharmacy setting. One DDI was divided into two different items because of feasibility of the management plan (oral antidiabetic/insulin + beta blocker replaced by: oral antidiabetic/insulin + non-selective beta-blocker and oral antidiabetic/insulin + cardioselective beta-blocker). The 83 items define the final GheOP³S-tool (Table 2.2.1 and Table 2.2.2). For all of these items, extended information with rationales, management plans and scientific literature was compiled (currently only available in Dutch and French[34]). Items with clinical relevance for primary care, but not (yet) applicable in the community pharmacy practice, are displayed in Table 2.2.5.

Table 2.2.5: Items deleted from each GheOP³S-part because of current inapplicability in the community pharmacy
Part 1: Drugs, inappropriate for older patients, independent of diagnosis
Sotalol for rate control
Part 2: Drugs, inappropriate for older patients, dependent on diagnosis
RAAS-inhibitors in renal impairment
Any potassium sparing diuretic in renal impairment
Chlortalidon and thiazides in renal impairment
Allopurinol in renal impairment
Amoxicillin with full dose clavulanic acid in renal impairment
Ciprofloxacin in renal impairment
Dabigatran in renal impairment
Digoxin in renal impairment
Diltiazem in congestive heart failure
Metformin in renal impairment
Nitrofurantoin in renal impairment
Norfloxacin in renal impairment
Sotalol in renal impairment
Verapamil in congestive heart failure
Part 3: PPOs for older patients
When a patients has elevated total cholesterol, a statin in secondary prevention should be started when the patient has a good life expectancy
Part 4: Drug-Drug interactions of specific relevance in older patients
None
Part 5: General care-related items for older patients to be addressed in the community pharmacy
None

DISCUSSION

Main finding of this study

In this study, we developed the GheOP³S-tool, a screening tool consisting of 83 items for identifying PIP in older patients in the community pharmacy practice. The items of the GheOP³S-tool were categorized in 5 different parts: Part 1: Potentially inappropriate drugs, independent of diagnosis, Part 2: Potentially inappropriate drugs, dependent on diagnosis, Part 3: PPOs, Part 4: DDIs of specific relevance and Part 5: General care-related items to be addressed in the community pharmacy (Table 2.2.1 and Table 2.2.2). For every item, an alternative therapeutic option was offered.

What is already known on this topic

Worldwide, the need for PIP-screening is rising in order to reduce prevalence of ADE[35 36]. As PIP-screening is part of pharmaceutical care, it is an assigned task of the community pharmacist[37 38]. Therefore, it is surprising that screening tools, specifically developed for this setting, are lacking. Community pharmacists have nevertheless shown to be effective in detecting PIP, even when non-specific or adapted tools were used[9 25 39]. The access to both the over the counter (OTC) and prescription medication record is also a major benefit, as missing OTC-data is an established risk factor for overlooking PIP in older patients[40]. Moreover, including a pharmacist in a multidisciplinary team to approach a patient's pharmacotherapy has been shown to be the safest and most rational way of prescribing[9].

What this study adds

An ideal screening tool for routine use in community pharmacy practice should be user-friendly, evidence-based, inexpensive to apply and interchangeable between countries. To meet these requirements, the GheOP³S-tool was developed as an explicit screening tool designed for community pharmacists. Where practical issues with implicit lists may arise (i.e. often lacking the necessary clinical and laboratory information), an explicit screening tool provides community pharmacists with a reference that supports pragmatic PIP-screening in a systematic and straightforward way. Moreover, the explicit character of the GheOP³S-tool allows future automatization of the screening, giving pharmacists the time to focus on checking patient-specific relevance, on inter-care giver communication and on drawing up a management plan. Furthermore, the grouping of items in Part 1a (e.g., "any non-steroidal anti-inflammatory drug (NSAID)" instead of naming each locally marketed NSAID) facilitates transition between countries, where different drugs in a particular drug class are available. Additionally, it anticipates the commercialisation of new molecules that were not yet marketed at the time of the tool-development.

A unique aspect of the GheOP³S-tool is the incorporation of a subset of items that evaluates the delivery of pharmaceutical care to the community-dwelling older patient (Table 2.2.1, Part 5: "General care-related items to be addressed in the community pharmacy"). In this section, the community pharmacist checks in an implicit way whether sufficient basic pharmaceutical care is provided. This includes – for example – verifying the need for a medication scheme or a regular evaluation of the medication adherence.

Limitations of this study

The development of the presented GheOP³S-tool using the RAND/UCLA methodology has some limitations. However, the methodological quality of the development was guaranteed by a thorough selection of the participating experts, extended scientific evidence for all included items and information about prevalence of ADEs attributable to PIP. Moreover, the setting in which the tool should be used was sufficiently taken into account by adding an extra step in the development process and by providing panellists with access to prescribing and sales data of the proposed items. Because the GheOP³S-tool is designed for routine implementation, it is evident that also a feasibility study, which in the meantime has been initiated, is necessary.

Additionally, as well as for all explicit screening tools, it is stressed that the screening is aimed at assisting in clinical decision making for the older patients and not at making the decision on its own. We emphasize that an eventual adaptation of the treatment plan remains the result of a shared decision-making process. Finally, although all currently employed pharmacists have an adequate education in pharmacology, basic pathophysiology, basic diagnostic testing and pharmacotherapy, PIP-screening, on the other hand, was barely a part of the curriculum. The delivery of continuing post-academic professional development will therefore be a prerequisite for the correct implementation of the GheOP³S-tool and correct interpretation of results.

Implications for future research

Since the GheOP³S-tool is specifically developed for use in the community pharmacy, it could address previously described and widely spread PIPs in community-dwelling older patients, such as long-term proton pump inhibitors (PPI) or benzodiazepine use[41-43]. As previous trials have shown that screening for PIP could have a positive clinical and economic impact[44 45], a routine use of the GheOP³S-tool in the community pharmacy practice could have an impact on patient's health and health care budgets. A future (cost-) effectiveness trial should therefore study the efficacy of a screening with the GheOP³S-tool by a community pharmacist on patient centred outcomes (i.e. hospital admissions, utilisation of health care resources, etc.). This way, the clinical and content validity of the screening tool as well as the efficacy of screening would be evaluated.

Since polypharmacy and older age are major risk factors for PIPs and ADEs[24 46], it is desirable to focus such a trial on an older population taking five or more drugs a day. However, if (limited) laboratory data such as renal function, would be available in trial context or in the community pharmacy because of policy changes, items from Table 2.2.5 can be added to the GheOP³S-tool.

Conclusion

The GheOP³S-tool is the first explicit screening tool, specifically designed for use in the community pharmacy practice. The developmental design of the GheOP³S-tool offers a high flexibility in terms of adding or modifying specific parts of the tool. The GheOP³S-tool is intended to be used for PIP-screening in routine community pharmacy practice and to facilitate patient and caregiver communication. Using this tool, community pharmacists could play a supportive role as an advocate for the patient in which the most beneficial and clinically effective medication with the lowest possible risk for ADEs is delivered. Future research is required to determine whether screening for PIP with this tool results in detection of clinically relevant drug related problems and in optimization of drug therapy for older patients and whether it can reduce the cost of PIP.

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AUTHOR CONTRIBUTIONS

Tommelein had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Conception and design: Tommelein, Petrovic, Somers, Mehuys, Boussery
Analysis of the data: Tommelein
Interpretation of the data: Tommelein
Drafting of the article: Tommelein
Critical revision and final approval of the article: Tommelein, Petrovic, Somers, Mehuys, van der Cammen, Boussery
Study supervision: Boussery

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COMPETING INTERESTS

All authors completed the ICMJE-form. No competing interests were declared.

REFERENCES

1. *Pammolli F, Riccaboni M, Magazzini L. The sustainability of European health care systems: beyond income and aging. Eur J Health Econ 2012;**13**(5):623-34.*
2. *Sikdar KC, Dowden J, Alaghehbandan R, et al. Adverse Drug Reactions in Elderly Hospitalized Patients: A 12-Year Population-Based Retrospective Cohort Study. Annals of Pharmacotherapy 2012;**46**(7-8):960-71.*
3. *Gallagher P, Barry P, O'Mahony D. Inappropriate prescribing in the elderly. J Clin Pharm Ther 2007;**32**(2):113-21.*
4. *Passarelli MCG, Jacob W, Figueras A. Adverse drug reactions in an elderly hospitalised population - Inappropriate prescription is a leading cause. Drugs & Aging 2005;**22**(9):767-77.*
5. *Spinewine A, Schmader KE, Barber N, et al. Appropriate prescribing in elderly people: how well can it be measured and optimised? Lancet 2007;**370**(9582):173-84.*
6. *Fu AZ, Jiang JZ, Reeves JH, et al. Potentially inappropriate medication use and healthcare expenditures in the US community-dwelling elderly. Med Care 2007;**45**(5):472-76.*
7. *Ryan C, O'Mahony D, Kennedy J, et al. Potentially inappropriate prescribing in an Irish elderly population in primary care. British Journal of Clinical Pharmacology 2009;**68**(6):936-47.*
8. *Opondo D, Eslami S, Visscher S, et al. Inappropriateness of Medication Prescriptions to Elderly Patients in the Primary Care Setting: A Systematic Review. PLoS One 2012;**7**(8).*
9. *Kaur S, Mitchell G, Vitetta L, et al. Interventions that can reduce inappropriate prescribing in the elderly: a systematic review. Drugs Aging 2009;**26**(12):1013-28.*
10. *Fick D, Semla T, Beizer J, et al. American Geriatrics Society Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults. J Am Geriatr Soc 2012;**60**(4):616-31.*
11. *Basger BJ, Chen TF, Moles RJ. Validation of prescribing appropriateness criteria for older Australians using the RAND/UCLA appropriateness method. BMJ open 2012;**2**(5).*
12. *Mann E, Bohmdorfer B, Fruhwald T, et al. Potentially inappropriate medication in geriatric patients: the Austrian consensus panel list. Wien Klin Wochen 2012;**124**(5-6):160-69.*
13. *Laroche ML, Charmes JP, Merle L. Potentially inappropriate medications in the elderly: a French consensus panel list. Eur J Clin Pharmacol 2007;**63**(8):725-31.*
14. *Rancourt C, Moisan J, Baillargeon L, et al. Potentially inappropriate prescriptions for older patients in long-term care. BMC geriatrics 2004;**4**:9.*
15. *Holt S, Schmiedl S, Thurmann PA. Potentially Inappropriate Medications in the Elderly: The PRISCUS List. Dtsch Arztebl Int 2010;**107**(31-32):543-U39.*
16. *Lindblad CI, Hanlon JT, Gross CR, et al. Clinically important drug-disease interactions and their prevalence in older adults. Clin Ther 2006;**28**(8):1133-43.*
17. *Rognstad S, Brekke M, Fetveit A, et al. The Norwegian General Practice (NORGEP) criteria for assessing potentially inappropriate prescriptions to elderly patients. Scand J Prim Health Care 2009;**27**(3):153-59.*
18. *McLeod PJ, Huang AR, Tamblyn RM, et al. Defining inappropriate practices in prescribing for elderly people: A national consensus panel. Can Med Assoc J 1997;**156**(3):385-91.*
19. *Naugler CT, Brymer C, Stolee P, et al. Development and validation of an improving prescribing in the elderly tool. The Canadian journal of clinical pharmacology = Journal canadien de pharmacologie clinique 2000;**7**(2):103-7.*
20. *Barry PJ, Gallagher P, Ryan C, et al. START (screening tool to alert doctors to the right treatment)an evidence-based screening tool to detect prescribing omissions in elderly patients. Age and Ageing 2007;**36**(6):632-38.*
21. *Gallagher P, Ryan C, Byrne S, et al. STOPP (Screening Tool of Older Person's Prescriptions) and START (Screening Tool to Alert Doctors to Right Treatment). Consensus validation. Int J Clin Pharmacol Ther 2008;**46**(2):72-83.*
22. *Winit-Watjana W, Sakulrat P, Kespichayawattana J. Criteria for high-risk medication use in Thai older patients. Arch Gerontol Geriatr 2008;**47**(1):35-51.*
23. *Zhan CL, Sangl J, Bierman AS, et al. Potentially inappropriate medication use in the community-dwelling elderly - Findings from the 1996 Medical Expenditure Panel Survey. Jama-Journal of the American Medical Association 2001;**286**(22):2823-29.*
24. *Lechevallier-Michel N, Gautier-Bertrand M, Alperovitch A, et al. Frequency and risk factors of potentially inappropriate medication use in a community-dwelling elderly population: results from the 3C Study. Eur J Clin Pharmacol 2005;**60**(11):813-9.*
25. *Ryan C, O'Mahony D, O'Donovan DO, et al. A comparison of the application of STOPP/START to patients' drug lists with and without clinical information. International journal of clinical pharmacy 2013;**35**(2):230-5.*
26. *Galvin R, Moriarty F, Cousins G, et al. Prevalence of potentially inappropriate prescribing and prescribing omissions in older Irish adults: findings from The Irish LongituDinal Study on Ageing study (TILDA). European journal of clinical pharmacology 2014;**70**(5):599-606.*
27. *Maio V, Yuen EJ, Novielli K, et al. Potentially inappropriate medication prescribing for elderly outpatients in Emilia Romagna, Italy: a population-based cohort study. Drugs Aging 2006;**23**(11):915-24.*
28. *Fick DM, Mion LC, Beers MH, et al. Health Outcomes Associated With Potentially Inappropriate Medication Use in Older Adults. Research in nursing & health 2008;**31**(1):42-51.*
29. *Fitch K, Bernstein SJ, Aguilar MS, et al. The RAND/UCLA Appropriateness Method User's Manual. Secondary The RAND/UCLA Appropriateness Method User's Manual. http://www.rand.org/pubs/monograph_reports/MR1269.html.*
30. *ACOVE quality indicators. Ann Intern Med 2001;**135**(8):653-67.*
31. *Ministry of Health WS. HARM-Wrestling report: a proposition from the expert group Medication Safety concerning specific intervention improving extramural medication safety on a short-term. 2009.*
32. *KNMP. Labwaarden en Nierfunctie, uitwisseling van gegevens. Secondary Labwaarden en Nierfunctie, uitwisseling van gegevens 2011. http://www.knmp.nl/downloads/samenwerken-kennis-delen/innovatieve-apotheken/LabwaardenenNierfunctieuitwisselingvangegevens.pdf.*
33. *Hines LE, Murphy JE. Potentially Harmful Drug-Drug Interactions in the Elderly: A Review. Am J Geriatr Pharmacother 2011;**9**(6):364-77.*
34. *Pharmaceutical Care Unit. Ghent Older People's Prescriptions community Pharmacy Screening tool: Rationales, management plans and additional information. Secondary Ghent Older People's Prescriptions community Pharmacy Screening tool: Rationales, management plans and additional information. 2014. http://www.ugent.be/fw/nl/onderzoek/bioanalyse/farmzorg/tools.htm/gheops.htm.*

35. *Price SD, Holman CD, Sanfilippo FM, et al. Association between potentially inappropriate medications from the Beers criteria and the risk of unplanned hospitalization in elderly patients. The Annals of pharmacotherapy 2014;**48**(1):6-16.*
36. *Lund BC, Carnahan RM, Egge JA, et al. Inappropriate prescribing predicts adverse drug events in older adults. The Annals of pharmacotherapy 2010;**44**(6):957-63.*
37. *World Health Organization. The role of the pharmacist in the health care system. Secondary The role of the pharmacist in the health care system 1994. http://apps.who.int/medicinedocs/en/d/Jh2995e/.*
38. *European Directorate for the Quality of Medicines & HealthCare. Pharmaceutical Care - Policies and Practices for a Safer, More Responsible and Cost-effective Health System. Secondary Pharmaceutical Care - Policies and Practices for a Safer, More Responsible and Cost-effective Health System 2012. http://www.edqm.eu/en/pharmaceutical-care-1517.html.*
39. *Kwint HF, Faber A, Gussekloo J, et al. Completeness of medication reviews provided by community pharmacists. J Clin Pharm Ther 2014;**39**(3):248-52.*
40. *Olesen C, Harbig P, Barat I, et al. Absence of 'over-the-counter' medicinal products in on-line prescription records: a risk factor of overlooking interactions in the elderly. Pharmacoepidemiol Drug Saf 2013;**22**(2):145-50.*
41. *Cahir C, Bennett K, Teljeur C, et al. Potentially inappropriate prescribing and adverse health outcomes in community dwelling older patients. Br J Clin Pharmacol 2014;**77**(1):201-10.*
42. *Nyborg G, Straand J, Brekke M. Inappropriate prescribing for the elderly--a modern epidemic? European journal of clinical pharmacology 2012;**68**(7):1085-94.*
43. *Barnett K, McCowan C, Evans JM, et al. Prevalence and outcomes of use of potentially inappropriate medicines in older people: cohort study stratified by residence in nursing home or in the community. BMJ quality & safety 2011;**20**(3):275-81.*
44. *Gallagher PF, O'Connor MN, O'Mahony D. Prevention of Potentially Inappropriate Prescribing for Elderly Patients: A Randomized Controlled Trial Using STOPP/START Criteria. Clin Pharmacol Ther 2011;**89**(6):845-54.*
45. *McMullin ST, Hennenfent JA, Ritchie DJ, et al. A prospective, randomized trial to assess the cost impact of pharmacist-initiated interventions. Arch Intern Med 1999;**159**(19):2306-9.*
46. *Pitkala KH, Strandberg TE, Tilvis RS. Inappropriate drug prescribing in home-dwelling, elderly patients: a population-based survey. Arch Intern Med 2002;**162**(15):1707-12.*
47. *Duran CE, Azermai M, Vander Stichele RH. Systematic review of anticholinergic risk scales in older adults. Eur J Clin Pharmacol 2013;**69**(7):1485-96.*
48. *World Health Organization Collaborating Centre for Metabolic Bone Diseases. Fracture Risk Assessment Tool. Secondary Fracture Risk Assessment Tool. https://www.shef.ac.uk/FRAX/tool.jsp.*

APPENDIX 2.2.1: CRITERIA TO WITHHOLD ITEMS FOR EVALUATION BY THE DELPHI-PANEL WERE DETERMINED FOR EACH PART OF THE TOOL

Criteria to withhold items in Part 1 (Potentially inappropriate medication for older patients, independent of diagnosis)

Starting from all existing lists with explicit criteria on potentially inappropriate medication for older patients, independent of diagnosis, we withheld all items that were mentioned on at least 4 lists, as well as all OTC-available drugs mentioned on at least 1 list. Subsequently, we retained only those items considering drugs that are available in at least 4 European countries.

Criteria to withhold items in Part 2 (Potentially inappropriate medication for older patients, dependent on diagnosis)

Starting from all existing lists with explicit criteria on potentially inappropriate medication for older patients with certain diseases, we withheld all items mentioned on ≥2 lists. Items considering drugs not available in at least 4 European countries were deleted. Because of clinical relevance, 10 recommendations of the Koninklijke Nederlandse Maatschappij ter bevordering der Pharmacie (KNMP)[32] and the HARM-Wrestling report[31] concerning drugs administered in patients with renal impairment were added to the list.

Criteria to withhold items in Part 3 (Potential Prescribing Omissions)

Starting from all existing lists with explicit criteria on potential prescribing omissions in older patients, we only withheld items confirmed by recommendations of the HARM-Wrestling report[31] or ACOVE quality indicators[30]. Items considering drugs not available in at least 4 European countries were deleted.

Criteria to withhold items in Part 4 (Drug-Drug interactions of specific relevance in older patients)

Starting from all existing lists with explicit criteria on drug-drug interactions (DDI) of specific relevance in older patients, we only withheld DDIs of which clinical relevance in older patients was confirmed through the HARM-Wrestling report[31] or the systematic review of Hines et al[33]. DDIs considering drugs not available in at least 4 European countries were deleted.

Criteria to withhold items in Part 5 (General care-related items for older patients to be addressed in the community pharmacy)

Starting from all existing lists with explicit criteria on General care-related items for older patients to be addressed in the pharmacy, we withheld items if they have a contribution to drug-related problems (e.g. recording of fall frequency and long-term benzodiazepine use). None of the lists mentioned care-centred items. However, ACOVE-criteria[30] and the HARM-Wrestling report[31] mentioned four care-related items. For each of these statements, scientific evidence for being on the list was evaluated.

PART 2.3:

DETECTION OF POTENTIALLY INAPPROPRIATE PRESCRIBING IN OLDER PATIENTS WITH THE GHEOP³S-TOOL: COMPLETENESS AND CLINICAL RELEVANCE

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ABSTRACT

***Purpose*:** The Ghent Older People's Prescriptions community Pharmacy Screening (GheOP³S-) tool was recently developed as an explicit screening method to detect Potentially Inappropriate Prescribing (PIP) in the community pharmacy. We aimed to validate the GheOP³S-tool as an effective screening method for PIP.

***Methods*:** All patients admitted to the acute geriatric ward at the Sint-Vincentius hospital (Deinze, Belgium) were consecutively screened for inclusion (≥70 years and ≥5 drugs chronically). PIP prevalence was evaluated by applying the GheOP³S-tool on the complete medication history. For each PIP-item, clinical relevance of the detected item, relevance of proposed alternative and subsequent acceptance by the geriatrician were evaluated. Additionally, contribution to the current admission and preventability were assessed. The completeness of a PIP-screening with the GheOP³S-tool was evaluated through comparison with the adapted Medication Appropriateness Index (aMAI).

***Results*:** We detected 250 GheOP³S-items in 57 of 60 included patients (95%) (Median: 4 PIP-items per patient; IQR: 3-5). Clinical relevance was scored 'serious' for 182 items (73%) and 'significant' for 67 items (26%). Proposed alternative treatment plans were accepted for 79% of the PIP-items (n=198). The aMAI detected 536 items, of which 145 were incorporated in 131 PIP-items detected by the GheOP³S-tool. 119 PIP-items were additionally detected by the GheOP³S-tool.

***Conclusion*:** The clinical relevance of the PIP-items detected with the GheOP³S-tool is high, likewise the acceptance rate of proposed alternatives. One third of the items detected by the aMAI were found using the GheOP³S-tool and a substantial amount (18%) of extra PIP-items, considered relevant by the physician, were only detected by the GheOP³S-tool.

INTRODUCTION

Multimorbidity and associated polypharmacy are very common in older people. Combined with changed pharmacodynamics and pharmacokinetics, this leads to a higher risk of drug related problems (DRPs) [1 2]. DRPs can cause hospitalization and about half of those admissions seem preventable[3 4]. Potentially Inappropriate Prescribing (PIP) is established as one of the main factors, associated with DRPs [5-9]. PIP is defined as "*the prescribing of medication that could introduce a significant risk of a DRP, in particular when there is an equally or more effective alternative with lower risk available"* [10 11]. There are three main categories of PIP: overprescribing, underprescribing and misprescribing [12].

Multiple screening methods are currently used to identify PIP, both implicit and explicit. Implicit methods such as the (adapted) Medication Appropriateness Index (MAI) judge the appropriateness of therapy using clinical information of an individual patient [13 14]. Explicit methods on the other hand, consist of lists of drugs that should be avoided or started in certain clinical conditions[15 16]. Both methods are most often applied by general practitioners, specialists or hospital pharmacists.

Recently however, the Ghent Older People's Prescription community Pharmacy Screening (GheOP³S-)tool was developed to identify PIP with high clinical relevance in primary care settings with limited or no information about the clinical situation of the patient. A screening with the GheOP³S-tool specifically aims at initiating a multidisciplinary medication review in primary care, on the basis of the detailed medication history available in the patient's pharmacy [17]. The GheOP³S-tool is an explicit method, consisting of 83 items, categorized into 5 parts (Table 2.3.1) [17]. For each PIP-item on the list a rationale, an alternative treatment plans and scientific background are provided. In a previous observational study, conducted in 204 Belgian community pharmacies, the usability and feasibility of the GheOP³S-tool were positively evaluated (personal communication, unpublished results). However, the clinical relevance of the detected items, as well as a possible contribution of the detected items to hospital admissions has not yet been evaluated. This is however essential in order to evaluate whether the initial goal of the GheOP³S-tool (detecting items with a high clinical relevance), was achieved. If this goal could be confirmed, a systematic application of the GheOP³S-tool by the community pharmacy, might uncover PIP in a very early stage and therefore prevent possible DRPs.

Therefore, in this study the GheOP³S-tool was applied on the medication history upon admission of older patients with polypharmacy, admitted to an acute geriatric ward. The results of the GheOP³S-screening by the pharmacist were communicated to the treating geriatrician. The specific aims were to evaluate the clinical relevance of the PIP-items, detected with the GheOP³S-tool, the acceptance of the proposed alternative treatment plans and the possible contribution of the detected PIP-items to the current hospitalization. Finally, we aimed to evaluate the completeness of a PIP screening using the GheOP³S-tool, compared to a full clinical medication review, conducted with the aMAI.

METHODS

Study design, setting and participants

From October 2014 to March 2015, a prospective observational single centre study was performed at the Sint-Vincentius hospital in Deinze (Belgium). All patients admitted to the acute geriatric ward were consecutively screened for inclusion. Patients could be included if they were 70 years or older and chronically taking 5 or more drugs. Patients were excluded if they were already admitted to the hospital during the 3 previous months. Failures and refusals were documented. The study was granted ethical approval from the Ghent University Hospital. A written informed consent was provided, either by the patient or by the legal representative.

Data collection

For each patient, data on age, gender, living situation, reason for admission, medical history, relevant laboratory data and drug use (dose, frequency of treatment) were obtained by the treating geriatrician, based on the (hetero-)anamnesis and the medical record. Drug use was obtained at admission, based on the procedure of Nielsen et al (Appendix 2.3.2), resulting in a *preliminary medication history* [18]. Additionally, the participants' community pharmacist was contacted to obtain all data about both prescribed and Over-The-Counter (OTC-)medication, previously stopped drugs and non-chronic therapy (e.g. vaccination), resulting in the *complete medication history*. Discrepancies between the preliminary and the complete medication history and their involvement in PIP were also recorded.

Table 2.3.1: The GheOP³S-tool & the adapted MAI

The GheOP³S-tool		**The adapted MAI**	
Part 1	Potentially inappropriate drugs, independent of diagnosis – Drug classes	**1**	Indication
	Potentially inappropriate drugs, independent of diagnosis – Specific molecules	**2**	Choice
Part 2	Potentially inappropriate drugs, dependent of diagnosis – Drug classes	**3**	Dosage
	Potentially inappropriate drugs, dependent of diagnosis – Specific molecules	**4**	Correct directions/Modalities
Part 3	Potential Prescribing Omissions	**5**	Drug–drug interactions
Part 4	Drug-Drug Interactions (DDIs) of specific relevance	**6**	Drug–disease interactions
Part 5	General care-related items to be addressed in the community pharmacy	**7**	Duration
		8	Adverse drug reaction
			Underuse

GheOP³S: *Ghent Older People's Prescription community Pharmacy Screening*
MAI: *Medication Appropriateness Index*

PIP prevalence

PIP prevalence was evaluated by applying the GheOP³S-tool. In this study, Part 1 to Part 4 was used (item 1 to item 77) (Table 2.3.1). The PIP-screening with the GheOP³S-tool was performed by a pharmacist (ET) within 24 hours after patient inclusion and was based on the complete medication history. For each patient, a report was made to the treating geriatrician (CK) containing information about detected PIP-items, rationale and a possible alternative treatment plan (e.g., withdrawal scheme, alternative therapy options etc.).

Estimating clinical relevance of detected PIP-items

The validated method of Overhage et al [19] was used to measure the severity of the detected PIP-items and the value of the pharmacist's recommendations. First, the severity of the detected PIP was analysed and classified into 'potentially lethal', 'serious', 'significant', 'minor' and 'no error'. This quantifies the potential impact of the adverse outcome that could have resulted if the pharmacist had not intervened. Second, evaluation of the value of the pharmacist's clinical intervention was categorized into 'extremely significant', 'very significant', 'significant', 'somehow significant', 'no significance' and 'adverse significance' (Appendix 2.3.1) [19]. This represents the potential impact of the pharmacist's recommendations on the patient's care. The clinical relevance of the detected PIP-items was evaluated by the treating geriatrician (CK). In case of doubt, another out-of-hospital geriatrician (MP) was consulted until consensus was reached.

Evaluating acceptance of proposed alternative treatment plans

The geriatrician's acceptance of the proposed alternative treatment plan was categorized as 'fully accepted', 'partially accepted' or 'not accepted'. The latter could be due to intolerance, the patient not accepting the change or insufficient reason for stopping or starting therapy. Furthermore, the patient could be palliative. If the drug information was incorrect or incomplete the term 'not applicable' was used.

Correlation with hospital admission

The determination of a (possible) contribution with the current hospital admission was based on a previously published method [20]. The contribution was categorized as 'dominant', 'partly contributing', 'less important' or 'non-contributing', meaning that the DRP is the main, the substantial or the minor reason for admission or had no influence on the admission, respectively. The correlation between the detected PIP-items and the current hospital admission was evaluated by the treating geriatrician (CK). In case of doubt, another out-of-hospital geriatrician (MP) was consulted until consensus was reached.

Furthermore, the preventability of the detected PIP-items that were positively associated with the current hospital admission was evaluated, using a previously published method[21]

Comparing GheOP³S to a full medication review

To evaluate the completeness of a PIP-screening, using the GheOP³S-tool, we compared it to the results of a full clinical medication review obtained by applying the aMAI. This is an implicit instrument developed for hospitalized older patients using 8 criteria to assess the appropriateness of each drug (Table 2.3.1). An overall MAI score is calculated using weighted factors for each item [14]. The aMAI was applied on the complete medication history, with access to medical file including diagnosis and laboratory data, by a clinical pharmacist (AS), extensively trained in geriatric pharmacotherapy.

Statistical Analysis

Prevalence of PIP-items is described as the number of patients with at least one PIP. Additionally, the median number of PIP-items with inter quartiles ranges (IQR) per patient is presented. Basic characteristics will be described appropriately by means of standard deviations, medians with IQRs and counts with percentages.

RESULTS

We screened 158 patients for eligibility, of which 60 were eventually included in the study (Figure 2.3.1). Mean age of the patients was 86 years (SD = 6) and 48 were female (80%) (Table 2.3.2). The included population used a total of 610 drugs, with a mean of 10.2 drugs per patient (SD = 3.2). Most frequent drug classes are reported in Table 2.3.2. For 25 of the included patients the preliminary medication history, obtained at admission, was not consistent with the information from the community pharmacy. We detected 63 medication discrepancies, mostly concerning missing drugs.

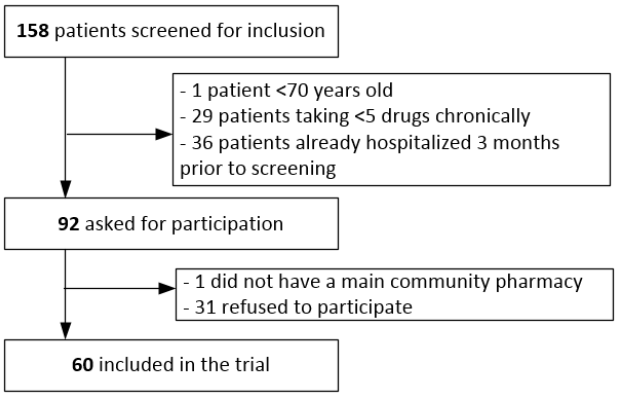

***Figure 2.3.1**: Flowchart of patient inclusion*

Table 2.3.2: Basic characteristics of the included population (n=60)		
Age, Mean (SD)	85.7	6.5
Age ≥ 85j, n (%)	31	52%
Female gender, n (%)	48	80%
No. of drugs, median (IQR)	10	8-12
No. of drugs, mean (SD)	10.2	3.2
Living situation, n (%)		
Ambulant with minimal (≤ 1 time a week) professional help[a]	18	30%
Ambulant with (> 1 time a week) professional help[a]	23	38%
Residential care	19	32%
Reason for admission, n (%)		
Fall incident	11	18%
Pneumonia	8	13%
Bronchitis	8	13%
Deterioration of general condition	6	10%
Severe gastro-enteritis	5	8%
Syncope	4	7%
Confusion	3	5%
Other	15	25%
Comorbidities, n (%)		
Cardiovascular Disease	47	78%
Dementia	17	28%
Osteoporosis	17	28%
Diabetes	16	27%
Obstructive Lung Disease	7	12%
Parkinson's disease	4	7%
Depression	1	2%

Table 2.3.2 (Continued): Basic characteristics of the included population (n=60)		
Drug use of the included population, n (%)		
ANTITHROMBOTIC AGENTS	**42**	**70%**
Platelet aggregation inhibitors excl. Heparin	*34*	*57%*
Vitamin K antagonists	*9*	*15%*
DRUGS FOR PEPTIC ULCER AND GASTRO-OESOPHAGEAL REFLUX DISEASE	**32**	**53%**
Proton pump inhibitors	*28*	*47%*
H_2-receptor antagonists	*5*	*8%*
OTHER ANALGESICS AND ANTIPYRETICS	**28**	**47%**
Anilides (i.e. paracetamol, possibly in combinations)	*27*	*45%*
Salicylic acid and derivatives	*2*	*3%*
ANTIDEPRESSANTS	**25**	**42%**
Other antidepressants	*13*	*22%*
Selective serotonin reuptake inhibitors	*12*	*20%*
Non-selective monoamine reuptake inhibitors	*2*	*3%*
DRUGS FOR CONSTIPATION	**25**	**42%**
Osmotically acting laxatives	*22*	*37%*
Contact laxatives	*4*	*7%*
Bulk-forming laxatives	*2*	*3%*
LIPID MODIFYING AGENTS, PLAIN	**26**	**43%**
HYPNOTICS AND SEDATIVES	**25**	**42%**
Benzodiazepine derivatives	*15*	*25%*
Benzodiazepine related drugs	*8*	*13%*
Other hypnotics and sedatives	*3*	*5%*
BETA BLOCKING AGENTS	**24**	**40%**
[a]Professional help defined as help by a nurse or 'home help' with a fixed visiting regimen		

PIP exposure according to the GheOP³S-tool

In total, 250 GheOP³s-items were detected in 57 patients (95%), resulting in a median of 4 PIP-items per patient (interquartile range: 3-5). Most frequent detected items are listed in Table 2.3.3. The complete prevalence list is presented in Appendix 2.3.3. The 63 detected medication discrepancies were involved in 20 PIP-items detected with GheOP³S-tool.

Table 2.3.3: Most prevalent PIP-items according to the GheOP³S-tool			
	GheOP³S-item	**No. of patients**	**% of patients (n=60)**
1	The patient has an elevated risk for osteoporosis (determined via FRAX-tool) and is not prescribed Calcium/Vitamin D supplementation	41	68%
2	Any intermediate acting benzodiazepine or Z-product at full dose or any dose ≥30 subsequent days	27	45%
3	Any antidepressant ≥1year	24	40%
4	The patient is not reminded and proposed to undergo yearly influenza vaccination	18	30%
5	Any combination of anticholinergic drugs	16	27%
6	Anticholinergics with constipation	15	25%
7	The patient is taking narcotic analgesics and is not prescribed appropriate preventative bowel regimen (preferably macrogol or lactulose)	10	17%
8	Any PPI at full dose ≥8 weeks	9	15%
9	Tramadol	7	12%
10	Any short or long-acting benzodiazepine	6	10%

Estimating clinical relevance of detected PIP-items

None of the detected GheOP³S items were estimated as potentially lethal. Of the 250 PIP-items detected by the GheOP³S-tool, 182 (73%) were classified as serious and 67 (27%) as significant. One item was classified as 'no error'.

Second, the evaluation of the value of the pharmacist's clinical interventions for these PIP-items resulted in the categorization of 6 items (2%) as 'very significant', 235 items (94%) as 'significant', 7 items (3%) as 'somehow significant' and 1 item as 'not significant' (Table 2.3.4).

Evaluating acceptance of proposed alternative treatment plans & contribution to hospital admission

The geriatrician fully accepted 52% of the proposed alternative treatment plans (n=130) and partially accepted 27% (n=68). Eighteen percent (n=44) of the alternative treatment plans were not accepted. Main reasons for not accepting are presented in Table 2.3.4, the majority being insufficient reason to stop or start.

Of the 250 PIP-items, 3 dominantly contributed to the current hospitalization. These 3 PIP-items appeared in 3 different patients. They consisted of the type and side-effects of an opioid in two cases and the long-term use of a high dose of benzodiazepine in the other case. Two of these 3 PIP-items were preventable, one not. Eleven detected PIP-items (present in 6 different patients) partially contributed to the hospitalization. All of these PIP-items were preventable. In total, for 9 patients (15%), the hospitalization was considered related to a PIP, detected with the GheOP³S-tool (Table 2.3.4).

Comparing the GheOP³S-tool to a full medication review

The screening with the aMAI detected a total of 536 items. Of these 536 items, 145 items (27%) had also been detected with the GheOP³S-tool, albeit within only 131 of the 250 items. This is a consequence of duplicate detections. For example, according to the aMAI-score, long-term treatment with a full dose PPI was noted as two items ('dosage' and 'duration'), where the GheOP³S-tool detects this as 1 PIP-item. On the other hand, the GheOP³S-tool detected 119 items that were not detected by the aMAI. Figure 2.3.2 describes in detail the type of items, the clinical relevance, acceptance, hospital contribution and most frequently detected ATC-codes of the 145 items commonly detected by the GheOP³S-tool and the aMAI, as well as of the 119 items additionally detected only by the GheOP³S-tool.

Table 2.3.4: Clinical relevance of the items detected with the GheOP³S-tool, the value of the pharmacist's clinical intervention, the acceptance of the proposed alternative treatment plans and contribution to hospital admission (n=250)

	No. of items detected by GheOP³S	**% (n=250)**
Severity of detected PIP		
Potentially lethal	0	0%
Serious	182	73%
Significant	67	27%
Minor	0	0%
No error	1	0%
	No. of items detected by GheOP³S	**% (n=249)**
Value of pharmacists' clinical intervention		
Extremely significant	0	0%
Very significant	6	2%
Significant	235	94%
Somehow significant	7	3%
No significance	1	0%
Adverse significance	0	0%
Acceptance of the proposed alternative treatment plans		
Fully accepted	130	52%
Partially accepted	68	27%
Not accepted	44	18%
Intolerance for higher dose	*0*	*0%*
Not accepted by the patient	*8*	*18%*
Insufficient reason for stop or start	*36*	*82%*
Palliative patient	*0*	*0%*
Not applicable	7	3%
Already applied by the patient	*7*	*100%*
Deceased patient	*0*	*0%*
Contribution with hospital admission		
Dominant	3	1%
Partly	11	4%
Less important	24	10%
Non-contributing	211	85%

GheOP³S: *Ghent Older People's Prescriptions community Pharmacy Screening;* ***MAI:*** *Medication Appropriateness Index*

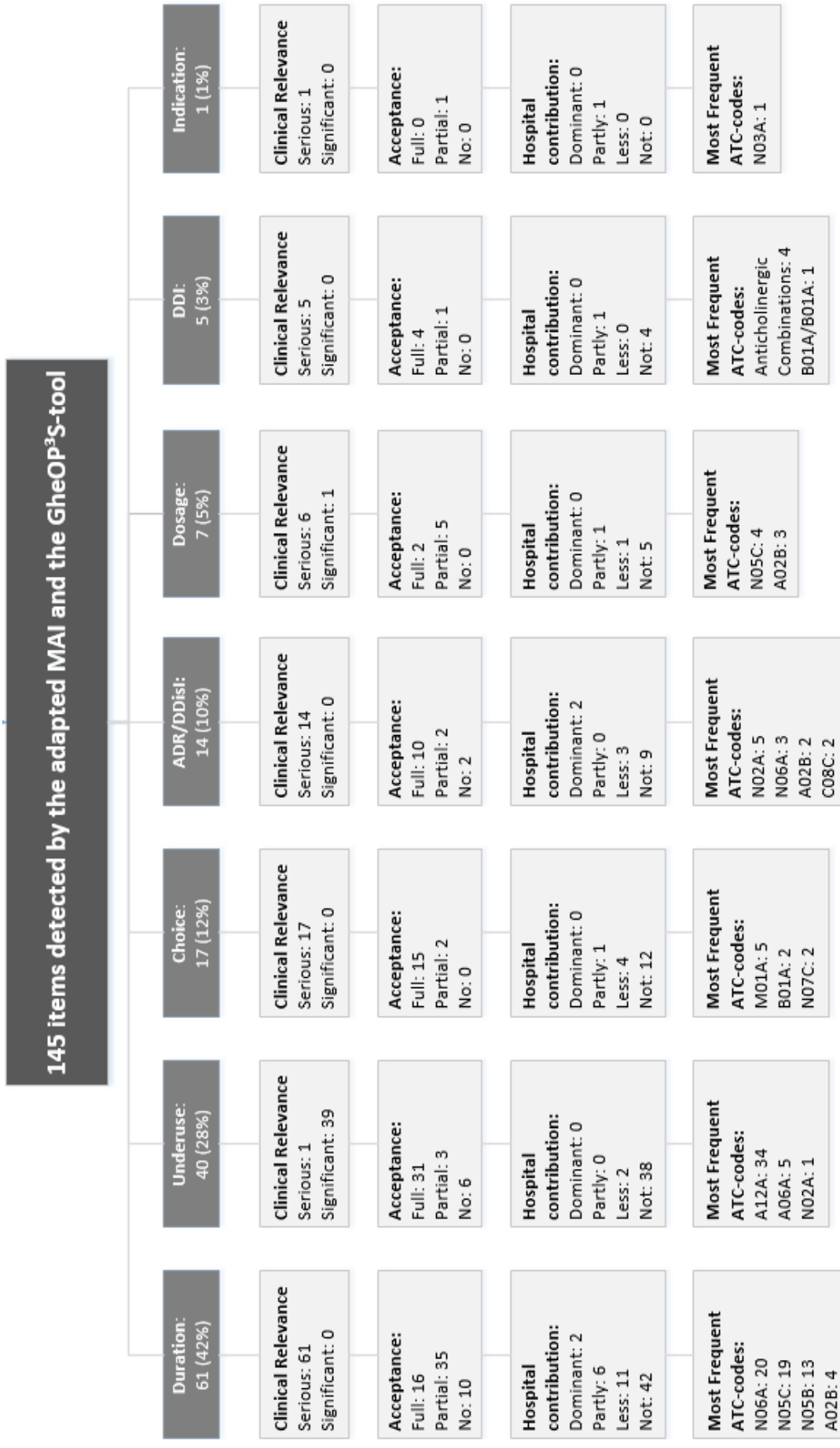

Figure 2.3.2a: *Detailed analyses of the items, commonly detected by the aMAI and the GheOP³S-tool (n=145)*

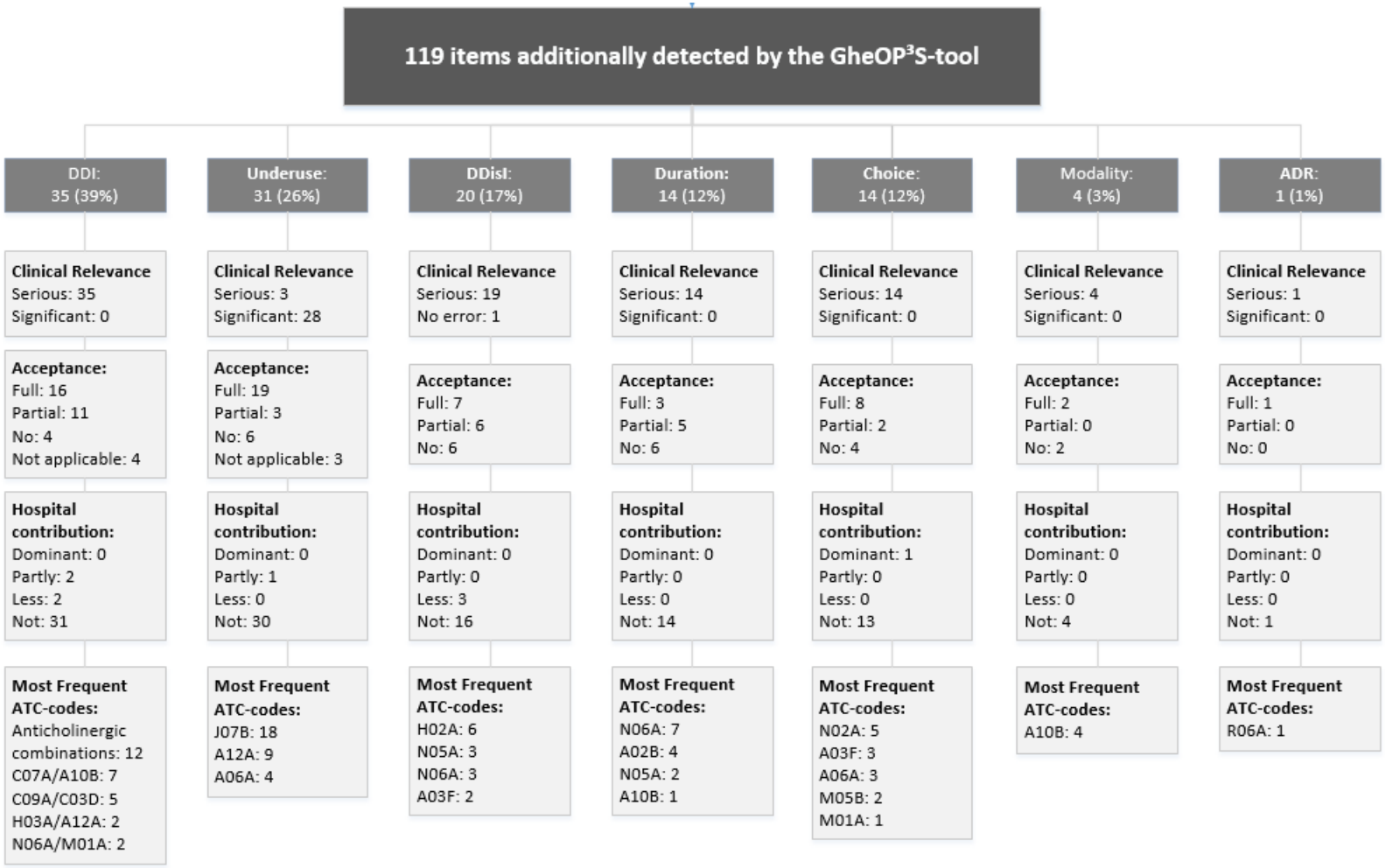

Figure 2.3.2b: *Detailed analyses of the items, detected with the GheOP³S-tool, additionally to the aMAI (n=119)*

DDI: *Drug-Drug Interaction;* ***DDisI****: Drug-Disease Interaction;* ***ADR****: Adverse Drug Reaction*
ATC-Codes: A02B*: Drugs for peptic ulcer and gastro-oesophageal reflux disease (GORD);* ***A03F****: Propulsives;* ***A06A****: Drugs for constipation;* ***A10B****: Blood glucose lowering drugs, excl. Insulins;* ***A12A****: Calcium;* ***B01A****: Antithrombotic agents;* ***C07A****: Beta Blocking Agents;* ***C08C****: Selective calcium channel blockers with mainly vascular effects;* ***C09A****: ACE inhibitors, plain;* ***C03D****: Potassium-sparing agents;* ***H02A****: Corticosteroids for systemic use, plain;* ***H03A****: Thyroid preparations;* ***J07B****: Viral vaccines;* ***M01A****: Anti-inflammatory and anti-rheumatic products, non-steroids;* ***M05B****: Drugs affecting bone structure and mineralization;* ***N02A****: Opioids;* ***N03A****: Anti-epileptics;* ***N05A****: Antipsychotics;* ***N05B****: Anxiolytics;* ***N05C****: Hypnotics and sedatives;* ***N06A****: Antidepressants;* ***N07C****: Anti-vertigo preparations;* ***R06A****: Antihistamines for systemic use*

DISCUSSION

In this study, we applied the GheOP³S-tool to the complete medication history of 60 older patients with polypharmacy, hospitalized at an acute geriatric ward. At least one PIP was detected in 95% of patients, with a median of 4 PIP-items per patients (IQR: 3-5). The clinical relevance of the detected PIP was considered 'serious' for 73% of the detected items and 'significant' for the remaining 27%. Additionally, acceptance rates were high, with a full or partial acceptance of the proposed alternative treatment plans in 79% of cases. Fourteen PIPs, detected in 9 patients, were dominantly or partly contributing to the current hospital admission.

The GheOP³S-tool mainly detects PIP-items related to duration of therapy, underuse of medication and DDIs. However, all types of PIP (underuse, overuse and misuse) were at least detected once. This supports the validity of the GheOP³S-tool as an all-round screening tool that tackles all types of PIP[17]. Also, as practically all detected items were considered relevant by a geriatrician, the developmental goal of the GheOP³S-tool – to deliver a tool that detects PIP-items with high clinical relevance – was confirmed[17].

The acceptance of the proposed alternative treatment plans was remarkably high (79% of proposed alternative treatment plans were accepted), since acceptance has been a troublesome step in the implementation process of multiple other trials[22 23]. This high rate could be explained by multiple factors. First, the pharmacist felt empowered by the availability of substantial scientific background. Second, the close collaboration between the geriatrician and pharmacist and the quick exchange of information to one another was a decisive factor for implementing specific recommendations. This suggests that the possibility for immediate mutual contact is an environmental prerequisite for an optimal medication review process. As well, all researchers had a positive attitude towards the implementation of medication review in the current practice. There were no constraints towards executing the review within the present time-frame, meeting for follow-up consultations or sharing necessary patient data.

For a significant amount of patients (15%), the hospitalization was to a certain extent related to a PIP-item detected with the GheOP³S-tool. Three PIPs in 2 patients seemed to dominantly contribute to the hospital admission, which could have been avoided if the PIP-item had been detected beforehand. This shows that medication review in the primary care setting may have a substantial impact on health care utilization. However, this has to be confirmed by a larger, controlled study.

The GheOP³S-tool detected one third of PIP in comparison with a full clinical medication review. The items that are commonly detected by the aMAI and the GheOP³S-tool mainly concern the long-term use of drugs that influence the central nervous system (i.e. antidepressants, anxiolytics, hypnotics and sedatives), the underuse of calcium/vitamin D supplements and the use of NSAIDs in pain management. In addition, concerning the 119 items that are solely detected by the GheOP³S-tool a significant amount of DDIs (mainly combinations of anticholinergic drugs) were observed, as well as the underuse of influenza vaccination and DDIs with corticosteroids for systemic use.

All of the items, whether commonly detected by the aMAI and the GheOP³S-tool or solely by the GheOP³S-tool, are considered of 'serious' or 'significant' relevance. Comparison with results from other studies is challenging as some studies used adapted classifications. The study of Bosma et al[23] for example rated a pharmacists' recommendations based upon drug related problems such as inappropriate drug choice, inappropriate dosing, therapeutic duplication, side effects, and drug–drug interactions using the method of Overhage et al [19], but merging the severity of the detected PIP-items and the value of the pharmacist's recommendations . Eventually, thirty to fifty percent of interventions were rated as (extremely) significant. Somers et al [24] on the other hand, only used the value of the pharmacist's recommendations part of the method of Overhage et al [19], however rating the recommendations as '(very) significant' in 58% of cases and 'somehow significant' in 38% [24]. Both studies observed lower significance than in our study, which could be due to the fact that the assessment was done retrospectively by independent raters, and that implicit detection methods were used in both trials. Implicit methods are all-embracing and therefore inherently also detect minor problems. During the developmental process of the GheOP³S-tool though, it was a specific goal to only withhold items with high clinical relevance for primary practice [17].

Furthermore, as the GheOP³S-tool detects additional clinically relevant PIP-items, our results confirm that using the GheOP³S-tool – an explicit method – is complementary to an implicit method and has therefore an added value for the medication review process. Other methods, such as the Systematic Tool to Reduce Inappropriate Prescribing, also effectively used the combination of implicit and explicit methods[25]. This can be explained by the fact that implicit methods rely on the knowledge and attitudes of the user and are therefore very much rater-dependent. It is evident that for example not all interactions are known by heart.

Strengths and limitations

Obtaining a complete medication history was a significant strength in this study. Contacting the patient's community pharmacy provided important additional information concerning the medication use of the patient. In almost half of the included population there were multiple discrepancies between the patient-provided list and the dispensing database provided by the community pharmacy, which delivered 20 extra PIP-items during screening by the GheOP³S-tool.

On the other hand, this study has some limitations. First, only one geriatrician estimated the clinical relevance, evaluated the proposed alternative treatment plan and determined a contribution with the hospital admission. However, this was partly corrected with the consensus method, made in case of doubt about the right categorization. Second, the study includes only 60 patients. Nevertheless, it still supports that using an explicit method such as the GheOP³S-tool is complementary to an implicit method in the medication review process.

Future perspectives

Performing medication review is an initiative that captures the priorities and aims of current guidelines concerning medicines optimisation[26]. However, the success of medication review on patient related outcomes relies on its integration into primary care as PIPs leading to hospitalization can then still be prevented. To achieve this, multiple barriers, including insufficient integration, underdeveloped relationships between a patient's pharmacist and general practitioner, relatively inaccessible patient records, poorly devised strategies for targeting services and the reluctance of some health care workers to involve in medication review processes, still have to be tackled and have – until now – hampered the implementation of community pharmacy-led clinical services [27-29].

Facilitation is needed but is however possible as the GheOP³S-tool is an explicit method. This enables a complete digital integration into the pharmacy software and would facilitate routine PIP-screening. Additionally, tailoring the software systems to ease (local) pharmacist-physician communication is required. Nevertheless, to confirm the value of a systematic screening with the GheOP³S-tool including follow-up pharmacist-physician contacts in the primary care setting, the application on a larger scale in a controlled trial is needed. Besides hospitalizations and health care utilization, such a study should also include patient centred outcomes such as quality of life and satisfaction.

Further analysis of the aMAI items not detected by the GheOP³S-tool will offer the opportunity to optimize the GheOP³S-tool. The current data will reveal the items with high clinical relevance and those that are highly related to hospital admissions.

Conclusion

The clinical relevance of the PIP-items detected with the GheOP³S-tool is high, as well as the acceptance of the proposed alternative treatment plan. About one third of the items detected by a clinical medication review were detected using the GheOP³S-tool. Furthermore, a substantial amount of extra PIP-items were detected by the GheOP³S-tool, all of which considered relevant by the clinician. The advantage of the GheOP³S-tool is the application on a regular basis in the community pharmacy, with limited or no information about clinical situation of the patient, but with detection of clinically relevant PIP-items. Therefore, application of the GheOP³S-tool has the potential of preventing drug related problems and hospitalizations in older community dwelling patients with polypharmacy.

REFERENCES

1. *Mangoni AA, Jackson SH. Age-related changes in pharmacokinetics and pharmacodynamics: basic principles and practical applications. Br J Clin Pharmacol 2004;**57**(1):6-14.*
2. *Goldberg RM, Mabee J, Chan L, et al. Drug-drug and drug-disease interactions in the ED: analysis of a high-risk population. The American journal of emergency medicine 1996;**14**(5):447-50.*
3. *Leendertse AJ, Egberts AC, Stoker LJ, et al. Frequency of and risk factors for preventable medication-related hospital admissions in the Netherlands. Arch Intern Med 2008;**168**(17):1890-6.*
4. *Juurlink DN, Mamdani M, Kopp A, et al. Drug-drug interactions among elderly patients hospitalized for drug toxicity. JAMA : the journal of the American Medical Association 2003;**289**(13):1652-8.*
5. *Lund BC, Carnahan RM, Egge JA, et al. Inappropriate Prescribing Predicts Adverse Drug Events in Older Adults. Annals of Pharmacotherapy 2010;**44**(6):957-63.*
6. *Hamilton H, Gallagher P, Ryan C, et al. Potentially inappropriate medications defined by STOPP criteria and the risk of adverse drug events in older hospitalized patients. Arch Intern Med 2011;**171**(11):1013-9.*
7. *Price SD, Holman CD, Sanfilippo FM, et al. Association between potentially inappropriate medications from the Beers criteria and the risk of unplanned hospitalization in elderly patients. The Annals of pharmacotherapy 2014;**48**(1):6-16.*
8. *Pasina L, Djade CD, Tettamanti M, et al. Prevalence of potentially inappropriate medications and risk of adverse clinical outcome in a cohort of hospitalized elderly patients: results from the REPOSI Study. J Clin Pharm Ther 2014;**39**(5):511-5.*
9. *Laroche ML, Charmes JP, Nouaille Y, et al. Is inappropriate medication use a major cause of adverse drug reactions in the elderly? Br J Clin Pharmacol 2007;**63**(2):177-86.*
10. *Opondo D, Eslami S, Visscher S, et al. Inappropriateness of Medication Prescriptions to Elderly Patients in the Primary Care Setting: A Systematic Review. PloS one 2012;**7**(8).*
11. *Fick DM, Cooper JW, Wade WE, et al. Updating the beers criteria for potentially inappropriate medication use in older adults - Results of a US consensus panel of experts. Archives of Internal Medicine 2003;**163**(22):2716-24.*
12. *Spinewine A, Schmader KE, Barber N, et al. Appropriate prescribing in elderly people: how well can it be measured and optimised? Lancet 2007;**370**(9582):173-84.*
13. *Hanlon JT, Schmader KE, Samsa GP, et al. A method for assessing drug therapy appropriateness. J Clin Epidemiol 1992;**45**(10):1045-51.*
14. *Somers A, Mallet L, van der Cammen T, et al. Applicability of an adapted medication appropriateness index for detection of drug-related problems in geriatric inpatients. The American journal of geriatric pharmacotherapy 2012;**10**(2):101-9.*
15. *Gallagher P, Ryan C, Byrne S, et al. STOPP (Screening Tool of Older Person's Prescriptions) and START (Screening Tool to Alert doctors to Right Treatment). Consensus validation. International journal of clinical pharmacology and therapeutics 2008;**46**(2):72-83.*
16. *Panel TAGSBCUE. American Geriatrics Society updated Beers Criteria for potentially inappropriate medication use in older adults. J Am Geriatr Soc 2012;**60**(4):616-31.*
17. *Tommelein E, Petrovic M, Somers A, et al. Older patients' prescriptions screening in the community pharmacy: development of the Ghent Older People's Prescriptions community Pharmacy Screening (GheOP(3)S) tool. J Public Health (Oxf) 2015.*
18. *Nielsen TR, Andersen SE, Rasmussen M, et al. Clinical pharmacist service in the acute ward. International journal of clinical pharmacy 2013;**35**(6):1137-51.*
19. *Overhage JM, Lukes A. Practical, reliable, comprehensive method for characterizing pharmacists' clinical activities. American journal of health-system pharmacy : AJHP : official journal of the American Society of Health-System Pharmacists 1999;**56**(23):2444-50.*
20. *Somers A, Robays H, Vander Stichele R, et al. Contribution of drug related problems to hospital admission in the elderly. The journal of nutrition, health & aging 2010;**14**(6):477-82.*
21. *Schumock GT, Thornton JP. Focusing on the preventability of adverse drug reactions. Hosp Pharm 1992;**27**(6):538.*
22. *Stuijt CC, Franssen EJ, Egberts AC, et al. Appropriateness of prescribing among elderly patients in a Dutch residential home: observational study of outcomes after a pharmacist-led medication review. Drugs Aging 2008;**25**(11):947-54.*
23. *Bosma L, Jansman FG, Franken AM, et al. Evaluation of pharmacist clinical interventions in a Dutch hospital setting. Pharm World Sci 2008;**30**(1):31-8.*
24. *Somers A, Robays H, De Paepe P, et al. Evaluation of clinical pharmacist recommendations in the geriatric ward of a Belgian university hospital. Clin Interv Aging 2013;**8**:703-9.*
25. *Keijsers CJ, van Doorn AB, van Kalles A, et al. Structured pharmaceutical analysis of the Systematic Tool to Reduce Inappropriate Prescribing is an effective method for final-year medical students to improve polypharmacy skills: a randomized controlled trial. J Am Geriatr Soc 2014;**62**(7):1353-9.*
26. *Royal Pharmaceutical Society. Helping patients to make the most of medicines: Good practice guidance for healthcare professionals in England, May 2013.*
27. *Cullinan S, Fleming A, O'Mahony D, et al. Doctors' perspectives on the barriers to appropriate prescribing in older hospitalized patients: a qualitative study. Br J Clin Pharmacol 2015;**79**(5):860-9.*
28. *Bardet JD, Vo TH, Bedouch P, et al. Physicians and community pharmacists collaboration in primary care: A review of specific models. Research in social & administrative pharmacy : RSAP 2015;**11**(5):602-22.*
29. *Kelly DV, Bishop L, Young S, et al. Pharmacist and physician views on collaborative practice: Findings from the community pharmaceutical care project. Canadian pharmacists journal : CPJ = Revue des pharmaciens du Canada : RPC 2013;**146**(4):218-26.*
30. *World Health Organization Collaborating Centre for Metabolic Bone Diseases. Fracture Risk Assessment Tool. Secondary Fracture Risk Assessment Tool. https://www.shef.ac.uk/FRAX/tool.jsp.*

APPENDIX 2.3.1: METHOD OF OVERHAGE ET AL TO MEASURE THE SEVERITY OF THE DETECTED PIP-ITEMS AND THE VALUE OF PHARMACIST'S RECOMMENDATION

Appendix 2.3.1: Method of Overhage et al to measure the severity of the detected PIP-items and the value of pharmacist's recommendation	
OVERHAGE ET AL – SEVERITY OF DETECTED PIP	**OVERHAGE ET AL – VALUE OF PHARMACIST'S RECOMMENDATION**
Potentially lethal	**Extremely significant**
• High potential for life-threatening adverse reactions • Potentially lifesaving drug at a dosage too low for the disease begin treated • High dosage (≥ 10 times normal) of drug with low therapeutic index	• Recommendation qualified by extremely serious consequences or potential life-and-death situation
Serious	**Very significant**
• Route of administration could lead to severe toxicity • Low dosage of drug for serious disease in patient with acute distress • High dosage (4-10 times normal) of drug with low therapeutic index • Dosage resulted in serum drug concentration in potentially toxic range • Drug could exacerbate the patient's condition (related to warnings or contraindications) • Misspelling or mix-up in medication order could lead to dispensing of wrong drug • Documented allergy to drug • High dosage (10 times normal) of drug without low therapeutic index • Omission of pre-test for drug hypersensitivity	• Recommendation qualified by a potential or existing dysfunction in a major organ • Avoidance of serious adverse drug interaction or contraindication to use
Significant	**Significant**
• High dosage (1.5-4 times normal) of drug with low therapeutic index • Drug dosage too low for patient's condition • High dosage (1.5-10 times normal) of drug without low therapeutic index • Errant dual-drug therapy for single condition • Inappropriate dosage interval • Omission from medical order	• Recommendation would bring patient care to a more acceptable, appropriate level (i.e., standard of practice), including quality-of-life issues with evidence from the patients or documentation elsewhere, as well as issues of cost and convenience.
Minor	**Somehow significant**
• Incomplete information in medication order • Unavailable or inappropriate dosage form • Nonformulary drug • Noncompliance with standard formulation and hospital policies • Illegible, ambiguous or nonstandard abbreviation	• Patient's benefit from the recommendation could be neutral depending on professional interpretation (to distinguish this rank from rank 3, where a standard of practice would support the recommendation) • More information or a clarification must be obtained by the pharmacist from the physician, nurse, or other appropriate health care professional before an order can be processed.
No error	**No significance**
• Information or clarification requested by physician or other health care professional from pharmacist • Cost savings only	• Information only • Recommendation not patient specific
	Adverse significance
	• Recommendation inappropriate; its implementation may lead to adverse outcomes

APPENDIX 2.3.2: PROCEDURE FOR RECRUITING AT THE GERIATRIC WARD

Appendix Table 2.3.2: Procedure for recruiting at the acute ward / geriatric wad

Workflow	Task	Procedure
Patient is admitted to acute ward and referred to the geriatric ward	Screen	• Inclusion criteria: - Patient ≥ 70 years - Unplanned hospitalization ▪ First hospitalization ▪ Repeated hospitalization: only one inclusion possible & no hospitalization till 3 months before - ≥ 5 chronic medications • Patient or legal representative wants to take part of the study (cfr. informed consent)
If inclusion criteria are fulfilled	Compile relevant medical information Compile preliminary medication list	• Check relevant sources for information on - Medications, if present: - Previous medical records - Referral papers - Home care or nursing home notes, or personal medication lists • Medication history - Compile medication history using the patient own medication and/or preliminary medication list as interview guide - Ask specifically for OTCs such as; pain-, allergy- or alimentary preparations. - Ask specifically for herbal- and dietary supplements - Ask specifically for non-oral medications, such as; inhalation-, ophthalmic-, dermatologic-, nasal-, sublingual-, or rectal preparations - Ask for the patient's perceived effect of the medication - Ask about compliance and adverse drug reactions - Ask about known allergies or alerts, such as; antibiotics, opiates, NSAIDs, iodide, food dyes - Also ask relatives or caregivers if they are present, especially if patient has aphasia, dyspnoea or otherwise cannot participate well in the interview • Explain purpose of the interview • Obtain patient's own medication if present • Comprise medication history using the patient own medication and/or preliminary medication list as interview guide • Ask if the patient has drug-related questions • Contact generalist if needed • Ask pharmacy
If medication history is complete as possible	Obtaining more information	• Contact community pharmacy by pharmacist (medication history past 6 months and OTC medication)

APPENDIX 2.3.3: COMPLETE PREVALENCE LIST ACCORDING TO THE GHEOP³S-TOOL

Appendix Table 2.3.3: Complete prevalence list according to the GheOP³S-tool

No.	GheOP³S-criterion	N, % (relative to total population, n=60)		N, % (relative to diagnosis positive patients)
Part 1b: Potentially inappropriate drugs, independent of diagnosis – Drug classes				
1	Any antidepressant ≥1year	24	40%	
2	Any antipsychotic drug ≥1 month	5	8%	
3	Any drug for arterial vascular disorders	3	5%	
4	Any intermediate acting benzodiazepine or Z-product at full dose or any dose ≥30 subsequent days	27	45%	
5	Any short or long-acting benzodiazepine	6	10%	
6	Any long-acting sulfonylurea derivative	5	8%	
7	Any nasal vasoconstrictor ≥1 month	0	0%	
8	Any oral NSAID	6	10%	
9	Any PPI at full dose[a] ≥8 weeks	9	15%	
10	Any recently marketed drug (black triangles)	2	3%	
11	Any sedating antihistaminic drug	2	3%	
Part 1b: Potentially inappropriate drugs, independent of diagnosis - Specific molecules				
12	Alizapride	2	3%	
13	Bisacodyl	1	2%	
14	Clonidine	0	0%	
15	Codeine and its derivatives for acute cough	0	0%	
16	Dabigatran	0	0%	
17	Digoxin >0,125mg/day	0	0%	
18	Dipyridamole monotherapy (without ASA)	2	3%	
19	Ginkgo biloba or Panax ginseng	1	2%	
20	Liquid paraffin	0	0%	
21	Methyldopa	0	0%	
22	Metoclopramide	1	2%	
23	Pentazocine	0	0%	
24	Phenobarbital	0	0%	
25	Pseudoephedrine oral	0	0%	
26	Rivaroxaban or Apixaban	0	0%	
27	Senna glycosides	0	0%	
28	Picosulfate	3	5%	
29	Theophylline	1	2%	
30	Ticlopidine, new prescription	0	0%	
31	Tramadol, new prescription	7	12%	
Part 2a: Potentially inappropriate drugs, dependent on diagnosis - Drug classes				
32	Any antipsychotic other than quetiapine and clozapine with Parkinson's disease	1	2%	1/3 (33%)
33	Anticholinergics (e.g. Antihistamines, Antidepressants, Antipsychotics, Antispasmodics…) with dementia or cognitive impairment	4	7%	4/8 (50%)
34	Anticholinergics (e.g. Antihistamines, Antidepressants, Antipsychotics, Antispasmodics…) with constipation	15	25%	15/23 (65%)
35	Anticholinergics (e.g. Antihistamines, Antidepressants, Antipsychotics, Antispasmodics…) with BPH	0	0%	0/1 (0%)
36	Calcium Channel Blockers with constipation	2	3%	2/17 (12%)
37	Non-selective beta-blockers with asthma or COPD	0	0%	0/5 (0%)
38	Oral corticosteroids >1 week with diabetes	2	3%	2/10 (20%)
39	Oral corticosteroids >1 week with hypertension	5	8%	5/36 (14%)
40	Thiazide and loop diuretics with gout	2	3%	2/4 (50%)
Part 2b: Potentially inappropriate drugs, dependent on diagnosis - Specific molecules				
41	Alizapride with Parkinson's disease	1	2%	1/4 (25%)
42	Metoclopramide with Parkinson's disease	0	0%	0/4 (0%)
Part 3: Potential prescribing omissions				
43	The patient is taking ≥ an equivalent of 7.5 mg of oral prednisone for ≥3 months and is not prescribed Ca/VitD supplementation and bisphosphonates.	0	0%	0/0 (-)
44	The patient is taking narcotic analgesics and is not prescribed appropriate preventative bowel regimen (preferably macrogol or lactulose).	10	17%	10/12 (83%)
45	The patient has an elevated risk for osteoporosis (determined via FRAX-tool[30]) and is not prescribed Calcium/Vitamin D supplementation.	41	68%	41/49 (84%)
46	The patient is taking oral corticosteroids for ≥1 month and is not prescribed Ca/VitD supplementation.	2	3%	2/4 (50%)
47	The patient is not reminded and proposed to undergo yearly influenza vaccination.	18	30%	18/59 (31%)
48	The patient is taking methotrexate and is not prescribed folic acid supplementation.	0	0%	0/1 (0%)

Part 4: Drug-Drug interactions of specific relevance				
49	VKA + oral NSAIDs	0	0%	
50	RAAS-inhibitor + potassium sparing diuretic/potassium supplements/potassium containing drugs[b]	0	0%	
51	VKA + Antiplatelet drugs (esp. ASA), unless prescribed by internist/cardiologist	6	10%	
52	VKA + TMP/SMX	2	3%	
53	Oral NSAID + Oral Corticosteroids	0	0%	
54	Oral NSAID + Diuretic	0	0%	
55	Digoxin + Macrolide antibiotics	1	2%	
56	Digoxin + Verapamil/Diltiazem	0	0%	
57	Lithium + RAAS-inhibitors	0	0%	
58	Lithium + Oral NSAID	0	0%	
59	Lithium + Diuretics	0	0%	
60	Theophylline + Quinolones/Macrolides	0	0%	
61	RAAS-inhibitor + Oral NSAID	1	2%	
62	Oral NSAID + SSRI/SNRI	2	3%	
63	RAAS-inhibitor + TMP/SMX	0	0%	
64	Oral antidiabetics/insulin + non-selective beta-blocker	1	2%	
65	Oral antidiabetics/insulin + cardioselective beta-blocker	6	10%	
66	Alprazolam/Midazolam/Triazolam/Zolpidem/Zopiclone + Strong CYP3A4 inhibitor	1	2%	
67	CCB + Strong CYP3A4 inhibitor	0	0%	
68	Oral NSAID + Antipletelet drugs	0	0%	
69	Phenytoin + TMP/SMX	0	0%	
70	First dose RAAS-inhibitor at full dosage + pre-treatment with diuretic	0	0%	
71	Tamoxifen + strong CYP2D6 inhibitors	0	0%	
72	Calcium + Quinolones/Tetracyclines	1	2%	
73	Calcium + Stontium ranelate	0	0%	
74	Calcium + Levothyroxine	2	3%	
75	Bisphosphonate + Calcium, Magnesium, Zinc, Iron or Aluminium	1	2%	
76	VKA + Vitamin K containing drugs/supplements[c]	0	0%	
77	Any combination of anticholinergic drug	16	27%	

***ASA**: Acetylsalicylic acid; **BPH**: Benign prostatic hyperplasia; **CCB**: Calcium Channel Blocker; **COPD**: Chronic Obstructive Pulmonary Disease; **CV-risk**: Cardiovascular risk; **GI-risk**: Gastro-intestinal risk; **GP**: General Practitioner; **NSAID**: Non Steroidal Anti-Inflammatory Drug; **INR**: International Normalized Ratio; **PPI**: Proton Pump Inhibitor; **RAAS-inhibitor**: Renin-Angiotensin-Aldosteron System Inhibitors; **SNRI**: Serotonin and Noradrenalin Reuptake Inhibitor; **SSRI**: Selective Serotonin Reuptake Inhibitor; **TMP/SMX**: Trimetoprim/Sulfamethoxazol; **VKA**: Vitamin K Antagonist.*

[a] Full dose defined as: >20 mg (es)omeprazole, >20mg pantoprazole, >30mg lansoprazole, >20mg rabeprazole
[b] Some drugs contain considerable potassium amounts: Glucosamine in potassium salt (up to 300mg/tablet), oral nutritional supplements (up to 200mg/unit).... (Recommended Daily Dose: 3000mg/day for ≥60 year old patients)
[c] Some supplements such as oral nutritional supplements contain considerable Vitamin K amounts (up to 13µg/unit). (Recommended Daily Dose: 50-70µg/day for ≥60 year old patients)

PART 2.4:

COMMUNITY PHARMACISTS' EVALUATION OF POTENTIALLY INAPPROPRIATE PRESCRIBING IN OLDER COMMUNITY-DWELLING PATIENTS WITH POLYPHARMACY: OBSERVATIONAL RESEARCH BASED ON THE GHEOP³S-TOOL.

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ABSTRACT

Purpose. In this study, we aimed to (1) determine the prevalence of potentially inappropriate prescribing (PIP) in community-dwelling older polypharmacy patients using the GheOP³S-tool, (2) identify the items that account for the highest proportion of PIP and (3) identify the patient variables that may influence the occurrence of PIP. Additionally, pharmacist-physician contacts emerging from PIP-screening with the GheOP³S-tool and feasibility of the GheOP³S-tool in daily practice were evaluated.

Methods. A prospective observational study was carried out between December 2013 and July 2014 in 204 community pharmacies in Belgium. Patients were eligible if they were (1) ≥70 years, (2), community-dwelling, (3) using ≥5 chronic drugs (4) a regular visitor of the pharmacy and (5) understanding Dutch or French. Community pharmacists used a structured interview to obtain demographic data and medication use and subsequently screened for PIP using the GheOP³S-tool. A Poisson regression was used to investigate the association between different covariates and the number of PIP.

Results. In 987 (97%) of 1016 included patients, 3721 PIP items were detected (median of 3 per patient; IQR: 2-5). Most frequently involved with PIP are drugs for the central nervous system such as hypnosedatives, antipsychotics and antidepressants. Risk factors for a higher PIP prevalence appeared to be a higher number of drugs (30% extra PIPs per 5 extra drugs), female gender (20% extra PIPs), higher BMI (20% extra PIPs per 10-unit increase in BMI) and poorer functional status (30% extra PIPs with 6-point increase). The feasibility of the GheOP³S-tool was acceptable although digitalization of the tool would improve implementation. Despite detecting at least one PIP in 987 patients, only 39 physicians were contacted by the community pharmacists to discuss the items.

Conclusion. A high prevalence of PIP in community-dwelling older polypharmacy patients in Belgium was detected which urges for interventions to reduce PIP.

INTRODUCTION

Potentially inappropriate prescribing (PIP) is defined as the prescribing of medication that significantly increases the risk of an adverse drug reaction (ADR), in particular when there is an equally or more effective alternative with lower risk available[1 2]. PIP encompasses three main categories: overuse, underuse and misuse[3]. As PIP is a major risk factor for ADRs, it can put substantial pressure on the safety of medication use[4 5].

A recent systematic review[6] showed that PIP prevalence in community dwelling European older adults is high (average estimated prevalence: 22.6%, confidence interval (CI): 19.5-26.7%). This shows that PIP is a wide-spread issue. Furthermore, a variety of factors seem to contribute to the prevalence of PIP in older community-dwelling adults, such as polypharmacy, older age, depression, moderate self-rated health quality, low activities of daily living (ADL)-score and poor economic situation[4-6]. A periodic screening for PIP could be a strategy to diminish its burden[7]. In the literature, there is agreement that such a periodic screening should be applied to older patients with polypharmacy or other additional risk factors. PIP screening in primary care could reduce the risk for ADR and ADR-related hospitalization[8] and research showed it is probably cost-neutral[9 10].

Community pharmacists are ideally placed to perform periodic screening for PIP because of their medication-specific knowledge and the availability of an electronic dispensing record in the pharmacy that ideally includes all dispensed over-the-counter (OTC) medication. Moreover, multiple studies showed that the community pharmacist can intervene and assist in significantly reducing the occurrence of a lot of specific PIPs. The EMPOWER-study for example showed that direct-to-consumer education from the community pharmacy effectively reduced overuse of benzodiazepines[11]. Another study, performed in French community pharmacies, shows that providing the community pharmacist with the patients' renal functions can resolve several PIPs concerning incorrect dosing[12].

However, general screening for PIP in the community pharmacy is more comprehensive and requires an evidence-based screening tool specifically suitable for this setting. The Ghent Older People's Prescriptions community Pharmacy Screening (GheOP³S-)tool[13] was recently developed to detect PIP with high clinical relevance for primary care, taking into account the limited availability of clinical data in the community pharmacy setting. The GheOP³S-tool consists of 83 items, addressing overuse, underuse and misuse of medication. For each item of the tool, an alternative therapeutic option is offered. Furthermore, pharmacists could perform a medication screening on a regular base or at every moment a change in pharmacotherapy is made.

This observational research was the first to use the GheOP³S-tool in the community-pharmacy setting. We aimed (1) to determine the prevalence of PIP in community-dwelling older polypharmacy patients with the GheOP³S-tool, (2) to identify the items that account for the highest proportion of PIP and (3) to identify the patient variables that may influence the occurrence of PIP. Additionally, (4) pharmacist-physician contacts resulting from PIP-screening with the GheOP³S-tool and (5) feasibility of the GheOP³S-tool in daily practice was evaluated.

METHODS

Study design & setting

This manuscript describes a prospective observational study, carried out between December 2013 and July 2014 in all 204 community pharmacies counselling a pharmacist in training from the Ghent University or the University of Liège, during the academic year of 2013-2014 (i.e. a final year pharmacy student, performing obligatory six-month pre-registration community pharmacy training). Ethical approval was granted by the ethical committees of the Ghent University Hospital (for Flanders) and Centre Hospitalier Universitaire de Liège (for Wallonia). All participants provided written informed consent. The STROBE standardized reporting guidelines for cross-sectional studies were followed to ensure the uniform conduct and reporting of the research[14].

Participants

All older patients filling a prescription at a participating pharmacy were consecutively approached and invited to participate in the study. They were eligible when meeting the following inclusion criteria: (1) aged 70 years of older, (2), community-dwelling, (3) using 5 of more chronic drugs (i.e. intake follows a fixed regimen) registered in the Belgian Commented Drugs Repertory[15] (4) being a regular visitor of the pharmacy and (5) speaking and reading Dutch or French. Each pharmacy planned to recruit 5 patients. Recruiting patients that regularly visited the pharmacy warranted a patient-pharmacist relationship of respect and trust.

Data collection and outcome measures

Participating patients were interviewed by a pharmacist in training using a structured questionnaire. The questionnaire assessed information about demographics, self-rated health[16], functional status, cognitive impairment (using the MiniCog[17]), fall incidents, hospitalizations and emergency visits in the previous year, and current medication use (including detailed information about dose, frequency, time of administration, starting date etc). For current medication use, the electronic dispensing records at the participating pharmacy were consulted as a starting point. In addition, patients were specifically asked about the use of over-the-counter (OTC-) and herbal drugs. The structured interview took place at the pharmacy or at the patient's home (according to patient preference), and was fully documented on paper.

Using the data from the structured interview and the electronic dispensing record, the pharmacist in training subsequently screened each patient's medication for PIP by applying the GheOP^{3}S-tool[13].

The choice to use this screening tool was deliberate. First, the GheOP³S-tool makes it possible to screen for PIP in settings where clinical data are not available. Second, the GheOP³S-tool is adapted to the European market and addresses all types of PIP. Third, the GheOP³S-tool offers the pharmacists a backbone to get started with the process of a medication review. An elaborate document describing rationale, alternative treatment plans and scientific background information of all included items empowers the pharmacists to initiate pharmacist-physician contacts to discuss the considered clinically relevant PIP-items.

The GheOP³S-tool is subdivided into 5 different parts: Part 1: Potentially inappropriate drugs, independent of diagnosis; Part 2: Potentially inappropriate drugs, dependent on diagnosis; Part 3: Potential prescribing omissions (PPOs); Part 4: Drug-drug interactions (DDIs) of specific relevance; and Part 5: General care-related items to be addressed in the community pharmacy. The items in the latter part are not strictly considered to be PIP, according to the definition in the introduction, but they are considered relevant to be checked for in community pharmacy practice as they evaluate the appropriateness of the provided pharmaceutical care. With regard to the diagnoses in Part 2, drug proxies were used. Only diagnoses that could unambiguously be derived from the patient's medication (e.g. diabetes from insulin, gout from allopurinol, etc) were taken into account. In this study, all 83 criteria of the GheOP³S-tool were used.

An extensive training session on the use of the GheOP³S-tool for PIP screening (with example cases as well as one real-life trial case) was completed by each pharmacist in training before the start of the study. In addition, all screenings included in the study were double-checked by a member of the research team (ET). As pharmacist-physician contacts considering PIP are not yet common practice in Belgium, the decision to initiate such a contact from the pharmacy was left to the supervising pharmacist, based on his/her personal judgement of the detected PIPs. All initiated physician contacts and their outcomes were documented. The acceptance of the proposed alternative treatment plans by the pharmacist was categorized as 'accepted', 'partially accepted' or 'not accepted'. Reasons for not accepting the treatment plan were also recorded.

Subsequently, all participating pharmacists evaluated the feasibility of the GheOP³S-tool, using a slightly adapted version of the system usability scale (SUS) (Appendix 2.4.1)[18 19]. The SUS is a validated tool for assessing feasibility, consisting of 10 items, each to be scored on a 5-point scale. It provides an easy-to-understand overall score from 0 (lowest feasibility) to 100 (highest feasibility). Although no explicit cut-off for feasibility is determined, it is generally accepted that SUS-scores >50 are sufficient to consider the tool feasible in current practice[19]. Research by Lewis et al. showed that SUS can be divided into two separate factors, specifically representing the usability (8 items) and learnability (2 items) of the evaluated tool[18].

The participating pharmacists transferred all obtained anonymized patient data and results of the written document through an electronic platform to the Ghent University study centre. Data input was double-checked using the written document by the principal investigator (ET) before processing. During this process, each medicine was assigned a seven-digit code in accordance with the Anatomical Therapeutic Chemical (ATC) Classification System formulated by the World Health Organization Collaborating Centre for Drug Statistics Methodology[20].

Statistical analysis

Descriptive statistics are provided as counts with percentages, means with standard deviations or medians with interquartile ranges as appropriate. Prevalence of PIP is represented as the proportion of patients with at least one PIP and the median number of PIPs per patient.

Poisson regression was used to investigate the association between different covariates and the number of PIP. Patient covariates considered as predictors in the model, were: number of drugs, age, gender, body mass index (BMI), smoking status, education, self-rated health status, functional status, living situation, cognitive impairment, emergency department visits, hospitalizations, recent falls and presence of ADRs. Continuous covariates, such as 'number of drugs', 'age' and 'BMI' were centered around 5, 70 years and 25 kg/m², respectively. After covariate selection, based on "backward elimination" at the 5% level of significance, the linearity assumption for the continuous covariates in the final model was assessed. Education (scale: 1-4 with 4 as highest education), functional status (scale: 0-6 with 6 as worst functional status), self-rated health status (scale: 1-5 with 5 as best health rate), and cognitive impairment (scale: 0-5 with 5 as no cognitive impairment) were set as ordinal variables. Furthermore, a likelihood-ratio-test was performed to test whether overdispersion should be accounted for. Finally, once the final model was developed, likelihood-ratio-testing was performed at the 5% level of significance to test whether 2-way interaction terms should be added to the model. Fitting of the models to the observed data and post-hoc evaluations of the model's goodness-of-fit was performed in R® (R foundation for statistical computing, Vienna, Austria).

RESULTS

Participants

In total, 2228 patients were screened for eligibility. 726 patients did not meet the inclusion criteria (547 took less than 5 drugs, 89 were not regular visitors of the participating pharmacy, 45 didn't sufficiently understand Dutch or French and 45 were not community-dwelling). Additionally, 486 refused to participate (221 did not have time to participate, 194 were not interested and 71 stated other reasons). Eventually, 1016 older community dwelling polypharmacy patients were included in the study. Mean age (± SD) was 78.8 (±5.5) years and 58% of the population was female. The total number of medicines taken was 10568, with a range of 5-29 per patient and a median of 10 per patient (interquartile range 8-12) (Table 2.4.1).

Table 2.4.1: Basic characteristics of the study population (n=1016)

Age, Mean (SD)	78.8	(5.5)
Age ≥ 85j, n (%)	162	(16%)
Female gender, n (%)	592	(58%)
BMI, Mean (SD)	26.6	(4.3)
No. of drugs, Median (IQR)	10	(8-12)
No. of drugs, Mean (SD)	10.4	(3.4)
Current smoker, n (%)	57	(6%)
Education [a]		
Primary school	257	(25%)
Secondary school	580	(57%)
Higher education	176	(17%)
Living alone, n (%)	434	(43%)
Functional status; need help with, n (%)		
Bathing/showering	110	(11%)
Dressing	54	(5%)
Toileting	19	(2%)
Community mobility	117	(12%)
Eating	39	(4%)
Cleaning	382	(38%)
Self-rated health status, n (%)		
Excellent	19	(2%)
Very good	104	(10%)
Good	497	(49%)
Fair / Moderate	343	(34%)
Poor	53	(5%)
Positive for cognitive impairment (according to the Mini-Cog), n (%)	335	(33%)
Emergency department visits		
Patients with emergency department visit in previous year, n (%)	229	(23%)
Number of emergency department visits per patient year, Median (IQR)	1	(1-2)
Hospitalizations		
Patients with hospitalization in previous year, n (%)	394	(39%)
Number of hospitalizations per patient year, Median (IQR)	1	(1-2)
Fall incidents		
Patients with fall incident in previous year, n (%)	333	(33%)
Number of fall incidents per patient year, Median (IQR)	1	(1-3)
[a] 3 patients did not answer this question		

Potentially inappropriate prescribing

Considering Part 1 to Part 4 of the GheOP³S-tool, a total of 3721 PIPs were detected in 987 (97%) of participants (Median: 3; IQR: 2-5). However, with regard to the full GheOP³S-tool, thus also including list 5 "General care-related items to be addressed in the community pharmacy", an additional 3186 items considering general care-related items were detected. This led to a total of 6907 items in 1008 (99%) participants (Median: 7; IQR: 5-8) (Figure 2.4.1).

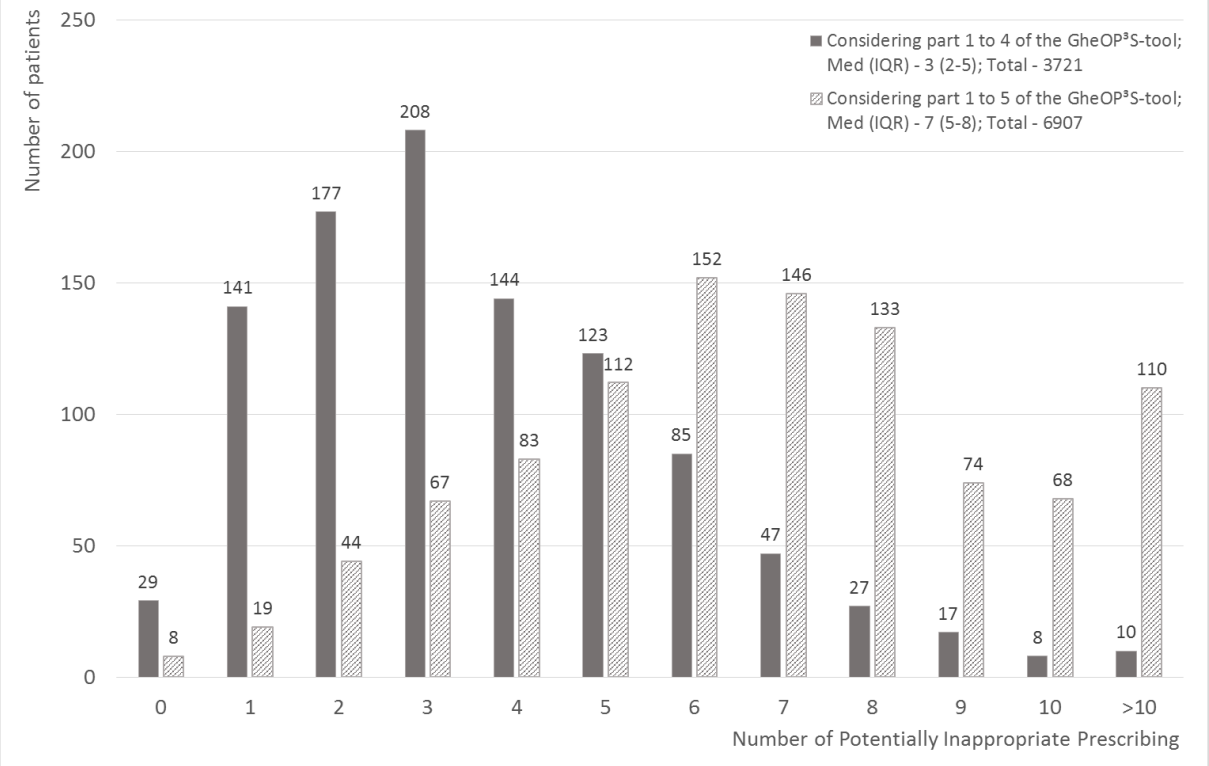

Figure 2.4.1*: Distribution of the number of GheOP³S-criteria detected per patient (n = 1016; Part 1: Potentially inappropriate drugs, independent of diagnosis, Part 2: Potentially inappropriate drugs, dependent on diagnosis, Part 3: Potential prescribing omissions, Part 4: Drug-drug interactions of specific relevance and Part 5: General care-related items to be addressed in the community pharmacy).*

The 5 most prevalent items of each part of the GheOP³S-tool are reported in Table 2.4.2. The items of Part 2 and Part 3 are displayed in two ways; relative to the total population and relative to the overall drug or disease prevalence. For example, of the 130 patients taking narcotic analgesics, 99 (76%) did not receive an appropriate preventative bowel regimen, however relative to the total population (n=1016), this considers only 10%. The full list of the prevalence of all GheOP³S-criteria is reported in Appendix 2.4.2.

Table 2.4.2: The 5 most prevalent[a] criteria of each part of the GheOP³S-tool, n = 1016

	GheOP³S-item	N, %[a] (relative to total population)	N, %[a] (relative to overall drug or disease prevalence)
Part 1: Potentially inappropriate drugs, independent of diagnosis		**791 (78%)**	
1	Any intermediate acting benzodiazepine or Z-product at full dose or any dose ≥30 subsequent days OR any short or long-acting benzodiazepine	510 (50%)	
	Any intermediate acting benzodiazepine or Z-product at full dose or any dose ≥30 subsequent days	448 (44%)	
	Any short or long-acting benzodiazepine	93 (9%)	
	Any intermediate acting benzodiazepine or Z-product at full dose or any dose ≥30 subsequent days AND any short or long-acting benzodiazepine	31 (3%)	
2	Any antidepressant ≥1 year	216 (21%)	
3	Any oral NSAID	146 (14%)	
4	Any PPI at full dose ≥8 weeks	145 (14%)	
5	Any antipsychotic drug ≥ 1 month	71 (7%)	
Part 2: Potentially inappropriate drugs, dependent on diagnosis		**276 (27%)**	
1	Thiazide and loop diuretics with gout	88 (9%)	88/151 (58%)
2	Anticholinergics with constipation	84 (8%)	84/147 (57%)
3	Calcium Channel Blockers with constipation	43 (4%)	43/144 (30%)
4	Oral corticosteroids >1 week with hypertension	43 (4%)	43/810 (5%)
5	Anticholinergics with benign prostate hyperplasia	40 (4%)	40/93 (43%)
Part 3: Potential prescribing omissions		**727 (72%)**	
1	The patient has an elevated risk for osteoporosis (determined via FRAX tool) and is not prescribed calcium/Vitamin D supplementation.	545 (54%)	545/710 (77%)
2	The patient is not reminded and proposed to undergo yearly influenza vaccination.	306 (30%)	
3	The patient is taking narcotic analgesics and is not prescribed appropriate preventative bowel regimen (preferably macrogol or lactulose).	99 (10%)	99/130 (76%)
4	The patient is taking oral corticosteroids for ≥1 month and is not prescribed calcium and vitamin D supplementation.	39 (4%)	39/54 (72%)
5	The patient is taking an equivalent of 7.5 mg of oral prednisone or more for ≥3 months and is not prescribed calcium/Vitamin D supplementation and bisphosphonates.	23 (2%)	23/24 (96%)
Part 4: Drug-drug interactions of specific relevance		**523 (51%)**	
1	Oral antidiabetics/insulin + beta-blocker	226 (22%)	
	Oral antidiabetics/insulin + non-selective beta-blocker	44 (4%)	
	Oral antidiabetics/insulin + cardioselective beta-blocker	187 (18%)	
2	Any combination of anticholinergic drug	135 (13%)	
3	RAAS-inhibitor + potassium sparing diuretic/ potassium supplements/ potassium containing drugs	81 (8%)	
4	RAAS inhibitor + oral NSAID	74 (7%)	
5	Oral NSAID + antiplatelet drugs	71 (7%)	
Part 5: General care-related items to be addressed in the community pharmacy		**872 (86%)**	
1	Adherence for all new medication was not checked or discussed at first refill during the past year. Adherence for all chronic medication was not checked or discussed during the past year (refill rate).	701 (69%) 681 (67%)	
2	Contra-indications that can unambiguously be derived from patient's medication were not added to the electronic patient record.	626 (62%)	
3	The patient was not asked which aspects of pharmaceutical care could be improved for him/her.	463 (46%)	
4	Polypharmacy patients (chronically taking ≥ 5 drugs) were not questioned about whether a clear medication scheme was available to him/her.	441 (43%)	
5	Dispensation of over-the-counter medication (NSAID, ASA…) was not added in the electronic patient record.	253 (25%)	

ASA: *Acetyl Salicylic Acid****; NSAID****: Nonsteroidal Anti-Inflammatory Drugs;* ***PPI:*** *Proton Pump Inhibitor*

[a] *Prevalence is expressed as the percentage of patients to whom this item applies, whether relative to the total population or whether relative to the overall disease/drug prevalence*

Factors associated with PIP

The estimated parameters from the final Poisson regression model are shown in Table 2.4.3. The number of drugs, gender, BMI and functional status were predictive for the observed number of PIPs. From the estimated parameters we can calculate that a baseline patient (female patient with a functional status of 0, a BMI of 25, taking 5 drugs) has an estimated average number of PIPs of 2.7 [= ^{e}log (intercept)]. Compared to this "baseline" patient, a very poor functional status (6 compared to 0) is associated with an average of 30% extra PIPs. Furthermore, male gender and BMI are associated with a decrease of 23% and an increase of 20% (BMI 35 vs 25) in the estimated number of PIPs, respectively. Finally, the number of PIPs increases with the number of drugs taken. For instance, patients taking an additional 5 drugs have a 30% increase in expected PIPs as compared to otherwise similar patients.

Table 2.4.3: Estimated parameters of the Poisson regression model (outcome: number of PIPs, considering list 1-4 of the GheOP^{3}S-tool) with calculation example.

Risk factor	Estimate	95% CI
Intercept	1.001***	0.932 – 1.071
No. of drugs (continuous, centered around 5)	0.057***	0.049 – 0.066
Gender (1 = male, 0 (female) as reference)	-0.266***	-0.958 – -0.197
BMI (continuous, centered around 25)	0.017***	0.009 – 0.024
Functional status (scale 0-6, 0 as reference)	0.043**	0.016 – 0.070

CI: *Confidence Interval;* ***PIP:*** *Potentially Inappropriate Prescribing;* ***No.****: Number;* ***BMI****: Body Mass Index;* ***GheOP^{3}S****: Ghent Older People's Prescriptions community Pharmacy Screening - *** p<0.001; **p<.01*

Calculation example: For a man with 6 chronic drugs, a BMI of 30 and a functional status of 1, the estimated number of PIPs can be determined through the following formula:

$$Ln(\text{estimated number of PIP}) = 1.001 + 0.057*(6-5) - 0.266*1 + 0.017*(30-25) + 0.043*(1-0)$$
$$\text{Estimated number of PIP} = e^{0,92} = 2,5$$

Pharmacist-physician contacts

In total, 22 supervising pharmacists decided to initiate contact with at least one prescribing physician to discuss the detected PIPs. In total 39 physicians were contacted. Thirteen refused to participate (reasons for refusal: no time (n=12), not interested (n=1)) and 1 could not be reached. The remaining 25 physicians agreed to participate and discussed a total of 77 detected PIP-items with the pharmacists. For 28 of the 77 items (36%), the alternative treatment plan proposed by the pharmacist was accepted. For 2 items, the alternative treatment plan was partially accepted. For 47 items, the physician did not accept the proposed treatment plan of the community pharmacists (Table 2.4.4).

Table 2.4.4: Reasons for the family physician not to accept the proposed alternative treatment plan (n = 47)

The family physician did not provide a rationale for not accepting the alternative treatment plan	13
The alternative treatment plan was not feasible due to clinical reasons (e.g. intolerance for alternative)	12
The alternative treatment plan had already been implemented before with insufficient result or relapse	7
The alternative treatment plan was not accepted by the patient	6
Adequate monitoring had already been provided (e.g. frequent measurement of kidney function)	3
Physician is unwilling to change a therapy initiated by a colleague (e.g. specialist or former family physician)	2
PIP was detected on the basis of incorrect data (e.g. flu vaccination was administered but incorrectly registered in pharmacy software)	4
PIP: *Potentially Inappropriate Prescribing*	

Usability and feasibility

The mean SUS-score was 61.2 (SD: 12.2), with a learnability score of 63.4 (SD: 17.5) and a usability score of 60.7 (SD: 12.9). Reviewing the comments of the users, the most frequent remark was the lack of digitalization or integration of the GheOP³S-tool in the software which renders the tool too time-consuming. Mean duration of an evaluation using the GheOP³S-tool including the estimation of the clinical relevance of the detected items was 38 minutes (SD = 27 min).

DISCUSSION

Main findings of the study

In this observational study, we found that in 99% of included patients, at least one GheOP³S-item was detected. Specifically focusing on PIPs (i.e. Part 1 to Part 4 of the GheOP³S-tool), a median of 3 (IQR: 2-5) PIPs per patient was observed. When the general care-related items of Part 5 of the GheOP³S-tool were also included, a median of 7 items (IQR: 5-8) per patient was detected. Risk factors most frequently associated with higher number of PIPs were higher number of drugs, female gender, higher BMI and poorer functional status.

What is already known on this topic

Similar studies, also conducted in community pharmacies, are scarce. A study in France using the Laroche-list[21] observed that 37.1% of the 393 included patients had at least one PIP[22], which is markedly lower than the observations in this study. A possible explanation might be that the French Laroche list does not include DDIs, drug-disease interactions (DDisI) or PPOs[21]. Additionally, in the French study, all older adults were included, regardless of polypharmacy, where in this study, only older adults taking 5 or more chronic drugs were included.

Studies conducted in other primary care settings but using similar inclusion criteria (older age and 5 or more chronic drugs), presented higher prevalence numbers for PIP[23-25]. A Spanish study using the START/STOPP criteria[24], a Danish study using the MAI-criteria[25] and an Austrian study using the PRISCUS list[23], detected at least one PIP in respectively 76.4%, 94.3% and 37.3% of patients. The low prevalence of the Austrian study should however be nuanced with the fact that 93.5% of patients took at least one non-evidence based medication, that 56.2% had at least one dosing error and that 59.2% had at least one clinically significant drug-drug interaction[23].

What this study adds

In the current study, the prevalence of all types of PIP (i.e. overuse, misuse and underuse) was remarkably high. The fact that almost all patients had at least one PIP could raise questions about whether the tool needs to be more discriminatory. During the development of the GheOP³S-tool however, the experts unanimously agreed that it was clinically relevant to check for all of the items included in the GheOP³S-tool in ambulatory older adults. Whether the detected *potential* problems are clinically relevant for the specific individual patient, still needs to be assessed during a pharmacist-physician and follow-up patient consultation. *Actual* inappropriate prescribing will therefore probably be somewhat lower. Nevertheless, these results show that there is a large potential for improvement in the appropriateness of prescribing and provided pharmaceutical care for ambulatory older patients with polypharmacy.

The specific criteria with the highest prevalence are the overuse of benzodiazepines and the underuse of preventive anti-osteoporotic medication, respectively in 50% and 54% of included patients. A review of studies using STOPP/START criteria also showed that both of these items are frequently detected[26]. At first instance, it appears that DDisIs are not very prevalent (up to 9% of included patients). However, relative to the number of patients with a certain diagnosis, this is still significant (e.g. 43% of patients using drugs for benign prostate hyperplasia receive anticholinergic medication).

Furthermore, taking into account that only DDIs with high risk for hospitalization were included in the GheOP³S-tool, the observed high frequency (i.e. in up to 22% of patients) implies serious potential health consequences and healthcare costs.

Risk factor assessment showed that a higher number of drugs, female gender, a higher BMI and a poorer functional status are associated with a higher prevalence of PIP. Recent systematic research on risk factors for PIP showed that polypharmacy and a poor functional status are indeed consistently positively associated with PIP[6]. BMI could be present due to its association with metabolic syndrome, however, literature is not consistent considering this risk factor's association with PIP[27 28]. Analogously, there is no consistency in the literature on the association between the female gender and a higher prevalence of PIP. However, this might be explained by differences in prescribing attitude towards the genders and by differences between genders in educational and socio-economic characteristics[29].

The evaluation of the feasibility of the GheOP³S-tool showed that the tool is functioning well in the current community pharmacy setting. There is, nevertheless, still room for improvement. It would be interesting to re-evaluate the feasibility of the GheOP³S-tool, once the tool is available in a digital format.

The low number of pharmacist-initiated contacts with physicians to discuss the detected PIPs must however be seen as a point of concern (only 39 initiated contacts for 987 patients with at least one PIP). These numbers are a real-world representation of the extensively present barriers for collaboration between pharmacists and physicians[30-32]. A Canadian research project identified barriers for pharmacist-physician collaboration which include lack of financial remuneration and insufficient time[32]. Furthermore, although community pharmacists considered patient counseling and advising physicians about drug interactions, dosages and drug information as core tasks, physicians did not perceive this as an important role for the community pharmacist[32]. Other recent research showed however that prescribers indicate that pharmacists' input is preferred as well as collaborations with other levels of care[30]. Additionally, potential facilitators have been established such as interprofessional experiences and facilitated communication[31].

Strengths and limitations of this study

This was the first study using the newly developed GheOP³S-tool, a community pharmacy specific list for settings in which limited clinical data are available. The study was protocol-based and reported following the STROBE statement[14]. Because of the prospective nature and the inclusion of patient interviews, accurate dosing information and complete medication use (i.e. OTC-medication, herbal therapies etc) was available. Additionally, this was the first study evaluating PIP in community dwelling older adults in Belgium. The study also evaluated usability and learnability of the GheOP³S-tool which is a very important aspect for future implementation research.

On the other hand, this study has some limitations. The first is inherently linked to the use of the GheOP³S-tool as screening method. As the GheOP³S-tool is an explicit list, it does not take into account all patient factors in evaluating a patient's pharmacotherapy, e.g. the diagnoses and evolution of the patient's diseases, the patient's own preferences and earlier attempts to prohibit the use of potentially inappropriate drugs. The few pharmacist-physician contacts to discuss the detected items made it difficult to estimate which part of the items were of no or limited clinical relevance.

Second, some limitations are linked to the study design. As the study was merely observational, the possible clinical effects of reduced inappropriate prescribing could not be assessed. Moreover, we only evaluated the feasibility of the GheOP³S-tool in the community pharmacy practice, where it also would have been interesting to evaluate how the tool performs in a broader primary health care team, including the general practitioner, nurses, physiotherapists, etc. Third, about 20% of potential participants refused study participation. Potential bias caused by those who refused could not be assessed as the ethical committee prohibited data collection in study refusers. The impact on the roll-out of any future intervention based on the current results is therefore unclear. Finally, generalizability of the results to other countries is difficult. Prescribing patterns vary along health care settings, which are very country-specific. However, throughout Belgium, we increased generalizability as much as possible by recruiting a patient sample using all 204 participating pharmacies as one recruitment center.

Future perspectives

A study evaluating the reduction of PIP in older ambulatory patients using the GheOP³S-tool should be conducted. Ideally, the impact (clinical and economic) of this improved pharmacotherapy should be measured. To reach this, we need to start with a study that evaluates the discrepancy between the *potential* inappropriate prescribing detected with the GheOP³S-tool and the *actual* inappropriate prescribing detected after pharmacist-physician consultation. Moreover, such a study could easily integrate an evaluation of all aspects of pharmacist-physician consultations upon PIP detection with the GheOP³S-tool (i.e. barriers, modalities, facilitators, etc).

As PIP is a complex matter, it is however unlikely that a single intervention will be sufficient to substantially improve the quality of prescribing and patient centred outcomes. Research showed that more integrated approaches are needed to significantly reduce the burden of PIP[33 34]. In that light, developing a complex intervention will be key. A proposition to such an intervention could be as follows. A digital screening of the medication history with the GheOP³S-tool is performed in the community pharmacy. This screening would yield a list of *potential* inappropriate pharmacotherapy. Subsequently, in consultation with a multidisciplinary healthcare team, these *potential* issues are discussed and a list of *actual* inappropriate pharmacotherapy with recommendations for change is decided on. After consultation with the patient, a final treatment plan is set up. This patient consultation could be performed by any healthcare provider of the multidisciplinary healthcare team. Final decisions are communicated to all healthcare providers of the team through a secure electronic platform.

To realize a significant degree of implementation, the proposed complex intervention would benefit from some optimization in different levels of care: the governmental level, the informatics level and the healthcare providers' level. First, governments could provide incentives to perform medication screening in the ambulatory setting by financing pilot projects at first and by eventually remunerating this service in case of positive results. Additionally, a clear legal outline of the specific role of each healthcare provider in the medication screening process could empower each one of them to take up their role[31 32 35]. In order to enhance interprofessional collaborations, governments could support the organization of local interdisciplinary conferences[31]. Other strategies could include financial rewards or penalties when specific quality indicators are (not) met.

Second, informatics and software companies could be of major help in facilitating interprofessional communication by developing communication channels that are secure and easy to use[31]. Furthermore, automatizing the screening of medication lists or medication histories, including clinical support systems could enhance the implementation of this intervention strategy as this would limit the time needed to perform the review. Both limited time and difficult communication are often mentioned as barriers to implement medication review[30 31].

Finally, healthcare providers should be educated to perform medication review and about their potential role in the process. This includes recognizing each healthcare provider's role while none claiming a position of superiority. As healthcare providers may not always feel confident prescribing for older adults or evaluating their pharmacotherapy, specific courses on geriatric pharmacotherapy should be organized[30].

With regard to this proposed complex intervention, our study is of help and reveals some pitfalls to which we can further anticipate. To start with, the high prevalence of PIP confirms there is an urge for initiatives such as the proposed complex intervention. The evaluation of risk factors for PIP in the

current study shows the intervention should be targeted towards older patients with polypharmacy and poor functional status. Community pharmacists feel it is feasible to perform medication screening using the GheOP³S-tool, but it could be helped by digitalization of the tool. Finally, and most importantly, this observational study confirms that the current pitfall lies in the extreme low number of initiated pharmacist-physician consultations to discuss detected PIP items. All strategies to improve these collaborations should therefore be exploited. At the same time, we have to be aware of the fact that the current differences between healthcare levels, IT systems and variability between healthcare providers will influence the results of the studies that will evaluate this complex intervention.

Conclusion

Screening with the GheOP³S-tool revealed a high prevalence of PIP in community-dwelling older polypharmacy patients in Belgium. Drugs or drug groups most often associated with PIP are drugs for the central nervous system such as hypnosedatives, antipsychotics and antidepressants. Also, potential prescribing omissions are highly present. A higher number of drugs, female gender, a higher BMI and a poorer functional status are risk factors for a higher PIP prevalence. The usability of the GheOP³S-tool is acceptable although digitalization of the tool would improve its feasibility. Despite the high number of detected PIPs however, only a small number of physicians were contacted by the community pharmacists.

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AUTHOR CONTRIBUTIONS

Tommelein had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Conception and design: Tommelein, Mehuys, Petrovic, Somers, Boussery
Analysis of the data: Tommelein, Colin
Interpretation of the data: Tommelein, Mehuys, Colin, Boussery
Drafting of the article: Tommelein
Critical revision and final approval of the article: Tommelein, Mehuys, Van Tongelen, Petrovic, Somers, Colin, Demarche, Van Hees, Christiaens, Boussery
Study supervision: Tommelein, Van Hees, Van Tongelen, Boussery

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COMPETING INTERESTS

All authors completed the ICMJE-form. No competing interests were declared.

REFERENCES

1. *Opondo D, Eslami S, Visscher S, et al. Inappropriateness of Medication Prescriptions to Elderly Patients in the Primary Care Setting: A Systematic Review. PloS one 2012;**7**(8).*
2. *Fick DM, Cooper JW, Wade WE, et al. Updating the beers criteria for potentially inappropriate medication use in older adults - Results of a US consensus panel of experts. Archives of Internal Medicine 2003;**163**(22):2716-24.*
3. *Spinewine A, Schmader KE, Barber N, et al. Appropriate prescribing in elderly people: how well can it be measured and optimised? Lancet 2007;**370**(9582):173-84.*
4. *Tache SV, Soennichsen A, Ashcroft DM. Prevalence of Adverse Drug Events in Ambulatory Care: A Systematic Review. Annals of Pharmacotherapy 2011;**45**(7-8):977-89.*
5. *Al Hamid A, Ghaleb M, Aljadhey H, et al. A systematic review of hospitalization resulting from medicine-related problems in adult patients. Br J Clin Pharmacol 2014;**78**(2):202-17.*
6. *Tommelein E, Mehuys E, Petrovic M, et al. Potentially inappropriate prescribing in community-dwelling older people across Europe: a systematic literature review. European journal of clinical pharmacology 2015;**71**(12):1415-27.*
7. *Wilson JMG, G J. Principles and practice of screening for disease: J R Coll Gen Pract. 1968 Oct;16(4):318., 1968.*
8. *Leendertse AJ, de Koning GH, Goudswaard AN, et al. Preventing hospital admissions by reviewing medication (PHARM) in primary care: an open controlled study in an elderly population. J Clin Pharm Ther 2013;**38**(5):379-87.*
9. *Donohue JM, Marcum ZA, Gellad WF, et al. Medicare Part D and Potentially Inappropriate Medication Use in the Elderly. The American journal of managed care 2012;**18**(9):e315-e22.*
10. *Zermansky AG, Silcock J. Is medication review by primary-care pharmacists for older people cost effective?: a narrative review of the literature, focusing on costs and benefits. PharmacoEconomics 2009;**27**(1):11-24.*
11. *Tannenbaum C, Martin P, Tamblyn R, et al. Reduction of Inappropriate Benzodiazepine Prescriptions Among Older Adults Through Direct Patient Education The EMPOWER Cluster Randomized Trial. JAMA internal medicine 2014;**174**(6).*
12. *Pourrat X, Sipert AS, Gatault P, et al. Community pharmacist intervention in patients with renal impairment. International journal of clinical pharmacy 2015;**37**(6):1172-9.*
13. *Tommelein E, Petrovic M, Somers A, et al. Older patients' prescriptions screening in the community pharmacy: development of the Ghent Older People's Prescriptions community Pharmacy Screening (GheOP(3)S) tool. J Public Health (Oxf) 2015.*
14. *von Elm E, Altman DG, Egger M, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. BMJ (Clinical research ed) 2007;**335**(7624):806-8.*
15. *Belgian Center for Pharmacotherapeutic Information B. Commented Drug Repertory. Secondary Commented Drug Repertory 2016. http://www.bcfi.be/*
16. *DeSalvo KB, Bloser N, Reynolds K, et al. Mortality Prediction with a Single General Self-Rated Health Question: A Meta-Analysis. Journal of general internal medicine 2006;**21**(3):267-75.*
17. *Borson S, Scanlan J, Brush M, et al. The mini-cog: a cognitive 'vital signs' measure for dementia screening in multi-lingual elderly. Int J Geriatr Psychiatry 2000;**15**(11):1021-7.*
18. *Lewis J, Sauro J. The Factor Structure of the System Usability Scale. In: Kurosu M, ed. Human Centered Design: Springer Berlin Heidelberg, 2009:94-103.*
19. *Aaron Bangor PK, James Miller. Determining what individual SUS scores mean: adding an adjective rating scale. Journal of Usability Studies 2009;**4**(3):114-23.*
20. *WHO Collaborating Centre for Drug Statistics Methodology - Norwegian Institute of Public Health. ATC/DDD Index. Secondary ATC/DDD Index 2016. http://www.whocc.no/atc_ddd_index/.*
21. *Laroche ML, Charmes JP, Merle L. Potentially inappropriate medications in the elderly: a French consensus panel list. Eur J Clin Pharmacol 2007;**63**(8):725-31.*
22. *Montastruc F, Laffont M, Bagheri H, et al. Potentially inappropriate medications in the elderly in France: a study in community pharmacies in 2011-2012. European journal of clinical pharmacology 2013;**69**(3):741-2.*
23. *Koper D, Kamenski G, Flamm M, et al. Frequency of medication errors in primary care patients with polypharmacy. Fam Pract 2013;**30**(3):313-9.*
24. *Filomena Paci J, Garcia Alfaro M, Redondo Alonso FJ, et al. [Inappropriate prescribing in polymedicated patients over 64 years-old in primary care]. Aten Primaria 2015;**47**(1):38-47.*
25. *Bregnhoj L, Thirstrup S, Kristensen MB, et al. Prevalence of inappropriate prescribing in primary care. Pharm World Sci 2007;**29**(3):109-15.*
26. *Hill-Taylor B, Sketris I, Hayden J, et al. Application of the STOPP/START criteria: a systematic review of the prevalence of potentially inappropriate prescribing in older adults, and evidence of clinical, humanistic and economic impact. Journal of clinical pharmacy and therapeutics 2013;**38**(5):360-72.*
27. *Bongue B, Naudin F, Laroche ML, et al. Trends of the potentially inappropriate medication consumption over 10 years in older adults in the East of France. Pharmacoepidemiol Drug Saf 2009;**18**(12):1125-33.*
28. *Klarin I, Wimo A, Fastbom J. The association of inappropriate drug use with hospitalisation and mortality: a population-based study of the very old. Drugs Aging 2005;**22**(1):69-82.*
29. *Bierman AS, Pugh MJ, Dhalla I, et al. Sex differences in inappropriate prescribing among elderly veterans. The American journal of geriatric pharmacotherapy 2007;**5**(2):147-61.*
30. *Cullinan S, Fleming A, O'Mahony D, et al. Doctors' perspectives on the barriers to appropriate prescribing in older hospitalized patients: a qualitative study. Br J Clin Pharmacol 2015;**79**(5):860-9.*
31. *Bardet JD, Vo TH, Bedouch P, et al. Physicians and community pharmacists collaboration in primary care: A review of specific models. Research in social & administrative pharmacy : RSAP 2015;**11**(5):602-22.*
32. *Kelly DV, Bishop L, Young S, et al. Pharmacist and physician views on collaborative practice: Findings from the community pharmaceutical care project. Canadian pharmacists journal : CPJ = Revue des pharmaciens du Canada : RPC 2013;**146**(4):218-26.*
33. *Kaur S, Mitchell G, Vitetta L, et al. Interventions that can reduce inappropriate prescribing in the elderly: a systematic review. Drugs Aging 2009;**26**(12):1013-28.*
34. *Meid AD, Lampert A, Burnett A, et al. The impact of pharmaceutical care interventions for medication underuse in older people: a systematic review and meta-analysis. Br J Clin Pharmacol 2015.*

*35. Hatah E, Braund R, Duffull SB, et al. General practitioners' views of pharmacists' current and potential contributions to medication review and prescribing in New Zealand. Journal of primary health care 2013;**5**(3):223-33.*

36. World Health Organization Collaborating Centre for Metabolic Bone Diseases. Fracture Risk Assessment Tool. Secondary Fracture Risk Assessment Tool. https://www.shef.ac.uk/FRAX/tool.jsp.

APPENDIX 2.4.1: ORIGINAL AND ADAPTED VERSION OF THE SYSTEM USABILITY SCALE

Appendix table 2.4.1: Original and adapted version of the system usability scale

Original version of the System Usability Scale	Adapted version of the System Usability Scale
1. I think that I would like to use this system frequently.	1. I think that I would like to use this tool frequently.
2. I found the system unnecessarily complex.	2. I found this tool unnecessarily complex.
3. I thought the system was easy to use.	3. I thought this tool was easy to use.
4. I think that I would need the support of a technical person to be able to use this system.	4. I think that I would need the support of someone with more knowledge about pharmacotherapy to be able to use this tool.
5. I found the various functions in this system were well integrated.	5. I found that the various types of potentially inappropriate prescribing were well integrated in this tool.
6. I thought there was too much inconsistency in this system.	6. I thought there was too much inconsistency in this tool.
7. I would imagine that most people would learn to use this system very quickly.	7. I would imagine that most people would learn to use this tool very quickly.
8. I found the system very cumbersome to use.	8. I found this tool very cumbersome to use.
9. I felt very confident using the system.	9. I felt very confident concerning the decision I made for each detected item of this tool.
10. I needed to learn a lot of things before I could get going with this system.	10. I needed to learn a lot of things before I could get going with this tool.

APPENDIX 2.4.2: FULL LIST OF PREVALENCE OF ALL GHEOP³S-CRITERIA

Appendix table 2.4.2: Full list GheOP³S-criteria prevalence

No.	GheOP³S-criterion	N, % (relative to total population, n=1016)		N, % (relative to diagnosis positive patients)
Part 1a: Potentially inappropriate drugs, independent of diagnosis – Drug classes				
1	Any antidepressant ≥1year	216	21%	
2	Any antipsychotic drug ≥1 month	71	7%	
3	Any peripheral vasodilator	33	3%	
4	Any intermediate acting benzodiazepine or Z-product at full dose or any dose ≥30 subsequent days	448	44%	
5	Any short or long-acting benzodiazepine	93	9%	
6	Any long-acting sulfonylurea derivative	69	7%	
7	Any nasal vasoconstrictor ≥1 month	11	1%	
8	Any oral NSAID	146	16%	
9	Any PPI at full dose[a] ≥8 weeks	145	14%	
10	Any recently marketed drug (black triangles)	54	5%	
11	Any sedating antihistaminic drug	21	2%	
Part 1b: Potentially inappropriate drugs, independent of diagnosis - Specific molecules				
12	Alizapride	3	0%	
13	Bisacodyl	15	1%	
14	Clonidine	2	0%	
15	Codeine and its derivatives for acute cough	15	1%	
16	Dabigatran	26	3%	
17	Digoxin >0,125mg/day	14	1%	
18	Dipyridamole monotherapy (without ASA)	2	0%	
19	Ginkgo biloba or Panax ginseng	43	4%	
20	Liquid paraffin	2	0%	
21	Methyldopa	0	0%	
22	Metoclopramide	9	1%	
23	Pentazocine	0	0%	
24	Phenobarbital	4	0%	
25	Pseudoephedrine oral	4	0%	
26	Rivaroxaban or Apixaban	45	4%	
27	Senna glycosides	15	1%	
28	Picosulfate	7	1%	
29	Theophylline	17	2%	
30	Ticlopidine, new prescription	0	0%	
31	Tramadol, new prescription	15	1%	
Part 2a: Potentially inappropriate drugs, dependent on diagnosis - Drug classes				
32	Any antipsychotic other than quetiapine and clozapine with Parkinson's disease	2	0%	2/26 (8%)
33	Anticholinergics (e.g. Antihistamines, Antidepressants, Antipsychotics, Antispasmodics…) with dementia or cognitive impairment	7	1%	7/21 (33%)
34	Anticholinergics (e.g. Antihistamines, Antidepressants, Antipsychotics, Antispasmodics…) with constipation	84	8%	84/147 (57%)
35	Anticholinergics (e.g. Antihistamines, Antidepressants, Antipsychotics, Antispasmodics…) with BPH	40	4%	40/93 (43%)
36	Calcium Channel Blockers with constipation	43	4%	43/147 (29%)
37	Non-selective beta-blockers with asthma or COPD	18	2%	18/145 (12%)
38	Oral corticosteroids >1 week with diabetes	13	1%	13/298 (4%)
39	Oral corticosteroids >1 week with hypertension	43	4%	43/810 (5%)
40	Thiazide and loop diuretics with gout	88	9%	88/151 (58%)
Part 2b: Potentially inappropriate drugs, dependent on diagnosis - Specific molecules				
41	Alizapride with Parkinson's disease	0	0%	0/26 (0%)
42	Metoclopramide with Parkinson's disease	0	0%	0/26 (0%)
Part 3: Potential prescribing omissions				
43	The patient is taking ≥ an equivalent of 7.5 mg of oral prednisone for ≥3 months and is not prescribed Ca/VitD supplementation and bisphosphonates.	23	2%	23/24 (96%)
44	The patient is taking narcotic analgesics and is not prescribed appropriate preventative bowel regimen (preferably macrogol or lactulose).	99	10%	99/130 (76%)
45	The patient has an elevated risk for osteoporosis (determined via FRAX-tool[36]) and is not prescribed Calcium/Vitamin D supplementation.	545	54%	545/710 (77%)
46	The patient is taking oral corticosteroids for ≥1 month and is not prescribed Ca/VitD supplementation.	39	4%	39/54 (72%)
47	The patient is not reminded and proposed to undergo yearly influenza vaccination.	306	30%	
48	The patient is taking methotrexate and is not prescribed folic acid supplementation.	5	0%	5/23 (22%)

Part 4: Drug-Drug interactions of specific relevance				
49	VKA + oral NSAIDs	4	0%	
50	RAAS-inhibitor + potassium sparing diuretic/potassium supplements/potassium containing drugs[b]	81	8%	
51	VKA + Antiplatelet drugs (esp. ASA), unless prescribed by internist/cardiologist	6	1%	
52	VKA + TMP/SMX	1	0%	
53	Oral NSAID + Oral Corticosteroids	14	1%	
54	Oral NSAID + Diuretic	67	7%	
55	Digoxin + Macrolide antibiotics	0	0%	
56	Digoxin + Verapamil/Diltiazem	3	0%	
57	Lithium + RAAS-inhibitors	0	0%	
58	Lithium + Oral NSAID	0	0%	
59	Lithium + Diuretics	0	0%	
60	Theophylline + Quinolones/Macrolides	2	0%	
61	RAAS-inhibitor + Oral NSAID	74	7%	
62	Oral NSAID + SSRI/SNRI	22	2%	
63	RAAS-inhibitor + TMP/SMX	0	0%	
64	Oral antidiabetics/insulin + non-selective beta-blocker	44	4%	
65	Oral antidiabetics/insulin + cardioselective beta-blocker	187	18%	
66	Alprazolam/Midazolam/Triazolam/Zolpidem/Zopiclone + Strong CYP3A4 inhibitor	8	1%	
67	CCB + Strong CYP3A4 inhibitor	5	0%	
68	Oral NSAID + Antipletelet drugs	71	7%	
69	Phenytoin + TMP/SMX	0	0%	
70	First dose RAAS-inhibitor at full dosage + pre-treatment with diuretic	0	0%	
71	Tamoxifen + strong CYP2D6 inhibitors	0	0%	
72	Calcium + Quinolones/Tetracyclines	1	0%	
73	Calcium + Stontium ranelate	1	0%	
74	Calcium + Levothyroxine	47	5%	
75	Bisphosphonate + Calcium, Magnesium, Zinc, Iron or Aluminium	46	5%	
76	VKA + Vitamin K containing drugs/supplements[c]	2	0%	
77	Any combination of anticholinergic drug	135	13%	
Part 5: General care-related items to be addressed in the community pharmacy				
78	Dispensation of over-the-counter medication (NSAID, ASA…) was not added in the electronic patient record.	253	25%	
79	Contra-indications that can unambiguously be derived from patient's medication were not added to the electronic patient record.	626	62%	
80	Availability of assistance in medication/health issues (by nurse, neighbour, children etc.) was not checked nor discussed in frail older patients or older patients with reduced cognition, especially when taking drugs needing strict intake scheme.	21	2%	
81	The patient was not asked which aspects of pharmaceutical care could be improved for him/her (Translated into practical questions for the specific patient: e.g. correct inhaler use, splitting tablets…).	463	46%	
82	**a/** Adherence for all chronic medication was not checked or discussed during the past year (refill rate). **b/** Adherence for all new medication was not checked or discussed at first refill during the past year?	681 701	67% 69%	
83	Polypharmacy patients (chronically taking ≥ 5 drugs) were not questioned about whether a clear medication scheme was available to him/her.	441	43%	

***ASA**: Acetylsalicylic acid; **BPH**: Benign prostatic hyperplasia; **CCB**: Calcium Channel Blocker; **COPD**: Chronic Obstructive Pulmonary Disease; **CV-risk**: Cardiovascular risk; **GI-risk**: Gastro-intestinal risk; **GP**: General Practitioner; **NSAID**: Non Steroidal Anti-Inflammatory Drug; **INR**: International Normalized Ratio; **PPI**: Proton Pump Inhibitor; **RAAS-inhibitor**: Renin-Angiotensin-Aldosteron System Inhibitors; **SNRI**: Serotonin and Noradrenalin Reuptake Inhibitor; **SSRI**: Selective Serotonin Reuptake Inhibitor; **TMP/SMX**: Trimetoprim/Sulfamethoxazol; **VKA**: Vitamin K Antagonist.*

[a] Full dose defined as: >20 mg (es)omeprazole, >20mg pantoprazole, >30mg lansoprazole, >20mg rabeprazole
[b] Some drugs contain considerable potassium amounts: Glucosamine in potassium salt (up to 300mg/tablet), oral nutritional supplements (up to 200mg/unit).... (Recommended Daily Dose: 3000mg/day for ≥60 year old patients)
[c] Some supplements such as oral nutritional supplements contain considerable Vitamin K amounts (up to 13µg/unit). (Recommended Daily Dose: 50-70µg/day for ≥60 year old patients)

PART 2.5:

POTENTIALLY INAPPROPRIATE PRESCRIBING IN NURSING HOME RESIDENTS DETECTED WITH THE COMMUNITY PHARMACIST SPECIFIC GHEOP³S-TOOL

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ABSTRACT

***Purpose*.** The emerging high level of medication use in nursing home residents makes prescribing in this setting a complex and challenging task. The Ghent Older People's Prescriptions community Pharmacy Screening (GheOP³S-)tool was recently developed to screen for potentially inappropriate prescribing (PIP) by community pharmacists. We aim (1) to determine the prevalence of PIP in older nursing home residents with polypharmacy using the GheOP³S-tool and (2) to identify those PIPs that are most frequently detected with the GheOP³S-tool.

***Methods*.** This was a cross-sectional study, carried out between February and June 2014 in 10 nursing homes in Belgium, supplied by a community pharmacy chain. For each nursing home, 40 residents aged 70 years or older, using 5 or more chronic drugs were included. The PIP prevalence was determined using the GheOP³S-tool.

***Results*.** Four hundred nursing home residents were included, with a mean age (± SD) of 86.2 (±6.3) years and a median number of 10 drugs per resident (Interquartile Range (IQR): 7-12). A total of 1728 PIPs were detected in 387 (97%) participants (Median: 4; IQR: 2-6). The most prevalent items can be assigned to three categories: long-term use of drugs that influence the central nervous system (i.e. benzodiazepines, antidepressants and antipsychotics), use of anticholinergic drugs (mutual combinations and with underlying constipation or dementia) and underuse of osteoporosis prophylaxis.

***Conclusion*.** Screening for PIP by means of the GheOP³S-tool revealed a high prevalence of PIP among older nursing home residents with polypharmacy. This finding urges for initiatives on the patient-level, but also on a broader, institutional level.

INTRODUCTION

Nursing home residents are particularly vulnerable to (potentially) inappropriate prescribing ((P)IP) as they are more fragile, receive therapy from multiple health care workers and are often prescribed a high number of drugs(1). It makes prescribing in this setting a complex and challenging task(2, 3). Additionally, PIP (i.e. overuse, underuse and misuse of drugs) is often associated with increased prevalence of adverse drug events (ADEs) and health care utilization(4). Other health care professionals such as pharmacists and nurses, could assist physicians in the medication management process to ensure the most effective and safe pharmacotherapy for the patient(5).

Screening of medication by pharmacists, preferably as a part of a full medication review with multidisciplinary consultation, is a proposed strategy to improve the appropriateness of prescribing(1, 6, 7) and has been shown to be effective (5). However, significant improvements on hospitalizations or mortality are currently lacking(7). This is probably due to the use of inappropriate outcome measures (i.e. number of drugs, MMSE-improvement etc), a lack of power to detect statistically significant differences or – most importantly – the poor acceptance rate and continuation of recommendations resulting from the reviews(5, 8). Additionally, there exist practical barriers to the systematic performance of a medication review among nursing home residents. This includes the lack of pharmacists with specific training in geriatric pharmacotherapy, the lack of centralized medical records and insufficient computerized support(8).

Recently, we developed the Ghent Older People's Prescriptions community Pharmacy Screening (GheOP³S-) tool, an explicit screening tool to detect PIPs with high clinical relevance for older patients(9). This screening tool provides the community pharmacist with the possibility to initiate a medication review process in a systematic and straightforward way, solely based on medication dispensing data available in the community pharmacy. Ideally, the results of a medication screening with the GheOP³S-tool should be discussed with the prescribing physician to confirm clinical relevance for the specific patient. Based on the outcomes of the pharmacist-physician consultation, suggestions for medication changes are proposed. Lastly, these suggestions are to be discussed with the patient, and a final treatment plan is to be decided on.

The GheOP³S-tool has already been tested in ambulatory patients(10), where it showed to detect all three categories of PIP: overuse, misuse and underuse. In the current observational study, we aim to perform a screening for PIP in nursing home residents using the GheOP³S-tool and to identify those PIPs that are most frequently detected.

METHODS

This manuscript describes a cross-sectional study, carried out between February and June 2014, in 10 nursing homes in Flanders (i.e. the Dutch speaking part of Belgium) supplied by a community pharmacy chain. The pharmacy chain provided the research centre with an anonymized dataset, previously set up to examine problems for robotic unit dose drug dispensing. This database was set up as follows: 10 nursing homes were randomly selected out of a sample of 33 nursing homes which are all supplied by the community pharmacy chain. From each selected nursing home, forty residents meeting the following inclusion criteria were randomly selected: (1) aged 70 years or older and (2) using 5 of more chronic (i.e. according to a set regimen) drugs registered in the Belgian Commented Drugs Repertory(11). The dataset contained the residents' medication records and basic demographics (age & gender). Each drug was assigned a seven-digit code in accordance with the Anatomical Therapeutic Chemical (ATC) Classification System formulated by the World Health Organization Collaborating Centre for Drug Statistics Methodology(12).

We applied the GheOP³S-tool(9) to the received dataset. The choice to use this screening-tool was deliberate. First, the GheOP³S-tool makes it possible to screen for PIP in settings where clinical data are not available. Second, the GheOP³S-tool is adapted to the European market and addresses all types of PIP. Third, the GheOP³S-tool offers the pharmacists a backbone to get started with the process of a medication review. An elaborate document describing rationale, alternative treatment plans and scientific background information empowers the pharmacists to initiate pharmacist-physician contacts to discuss the considered clinically relevant PIP-items. The GheOP³S-tool consists of 83 items, categorized in 5 different parts *(Part 1: Potentially inappropriate drugs, independent of diagnosis, Part 2: Potentially inappropriate drugs, dependent on diagnosis, Part 3: Potential Prescribing Omissions (PPOs), Part 4: Drug Drug Interactions (DDIs) of specific relevance and Part 5: General care-related items to be addressed in the community pharmacy)*. Part 5 of the GheOP³S-tool was not applied in the current study as this part reflects on pharmacy work processes and is not applicable to the bulk supplying for nursing homes. With regard to the diagnoses in Part 2, drug proxies were used. Only diagnoses that unambiguously could be derived from the patient's medication (e.g. diabetes from insulin, gout from allopurinol, etc) were taken into account. We also identified the GheOP³S-criteria that accounted for the highest proportion of PIP. The PIP screening with the GheOP³S-tool was performed manually by 3 researchers (EP, CVD and KM) and double-checked by the main investigator (ET). The STROBE standardized reporting guidelines for cross-sectional studies were followed to ensure the uniform conduct and reporting of the research(13).

Descriptives were displayed as counts with percentages and means with standard deviations or medians with interquartile ranges as appropriate. The PIP prevalence is represented as the proportion of residents with at least one PIP and the median number of PIPs per resident.

RESULTS

The 400 randomly included residents had a mean age (± SD) of 86.2 (±6.3) years with 63% of residents (250) being older than 85 years. Three quarters (298 residents) of the population was female. The total number of medicines taken was 4079, with an absolute range varying between 5 to 34 drugs per resident and a median of 10 per resident (Interquartile Range (IQR): 7-12).

Considering Part 1 to Part 4 of the GheOP³S-tool, a total of 1728 PIPs were detected in 387 (97%) participants (Median: 4; IQR: 2-6). Figure 2.5.1 represents the distribution of number of PIPs detected per patient according to the full GheOP³S-tool, as well as according to each part of the tool. All types of PIP (overuse, underuse and misuse) are detected. The 5 most prevalent items for each part of the GheOP³S-tool are reported in Table 2.5.1. The items of Part 2 and Part 3 are displayed in two ways; relative to the total population and relative to the overall drug or disease prevalence. A complete list of the prevalence of all individual GheOP³S-criteria is reported as Online Supplement.

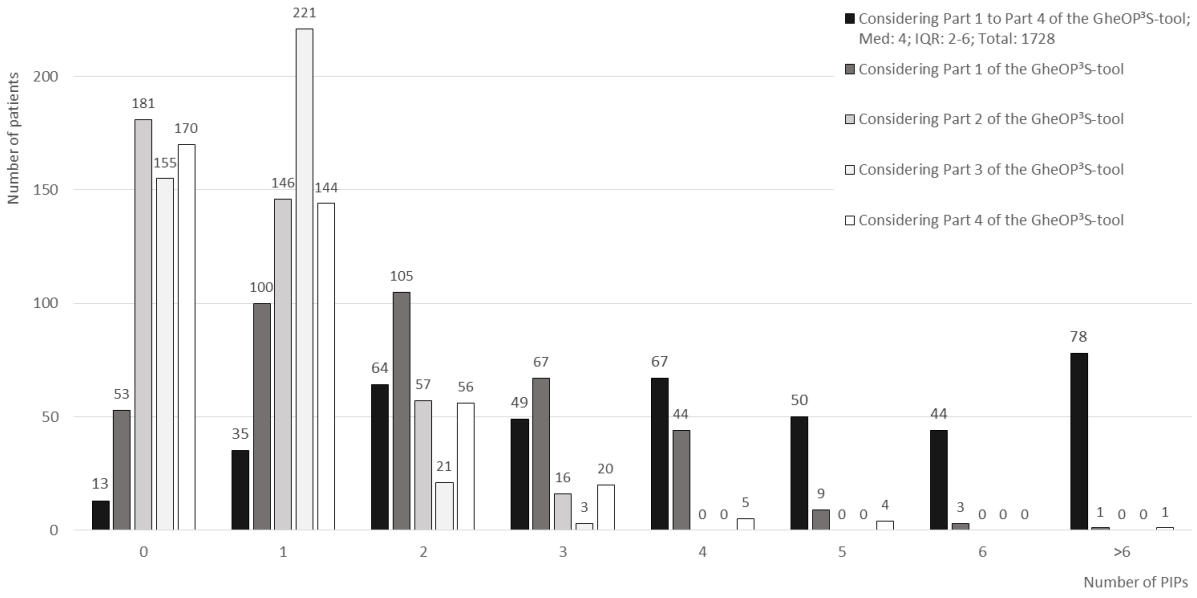

***Figure 2.5.2**: Distribution of the number of PIP-items detected per patient, using the GheOP³S-tool (n = 400; Part 1: Potentially inappropriate drugs, independent of diagnosis, Part 2: Potentially inappropriate drugs, dependent on diagnosis, Part 3: Potential prescribing omissions and Part 4: Drug-drug interactions of specific relevance)*

Table 2.5.1: Most prevalent GheOP³S-criteria of each part of the GheOP³S-tool, n = 400

	GheOP³S-criterion	N, % (relative to total population)	N, % (relative to overall drug or disease prevalence)
Part 1: Potentially inappropriate drugs, independent of diagnosis		**341 (85%)**	
1	Any intermediate acting benzodiazepine or Z-product at full dose or any dose ≥30 subsequent days OR Any short- or long-acting benzodiazepine	212 (53%)	
	Any intermediate acting benzodiazepine or Z-product at full dose or any dose ≥30 subsequent days	195 (49%)	
	Any short- or long-acting benzodiazepine	35 (9%)	
	Any intermediate acting benzodiazepine or Z-product at full dose or any dose ≥30 subsequent days AND Any short- or long-acting benzodiazepine	18 (5%)	
2	Any antidepressant ≥1 year	169 (42%)	
3	Any antipsychotic drug ≥1 month	117 (29%)	
4	Any PPI at full dose ≥8 weeks	73 (18%)	
5	Any oral non-steroidal anti-inflammatory drug	35 (9%)	
Part 2: Potentially inappropriate drugs, dependent on diagnosis		**219 (55%)**	
1	Anticholinergics with constipation	149 (37%)	149/199 (75%)
2	Calcium channel blockers with constipation	43 (11%)	43/197 (22%)
3	Anticholinergics with dementia or cognitive impairment	36 (9%)	36/51 (71%)
4	Oral corticosteroids >1 week with hypertension	19 (5%)	19/221 (9%)
5	Thiazide and loop diuretics with gout	18 (5%)	18/27 (67%)
Part 3: Potential prescribing omissions		**245 (61%)**	
1	The patient has an elevated risk for osteoporosis and is not prescribed Calcium and Vitamin D supplementation.	214 (54%)	214/295 (73%)
2	The patient is taking narcotic analgesics and is not prescribed appropriate preventative bowel regimen.	35 (9%)	35/84 (42%)
3	The patient is taking oral corticosteroids for ≥1 month and is not prescribed a Calcium and Vitamin D supplementation.	15 (4%)	15/25 (60%)
4	The patient is taking an equivalent of 7.5 mg of oral prednisone or more for ≥3 months and is not prescribed calcium/Vitamin D supplementation and bisphosphonates.	7 (2%)	7/11 (64%)
5	The patient is taking methotrexate and is not prescribed folic acid supplementation.	1 (0%)	1/1 (100%)
Part 4: Drug-drug interactions of specific relevance		**230 (58%)**	
1	Any combination of anticholinergic drug	163 (41%)	
2	Oral antidiabetics/insulin and β-blocker	41 (10%)	
	Oral antidiabetics/insulin and non-selective β-blocker	8 (2%)	
	Oral antidiabetics/insulin and selective β-blocker	37 (9%)	
3	Oral non-steroidal anti-inflammatory drug and diuretic	22 (6%)	
4	Bisphosphonate and calcium, magnesium, zinc, iron or aluminium	22 (6%)	
5	RAAS inhibitor and potassium sparing diuretic, potassium supplements or potassium containing drugs	20 (5%)	

***RAAS**: Renin angiontensin aldosteron system*

DISCUSSION

In this observational study, we detected at least one PIP in 97% of the 400 randomly included nursing home residents, with a median of 4 PIPs per resident. This is in concordance with two other Belgian studies and with studies from other European countries(3, 5, 14, 15). Some studies report lower prevalence rates, however in these cases, the researchers evaluated PIP with a smaller subset of published criteria or only screened for one aspect of PIP (e.g. underuse)(16, 17). On the other hand, compared with a recent systematic review, estimating PIP prevalence in the ambulatory setting(18), the prevalence in nursing homes is markedly higher. Although, one previously performed study with the GheOP³S-tool in the ambulatory setting observed a comparable PIP prevalence (at least one PIP in 97% of patients, median of 3 PIP per patient)(10).

The fact that nearly all patients had at least one PIP shows that there is a large room for improvement on the appropriateness of prescribing. During the development of the GheOP³S-tool, the experts unanimously agreed on the clinical relevance of screening for all included items in older patients in general. Whether the detected problems are also clinically relevant for the individual patient, still needs to be assessed during a pharmacist-physician consultation and agreement. The actual rate of inappropriate prescribing will therefore probably be somewhat lower.

The most prevalent PIP-items identified by the GheOP³s-tool can be assigned to the following three main categories: long-term use of drugs that influence the central nervous system (i.e. hypnosedatives, antidepressants and antipsychotics), use of anticholinergic drugs (mutual combinations and with underlying constipation or dementia) and underuse of osteoporosis prophylaxis. Additionally, the use of systemic NSAIDs and the long-term use of high-dose PPIs is frequent in this population. All of these items are also mentioned by other European observational studies(2, 8, 19). In the observational study, using the GheOP³S-tool in the ambulatory setting, the same items (except for the use of anticholinergic drugs) significantly added to the number of PIP(10). As the use of drugs that influence the central nervous system and drugs with anticholinergic effectssignificantly adds to the high number of PIP, with possible significant clinical consequences as a result, the inappropriate use of these drug classes should be targeted first. Multiple trials already addressed these specific issues and showed that deprescribing in nursing homes is possible, improves the quality of prescribing and has a positive effect on the quality of life of the patient.

One example is the study by Bourgeois et al(20), in which 66% of chronic benzodiazepine users were successfully discontinued after 8 months, with an improved self-perceived sleep quality and significantly less midnight awakenings(20). Another example, a randomized controlled trial performed in 22 nursing homes, showed that the anticholinergic burden was significantly reduced by a pharmacist-initiated medication review(21).

Despite the fact that the GheOP³S-tool was developed to detect PIP on the patient level, this study also shows that an overall analysis, applied to all residents of one institution, could expose the most urgent issues on a more general level. This way, the GheOP³S-tool might serve as a benchmarking instrument for the prescribing behaviour in a nursing home. The result of such an overall analysis would be the ideal starting point for interdisciplinary case-conferences or the basis for targeted action plans. Using the GheOP³S-tool, the dispensing pharmacist is able to assist prescribers and the nursing home management to increase the quality of prescribing.

Strengths and limitations

This study shows that the recently developed GheOP³S-tool, a validated community pharmacy specific list where limited clinical data are available, is practical and straightforward in screening for PIPs in nursing home residents. This study has nevertheless some limitations. As the GheOP³S-tool is explicit of nature, it does not take into account all patient factors in evaluating the pharmacotherapy, e.g. diagnoses, patient preferences or earlier attempts to tackle PIP. Also, some relevant items might have been missed. To tackle this, a future study will compare a GheOP³s-screening with a full medication review. This way, the items that are systematically missed will be identified and added to the GheOP³S-tool in a future update. Additionally, there were no pharmacist-prescriber contacts to discuss the clinical relevance of the detected items. E.g. the clinical relevance of the interaction between a selective β-blocker and oral antidiabetics/insulin is minimal if glycemic control is good. Also, it is difficult to estimate generalizability to other countries as prescribing behavior can largely differ between geographical regions. Despite the fact that our results match findings from other European countries, it would still be interesting to compare our results to a GheOP³S-tool application in other European countries.

Conclusion

Screening for PIP by means of the GheOP³S-tool showed a high PIP prevalence in older nursing home residents with polypharmacy. This urges for initiatives on the patient-level, but also on a broader, institutional level. The GheOP³S-tool could be part of such an evaluation process in which it could be the starting point for multidisciplinary interventions, initiated by the pharmacist. Such a process aims to improve the quality of prescribing for nursing home residents with polypharmacy.

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AUTHOR CONTRIBUTIONS

Tommelein had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Conception and design: Tommelein, Boussery
Analysis of the data: Tommelein, Van Damme, Mattelin, Pattyn
Interpretation of the data: Tommelein, Mehuys, Boussery
Drafting of the article: Tommelein
Critical revision and final approval of the article: Tommelein, Mehuys, Boussery, Petrovic, Somers
Study supervision: Boussery

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COMPETING INTERESTS

All authors completed the ICMJE-form. No competing interests were declared.

REFERENCES

1. *Loganathan M, Singh S, Franklin BD, Bottle A, Majeed A. Interventions to optimise prescribing in care homes: systematic review. Age Ageing. 2011;40(2):150-62.*
2. *Haasum Y, Fastbom J, Johnell K. Institutionalization as a risk factor for inappropriate drug use in the elderly: a Swedish nationwide register-based study. The Annals of pharmacotherapy. 2012;46(3):339-46.*
3. *O'Sullivan DP, O'Mahony D, Parsons C, Hughes C, Murphy K, Patterson S, et al. A prevalence study of potentially inappropriate prescribing in Irish long-term care residents. Drugs Aging. 2013;30(1):39-49.*
4. *Perri M, 3rd, Menon AM, Deshpande AD, Shinde SB, Jiang R, Cooper JW, et al. Adverse outcomes associated with inappropriate drug use in nursing homes. The Annals of pharmacotherapy. 2005;39(3):405-11.*
5. *Verrue C, Mehuys E, Boussery K, Adriaens E, Remon JP, Petrovic M. A pharmacist-conducted medication review in nursing home residents: impact on the appropriateness of prescribing. Acta Clin Belg. 2012;67(6):423-9.*
6. *Verrue CL, Petrovic M, Mehuys E, Remon JP, Vander Stichele R. Pharmacists' interventions for optimization of medication use in nursing homes : a systematic review. Drugs Aging. 2009;26(1):37-49.*
7. *Wallerstedt SM, Kindblom JM, Nylen K, Samuelsson O, Strandell A. Medication reviews for nursing home residents to reduce mortality and hospitalization: systematic review and meta-analysis. Br J Clin Pharmacol. 2014;78(3):488-97.*
8. *Mestres C, Agusti A, Puerta L, Barba M. Prescription of potentially inappropriate drugs for geriatric patients in long-term care: improvement through pharmacist's intervention. European Journal of Hospital Pharmacy-Science and Practice. 2015;22(4):198-201.*
9. *Tommelein E, Petrovic M, Somers A, Mehuys E, van der Cammen T, Boussery K. Older patients' prescriptions screening in the community pharmacy: development of the Ghent Older People's Prescriptions community Pharmacy Screening (GheOP(3)S) tool. J Public Health (Oxf). 2015.*
10. *Tommelein EM, E; Van Tongelen, I; Petrovic, M; Somers, A; Colin, P; Demarche, S; Van Hees, T; Christiaens, T; Boussery, K. Community pharmacists' evaluation of potentially inappropriate prescribing in older community-dwelling patients with polypharmacy: observational research based on the GheOP³S-tool. Submitted. 2016.*
11. *Belgian Center for Pharmacotherapeutic Information B. Commented Drug Repertory 2016 [cited 2016 March 25]. Available from: http://www.bcfi.be/*
12. *WHO Collaborating Centre for Drug Statistics Methodology - Norwegian Institute of Public Health. ATC/DDD Index 2016 [cited 2016 March 26]. Available from: http://www.whocc.no/atc_ddd_index/.*
13. *von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. BMJ (Clinical research ed). 2007;335(7624):806-8.*
14. *Elseviers MM, Vander Stichele RR, Van Bortel L. Quality of prescribing in Belgian nursing homes: an electronic assessment of the medication chart. Int J Qual Health Care. 2014;26(1):93-9.*
15. *Bergman Å, Olsson J, Carlsten A, Waern M, Fastbom J. Evaluation of the quality of drug therapy among elderly patients in nursing homes: A computerized pharmacy register analysis. Scandinavian journal of primary health care. 2007;25(1):9-14.*
16. *Shah SM, Carey IM, Harris T, DeWilde S, Cook DG. Quality of prescribing in care homes and the community in England and Wales. Br J Gen Pract. 2012;62(598):e329-36.*
17. *Kolzsch M, Kopke K, Fischer T, Hofmann W, Kuhnert R, Bolbrinker J, et al. Prescribing of inappropriate medication in nursing home residents in Germany according to a French consensus list: a cross-sectional cohort study. Pharmacoepidemiol Drug Saf. 2011;20(1):12-9.*
18. *Tommelein E, Mehuys E, Petrovic M, Somers A, Colin P, Boussery K. Potentially inappropriate prescribing in community-dwelling older people across Europe: a systematic literature review. European journal of clinical pharmacology. 2015;71(12):1415-27.*
19. *Ryan C, O'Mahony D, Kennedy J, Weedle P, Cottrell E, Heffernan M, et al. Potentially inappropriate prescribing in older residents in Irish nursing homes. Age Ageing. 2013;42(1):116-20.*
20. *Bourgeois J, Elseviers MM, Van Bortel L, Petrovic M, Vander Stichele RH. Feasibility of discontinuing chronic benzodiazepine use in nursing home residents: a pilot study. European journal of clinical pharmacology. 2014;70(10):1251-60.*
21. *Kersten H, Molden E, Tolo IK, Skovlund E, Engedal K, Wyller TB. Cognitive effects of reducing anticholinergic drug burden in a frail elderly population: a randomized controlled trial. The journals of gerontology Series A, Biological sciences and medical sciences. 2013;68(3):271-8.*
22. *World Health Organization Collaborating Centre for Metabolic Bone Diseases. Fracture Risk Assessment Tool United Kingdom: University of Sheffield; [cited 2016 March 25]. Available from: https://www.shef.ac.uk/FRAX/tool.jsp.*

APPENDIX 2.5.1: FULL LIST OF PREVALENCE OF ALL GHEOP³S-CRITERIA

Appendix Table 2.5.1: Full list of prevalence of all GheOP³S-criteria

No.	GheOP³S-criterion	N, % (relative to total population, n=400)		N, % (relative to overall drug or disease prevalence)
Part 1b: Potentially inappropriate drugs, independent of diagnosis – Drug classes				
1	Any antidepressant ≥1year	169	42%	
2	Any antipsychotic drug ≥1 month	117	29%	
3	Any drug for arterial vascular disorders	9	2%	
4	Any intermediate acting benzodiazepine or Z-product at full dose or any dose ≥30 subsequent days	195	49%	
5	Any short or long-acting benzodiazepine	35	9%	
6	Any long-acting sulfonylurea derivative	18	5%	
7	Any nasal vasoconstrictor ≥1 month	3	1%	
8	Any oral NSAID	35	9%	
9	Any PPI at full dose[a] ≥8 weeks	73	18%	
10	Any recently marketed drug (black triangles)	13	3%	
11	Any sedating antihistaminic drug	14	4%	
Part 1b: Potentially inappropriate drugs, independent of diagnosis - Specific molecules				
12	Alizapride	5	1%	
13	Bisacodyl	5	1%	
14	Clonidine	3	1%	
15	Codeine and its derivatives for acute cough	6	2%	
16	Dabigatran	3	1%	
17	Digoxin >0,125mg/day	8	2%	
18	Dipyridamole monotherapy (without ASA)	0	0%	
19	Ginkgo biloba or Panax ginseng	3	1%	
20	Liquid paraffin	1	0%	
21	Methyldopa	0	0%	
22	Metoclopramide	13	3%	
23	Pentazocine	0	0%	
24	Phenobarbital	1	0%	
25	Pseudoephedrine oral	0	0%	
26	Rivaroxaban or Apixaban	10	3%	
27	Senna glycosides	1	0%	
28	Picosulfate	4	1%	
29	Theophylline	10	3%	
30	Ticlopidine, new prescription	0	0%	
31	Tramadol, new prescription	30	8%	
Part 2a: Potentially inappropriate drugs, dependent on diagnosis - Drug classes				
32	Any antipsychotic other than quetiapine and clozapine with Parkinson's disease	13	3%	13/54 (24%)
33	Anticholinergics (e.g. Antihistamines, Antidepressants, Antipsychotics, Antispasmodics…) with dementia or cognitive impairment	36	9%	36/51 (71%)
34	Anticholinergics (e.g. Antihistamines, Antidepressants, Antipsychotics, Antispasmodics…) with constipation	149	37%	149/199 (75%)
35	Anticholinergics (e.g. Antihistamines, Antidepressants, Antipsychotics, Antispasmodics…) with BPH	13	3%	13/21 (62%)
36	Calcium Channel Blockers with constipation	43	11%	43/197 (22%)
37	Non-selective beta-blockers with asthma or COPD	9	2%	9/90 (10%)
38	Oral corticosteroids >1 week with diabetes	8	2%	8/103 (8%)
39	Oral corticosteroids >1 week with hypertension	19	5%	19/221 (9%)
40	Thiazide and loop diuretics with gout	18	5%	18/27 (67%)
Part 2b: Potentially inappropriate drugs, dependent on diagnosis - Specific molecules				
41	Alizapride with Parkinson's disease	0	0%	0/54 (0%)
42	Metoclopramide with Parkinson's disease	0	0%	0/54 (0%)
Part 3: Potential prescribing omissions				
43	The patient is taking ≥ an equivalent of 7.5 mg of oral prednisone for ≥3 months and is not prescribed Ca/VitD supplementation and bisphosphonates.	7	2%	7/11 (64%)
44	The patient is taking narcotic analgesics and is not prescribed appropriate preventative bowel regimen (preferably macrogol or lactulose).	35	8%	35/84 (42%)
45	The patient has an elevated risk for osteoporosis (determined via FRAX-tool(22)) and is not prescribed Calcium/Vitamin D supplementation.	214	54%	214/295 (73%)
46	The patient is taking oral corticosteroids for ≥1 month and is not prescribed Ca/VitD supplementation.	15	4%	15/25 (60%)
47	The patient is not reminded and proposed to undergo yearly influenza vaccination.	0	0%	0%

48	The patient is taking methotrexate and is not prescribed folic acid supplementation.	1	0%	1/1 (100%)
Part 4: Drug-Drug interactions of specific relevance				
49	VKA + oral NSAIDs	2	1%	
50	RAAS-inhibitor + potassium sparing diuretic/potassium supplements/potassium containing drugs[b]	20	5%	
51	VKA + Antiplatelet drugs (esp. ASA), unless prescribed by internist/cardiologist	11	3%	
52	VKA + TMP/SMX	0	0%	
53	Oral NSAID + Oral Corticosteroids	4	1%	
54	Oral NSAID + Diuretic	22	6%	
55	Digoxin + Macrolide antibiotics	1	0%	
56	Digoxin + Verapamil/Diltiazem	0	0%	
57	Lithium + RAAS-inhibitors	0	0%	
58	Lithium + Oral NSAID	0	0%	
59	Lithium + Diuretics	0	0%	
60	Theophylline + Quinolones/Macrolides	2	1%	
61	RAAS-inhibitor + Oral NSAID	8	2%	
62	Oral NSAID + SSRI/SNRI	9	2%	
63	RAAS-inhibitor + TMP/SMX	2	1%	
64	Oral antidiabetics/insulin + non-selective beta-blocker	8	2%	
65	Oral antidiabetics/insulin + cardioselective beta-blocker	37	9%	
66	Alprazolam/Midazolam/Triazolam/Zolpidem/Zopiclone + Strong CYP3A4 inhibitor	3	1%	
67	CCB + Strong CYP3A4 inhibitor	0	0%	
68	Oral NSAID + Antipletelet drugs	16	4%	
69	Phenytoin + TMP/SMX	0	0%	
70	First dose RAAS-inhibitor at full dosage + pre-treatment with diuretic	5	1%	
71	Tamoxifen + strong CYP2D6 inhibitors	0	0%	
72	Calcium + Quinolones/Tetracyclines	13	3%	
73	Calcium + Stontium ranelate	5	1%	
74	Calcium + Levothyroxine	10	3%	
75	Bisphosphonate + Calcium, Magnesium, Zinc, Iron or Aluminium	22	6%	
76	VKA + Vitamin K containing drugs/supplements[c]	1	0%	
77	Any combination of anticholinergic drug	163	41%	

***ASA**: Acetylsalicylic acid; **BPH**: Benign prostatic hyperplasia; **CCB**: Calcium Channel Blocker; **COPD**: Chronic Obstructive Pulmonary Disease; **CV-risk**: Cardiovascular risk; **GI-risk**: Gastro-intestinal risk; **GP**: General Practitioner; **NSAID**: Non Steroidal Anti-Inflammatory Drug; **INR**: International Normalized Ratio; **PPI**: Proton Pump Inhibitor; **RAAS-inhibitor**: Renin-Angiotensin-Aldosteron System Inhibitors; **SNRI**: Serotonin and Noradrenalin Reuptake Inhibitor; **SSRI**: Selective Serotonin Reuptake Inhibitor; **TMP/SMX**: Trimetoprim/Sulfamethoxazol; **VKA**: Vitamin K Antagonist.*

[a] Full dose defined as: >20 mg (es)omeprazole, >20mg pantoprazole, >30mg lansoprazole, >20mg rabeprazole
[b] Some drugs contain considerable potassium amounts: Glucosamine in potassium salt (up to 300mg/tablet), oral nutritional supplements (up to 200mg/unit).... (Recommended Daily Dose: 3000mg/day for ≥60 year old patients)
[c] Some supplements such as oral nutritional supplements contain considerable Vitamin K amounts (up to 13µg/unit). (Recommended Daily Dose: 50-70µg/day for ≥60 year old patients)

Chapter 3

Medication counselling for patients with COPD in the community pharmacy

PART 3.1:

INTRODUCTION ON COPD AND COPD MANAGEMENT

PATHOLOGY, PATHOPHYSIOLOGY, EPIDEMIOLOGY AND COPD MANAGEMENT

1. COPD PATHOLOGY AND PATHOGENESIS[1-3]

COPD is characterised by poorly reversible airflow obstruction and an abnormal inflammatory response in the lungs to long term exposure to noxious particles and gases, particularly cigarette smoke. In general, the inflammatory response and the consequent structural changes in the airways increase with disease severity and persist even after smoking cessation. Two other processes further modify COPD pathogenesis; an imbalance between proteases and anti-proteases and oxidative stress.

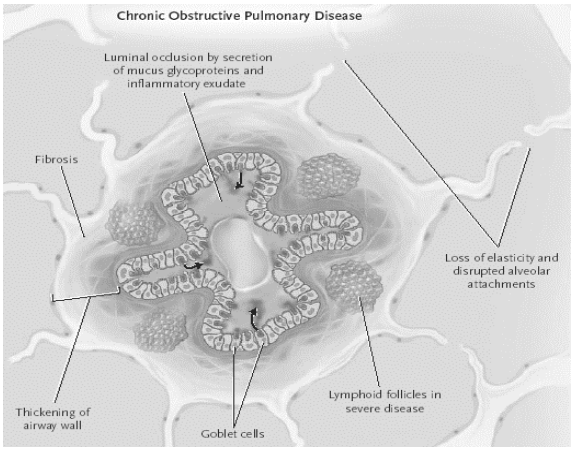

***Figure 3.1.1**: Pathology of Chronic Obstructive Pulmonary Disease.*

1.1. Inflammatory response in COPD

The inflammatory response in patients with COPD is amplified compared to the normal inflammatory response of the respiratory tract to chronic irritants such as cigarette smoke. In patients with COPD there is an increased number of CD8+ Tc1 lymphocytes, neutrophils and macrophages, releasing inflammatory mediators. These mediators attract inflammatory cells from the circulation, amplify inflammatory processes and induce structural changes in the airways, lung parenchyma and pulmonary vasculature.

1.2. Imbalance between proteases and anti-proteases

In patients with COPD, an imbalance between proteases that break down connective tissue and anti-proteases that protect against it, is observed. The imbalance originates in an increased production and release of proteases in the macrophages and neutrophils and an augmented inactivation of anti-proteases. Protease-mediated destruction of elastin, a major component of lung parenchyma, is believed to be an important feature of emphysema and is likely to be irreversible.

1.3. Oxidative Stress

Oxidative stress is a significant contributor to COPD pathogenesis. Sources of oxidants include cigarette smoke and reactive oxygen and nitrogen species released from inflammatory cells (e.g. macrophages, neutrophils). Biomarkers of oxidative stress (e.g. hydrogen peroxide) are increased in the exhaled breath condensate, sputum and systemic circulation of patients with stable COPD and even further amplified during exacerbations. Excessive oxidative stress leads to altered (anti-)protease activities and stimulation of mucous production. It can also amplify inflammation by enhancing transcription factor activation and hence the gene expression of pro-inflammatory mediators.

2. PATHOPHYSIOLOGY[1-3]

The pathogenic mechanisms result in the pathological changes found in COPD such as parenchymal tissue destruction. On their turn, they result in physiological abnormalities such as mucus hypersecretion, progressive airway obstruction and air trapping, gas exchange abnormalities, and systemic effects.

2.1. Mucus Hypersecretion

Mucus hypersecretion is not necessarily associated with COPD and conversely, not all patients with COPD have mucus hypersecretion. However when present, it results in a chronic productive cough and is due to an increased number of goblet cells and enlarged submucosal glands in response to chronic airway irritation.

2.2. Airflow obstruction and air trapping

The airflow obstruction mainly occurs in the small airways, because of fibrosis and inflammatory exudates. Other contributing factors include loss of the lung elastic recoil (due to destruction of alveolar walls) and destruction of alveolar support (from alveolar attachments). The airway obstruction progressively traps air during expiration, resulting in hyperinflation. Hyperinflation diminishes inspiratory capacity and increases functional residual capacity, particularly during exercise. This results in the typical breathlessness and limited exercise capacity for patients witch COPD.

2.3. Gas exchange abnormalities

Abnormalities in gas exchange appear in advanced COPD and result in characteristic arterial hypoxaemia with or without hypercapnia. Multiple processes contribute to this observation. First, gas transfer of both oxygen and carbon dioxide worsens as the disease progresses, and second, reduced ventilation leads to a decreased ventilator drive.

2.4. Exacerbations

Exacerbations of respiratory symptoms often occur in patients with COPD. They can be triggered by (concomitant) bacterial or viral infection, environmental pollution or other, unknown factors. However, bacterial and viral episodes have a characteristic response with increased inflammation. During exacerbations, there is increased hyperinflation and air trapping, with reduced expiratory flow and hence accounting for the increased dyspnoea. There is also a worsening in gas exchange abnormalities, possible resulting in hypoxaemia and respiratory acidosis.

3. EPIDEMIOLOGY & BURDEN OF COPD

As COPD is the result of cumulative exposure to tobacco smoke, occupational and indoor air pollution over decades, the prevalence varies widely across countries and across different groups within countries[4]. In Belgium and in the Netherlands, the prevalence of COPD is currently estimated to be about 2 to 3%, which increased since the early nineties[5 6]. Equal to the prevalence, the incidence of COPD is dependent on age and gender. Based on data of the Rotterdam Study[7], the incidence of COPD is estimated to be about 9.2/1000 person-years (PY), with a higher incidence for men (14/1000 PY) compared to women (6/1000 PY) in a cohort of patients ≥55 year. COPD appears to be a leading cause of morbidity and mortality worldwide and results in a substantial economic and social burden.

Morbidity traditionally includes physician visits, emergency department visits and hospitalizations. As patients with COPD are often affected by multiple comorbid conditions, data about morbidity specifically related to COPD are less available and difficult to interpret. Mortality data on the other hand are more readily available. According to a study in 2010, COPD was the 5th ranked cause of death in the United States. Mortality increased in the last 30–40 years, however, more recently, it decreased in men in several countries, while increasing or stabilizing in women. This may be explained by differences in smoking patterns and a greater vulnerability in women to the adverse effects of smoking. A main reason for this increase in mortality is mainly driven by the expanding epidemic of smoking, reduced mortality from other common causes of death and aging of the world population. Under-recognition and under-diagnosis of COPD still affect the accuracy of morbidity and mortality data. Actual numbers are probably much higher.

The economic burden for treating COPD is substantial. Direct costs can be divided into specialty care and hospitalization costs (± 45%), medication costs (± 35%), primary care and physiotherapy costs (± 15%) and other therapies (± 5%). In addition, indirect costs related to COPD are considerable, due to work productivity losses and disability pension paid[8]. Treatment of COPD and its exacerbations contribute substantially to overall healthcare costs. In the European Union the costs approximately account for 6% of the total European healthcare budget[1]. According to the National Institute for Health and Disability Insurance (INAMI), in Belgium, the expenditures of reimbursed drugs for COPD for patients >45 years is increasing, up to € 149 million in 2010[9].

Where mortality offers a limited perspective on the human burden of a disease, the Disability-Adjusted Life Years (DALY[i]) can be used. In 2010, COPD was ranked second, based on number of DALYs lost in the United States[10], and was ranked 4th based on number of life-years lost. Finally, COPD was ranked 6th for years lived with disability[10].

[i] The DALYs for a specific condition are the sum of years lost because of premature mortality and years of life lived with disability, adjusted for the severity of disability.

4. GLOBAL INITIATIVE FOR CHRONIC OBSTRUCTIVE LUNG DISEASE (GOLD)

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) is a worldwide organization that works together with health care professionals and public health officials. The primary goals are to raise awareness of COPD and to improve the prevention and treatment of this disease. GOLD started with the development of evidence-based strategy documents for COPD management in 1997 and regularly updated this document ever since, with the last update in January 2015[1]. The GOLD report is to be used by health care professionals to implement effective management programs based on available health care systems and evidence.

4.1. Classification of COPD

The classification of COPD helps to determine the severity of the disease, including its impact on the patient's health status and the risk of future events (such as exacerbations or hospital admissions)[1]. Before 2011, COPD was classified based on spirometry. Spirometry is a physiological test, measuring exhalation or inhalation volumes of air as a function of time[11]. To classify COPD, the Forced Vital Capacity (FVC) and Forced Expiratory Volume in one second (FEV_1) are used. The FVC is the volume delivered during an expiration made as forcefully and completely as possible starting from full inhalation. The FEV_1 is the volume delivered in the first second of that attempt[11]. Both can be measured before and after the use of a bronchodilator. The presence of a post-bronchodilator $FEV_1/FVC < 0.70$ confirms the diagnosis of COPD[1]. The FEV_1 is consequently used to estimate the severity of disease (Table 3.1.1).

Table 3.1.1: Spirometric classification of COPD, before 2011

GOLD stage	Spirometry
I: Mild	$FEV_1/FVC < 0.70$ $FEV_1 \geq 80\%$ of FEV_1 predicted[ii]
II: Moderate	$FEV_1/FVC < 0.70$ $50\ \% \leq FEV_1 < 80\%$ of FEV_1 predicted
III: Severe	$FEV_1/FVC < 0.70$ $30\ \% \leq FEV_1 < 50\%$ of FEV_1 predicted
IV: Very severe	$FEV_1/FVC < 0.70$ $FEV_1 < 30\%$ of FEV_1 predicted

***FEV_1**: Forced Expiratory Volume in one second; **FVC**: Forced Vital Capacity*

However, lung function alone does not cover the burden of the disease completely. Therefore, breathlessness (according to the mMRC-scale[iii]), health status impairment (according to the CAT-scale[iv]) and exacerbations are currently also included to estimate COPD severity (Figure 3.1.2)[1].

[ii] The FEV_1 predicted is defined as the FEV_1 of the patient divided by the average FEV_1 in the population for any person of similar age, sex and body composition.
[iii] Scores on the modified Medical Research Council dyspnea scale can range from 0 to 4, with a score of 4 indicating the patient is too breathless to leave the house or becomes breathless when (un)dressing.
[iv] The COPD Assessment Test scale is a unidimensional scale evaluation patients' COPD symptoms; ranges from 0-40, a higher score indicates a worse health status

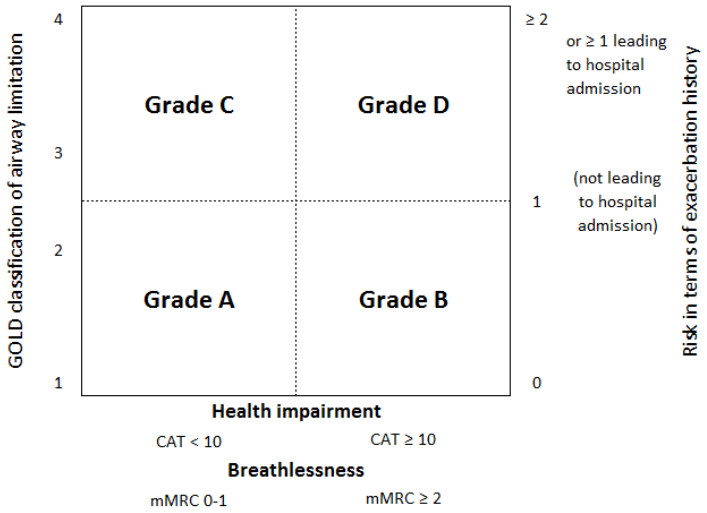

***Figure 3.1.2**: Classification of COPD severity (after 2011)*

***CAT**: COPD Assessment Test; **GOLD**: Global Initiative for Chronic Obstructive Lung Disease; **mMRC**: modified Medical Research Council*

4.2. Non-pharmacologic treatment of COPD

Non-pharmacologic strategies for patients with COPD are mainly aimed at reducing symptoms, improving quality of life and increasing participation in everyday activities[1]. At first instance, smoking cessation counselling should be offered to every patient diagnosed with COPD that is still smoking[12]. Second, individualized exercise training and nutrition counselling are recommended to increase exercise capacity and prevent muscle wasting and weight loss[13 14]. Finally, education about the disease can help patients playing a pro-active role in their disease management. These four action points are merged under the term 'pulmonary rehabilitation'[1]. Furthermore, for patients with COPD and chronic respiratory failure, oxygen therapy has demonstrated to increase survival when there is resting hypoxemia present[15]. Ventilator support, lung volume reduction surgery and lung transplantation are optional possibilities for patients with very advanced COPD[1].

4.3. Pharmacologic treatment of COPD

As COPD is an irreversible and progressive disease, the main goals of pharmacologic treatment are to reduce symptoms and to reduce the number of exacerbations. As COPD is a respiratory disease, a great deal of the medication is administered locally, through inhalation therapy. This can be on an as needed basis or on a regular basis. Besides, there are some oral possibilities, including methylxanthines, oral corticosteroids and antibiotics. However, the latter two are mostly used during exacerbations.

4.3.1. Inhalation therapy

Bronchodilators, including anticholinergics and β_2-agonists, and inhaled corticosteroids are administered through inhalation for the treatment of patients with COPD (Table 3.1.2).

4.3.1.1. Anticholinergics

Anticholinergics act by blocking muscarinic receptors in respiratory tissue. Both short- and long-acting anticholinergic agents exist where long-acting agents such as tiotropium have a duration of action of more than 24 hours[16]. Tiotropium reduces exacerbations and related hospitalisations compared to placebo and ipratropium[17]. It also improves health-related quality-of-life and symptoms among patients with moderate and severe disease[17]. Aclidinium and glycopyrronium seem to have similar action on lung function and breathlessness as tiotropium[18 19], however, less data are available for other outcomes[18].

4.3.1.2. β_2-agonists

β_2-agonists stimulate the β_2-receptors in the airways and consequently relax airway smooth muscle cells. As well, both short-acting (4 to 6 hours) and long-acting (up to 12 hours and more) β_2-agonists agents exist[16]. Formoterol and salmeterol significantly improve spirometry measures, dyspnea, health-related quality of life and exacerbation rate[20]. However no effect on decline in lung function or mortality is observed[20]. Similar effects are seen for indacaterol (long-acting, up to 24 hours)[21].

4.3.1.3. Inhaled corticosteroids

The inhibitory effects of inhaled corticosteroids on both pulmonary and systemic inflammation in patients with COPD are controversial. Their role in the management of stable COPD is therefore limited[1]. For patients with an FEV_1 < 60% predicted, regular treatment with inhaled corticosteroids may reduce exacerbation frequency[22 23]. However, it shows no effect on decline in lung function or mortality[24]. Additionally, they have significant local side-effects.

Table 3.1.2: Drugs, available through inhalation for treatment of COPD on the Belgian market[25]

Anticholinergics	β_2-agonists	Anticholinergic/ β_2-agonist combinations	Inhaled corticosteroids	Inhaled corticosteroid/ β_2-agonist combinations
Ipratropium (S)	*Fenoterol (S)*	*Ipratropium/Salbutamol (S)*	*Beclometason*	*Beclometason/Formoterol (L)*
Aclidinium (L)	*Salbutamol (S)*	*Ipratropium/Fenoterol (S)*	*Budesonide*	*Budesonide/Formoterol (L)*
Umeclidinium (L)	*Indacaterol (L)*	*Glycopyrronium/Indacaterol (L)*	*Fluticason*	*Fluticason/Formoterol (L)*
Glycopyrronium (L)	*Salmeterol (L)*	*Umeclidinium/Vilanterol (L)*		*Fluticason/Vilanterol (L)*
Tiotropium (L)	*Formoterol (L)*	*Aclidinium/Formoterol (L)*		*Fluticason/Salmeterol (L)*
	Vilanterol (L)			

***L**: Long-acting drug; **S:** Short-acting drug*

4.3.1.4. Inhalation therapy difficulties

Administration through inhalation requires very specific handling and leads to practical issues. The correct handling of inhalation devices seems to be problematic for many patients with COPD. Mehuys et al reported that 21% of patients with COPD made major inhalation errors, such as failing to remove the inhaler cap and/or failing to shake the pMDI[26]. Indeed, other research confirmed that inhaler mishandling remains common and is even associated with reduced disease control[27]. It is suggested that repeated training is necessary as positive effects of interventions disappear over time. This would require long-term and continuous monitoring of patients with COPD[28].

4.3.2. Oral treatment options

4.3.2.1. Methylxanthines

Methylxanthines act as non-selective phosphodiesterase inhibitors[16]. They increase intracellular cAMP by inhibiting breakdown, consequently stimulating airway smooth muscle cells to relax[16]. Theophylline is the most used methylxanthine in treatment of COPD. However, it is less effective and less well tolerated than inhaled long-acting bronchodilators. Therefore, and because of its narrow therapeutic window it is not recommended as first-line therapy[29].

4.3.2.2. Oral corticosteroids & Antibiotics

Oral corticosteroids and antibiotics are not recommended for maintenance therapy in patients with COPD as long-term use causes significant adverse effects such as increased risk of pneumonia and osteoporosis[16 25]. However, they play a significant role in the management of exacerbations (see further)[1].

4.3.3. Treatment guidelines

4.3.3.1. Managing stable COPD

For all patients with COPD, all non-pharmacological measures should be taken (e.g. smoking cessation, flu vaccination etc.). Additionally, to control symptoms and reduce severity and frequency of exacerbations, pharmacological therapy should be added. All patients are advised SABA/SAMA therapy in case of symptoms of shortness of breath (as needed) and during acute exacerbations. From COPD GOLD B stage onwards, a maintenance treatment with one or two long-acting bronchodilators is warranted. In patients with frequent exacerbations, inhaled corticosteroids might be added to long-acting bronchodilator(s).

4.3.3.2. Managing exacerbations

An exacerbation is defined as an '*acute event characterized by a worsening of the patient's respiratory symptoms that is beyond normal day-to-day variations and leads to a change in medication*'[1]. As severe exacerbations accelerate the rate of lung function decline and are associated with significant mortality[30], fast and effective treatment is needed. In all cases, immediate relief of bronchoconstriction is necessary, for which short-acting bronchodilators are the first-choice[1]. Consequently, systemic corticosteroids are the first option as they improve airflow, decrease the rate of treatment failure and risk of relapse, and decrease the length of hospital stay[31]. Antibiotics for COPD exacerbations showed inconsistent beneficial effects across outcomes of patients with a COPD exacerbation[32]. Also, antibiotics had no statistically significant effect on mortality and length of hospital stay in inpatients and almost no data on patient-reported outcomes exist[32]. Hence, antibiotics should only be given to patients where clear bacterial colonisation is observed. This can be assessed by three cardinal symptoms: increase in dyspnoea, sputum volume and sputum purulence[1].

Table 3.1.3: Management of stable COPD and exacerbations

	Stable COPD	**Exacerbation**
Goal	Symptom reduction Reduction of exacerbation risk	Minimize impact Prevent development of subsequent exacerbation
Non-pharmacologic treatment options	Smoking cessation Vaccination Pulmonary rehabilitation	Oxygen therapy *(optional)* Ventilator support *(optional)*
Pharmacologic treatment options	(long-acting) Bronchodilators Inhaled corticosteroids (Theophylline)	Short-acting bronchodilators Corticosteroids (oral and inhaled) Antibiotics

5. MEDICATION ADHERENCE IN PATIENTS WITH COPD

5.1. Medication adherence[33]

When a patient takes his or her medication as recommended, the patient is defined 'adherent'. Adherence to medication is a process that encompasses 3 different parts: (1) the initiation of the therapy, (2) correct implementation of the therapy in the patient's daily life, and (3) discontinuation of the therapy. Nonadherence to medications can subsequently occur in the following situations: late or non-initiation of the prescribed treatment, suboptimal implementation of the dosing regimen[v], or early discontinuation of the treatment.

When nonadherent behaviour is observed, this can be a deliberate choice of the patient, in which case we use the term '*intentional nonadherence'*. In case the patient is unaware of the exhibited behaviour, the term '*unintentional nonadherence'* is used. Patients may exhibit both behaviours, in which case the term '*overlapping nonadherence'* is used.

5.2. Measures of (non)adherence

A number of direct and indirect methods are available to measure the extent of (non)adherence (Table 3.1.4). All methods have advantages and disadvantages. In real-world situations however, pharmacy dispense records are preferred as they have shown a good correlation with actual use and are easy and cheap to obtain[34]. However, this method lacks discriminative properties to determine exhibited types of nonadherence. Therefore, qualitative patient interviews are required. To date, no gold standard to measure and define adherence in an unbiased, reliable, quick and low-cost way is defined.

Table 3.1.4: Methods to measure nonadherence; advantages and disadvantages (Adopted and adapted from Lareau et al.[35])

	Advantages	**Disadvantages**
Clinicians' estimates	Easy to obtain	Unreliable
Patients' self-report	Easy to obtain	Unreliable, overestimation
Pill counts	Easy to obtain	Overestimates, pill dumping
Pharmacy records	Confirms prescription filling	Incomplete, biased estimates
Biologic measures	Confirms ingestion	Expensive, invasive, insensitive to inhaled drugs, affected by pharmacokinetic patient properties and polypharmacy
Electronic monitoring	Provides use patterns	Expensive, limited availability and use, malfunctions

[v] *This includes (1) the proportion of prescribed drugs taken, (2) the proportion of days with the correct number of doses taken (3) the proportion of doses taken on time, (4) the number of drug holidays and (5) the longest interval between two doses.*

5.3. Nonadherence, its determinants, and impact for patients with COPD

Although COPD can be managed well with both non-pharmacological and pharmacological options[1], adherence to therapy is often suboptimal[36]. Adherence rates reported in asthma and COPD vary largely with rates between 22% and 78%, depending on the population assessed and the methods of measure[37]. For patients witch COPD, adherence rates are mainly estimated to be about 50%[36]. An observational study performed in Belgian community pharmacies detected underadherence in 48% of patients and overadherence in 5% of patients[26].

There is no single factor that determines nonadherent behaviour in a patient. Nonadherence to COPD medication is multi-factorial and is influenced by the patient, the treatment and the society (Figure 3.1.3)[36]. Therefore, interventions aimed at improving adherence could never follow a 'one-size-fits-all' approach, but need to be tailored to the individual's need.

Suboptimal adherence in patients with COPD has been associated with higher morbidity and healthcare use (i.e., general practitioner (GP) visits, emergency room visits and hospitalizations) due to more frequent episodes of worsening of symptoms, i.e. exacerbations[38-40]. Similarly, an association with increased mortality has been reported[38 40].

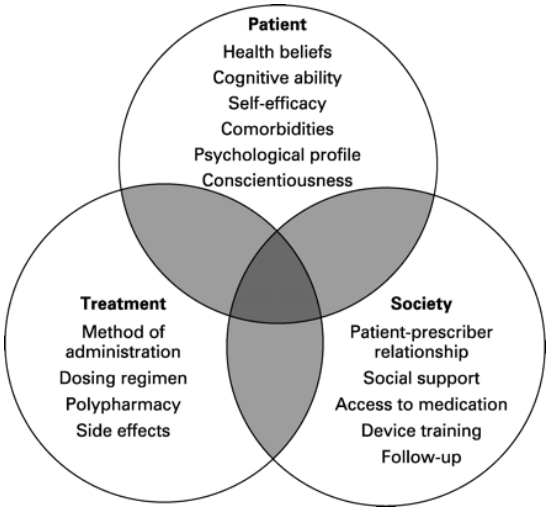

***Figure 3.1.3**: Determinants of nonadherence in patients with COPD (Adopted from Bourbeau et al.[36])*

REFERENCES

1. *Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: Available at: http://www.goldcopd.org/, Global Initiative for chronic Obstructive Lung Disease 2011.*
2. *UpToDate®. Chronic obstructive pulmonary disease: Definition, clinical manifestations, diagnosis, and staging Secondary Chronic obstructive pulmonary disease: Definition, clinical manifestations, diagnosis, and staging Sep 29, 2015.*
3. *MacNee W. Pathology, pathogenesis, and pathophysiology: BMJ. 2006 May 20;332(7551):1202-4.*
4. *Rycroft CE, Heyes A, Lanza L, et al. Epidemiology of chronic obstructive pulmonary disease: a literature review. International journal of chronic obstructive pulmonary disease 2012;**7**:457-94.*
5. *Nationaal Kompas Volksgezondheid. Hoe vaak komt COPD voor en hoeveel mensen sterven eraan? The Netherlands, 2011.*
6. *Agentschap Zorg & Gezondheid. Chronische aandoeningen: incidentie en prevalentie, 2014.*
7. *van Durme YM, Verhamme KM, Stijnen T, et al. Prevalence, incidence, and lifetime risk for the development of COPD in the elderly: the Rotterdam study. Chest 2009;**135**(2):368-77.*
8. *Rijksinstituut voor Volksgezondheid en Milieu. Societal costs of asthma, COPD and allergic rhinitis in The Netherlands, 2013.*
9. *National Institute for Health and Disability Insurance. Doelmatige behandeling van COPD. Belgium, 2011.*
10. *Murray CJ, Lopez AD. Measuring the global burden of disease. The New England journal of medicine 2013;**369**(5):448-57.*
11. *Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. The European respiratory journal 2005;**26**(2):319-38.*
12. *Tashkin DP, Murray RP. Smoking cessation in chronic obstructive pulmonary disease. Respir Med 2009;**103**(7):963-74.*
13. *Collins PF, Stratton RJ, Elia M. Nutritional support in chronic obstructive pulmonary disease: a systematic review and meta-analysis. The American journal of clinical nutrition 2012;**95**(6):1385-95.*
14. *Lee AL, Holland AE. Time to adapt exercise training regimens in pulmonary rehabilitation – a review of the literature. International journal of chronic obstructive pulmonary disease 2014;**9**:1275-88.*
15. *Stoller JK, Panos RJ, Krachman S, et al. Oxygen Therapy for Patients With COPD: Current Evidence and the Long-Term Oxygen Treatment Trial. Chest 2010;**138**(1):179-87.*
16. *College voor zorgverzekeringen C. Farmacotherapeutisch Kompas. Secondary Farmacotherapeutisch Kompas. ww.fk.cvz.nl/.*
17. *Barr RG, Bourbeau J, Camargo CA, et al. Inhaled tiotropium for stable chronic obstructive pulmonary disease. The Cochrane database of systematic reviews 2005(2):Cd002876.*
18. *Kerwin E, Hebert J, Gallagher N, et al. Efficacy and safety of NVA237 versus placebo and tiotropium in patients with COPD: the GLOW2 study. The European respiratory journal 2012;**40**(5):1106-14.*
19. *Jones PW, Singh D, Bateman ED, et al. Efficacy and safety of twice-daily aclidinium bromide in COPD patients: the ATTAIN study. The European respiratory journal 2012;**40**(4):830-6.*
20. *Tashkin DP, Fabbri LM. Long-acting beta-agonists in the management of chronic obstructive pulmonary disease: current and future agents. Respiratory research 2010;**11**:149.*
21. *Kornmann O, Dahl R, Centanni S, et al. Once-daily indacaterol versus twice-daily salmeterol for COPD: a placebo-controlled comparison. The European respiratory journal 2011;**37**(2):273-9.*
22. *Spencer S, Calverley PM, Burge PS, et al. Impact of preventing exacerbations on deterioration of health status in COPD. The European respiratory journal 2004;**23**(5):698-702.*
23. *Calverley P, Pauwels R, Vestbo J, et al. Combined salmeterol and fluticasone in the treatment of chronic obstructive pulmonary disease: a randomised controlled trial. Lancet 2003;**361**(9356):449-56.*
24. *Drummond MB, Dasenbrook EC, Pitz MW, et al. Inhaled corticosteroids in patients with stable chronic obstructive pulmonary disease: a systematic review and meta-analysis. JAMA : the journal of the American Medical Association 2008;**300**(20):2407-16.*
25. *Gecommenariëerd Geneesmiddelen Repertorium, Belgisch Centrum voor Farmacotherapeutische Informatie, 2013.*
26. *Mehuys E, Boussery K, Adriaens E, et al. COPD management in primary care: an observational, community pharmacy-based study. The Annals of pharmacotherapy 2010;**44**(2):257-66.*
27. *Melani AS, Bonavia M, Cilenti V, et al. Inhaler mishandling remains common in real life and is associated with reduced disease control. Respir Med 2011;**105**(6):930-8.*
28. *Basheti IA, Qunaibi EA, Hamadi SA, et al. Inhaler technique training and health-care professionals: effective long-term solution for a current problem. Respiratory care 2014;**59**(11):1716-25.*
29. *Barnes PJ. Theophylline for COPD. Thorax 2006;**61**(9):742-4.*
30. *Donaldson GC, Seemungal TA, Bhowmik A, et al. Relationship between exacerbation frequency and lung function decline in chronic obstructive pulmonary disease. Thorax 2002;**57**(10):847-52.*
31. *Woods JA, Wheeler JS, Finch CK, et al. Corticosteroids in the treatment of acute exacerbations of chronic obstructive pulmonary disease. International journal of chronic obstructive pulmonary disease 2014;**9**:421-30.*
32. *Vollenweider DJ, Jarrett H, Steurer-Stey CA, et al. Antibiotics for exacerbations of chronic obstructive pulmonary disease. The Cochrane database of systematic reviews 2012;**12**:Cd010257.*
33. *Vrijens B, De Geest S, Hughes DA, et al. A new taxonomy for describing and defining adherence to medications. Br J Clin Pharmacol 2012;**73**(5):691-705.*
34. *Hess LM, Raebel MA, Conner DA, et al. Measurement of adherence in pharmacy administrative databases: A proposal for standard definitions and preferred measures. Ann Pharmacother 2006;**40**(7-8):1280-88.*
35. *Lareau SC, Yawn BP. Improving adherence with inhaler therapy in COPD. International journal of chronic obstructive pulmonary disease 2010;**5**:401-6.*
36. *Bourbeau J, Bartlett SJ. Patient adherence in COPD. Thorax 2008;**63**(9):831-38.*
37. *Makela MJ, Backer V, Hedegaard M, et al. Adherence to inhaled therapies, health outcomes and costs in patients with asthma and COPD. Respir Med 2013;**107**(10):1481-90.*
38. *Vestbo J, Anderson JA, Calverley PMA, et al. Adherence to inhaled therapy, mortality and hospital admission in COPD. Thorax 2009;**64**(11):939-43.*
39. *Toy EL, Beaulieu NU, McHale JM, et al. Treatment of COPD: Relationships between daily dosing frequency, adherence, resource use, and costs. Respir Med 2011;**105**(3):435-41.*
40. *Butler RJ, Davis TK, Johnson WG, et al. Effects of Nonadherence With Prescription Drugs Among Older Adults. Am J Manag Care 2011;**17**(2):153-60.*

PART 3.2

EFFECTIVENESS OF PHARMACEUTICAL CARE FOR PATIENTS WITH COPD (PHARMACOP): A RANDOMIZED CONTROLLED TRIAL

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ABSTRACT

Aim. Few well-designed randomized controlled trials (RCT) regarding the impact of community pharmacist interventions on pharmacotherapeutic monitoring of patients with Chronic Obstructive Pulmonary Disease (COPD) have been conducted. We assessed the effectiveness of a pharmaceutical care program for patients with COPD.

Methods*.* The PHARMACOP-trial is a single-blind 3-month RCT, conducted in 170 community pharmacies in Belgium, enrolling patients prescribed daily COPD medication, aged ≥50 years, and with a smoking history ≥10 pack-years. A computer-generated randomization sequence allocated patients to intervention (n=371), receiving protocol-defined pharmacist care, or control group (n=363), receiving usual pharmacist care (1:1 ratio, stratified by center). Interventions, focusing on inhalation technique and adherence to maintenance therapy, were carried out at start of the trial and at one month follow-up. Primary outcomes were inhalation technique and medication adherence. Secondary outcomes were exacerbation rate, dyspnea, COPD specific and generic health status and smoking behavior.

Results. From December 2010 to April 2011, 734 patients were enrolled. 42 patients (5.7%) were lost to follow-up. At the end of the trial, inhalation score (Mean estimated difference [Δ],13.5%; 95% Confidence Interval [CI], 10.8-16.1; P<.0001) and medication adherence (Δ, 8.51%; 95%CI, 4.63-12.4; P<.0001) were significantly higher in the intervention group compared to the control group. In the intervention group, a significantly lower hospitalization rate was observed (9 vs 35; Rate Ratio, 0.28; 95%CI, 0.12-0.64; P=.003). No other significant between-group differences were observed.

Conclusion. Pragmatic pharmacist care programs improve the pharmacotherapeutic regime in patients with COPD and could reduce hospitalization rates.

INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is a highly prevalent, chronic lung disease, characterized by a not fully reversible airflow limitation. Although preventable and treatable, COPD remains a leading cause of morbidity, mortality and elevated health care costs worldwide[1]. The natural decline in lung function can be aggravated by a temporarily worsening of symptoms – exacerbations, which contribute substantially to the overall economic and social disease burden. COPD is projected to be the seventh leading cause of lost Disability-Adjusted Life Years in 2030 and the third leading cause of death in 2020[1 2].

To further improve management of COPD, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) develops and updates treatment guidelines[1]. As part of the management of stable COPD, GOLD recommends close monitoring of the patient's pharmacotherapy, including patient's adherence and inhalation technique. Indeed, in many COPD patients, inhalation technique and medication adherence have been shown to be suboptimal [3-5].

Multidisciplinary collaborations addressing these topics in primary care could be successful strategies to improve disease management[1 6-8]. In Belgium, COPD management programs are mainly provided in hospital settings, while community pharmacists are only occasionally involved[3 7 9]. However, pharmacists are well-placed to engage in COPD care programs due to their frequent patient contacts upon prescription refill, and their specific medication-related expertise. Furthermore, recent research showed that mere self-management programs are insufficient to reduce severe exacerbations[10]. Consequently, monitoring and optimizing COPD maintenance therapy in a community pharmacy to improve COPD management could be a good balance between unsupervised self-management and extensive hospital monitoring [8 11].

In the present 3-month randomized controlled trial (RCT), we investigated the effectiveness of a community pharmacist intervention, focusing on optimal use of COPD maintenance therapy. In accordance with the GOLD guidelines about monitoring COPD pharmacotherapy, patient's adherence and inhalation technique were chosen as primary outcomes. Given their association with suboptimal disease management[4 5], improvements in both primary outcomes could serve as surrogate markers for enhanced effectiveness of the current pharmacotherapeutic regimen. Secondary outcomes were exacerbation rates, dyspnea, COPD specific and generic health status and smoking behavior.

METHODS

Design Overview

The PHARMACOP (PHARMAceutical Care for COPD) trial is a 3-month randomized, controlled, parallel group trial carried out between December 2010 and July 2011 in 170 community pharmacies, well-spread throughout Belgium. The study protocol was approved by the Ethical Committees of the Ghent University Hospital (for Flanders) and Centre Hospitalier Universitaire de Liège (for Wallonia). All patients provided written informed consent. General practitioners (GP) of all participants were notified about the study by letter. **Clinicaltrials.gov Identifier**: NCT01260389.

Setting and Participants

Patients filling a prescription for COPD medication (R03, Anatomical Therapeutic Chemical classification) at participating pharmacies were consecutively invited to participate when meeting following inclusion criteria: (1) prescription for daily COPD maintenance medication, (2) aged 50 years or older, (3) smoking history of at least 10 pack-years, (4) regular visitor to the pharmacy and (5) providing written informed consent. Patients with current asthma and analphabetic patients were excluded. Each pharmacy planned a maximum of 6 COPD patients to be recruited. Recruitment period ran from December 2010 through April 2011.

Eligible patients were randomized to either control or intervention group (1:1 ratio), stratified by center, with each pharmacy accounting for one recruitment center. To conceal assignments, pharmacists performed allocation through a central web based randomization system, created by an independent investigator. As the intervention was educational, blinding of pharmacists was not possible. Patients, however, were not told to which study group they were assigned. After randomization, pharmacy visits were planned at 1 and 3 months.

Intervention

Before initiation of the trial, all participating pharmacists received a training session addressing pathophysiology of COPD, its nonpharmacological and pharmacological treatment (GOLD guidelines), important referral criteria and study protocol. Control group patients were given usual non protocol-based pharmacist care. Patients in the intervention group received a protocol-defined two-sessions intervention; one session at the start of the study and one session at the 1-month follow-up visit (Table 3.2.1), as described in detail in the trial's protocol. All interventions were given during one-on-one counselling sessions. The content of the sessions was set around predefined themes, but adapted according to patients' needs. Electronic medication records, performed inhalation technique and questionnaires completed at start of the study, served as starting point. Questionnaires included questions about behavioural issues concerning adherence, health issues etc.

Consequently, the focus of each counselling session could have been different. The duration of interventions was not predetermined, however, we estimate the duration between 15 and 25 minutes.To support interventions, pharmacists were provided with information leaflets on COPD, demo inhaler units, and a list of practical solutions to specific nonadherent behavior[12].

Table 3.2.1: Overview of pharmacist intervention
Session 1: At start of trial (T = 0)
Structured patient education (verbal and written form) about:
COPD pathophysiology
COPD medication
Dose and time of intake
Inhalation technique (including physical demonstration with demo inhaler unit)
Importance of adherence to maintenance therapy and current problems with adherence
Possible side effects
Self-management (e.g lifestyle advice)
Smoking cessation (if patient was current smoker)
Session 2: 1-month follow-up (T = 1 month)
Structured patient education (verbal only) about:
COPD medication
Inhalation technique (including physical demonstration with demo inhaler unit)
Changes in adherence to maintenance therapy since last visit
Self-management (e.g lifestyle advice)
Smoking cessation (if patient was current smoker)

Primary outcomes

Inhalation Technique. The participating pharmacist scored inhalation technique using a checklist (eight-point checklist for metered-dose inhalers (MDIs), ten-point checklist for MDIs with spacer and seven-point checklist for dry powder inhalers (DPIs)) at the start of the study and at 1- and 3-month follow-ups[3] (Appendix 3.2.1). One point was assigned for each correctly performed step and the sum score was expressed as percentage of correct steps. Patients committing major inhalation technique errors (for MDI: failure to remove cap and/or fail to shake MDI; for DPI: failure to load device correctly and/or fail to inhale quickly and deeply through device) were assigned a sum score of zero. For ethical reasons, major inhalation technique errors were also corrected in control group patients.

Adherence to maintenance therapy. Adherence was assessed at baseline and after 3 months, using a recommended measure of administrative data, i.e. Medication Refill Adherence (MRA)[13]. For each patient, MRA score was calculated by dividing the total days' supply by the number of days of study participation. The number of days of study participation represents the number of days between inclusion date and the date of the second follow-up visit (after 3 months), which is more or less 90 days. We refer to the protocol for technical aspects regarding MRA calculations. Patients with an MRA value ≥80 were considered adherent (cut-off selected based on previous use by other investigators[5] [14]).

For patients using more than one inhaled drug, only inhalation technique and MRA score of the principal maintenance therapy was checked or calculated.

Secondary outcomes

Dyspnea. The severity of dyspnea was determined by the modified Medical Research Council (mMRC) dyspnea scale[15]. This scale comprises five statements describing the entire range of respiratory disability from none (score 0) to almost complete incapacity (score 4). Patients completed the mMRC dyspnea scale at baseline and after 3 months.

COPD specific health status. The COPD specific health status was measured using the COPD Assessment Test (CAT). The CAT is a simple and reliable questionnaire for quantifying the impact of COPD on the patient's health[16 17]. It comprises 8 items: cough, phlegm, chest tightness, breathlessness going up hills/stairs, activity limitations at home, confidence leaving home, sleep and energy. Each item is scored from 0 to 5, giving an overall value ranging from 0 to 40 (corresponding to best and worst health status in patients with COPD, respectively). Patients completed CAT at baseline, after 1 month and after 3 months.

Generic health status. Generic health status was assessed at start and at end of the trial, using the EuroQol five-dimension questionnaire (EQ-5D)[18 19]. The EQ-5D is a standardized, self-administered quality-of-life questionnaire that comprises a descriptive and a valuation section. The descriptive section inquires 5 domains: mobility, self-care, usual activities, pain/discomfort and anxiety/depression, each to be scored from 1 (no problem) to 3 (extreme problems). These numbers provide a 5-digit code that can be converted into a single index (utility score) through a set of weights. The index ranges from -0.18 (worst possible health status) to 1 (full health), using the weights for Belgium. The valuation section is a visual analogue scale (VAS), ranging from 0 (worst possible health status) to 100 (full health), where the respondent points out his self-perceived overall quality of life.

Smoking. The smoking status of patients was assessed through a questionnaire, including following questions: "Do you currently smoke?","Did you previously smoke?", "How long do/did you smoke?" and "How many cigarettes do/did you smoke a day?", at start and end of the study.

Exacerbations. Participants were asked to record occurrence and duration of moderate and severe exacerbations during the study period. We estimated the mean annual exacerbation rate by dividing the total number of exacerbations in both study groups by the total follow-up time of the considered group (i.e. weighted approach)[20]. Exacerbations were defined functionally: exacerbations requiring treatment with oral corticosteroids or antibiotics were regarded as "moderate". Exacerbations requiring an emergency department visit or hospitalization were regarded as "severe"[21].

Statistical Analysis

Descriptives were displayed as counts with percentages and means with standard deviations as appropriate. Minimal sample size was calculated based on the ability to simultaneously detect a 10% difference in inhalation technique score (SD=0.2) and a 5% difference in MRA score (SD=0.2) between the intervention group and the control group (i.e. equivalent of a 50%-increase in the number of patients with perfect inhalation technique or ≥80% adherence) with 90% power at the 5% two-sided significance level. Allowing for a dropout rate of 5%, we aimed to enroll 706 patients.

Consistent with the hypothesis, we compared the intervention group with the control group performing an intention-to-treat analysis for all primary and secondary outcomes. Missing data were handled as missing completely at random. To test for differences in mean changes between intervention and control group, we used mixed effect models for repeated measurements. For binary outcomes we used logistic regression models. Both models included terms for baseline measurement, study group, time, and timeXgroup interaction. Least-square means and Odds ratios, respectively, each with 95% confidence limits are reported. For exacerbations, a generalized linear model (i.e. Poisson regression analysis) was used as recommended in literature[20]. Subgroup analysis was performed to investigate the consistency of the trial conclusions among different subpopulations (age, gender, region). All statistical analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC) by an academic statistician. Two-sided p-values of less than .05 were considered significant.

RESULTS

The flow of participants through the study is shown in Figure 3.2.1. In 170 community pharmacies, 1648 patients were pre-screened, of which 1067 (64.7%) were eligible. About 70% (n=734) of them agreed to participate and were randomized to control (n=363) or intervention (n=371). Both study groups showed similar baseline characteristics (Table 3.2.2). Almost 95% of patients (n=692) completed the trial, with a median follow-up time of 3 months (IQR, 3-3). Main reasons for dropout (n=42) were hospitalization and death. There was no significant difference between the number of dropouts in both study groups.

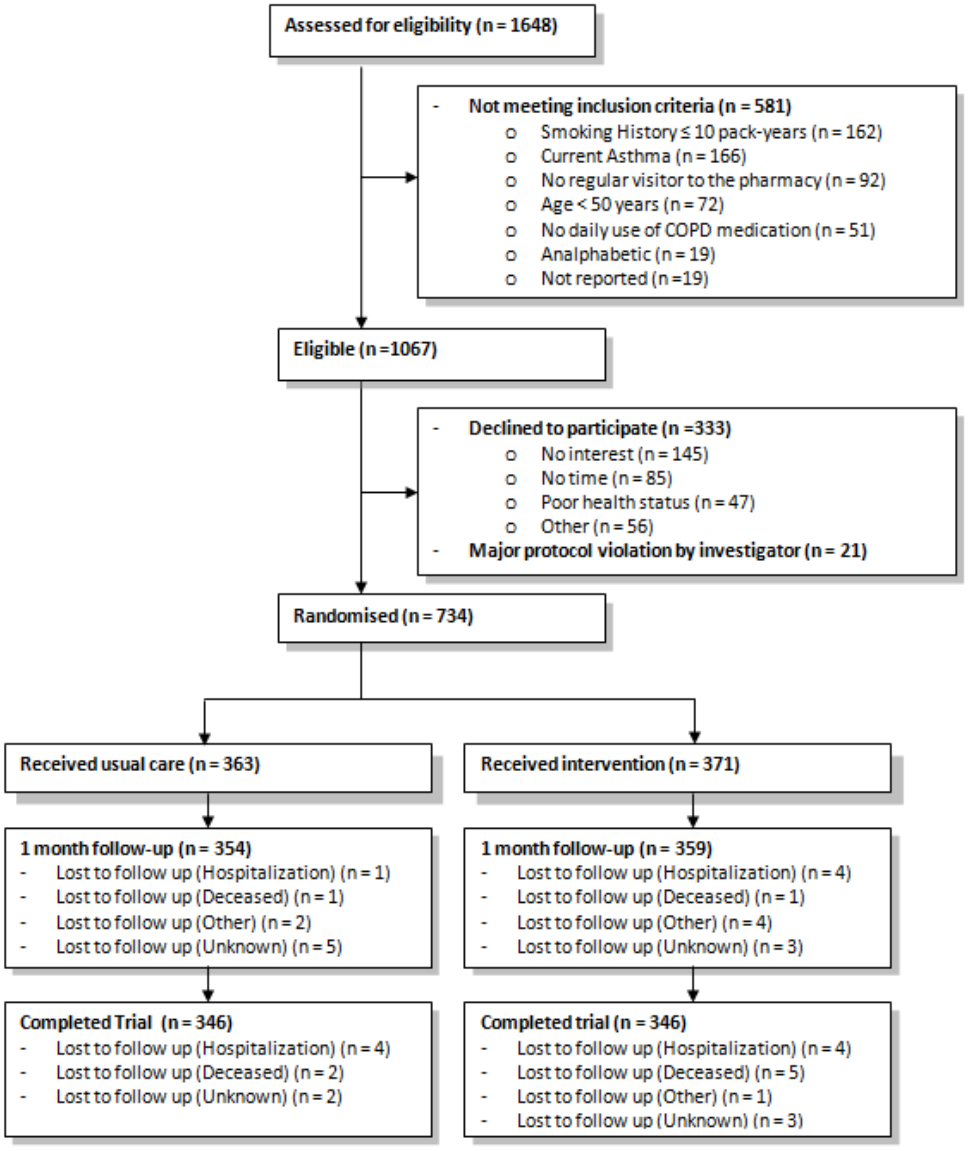

***Figure 3.2.1**: Flow of participants through the study*

Table 3.2.2: Baseline Characteristics

Parameter	Control group (n = 363)	Intervention group (n = 371)
Male Sex, No. (%)	249 (69)	236 (64)
Age (y), mean (SD)	68.9 (9.7)	68.4 (9.6)
BMI, kg/m², mean (SD)	25.9 (4.8)	25.9 (5.4)
Smoking status, No. (%)		
Current smoker	148 (41)	170 (46)
Ex-smoker	213 (59)	200 (54)
Pack-years of current smokers, mean (SD)	40.8 (24.4)	38.54 (22.9)
Pack-years of ex-smokers, mean (SD)	45.7 (31.3)	46.49 (29.1)
COPD, duration (y), mean (SD)	11.2 (9.4)	10.84 (9.7)
COPD management supervised by, No. (%)		
GP only	134 (37)	149 (40)
Pneumologist only	46 (13)	43 (12)
Both GP and pneumologist	181 (50)	179 (48)
Influenza vaccination, No. (%)	282 (78)	296 (80)
mMRC score*, No. (%)		
mMRC = 0	99 (28)	96 (26)
mMRC = 1	124 (34)	122 (33)
mMRC = 2	61 (17)	60 (16)
mMRC = 3	44 (12)	51 (14)
mMRC = 4	32 (9)	40 (11)
CAT score†, mean (SD)	16.4 (7.6)	16.7 (7.8)
History of exacerbations in preceding year		
≥ 1 in preceding yr, No. (%)	197 (54.3)	200 (54.1)
Moderate exacerbation rate‡, mean	0.47	0.50
Severe exacerbation rate‡, mean	0.23	0.21
COPD maintenance medication, No. (%)		
Short Acting β_2-agonists – SABA	36 (10)	28 (8)
Long Acting β_2-agonists – LABA	22 (6)	18 (5)
Short Acting Anticholinergics – SAAC	11(3)	6 (2)
Long Acting Anticholinergics – LAAC	284 (78)	260 (70)
SAAC + SABA	105 (29)	120 (32)
Inhaled Corticosteroids – ICS	26 (7)	37 (10)
ICS + LABA	296 (82)	269 (73)
Triple Therapy (LAAC+LABA+ICS)	236 (65)	192 (52)
Theophylline	6 (2)	10 (3)
Oral Corticosteroids	12 (3)	7 (2)
Mean Number of COPD medications, mean (SD)	2.3 (1.0)	2.2 (1.0)

***BMI** = Body Mass Index. **COPD** = Chronic Obstructive Pulmonary Disease. **GP** = General practitioner. **SD** = standard Deviation*

* Scores on the modified Medical Research Council dyspnea scale (mMRC) can range from 0 to 4, with a score of 4 indicating that a patient is too breathless to leave the house or becomes breathless when (un)dressing.

† CAT: COPD Assessment Test; a higher score indicates a worse health status (range: 0 – 40)

‡ Exacerbation rates are expressed as No./patient-year and calculated based on retrospective self-reported patient data.

Primary outcomes

At baseline, mean percentages of correctly performed inhalation steps were about 68% in both groups (Table 3.2.3). At the end of follow-up, the improvement in inhalation technique was significantly higher in the intervention arm compared to the control arm (Mean estimated difference [Δ], 13.5%; 95% confidence interval [CI], 10.8%-16.1%; P<.0001). The intervention corrected almost all major inhalation technique errors: 15.6% of intervention group patients received an inhalation score of 0% at baseline, which was reduced to 1.2% by the end of the trial, whereas in the control group, these percentages were 11.6% and 4.6% respectively (Odds Ratio [OR], 0.18; 95%CI, 0.06-0.53; P=.002). The increase in inhalation technique scores in the control group is predominantly caused by correction of major inhalation technique errors, as requested in the study protocol (for ethical reasons).

After 3 months, the odds of obtaining an inhalation score of 100% after receiving the intervention protocol vs no intervention was 3.03 (95%CI, 2.12-4.34; P<.0001) (Table 3.2.3). A supplementary table is included in Appendix 3.2.1, addressing detailed information on patients' inhalation technique errors per inhaler device and per checklist item.

Mean MRA scores were 82.7(23.9) in the control group and 84.0(23.5) in the intervention group at baseline. At three months, we detected a significantly higher improvement from baseline in the intervention group, compared to the control group (Δ, 8.51; 95%CI, 4.63-12.4; P<.0001). Additionally at three months, the odds to obtain an MRA score ≥80 in the intervention group compared to the control group was 2.15 (95%CI, 1.46-3.14; P<.0001) (Table 3.2.3).

COPD specific and generic health status

At the end of the study, the number of patients having an mMRC score <2 did not differ between groups (P=.97). Similarly, no beneficial effects of the intervention were seen in CAT scores (P=.83), EQ-5D utility scores (P=.19) or EQ-5D VAS (P=.15) (Table 3.2.3). At baseline, approximately 42% of patients reported to be current smokers. After three months, 9 (6.1%) control group patients and 15 (8.8%) intervention group patients had quit smoking. No significant between-group differences were observed (P=.33) (Table 3.2.3).

Exacerbations

During trial, 450 independent episodes of exacerbations among 302 patients were observed (Table 3.2.4). There was no difference in estimated annual rate of moderate exacerbations between the two treatment arms (P=.14). In contrast, there was a significantly lower number of intervention group patients reporting to have had at least one severe exacerbation during the trial, compared to the control group (19 vs 33; OR, 0.55; 95%CI, 0.31-0.98; P=.038). Fifty-three independent severe exacerbations were reported in the control arm, compared to 24 in the intervention arm, which generated a significantly lower estimated annual severe exacerbation rate in the intervention group compared to the control group (0.27 vs. 0.61; Rate Ratio [RR], 0.45; 95%CI, 0.25-0.80; P<.007), mainly due to less hospitalizations in the intervention arm, compared to the control arm (9 vs. 35). The estimated annual hospitalization rate was 72% lower in the intervention group, compared to the control group (0.10 vs 0.40; RR, 0.28; 95%CI, 0.12-0.64; P=.003). No significant difference in the rate of ER-visits (P=.20), nor in the duration of the hospital stay (P=.84) was seen, but hospitalization days rate was reduced by 73% (0.87 vs 3.51; RR, 0.27; 95%CI, 0.21-0.35; P<.0001).

Table 3.2.3: Primary and Secondary Outcomes

	Control group		Intervention group		Statistical analysis		
	No. of patients	Mean (SD) or %	No. of patients	Mean (SD) or %	Difference [95% CI]	Odds ratio [95%CI]	p-value
Inhalation Technique							
% correct steps							
Baseline	363	68.8 (28.8)	371	67.7 (32.5)	-	-	-
1 month	354	76.4 (22.3)	359	86.0 (23.1)	10.0 [7.2-12.9]	-	**<.0001**
3 months	346	79.0 (23.3)	346	93.4 (13.8)	13.5 [10.8-16.1]	-	**<.0001**
Patients scoring 0%							
Baseline	363	11.6	371	15.6	-	-	-
1 month	354	4.8	359	5.0	-	0.73 [0.39-1.36]	.323
3 months	346	4.6	346	1.2	-	0.18 [0.06-0.53]	**.002**
Patients scoring 100%							
Baseline	363	16.5	371	22.4	-	-	-
1 month	354	20.3	359	51.0	-	2.83 [2.05-3.90]	**<.0001**
3 months	346	32.9	346	68.5	-	3.03 [2.12-4.34]	**<.0001**
Adherence to maintenance medication							
MRA-score*							
Previous year	308¶	82.7 (23.9)	307ᶠ	84.0 (23.5)	-	-	-
During trial	307¶	85.7 (26.6)	292ᶠ	93.9 (21.5)	8.51 [4.63-12.4]	-	**<.0001**
Patients with MRA ≥ 80*							
Baseline	308¶	63.0	307ᶠ	62.9	-	-	-
3 months	307¶	62.5	292ᶠ	78.1	-	2.15 [1.46-3.14]	**<.0001**
Health Status							
CAT score† (scale 0 – 40)							
Baseline	363	16.4 (7.6)	371	16.7 (7.8)	-	-	-
1 month	354	15.0 (7.6)	359	15.1 (8.0)	-0.16 [-0.89-0.57]	-	.670
3 months	346	15.9 (7.7)	346	15.9 (7.8)	-0.08 [-0.82-0.66]	-	.832
Patients with mMRC score ≥ 2‡							
Baseline	363	38.1	371	40.9	-	-	-
1 month	354	37.6	359	39.8	-	0.99 [0.77-1.28]	.949
3 months	346	36.1	346	37.6	-	1.00 [0.76-1.32]	.973
EQ-5D utility score§ (scale -0.18 – 1)							
Baseline	363	0.71 (0.25)	371	0.68 (0.25)	-	-	-
3 months	346	0.73 (0.25)	346	0.72 (0.24)	0.02 [-0.01-0.04]	-	.190
EQ-VAS score‖ (scale 0 – 100)							
Baseline	363	64.9 (16.0)	371	63.3 (16.4)	-	-	-
3 months	346	64.6 (16.2)	346	65.2 (16.3)	1.31 [-0.48-3.09]	-	.151

Table 3.2.3 (Continued): Primary and Secondary Outcomes							
Smoking Status							
Current smokers							
Baseline	363	40.5	371	45.8	-	-	-
3 months	346	39.0	346	43.6	-	0.98 [0.86-1.12]	.760
Quit smoking	147	6.1	170	8.8	-	1.53 [0.65-3.61]	.331

No. *= Number;* ***SD*** *= Standard Deviation;* ***CI*** *= Confidence Interval*

*The Medication Refill Adherence (MRA) score for each patient was calculated by dividing his total days' supply by the number of days of study participation. Patients with a value ≥80 were considered adherent.

† CAT: COPD Assessment Test; a higher score indicates a worse health status.

‡ Scores on the modified Medical Research Council dyspnea (mMRC) scale can range from 0 to 4, with a score of 4 indicating the patient is too breathless to leave the house or becomes breathless when (un)dressing.

§ The EuroQol five-Dimension questionnaire (EQ-5D) provides a 5-digit code that can be converted into a single index (utility score) through a set of weights. Using the value set for Belgium, these scores can range from -0.18 (worst health status) to 1 (full health status).

|| The EQ-5D visual analogue scale (VAS) can range from 0 (worst health status) to 100 (full health). The respondent points out his self-perceived overall quality of life.

¶ Scores are calculated only for patients with complete pharmacy refill records.

Table 3.2.4: Exacerbations

	Control group n = 363	**Intervention group n = 371**	**Odds ratio [95% CI]**	**Statistical analysis Estimated Rate Ratio [95% CI]**	**p-value**
Moderate Exacerbations*					
Patients with event, No. (%)	125 (34.4)	125 (33.7)	1.02 [0.75-1.39]	-	.890
Total events, No.	194	179	-	-	-
Event rate, per patient-year	2.22	2.05	-	0.82 [0.64-1.06]	.135
Severe Exacerbations†					
Patients with event, No. (%)	33 (9.1)	19 (5.1)	0.55 [0.31-0.98]	**-**	**.038**
Total events, No.	53	24	-	-	-
Event rate, per patient-year	0.61	0.27	-	0.45 [0.25-0.80]	**.007**
ER visits					
Patients with event, No. (%)	14 (3.9)	13 (3.5)	0.91 [0.42-1.97]	-	.815
Total ER visits, No.	18	15	-	-	-
Rate of ER visits – per patient-year	0.21	0.17	-	0.59 [0.27-1.31]	.195
Hospitalizations					
Patients with event, No. (%)	24 (6.6)	8 (2.2)	0.31 [0.14-0.71]	-	**.003**
Total Hospitalizations, No.	35	9	-	-	**-**
Rate of hospitalizations, per patient-year	0.40	0.10	-	0.28 [0.12-0.64]	**.003**
Total hospitalization days, No.	307	76	-	-	**-**
Hospitalization duration, mean days	8.77	8.44	-	-	.835‡
Rate of hospitalization days, per patient-year	3.51	0.87	-	0.27 [0.21-0.35]	**<.0001**

*Exacerbations requiring treatment with oral corticosteroids or antibiotics were regarded as "moderate".

†Exacerbations requiring an emergency department visit or hospitalization were regarded as "severe".

‡ p-value is the result of a Mann-Whitney U test.

Subgroup Analysis

Prespecified subgroup analyses on age, gender and region were performed (Figure 3.2.2). No significant interactions between study group and any subgroup were found (predetermined value for interaction: P<.01). However, subgroup analyses were slightly underpowered to detect modest differences in subgroup effects if they might exist.

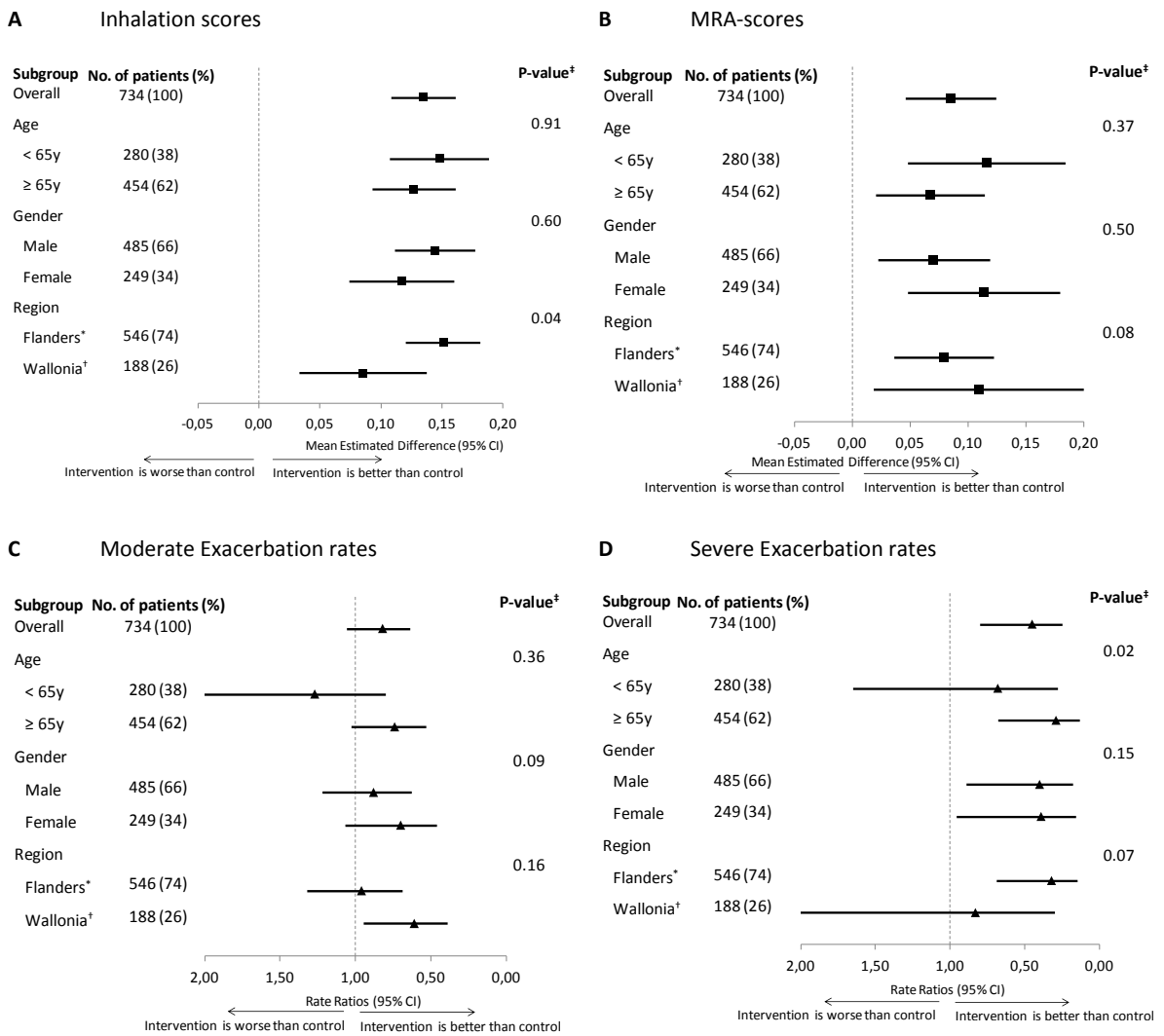

***Figure 3.2.2**: Subgroup Analysis. Mean estimated differences (black squares), rate ratios (black triangles), 95% confidence limits (horizontal Lines) and P values for the interaction between the study group effect and any subgroup variable.*

** The Dutch-speaking part of Belgium*
† The French-speaking part of Belgium
‡ No significant interaction between the study group and subgroup variables was found, according to the predetermined value for interaction (P<.01).

DISCUSSION

In the PHARMACOP-trial, we assessed the effectiveness of a protocol-based community pharmacist intervention in 734 patients with COPD. Outcomes were selected based on their association with suboptimal disease management[3-5]. The intervention significantly improved both primary outcomes, i.e. inhalation technique and medication adherence, and significantly decreased the estimated annual severe exacerbation rate. No significant differences in other health outcomes were observed.

Only few studies have investigated community pharmacist interventions to improve pharmacotherapeutic management of COPD[8 9 22]. None of these trials distinguished between asthma and COPD patients, although management and health outcomes for both diseases are distinct. This 3-month RCT confirms earlier indications that a pharmacist intervention can significantly improve inhalation technique[9 22]. Moreover, our trial is the first to demonstrate the positive effects of a community pharmacist intervention on medication adherence in patients with COPD, although comparable with results from trials performed in a hospital environment and led by a clinical pharmacist[23 24]. Most likely, improvements are due to the pharmacist-conducted patient education about correct use of the inhalers, their therapeutic effects and possible side effects. All intervention group patients received oral and written education along with a physical demonstration of inhalation technique, shown to be the most effective mode of instruction[9 25]. When entering the trial, 7% of patients had never been instructed about inhalation medication and only about 30% had yet received explanation from his pharmacist, offering a large room for improvement[9].

The significant decrease in severe exacerbation rate should be interpreted with caution, considering it being a secondary outcome and the short study duration. However, previous research indicated that integrated care[7], as well as clinical pharmacy interventions[23 24], similarly prevented hospitalizations. This effect of multidisciplinary care programs could be explained by diverse factors. Firstly, the intervention could result in enhanced self-management of the disease. Secondly, intervention patients could have perceived higher accessibility to primary healthcare professionals, prompting earlier detection and, consequently, better exacerbation management (i.e. decreased exacerbation recovery time and hospitalization risk)[26]. Hence it is plausible that pharmaceutical care protocols diminish the high health-care costs of severe COPD exacerbations, a presumption to be confirmed by proper pharmaco-economic analysis[1 2].The exacerbation rate in the control group during the trial seems higher compared to other clinical trials in patients with COPD[27 28]. Because of the heterogeneous nature of COPD, different geography and the specific population under study, caution is needed when comparing exacerbation rates between trials[29]. Nevertheless, the time set of the trial (i.e. during winter) could be a main factor contributing to the perceived higher exacerbation rate[30 31].

Our trial did not detect significant changes in health status after 3 months, which is in accordance with other studies, although it concerns heterogenous pharmaceutical care programs and health-care

settings[24 32 33]. This might be due to the short time span of the trial and the progressive nature of COPD. Furthermore, health status of our sample was relatively high at start of the trial (mean CAT of 16, and 39% with mMRC≥2), which decreases the available room for improvement. Furthermore, next to inhalation technique and medication adherence, other factors such as physical activity, motivation and nutrition could have influenced health related outcomes[1]. Though other trials have reported clinically relevant changes in health status after a pharmacist intervention, they ran over a longer period in time, recruited patients with worse baseline health status or were performed in a hospital setting[8 23 34]. Long-term trials are needed to confirm whether this pharmaceutical care protocol in a primary care setting has a positive effect on health or smoking status.

This RCT is the largest trial to investigate the effectiveness of a protocol-based community pharmacist intervention in patients with COPD and was conducted and reported following CONSORT guidelines[35]. The intervention was protocol-based and designed to be easily applicable in community pharmacies by different pharmacists. All actions executed during the trial's scheduled intervention points were documented, both electronically and in written form. However, the trial has some limitations. A first limitation is the relatively short study duration. Regarding exacerbation frequency, this could lead to false negative results; however, observed differences confirm that the trial length is sufficient. Moreover, a recent meta-analysis detected no differences between short or long-term trials regarding hospitalizations due to COPD exacerbations[36 37]. Secondly, the absence of spirometric confirmation of COPD could be considered an important limitation; however, it supports the pragmatic aspect of the trial, since in practice, pharmacists do not have access to such data. The operational definition of COPD (prescription for COPD medication, aged ≥50 years, smoking history ≥10 pack-years and excluding patients with current asthma) was chosen in consultation with specialists and provided pharmacists with satisfactory certainty of COPD presence. Thirdly, pharmacists, carrying out the intervention, measured their own performance in teaching and training. This may be a potential source of bias. However, pharmacists had no gain in untruly reporting of an improvement. Counselling was not individually evaluated, nor did pharmacists receive a remuneration for improved patients. Finally, selection bias cannot be fully excluded, since participation to trials is usually accepted more frequently by motivated patients.

To increase external generalizability of our study findings, we attempted recruiting a patient sample as representative as possible, using every pharmacy as one recruitment center. To confirm generalizability, we compared inhalation scores and medication adherence to results of other trials and similar scores were observed[3 9 22]. Moreover, subgroup analysis confirmed consistency of results in different regions and patient subgroups (Figure 3.2.2).

In conclusion, we conducted a 3-month RCT in 170 community pharmacies assessing the effectiveness of a protocol-based pharmaceutical care program in patients with COPD. Both primary outcomes, i.e. inhalation technique and medication adherence, were significantly more improved in the intervention group, compared to the control group. Furthermore, a trend towards a reduction in severe exacerbations was observed. This trial should encourage community pharmacists to engage in COPD care aiming to sustain an effective and safe pharmacotherapeutic treatment in patients with COPD.

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AUTHOR CONTRIBUTIONS:
Tommelein had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Conception and design: Mehuys, Van Tongelen, Boussery, Brusselle, Van Bortel, Christiaens, Remon, Van Hees
Analysis and interpretation of the data: Tommelein, Mehuys, Brusselle, Boussery
Drafting of the article: Tommelein
Critical revision of the article for important intellectual content: Tommelein, Mehuys, Van Hees, Van Bortel, Christiaens, Van Tongelen, Remon, Boussery, Brusselle
Final approval of the article: Tommelein, Mehuys, Boussery Brusselle
Statistical expertise: Tommelein, Adriaens
Obtaining of funding: Brusselle
Administrative, technical, or material support: Van Tongelen
Study supervision: Tommelein, Mehuys, Brusselle, Boussery

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POTENTIAL CONFLICT OF INTEREST*:*
All authors have completed and submitted the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare the following: Dr Brusselle reported to have received a grant from GlaxoSmithKline; is a member of the board for Astra-Zenica, Boehringer-Ingelheim, GlaxoSmithKline and Novartis; has received payment for lectures at Astra-Zenica, Boehringer-Ingelheim, Chiesi, GlaxoSmithKline, MerckSharp&Dohme, Novartis, Pfizer and UCB. Dr Remon reported to have received grants from IOF fund, FWO Vlaanderen and IWT; has received royalties from Tibotec/Biovail. Dr Van Bortel reported that he has been a consultant at the Drug Research Unit Maastricht; is employed by the Ghent University; has received royalties concerning educational pharmacological books; has received payment for travel accommodations concerning expenses unrelated to the trial from Daiichi-Sankyo and Servier. No other disclosures were reported.

REFERENCES

1. *Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: Available at: http://www.goldcopd.org/, Global Initiative for chronic Obstructive Lung Disease 2011.*
2. *Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. PLos Med 2006;**3**(11).*
3. *Mehuys E, Boussery K, Adriaens E, et al. COPD Management in Primary Care: An Observational, Community Pharmacy-Based Study. Ann Pharmacother 2010;**44**(2):257-66.*
4. *Melani AS, Bonavia M, Cilenti V, et al. Inhaler mishandling remains common in real life and is associated with reduced disease control. Respir Med 2011;**105**(6):930-38.*
5. *Vestbo J, Anderson JA, Calverley PMA, et al. Adherence to inhaled therapy, mortality and hospital admission in COPD. Thorax 2009;**64**(11):939-43.*
6. *Valero C, Monteagudo M, Llagostera M, et al. Evaluation of a combined strategy directed towards health-care professionals and patients with chronic obstructive pulmonary disease (COPD): Information and health education feedback for improving clinical monitoring and quality-of-life. BMC Public Health 2009;**9**.*
7. *Casas A, Troosters T, Garcia-Aymerich J, et al. Integrated care prevents hospital isations for exacerbations in COPD patients. Eur Resp J 2006;**28**(1):123-30.*
8. *Weinberger M, Murray MD, Marrero DG, et al. Effectiveness of pharmacist care for patients with reactive airways disease - A randomized controlled trial. JAMA-J Am Med Assoc 2002;**288**(13):1594-602.*
9. *Bosnic-Anticevich SZ, Sinha H, So S, et al. Metered-Dose Inhaler Technique: The Effect of Two Educational Interventions Delivered in Community Pharmacy Over Time. J Asthma 2010;**47**(3):251-56.*
10. *Fan VS, Gaziano JM, Lew R, et al. A Comprehensive Care Management Program to Prevent Chronic Obstructive Pulmonary Disease Hospitalizations A Randomized, Controlled Trial. Ann Intern Med 2012;**156**(10):673-U46.*
11. *Brown P, Bluml BM, Kritzler R, et al. White paper on expanding the role of pharmacists in chronic obstructive pulmonary disease. J Am Pharm Assoc 2011;**51**(2):203-11.*
12. *NICE Clinical Guideline 76: Medicines adherence: National Institute for Health and Clinical Excellence 2009.*
13. *Hess LM, Raebel MA, Conner DA, et al. Measurement of adherence in pharmacy administrative databases: A proposal for standard definitions and preferred measures. Ann Pharmacother 2006;**40**(7-8):1280-88.*
14. *Simpson SH, Eurich DT, Majumdar SR, et al. A meta-analysis of the association between adherence to drug therapy and mortality. Br Med J 2006;**333**(7557):15-18.*
15. *Bestall JC, Paul EA, Garrod R, et al. Usefulness of the Medical Research Council (MRC) dyspnoea scale as a measure of disability in patients with chronic obstructive pulmonary disease. Thorax 1999;**54**(7):581-86.*
16. *Jones PW, Brusselle G, Dal Negro RW, et al. Properties of the COPD assessment test in a cross-sectional European study. Eur Resp J 2011;**38**(1):29-35.*
17. *Jones PW, Harding G, Berry P, et al. Development and first validation of the COPD Assessment Test. Eur Resp J 2009;**34**(3):648-54.*
18. *Molken M, Ostenbrink JB, Tashkin DP, et al. Does quality of life of COPD patients as measured by the generic EuroQol five-dimension questionnaire differentiate between COPD severity stages? Chest 2006;**130**(4):1117-28.*
19. *Rabin R, de Charro F. EQ-5D: a measure of health status from the EuroQol Group. Ann Med 2001;**33**(5):337-43.*
20. *Suissa S. Statistical treatment of exacerbations in therapeutic trials of chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2006;**173**(8):842-46.*
21. *Wedzicha JA, Seemungal TAR. COPD exacerbations: defining their cause and prevention. Lancet 2007;**370**(9589):786-96.*
22. *Hammerlein A, Muller U, Schulz M. Pharmacist-led intervention study to improve inhalation technique in asthma and COPD patients. J Eval Clin Pract 2011;**17**(1):61-70.*
23. *Khdour MR, Kidney JC, Smyth BM, et al. Clinical pharmacy-led disease and medicine management programme for patients with COPD. Br J Clin Pharmacol 2009;**68**(4):588-98.*
24. *Jarab AS, Alqudah SG, Khdour M, et al. Impact of pharmaceutical care on health outcomes in patients with COPD. International journal of clinical pharmacy 2012;**34**(1):53-62.*
25. *Self TH, Brooks JB, Lieberman P, et al. The value of demonstration and role of the pharmacist in teaching the correct use of pressurized bronchodilators. Can Med Assoc J 1983;**128**(2):129-31.*
26. *Wilkinson TMA, Donaldson GC, Hurst JR, et al. Early therapy improves of chronic obstructive outcomes of exacerbations pulmonary disease. Am J Respir Crit Care Med 2004;**169**(12):1298-303.*
27. *Hurst JR, Vestbo J, Anzueto A, et al. Susceptibility to Exacerbation in Chronic Obstructive Pulmonary Disease. N Engl J Med 2010;**363**(12):1128-38.*
28. *Welte T, Miravitlles M, Hernandez P, et al. Efficacy and Tolerability of Budesonide/Formoterol Added to Tiotropium in Patients with Chronic Obstructive Pulmonary Disease. American Journal of Respiratory and Critical Care Medicine 2009;**180**(8):741-50.*
29. *Seemungal TA, Hurst JR, Wedzicha JA. Exacerbation rate, health status and mortality in COPD--a review of potential interventions. International journal of chronic obstructive pulmonary disease 2009;**4**:203-23.*
30. *Jenkins CR, Celli B, Anderson JA, et al. Seasonality and determinants of moderate and severe COPD exacerbations in the TORCH study. European Respiratory Journal 2012;**39**(1):38-45.*
31. *Rabe KF, Fabbri LM, Vogelmeier C, et al. Seasonal Distribution of COPD Exacerbations in the Prevention of Exacerbations With Tiotropium in COPD Trial. Chest 2013;**143**(3):711-19.*
32. *Engstrom CP, Persson LO, Larsson S, et al. Long-term effects of a pulmonary rehabilitation programme in outpatients with chronic obstructive pulmonary disease: A randomized controlled study. Scand J Rehabil Med 1999;**31**(4):207-13.*
33. *Gallefoss F, Bakke PS, Kjaersgaard P. Quality of life assessment after patient education in a randomized controlled study on asthma and chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1999;**159**(3):812-17.*
34. *Rea H, McAuley S, Stewart A, et al. A chronic disease management programme can reduce days in hospital for patients with chronic obstructive pulmonary disease. Intern Med J 2004;**34**(11):608-14.*
35. *Moher D. CONSORT 2010 Explanation and Elaboration: updated guidelines for reporting parallel group randomised trials. Br Med J 2011;**343**.*
36. *Barr RG, Bourbeau J, Camargo CA, et al. Tiotropium for stable chronic obstructive pulmonary disease: a meta-analysis. Thorax 2006;**61**(10):854-62.*
37. *Halpin DMG, Menjoge S, Viel K. Patient-level pooled analysis of the effect of tiotropium on COPD exacerbations and related hospitalisations. Primary Care Respiratory Journal 2009;**18**(2):106-13.*

APPENDIX 3.2.1: INHALATION TECHNIQUE SCORES PER INHALER DEVICE AND PER CHECKLIST ITEM

Appendix Table 3.2.1: Inhalation technique scores per inhaler device and per checklist item

Metered Dose Inhaler	**CONTROL**				**INTERVENTION**			
Item (% of patients performing this item correctly)	**n**	**Baseline**	**1 month**	**3 months**	**n**	**Baseline**	**1 month**	**3 months**
Removes cap*	20	100,0%	95,5%	100,0%	40	97,6%	100,0%	100,0%
Shakes inhaler*	20	65,0%	81,8%	90,0%	40	41,5%	89,5%	97,4%
Holds inhaler upright with mouthpiece down	20	85,0%	90,9%	90,0%	40	95,1%	94,7%	100,0%
Breathes out before inhalation	20	55,0%	72,7%	70,0%	40	51,2%	76,3%	79,5%
Puts mouthpiece between lips and seals lips tightly around it	20	100,0%	100,0%	100,0%	40	97,6%	100,0%	100,0%
Takes a slow deep breath at the same time as pressing the canister down	20	95,0%	95,5%	100,0%	40	80,5%	89,5%	97,4%
Holds breath for 10 sec	20	75,0%	72,7%	75,0%	40	51,2%	86,8%	82,1%
If corticosteroids: rinses mouth with water	16	43,8%	52,9%	52,9%	32	37,5%	66,7%	73,3%
Mean inhalation technique score†	**20**	**54,3%**	**77,0%**	**75,1%**	**40**	**34,0%**	**76,9%**	**75,1%**
Metered Dose Inhaler + Spacer	**CONTROL**				**INTERVENTION**			
Item (% of patients performing this item correctly)	**n**	**Baseline**	**1 month**	**3 months**	**n**	**Baseline**	**1 month**	**3 months**
Removes cap*	14	100,0%	100,0%	100,0%	18	100,0%	100,0%	100,0%
Shakes inhaler*	14	78,6%	91,7%	92,3%	18	66,7%	83,3%	93,3%
Holds inhaler upright with mouthpiece down and places mouthpiece into the spacer	14	100,0%	100,0%	100,0%	18	94,4%	100,0%	100,0%
Breathes out before inhalation	14	57,1%	50,0%	38,5%	18	61,1%	83,3%	80,0%
Puts spacer between lips and seals lips tightly around it	14	100,0%	100,0%	100,0%	18	100,0%	100,0%	100,0%
Presses the canister down	14	100,0%	100,0%	100,0%	18	100,0%	100,0%	93,3%
Breathes in slowly within 5 sec after pressing down the canister	14	92,9%	91,7%	92,3%	18	83,3%	94,4%	100,0%
Holds breath for 10 sec	14	50,0%	58,3%	53,8%	18	44,4%	50,0%	60,0%
Breathes 5 times in and out in the spacer	14	42,9%	75,0%	61,5%	18	50,0%	66,7%	86,7%
If corticosteroids: rinses mouth with water	4	64,3%	63,6%	61,5%	15	60,0%	75,0%	100,0%
Mean inhalation technique score†	**14**	**63,6%**	**79,1%**	**74,6%**	**18**	**54,3%**	**75,2%**	**87,1%**
Dry Powder Inhaler	**CONTROL**				**INTERVENTION**			
Item (% of patients performing this item correctly)	**n**	**Baseline**	**1 month**	**3 months**	**n**	**Baseline**	**1 month**	**3 months**
Loads dry powder inhaler correctly (depending on the type of DPI)*	329	96,9%	98,8%	98,4%	313	94,2%	98,3%	99,0%
Breathes out before inhalation	329	45,7%	55,3%	60,3%	313	50,8%	72,3%	85,5%
Puts mouthpiece between lips and seals lips tightly around it	329	98,5%	98,8%	98,4%	313	98,7%	99,3%	99,7%
Inhales forcefully and deeply*	329	93,3%	96,3%	96,8%	313	94,8%	98,3%	99,3%
Removes dry powder inhaler from the mouth	329	91,7%	93,4%	92,6%	313	93,5%	96,3%	97,9%
Holds breath for 10 sec	329	47,9%	54,7%	57,1%	313	47,6%	72,6%	87,2%
If corticosteroids: rinses mouth with water	167	28,1%	40,6%	49,1%	138	46,6%	66,4%	87,0%
Mean inhalation technique score†	**329**	**70,0%**	**76,3%**	**79,4%**	**313**	**72,9%**	**87,9%**	**94,0%**

* Patients committing inhalation technique errors in steps marked with an *, were assigned a sum score of zero.
† Mean inhalation technique scores are expressed as mean percentage of correctly performed steps.

PART 3.3:

PHARMACEUTICAL CARE FOR PATIENTS WITH COPD IN BELGIUM AND VIEWS ON PROTOCOL IMPLEMENTATION.

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ABSTRACT

Background. A protocol-based pharmaceutical care program (the PHARMACOP-protocol) focusing on patient counselling during prescription filling has shown to be effective in patients with Chronic Obstructive Pulmonary Disease (COPD). However, implementation of this protocol in daily practice has not yet been studied.

Objective. To describe current implementation level of the items included in the PHARMACOP-protocol in Belgian community pharmacies and to evaluate pharmacists' perspectives on the implementation of this protocol in daily practice.

Method. A cross-sectional study was conducted from April to June 2012, in randomly selected community pharmacies in Flanders. Pharmacists were questionned using structured interviews.

Results. 125 pharmacies were contacted and 80 managing pharmacists (64%) participated. In >70% of pharmacies, 4/7 protocol items for first prescriptions and 3/5 protocol items for follow-up prescriptions were already routinely implemented. For first and follow-up prescriptions, respectively 39 (49%) and 34 pharmacists (43%) stated they would need to spend at least 5 minutes extra to offer optimal patient counselling. Most mentioned barriers preventing protocol implementation included lack of time (80%), no integration in pharmacy software (61%) and too much administrative burden (58%).

Conclusion. Approximately 50% of the PHARMACOP-protocol items are currently routinely provided in Belgian community pharmacies. Nearly all interviewed pharmacists are willing to implement the protocol fully or partially in daily practice.

INTRODUCTION

For patients with Chronic Obstructive Pulmonary Disease (COPD), the close monitoring of patients' pharmacotherapy is considered indispensable[1]]. Community pharmacists are ideally placed to engage in care for patients with COPD because of their frequent patient contacts upon prescription filling and their specific medication-related expertise concerning inhalation technique, adverse effects, etc[1 2]. Additional important roles for pharmacists in counselling patients with COPD are improving adherence to medication regimens, participating in education programmes, smoking cessation counselling and performing annual medication regimen reviews[1 2]. Pharmaceutical care programs focusing on these aspects, aim at reducing overall health care costs, as well as improving patients' quality of life and productivity[2].

Previously, we conducted a randomized controlled trial, investigating the impact of a pharmaceutical care protocol for patients with COPD (the PHARMACOP-protocol)[3]. The PHARMACOP-protocol showed to be effective in improving inhalation technique and adherence to inhaled medication[3]. Moreover, tailoring the follow-up may reduce the number of smoking patients and diminish the number of hospitalizations due to severe exacerbations[3 4]. However, implementation of the PHARMACOP-protocol in daily practice has not yet been promoted or studied.

The aims of the present study are (1) to describe the current level of implementation of the different items of the PHARMACOP-protocol in Belgian community pharmacies and (2) to evaluate pharmacists' perspectives on the implementation of this protocol in daily practice.

METHOD

Pharmacy sample

This cross-sectional observational study was conducted from April to June 2012, in randomly selected community pharmacies in Flanders (the Dutch-speaking part of Belgium, total number of pharmacies: 2657). Zipcodes were randomly selected and pharmacies in this zipcode were telephoned in alphabetical order to request participation until a maximum of 8 pharmacies per zipcode were included. Recruitment was continued until 80 managing pharmacists agreed upon participating. A pharmacy was eligible for participation if the managing pharmacist was available the day the researcher planned to visit the concerning geographical region. The Ethical Committee of Ghent University does not require an approval for studies that merely describe current practice without collecting patient data.

The PHARMACOP-protocol

The PHARMACOP-protocol was originally developed for the randomized controlled PHARMACOP-trial[3]. One item (i.e. "influenza vaccination") was added to the original protocol, since the PHARMACOP-trial was conducted out of the influenza-vaccination season. The items of the protocol are presented in Table 3.3.1.

Data collection

The managing pharmacist of each participating pharmacy was interviewed using a structured interview. A questionnaire was specifically developed for this study and the interview was piloted with two pharmacists. It questioned (1) used sources for COPD information, (2) current provision of the protocol items for first and follow-up prescriptions for COPD medication in the participating pharmacy, (3) the pharmacist's opinion about the relevance of the items of the protocol, and (4) the current duration and the presumed optimal duration of a first and follow-up prescription filling (including the counselling aspects).

Subsequently, feasibility of implementing the PHARMACOP-protocol in daily practice was evaluated by registering pharmacists' intention to implement the protocol if it was available to them and by asking for barriers and facilitators for implementation. Pharmacists were asked to estimate the percentage of patients with COPD that would be receptive for pharmacist counselling and whether they presume implementation of this protocol would increase patient satisfaction towards provided care in the pharmacy. Clarity of reporting is obtained by following STROBE-guidelines[5].

Statistical analysis

Data were analyzed in SPSS statistics 21 (SPSS Inc. Chicago, IL, USA). Results of open-ending questions were categorized since pharmacists were often unaware of exact numbers. For answers to specific questions, means with standard deviations or sum-scores with percentages are displayed. For relevancy, items were scored as “essential, neutral or unnecessary”. We checked if baseline factors were associated with current and presumed optimal duration of a first and follow-up prescription with regression analysis.

Table 3.3.1: Items of the PHARMACOP-protocol: current implementation and pharmacists' opinions on their relevancy (n=80)

First prescription	Pharmacists currently implementing this item, no. (%)	Pharmacists considering this item essential, no. (%)	neutral, no. (%)	unnecessary, no. (%)
Structured patient education about:				
COPD pathophysiology	29 (36)	39 (49)	14 (17)	27 (34)
COPD medication				
Dosing instructions	74 (93)	75 (94)	3 (4)	2 (3)
Inhalation technique (including physical demonstration with demo inhaler unit)	80 (100)	80 (100)	0 (0)	0 (0)
Importance of adherence to maintenance therapy and current problems with adherence	61 (76)	70 (88)	6 (8)	4 (5)
Possible side effects	74 (93)	75 (94)	3 (4)	2 (3)
Smoking cessation (if patient was current smoker)	34 (43)	61 (76)	10 (13)	9 (11)
Provision of a patient information leaflet about COPD	26 (33)	51 (64)	21 (26)	8 (10)
Follow-up prescription				
Structured patient education about:				
COPD medication				
Inhalation technique (including physical demonstration with demo inhaler unit)	60 (75)	75 (94)	3 (4)	2 (3)
Changes in adherence to maintenance therapy since last visit	59 (74)	72 (90)	7 (9)	1 (1)
Self-management (e.g lifestyle advice, exacerbation recognition, etc)	37 (46)	38 (48)	25 (31)	17 (21)
Smoking cessation (if patient was current smoker)	25 (31)	51 (64)	19 (24)	10 (13)
Influenza vaccination	58 (73)	61 (76)	13 (16)	6 (8)

RESULTS

Pharmacy sample

In total, 125 pharmacies in 25 different zipcodes were contacted and 80 managing pharmacists (64%) agreed upon participating. Main reasons for declining were lack of time and absence of the managing pharmacist on the day the study investigator visited the pharmacy. The mean age of the managing pharmacists was 43.3 years (SD=11.8) and 50 of them (63%) were female. Pharmacies served an average of 82.5 prescriptions per day (SD=42.7) and an average of 123 patients per day (SD=56). Pharmacies employed a mean of 1.8 pharmacists (SD=0.8), and 0.8 pharmacy-assistants (SD=1.0), both expressed in full time equivalents. The mean number of patients per full-time equivalent employee per day was 53.9 (SD=21.8). Seven pharmacies (9%) had 1 to 5 regular visitors with COPD, 20 pharmacies (25%) had 6 to 10 regular visitors with COPD and 53 (66%) pharmacies had more than 10 regular visitors with COPD.

Current and presumed optimal pharmaceutical care

Sixty-six pharmacists (83%) stated they used their pharmacy software as a source for information about COPD and COPD medication, 46 pharmacists (58%) used the pharmacy guidelines for asthma and COPD from the Belgian Pharmacist Association and 41 (51%) used course material of post-graduate courses. Three pharmacists (4%) stated to use GOLD-guidelines[1].

Table 3.3.1 represents the different items of the PHARMACOP-protocol, their level of implementation in current practice, and their relevance as perceived by the managing pharmacists. The current duration and the presumed optimal duration of a prescription filling, including the counselling aspect, is presented in Table 3.3.2. For first and follow-up prescriptions respectively, 39 (49%) and 34 pharmacists (43%) stated they would need to spend at least 5 minutes extra during dispensing in order to provide optimal patient counselling.

Age, occupation and number of regular visitors with COPD in the pharmacy did not correlate with current duration or presumed optimal duration of prescription filling (i.e. including counselling).

Table 3.3.2: Current and presumed optimal duration of presciription filling (i.e. including the counselling part) for patients with COPD

	First prescription		Follow-up prescription	
Duration of counselling	Current practice, no (%)	Presumed optimal practice, no (%)	Current practice, no (%)	Presumed optimal practice, no (%)
0 to 5 minutes	18 (23)	4 (5)	69 (86)	36 (45)
6 to 10 minutes	46 (57)	39 (49)	10 (13)	40 (50)
11 to 15 minutes	14 (18)	26 (33)	1 (1)	3 (4)
> 15 minutes	2 (3)	11 (14)	0 (0)	1 (1)

Feasibility of the PHARMACOP-protocol

Forty pharmacists (50%) would fully implement the proposed protocol if it were available to them, 37 (46%) would implement it partially and 3 (4%) would not implement it. Most mentioned barriers to implement the proposed protocol in daily practice included lack of time (80%), no integration in pharmacy software (61%) and too much administrative burden (58%). Lack of remuneration and insufficient knowledge about COPD were only mentioned as barriers by 25% and 18% of pharmacists respectively.

Seventy-three pharmacists (91%) indicated that a complete integration of the protocol in the pharmacy software would facilitate implementation. Other facilitators were less administrative burden in general (71%), a remuneration for the extra service (54%) and provision of more background information (39%). Being asked to estimate the portion of patients that would be receptive for the full PHARMACOP-protocol, pharmacists reported a mean score of 58% (SD=21%). Nevertheless, 75 pharmacists (94%) think that fully implementing the PHARMACOP-protocol would generate an increased satisfaction in patients with COPD. Almost all pharmacists (93%) felt the need for further education about the protocol to confidently implement it.

DISCUSSION

This study evaluated which items of the PHARMACOP-protocol have already been implemented in current practice of Belgian community pharmacies. Additionally, we evaluated the perspectives of pharmacists on the implementation of the protocol.

Concerning patient counselling when filling a first or follow-up prescription for COPD medication, the short duration of current counselling practice is in accordance with findings in other studies[6]. Only items related to COPD medication (e.g. inhalation technique demonstration, dosing, adherence, etc) and the recommendation for influenza vaccination are currently routinely provided by ≥70% of pharmacists. Nevertheless, all but two items of the PHARMACOP-protocol are considered essential by a majority of pharmacists. Only patient education about the pathophysiology of COPD and self-management advice were considered less essential. Although it is not clear which educational topics contribute to successful COPD management, current practice guidelines recommend education tailored to the patient[7]. In this respect, the provision of simple and structured information about the pathophysiology and self-management of COPD could be additional to the information provided by the general practitioner. Indeed, patients experience the latter often as insufficient and efficacy of informing patients about self-management has been demonstrated[6 8]. Nevertheless, interviewed pharmacists indicated that they did not consider this a part of their job, that they were not aware of positive consequences, or that they had insufficient knowlegde about these topics.

Opinions about the necessity of smoking cessation counselling and the provision of patient leaflets were very divergent. However, especially smoking cessation counselling should be routinely offered to smokers with COPD, as pharmacist counselling is proven effective[4] and smoking cessation is the only intervention that can positively influence the natural course of COPD[1]. The provision of patient leaflets that can be looked into at home is reported to be essential for reinforcing verbal information[9].

Recommendation

Multiple parties could engage in addressing barriers and implementing facilitators in order to optimize current provision of pharmaceutical care for patients with COPD. The government could simplify the administrative burden experienced by pharmacists and could provide a remuneration for delivered services. The lack of remuneration has been reported elsewhere as a barrier to implementation of pharmaceutical care interventions[4]. This was not confirmed in our study although pharmacists mentioned remuneration as a facilitating factor. The barrier 'lack of time' could be overcome by the pharmacists by making an appointment for first and follow-up prescriptions. This would provide pharmacists with sufficient time to prepare the conversation, including the collection of counselling aids such as demo inhaler units and patients leaflets and getting themselves updated with the most current guidelines, thereby also tackling the barrier 'insufficient knowledge'.

Finally, software companies could integrate the PHARMACOP-protocol, including easy access to relevant patient leaflets, into the pharmacy software without however overlooking communication aspects because of a strong focus on computer checklists[6].

Limitations

Neither a participation bias, nor socially desirable answersing by the interviewees could be excluded. The sample size was also limited, although baseline data are comparable with previously reported demographic data of Flemish pharmacists[10].

Conclusion

In conclusion, approximately 50% of the PHARMACOP-protocol items are currently routinely provided by Belgian community pharmacists. Furthermore, nearly all interviewed pharmacists (96%) are willing to implement the protocol fully or partially in daily practice. Most mentioned barriers to implement the PHARMACOP-protocol were lack of time, no integration in pharmacy software and too much administrative burden.

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AUTHOR CONTRIBUTIONS:
Tommelein had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Conception and design: Tommelein, Mehuys, Boussery
Analysis and interpretation of the data: Tommelein, Tollenaere
Drafting of the article: Tommelein
Critical revision of the article for important intellectual content: Tommelein, Mehuys, Boussery
Final approval of the article: Tommelein, Mehuys, Boussery
Statistical expertise: Tommelein
Study supervision: Boussery

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REFERENCES

1. *Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: Available at: http://www.goldcopd.org/, Global Initiative for chronic Obstructive Lung Disease 2011.*
2. *Brown P, Bluml BM, Kritzler R, et al. White paper on expanding the role of pharmacists in chronic obstructive pulmonary disease. J Am Pharm Assoc 2011;**51**(2):203-11.*
3. *Tommelein E, Mehuys E, Van Hees T, et al. Effectiveness Of PHARMAceutical Care For Patients with COPD (PHARMACOP): a Randomized Controlled Trial. Br J Clin Pharmacol 2013.*
4. *Maguire TA, McElnay JC, Drummond A. A randomized controlled trial of a smoking cessation intervention based in community pharmacies. Addiction (Abingdon, England) 2001;**96**(2):325-31.*
5. *von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. J Clin Epidemiol 2008;**61**(4):344-49.*
6. *van Hulten R, Blom L, Mattheusens J, et al. Communication with patients who are dispensed a first prescription of chronic medication in the community pharmacy. Patient Education and Counseling 2011;**83**(3):417-22.*
7. *Stoilkova A, Janssen DJ, Wouters EF. Educational programmes in COPD management interventions: A systematic review. Respir Med 2013.*
8. *Gallefoss F, Bakke PS. How does patient education and self-management among asthmatics and patients with chronic obstructive pulmonary disease affect medication? Am J Respir Crit Care Med 1999;**160**(6):2000-05.*
9. *ASHP guidelines on pharmacist-conducted patient education and counseling. American journal of health-system pharmacy : AJHP : official journal of the American Society of Health-System Pharmacists 1997;**54**(4):431-4.*
10. *Liekens S, Smits T, Laekeman G, et al. Pharmaceutical care for people with depression: Belgian pharmacists' attitudes and perceived barriers. International journal of clinical pharmacy 2012;**34**(3):452-9.*

PART 3.4:

ACCURACY OF THE MEDICATION ADHERENCE REPORT SCALE (MARS-5) AS A QUANTITATIVE MEASURE OF ADHERENCE TO INHALATION MEDICATION IN PATIENTS WITH COPD

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ABSTRACT

Background. Self-report is considered the most suitable method to measure medication adherence in routine clinical practice. However, accuracy of self-report as a quantitative measure of adherence is not well documented.

Objective. To assess accuracy of a self-report measure of adherence (the Medication Adherence Report Scale, MARS-5) for identifying nonadherent users of inhalation medication among patients with COPD, compared to medication refill adherence (MRA) as reference.

Methods. We used baseline data from the Pharmaceutical Care for Patients with COPD (PHARMACOP) trial (n=734): MARS-5 as self-report measure and MRA as reference measure of adherence to inhalation medication. Patients with incomplete MARS-5 and/or incomplete pharmacy refill records were excluded from analysis (n=121). Internal consistency of MARS-5 (Crohnbach α) and the Spearman's rank correlation (ρ) with MRA were calculated. To assess accuracy of MARS-5 for identifying nonadherence, different thresholds for nonadherence were used to calculate sensitivity, specificity and Positive Predictive Value (PPV), compared to dichotomized MRA (MRA≥80% = adherent). A Receiver Operating Characteristic (ROC) curve was plotted to determine the goodness of test and to detect an optimal cut-off threshold for the MARS-5 scale.

Results. A total of 613 patients were included in the analysis. Mean adherence score by MARS-5 (range: 5-25) was 23.5 (SD=2.6); mean adherence by MRA was 83.4% (SD=23.8%). Internal consistency of MARS-5 was high (α=0.77). Continuous MARS-5 scores correlated poorly with continuous MRA scores (ρ=0.10; P=.011). When lowering adherence threshold stepwise from 25 to 20, MARS-5 did not reach sufficient sensitivity (53% to 13%), specificity (57% to 94%) and PPV (42% to 57%) to detect nonadherers, compared to dichotomized MRA. ROC-curve plotting resulted in an area under the curve value of 0.56 (95% Confidence Interval, [0.521-0.616]; P=.005).

Conclusion. Self-reported adherence measured by MARS-5 is inaccurate in identifying nonadherence to inhalation medication in patients with COPD.

INTRODUCTION

Adherence to inhaler maintenance therapy is an important parameter in the management of chronic obstructive pulmonary disease (COPD)[1]. However, adherence to inhaler medication among patients with COPD is generally considered low[2-5]. Suboptimal adherence has been associated with higher morbidity and health care use (i.e., general practitioner (GP) visits, emergency room visits and hospitalizations) due to more frequent episodes of worsening of symptoms – exacerbations – in nonadherent patients[6-8]. Similarly, an association with increased mortality has been reported[6, 8]. Furthermore, treatment of COPD and its exacerbations contributes substantially to overall health care costs. In the United States, the direct costs of COPD are estimated to be around $29.5 billion and the indirect costs around $ 20.4 billion. In the European Union the costs approximately count for 6% of the total European health care budget[1].

The availability of an accurate method to measure adherence is therefore essential to health-care workers in detecting nonadherent patients and evaluating the effectiveness of the prescribed treatment. To measure adherence, a number of direct (e.g., observation, serum level checking, etc.) and indirect methods (e.g., prescription refill, self-report, pill counts, etc.) are available[9]. One indirect method, the use of self-report questionnaires, has been recommended as the measure most suitable for clinical practice[10, 11], since these questionnaires are easy to use, inexpensive, and do not require a lot of time for both questioner and patient. However, self-report questionnaires require a patient-questioner relationship based on mutual trust and only provide information when patients are aware of their nonadherent behavior. Partially because of these drawbacks, self-reported questionnaires generally tend to overestimate adherence[10]. Nevertheless, self-report measures have been increasingly applied during the last decade to assess drug adherence in multiple patient populations[2, 10, 12, 13], even though no 'gold standard' self-report questionnaire has been defined yet[10].

Only few studies have compared patients' self-report with more objective measures such as prescription refill[12, 14-17], electronic monitoring[18, 19] or serum concentrations[13, 20, 21]. Overall, these studies described low correlations with the reference measure, unfavorable predictive values (PPV) and both low and high internal consistencies of the self-report questionnaire[12-22]. Furthermore, none of these studies exclusively focused on patients with COPD, although studies addressing adherence in patients with COPD, often use the Medication Adherence Report Scale (MARS-5) as a self-report measure of adherence[2, 4, 23]. As validation of self-report questionnaires as a measure of adherence in patients with COPD is lacking, this study aims to evaluate the accuracy of a self-report measure of adherence (MARS-5) in identifying nonadherent users of inhalation medication with pharmacy refill adherence as a reference.

METHODS

Design and patient sample

The data are drawn from a 3-month randomized controlled trial, the PHARMACOP-trial. The methods and results of the main study are reported in full elsewhere[24]. In brief, the PHARMACOP-trial was a longitudinal trial in 170 community pharmacies in Belgium, investigating the effectiveness of a pharmaceutical care program for patients with COPD. Patients filling a prescription for COPD maintenance medication (R03, Anatomical Therapeutic Chemical classification, which includes inhaled anticholinergics, inhaled β_2-mimetics, inhaled corticosteroids, xanthine-derivatives, leukotriene receptor antagonist or any combination of these drugs) in a participating community pharmacy, were consecutively invited to participate in the PHARMACOP-trial when meeting following inclusion criteria: (1) prescription for daily COPD maintenance medication, (2) aged 50 years or older, (3) smoking history of at least 10 pack-years, (4) regular visitor to the pharmacy and (5) providing written informed consent. Patients with current asthma or with limited health literacy were excluded. The recruitment period ran from December 2010 to April 2011. The study was approved by the Ethical Committee of the Ghent University Hospital (Ghent, Belgium).

The present cross-sectional analysis included patient data from self-administered written questionnaires and pharmacy records obtained at start of the PHARMACOP-trial. These data were only included if (1) a complete pharmacy refill record (i.e., at least six months of pharmacy records available for review) and (2) a fully completed self-report adherence questionnaire were available.

Self-reported adherence

Self-reported adherence was assessed using the Medication Adherence Report Scale (MARS-5)[12, 13, 15, 19, 25]. The MARS-5 consists of 5 common patterns of nonadherent behavior that respondents score on a 5-point Likert scale (with 1=always, 2=often, 3=sometimes, 4=rarely, and 5=never). The exact wording of the questions is given in Table 3.4.1. The first statement of the MARS-5 questions patients about unintentional nonadherence, while the other four statements question intentional nonadherence. Scores are summed and totals range from 5 to 25, with higher scores indicating higher self-reported adherence. The MARS-5 was introduced to the patients in a way that it was clear it only considered their principal maintenance therapy.

Table 3.4.1: Descriptives of the Medication Adherence Report Scale (MARS-5) and its individual items

Item	Mean (SD) *(n=613)*	Median (IQR) *(n=613)*	Range
Item 1: "I forget to take my inhalation medication"	4.58 (0.71)	5 (4-5)	1 – 5
Item 2: "I change the dosage of my inhalation medication"	4.65 (0.80)	5 (5-5)	1 – 5
Item 3: "I stop taking my inhalation medication for a while"	4.83 (0.56)	5 (5-5)	1 – 5
Item 4: "I decide to skip one of my inhalation medication dosages"	4.72 (0.70)	5 (5-5)	1 – 5
Item 5: "I use my inhalation medication less than is prescribed"	4.70 (0.79)	5 (5-5)	1 – 5
Sum score MARS-5[a]	23.49 (2.60)	25 (23-25)	7 – 25

[a]The Medication Adherence Report Scale (MARS-5) sum score was calculated by summing scores from each individual question (range: 5-25). Higher scores indicate higher self-reported adherence.

Medication refill adherence

A more objective adherence measurement was performed using a recommended measure of administrative data, i.e. the Medication Refill Adherence (MRA)[26]. Pharmacy records of one year prior to the trial were used. The MRA score for each patient was calculated by dividing the total days' supply in the year preceding enrollment into the trial, by the number of days the patient is prescribed his/her medication, with a minimum of 6 months and a maximum of one year. Patients with an MRA score ≥80% were considered adherent. This cut-off point was selected based on previous use by other investigators[6, 15, 27]. MRA-scores ≤60% were double-checked, which included the verification that the considered patient had started his/her COPD medication for more than six months, that the patient hadn't moved in the six months previous to the start of the trial, that the patient collected his/her medication at least every two months and that the patient was not frequently admitted to the hospital, in which case hospital supply would lead to incomplete dispensing records. If a patients was prescribed multiple inhalers, MRA was only calculated for the principal maintenance therapy (see Appendix 3.4.3).

Statistical Analysis

Data were analyzed in SPSS statistics 20 (SPSS Inc. Chicago, IL, USA). Descriptive statistics were displayed as counts with percentages, means with standard deviations or median with interquartile range as appropriate.

Internal consistency of MARS-5 was determined using Cronbach's α. Cronbach's α indicates whether each item of the scale is appropriate for assessing the underlying concept and summarizes inter-item correlations between responses and individual MARS-5 questions. Values for Cronbach's α theoretically range between 0 and 1; the closer they are to 0 the less the items are related to one another. Values above 0.70 are generally considered indicating good internal consistency. Values should not exceed 0.90[28].

To evaluate correlation between MARS-5 and MRA, Spearman's rank correlation coefficient (ρ) was determined. To assess accuracy by sensitivity, specificity and PPV, the MARS-5 sum score was dichotomized into either 'adherent' or 'nonadherent' using different thresholds and compared to dichotomized MRA as reference (MRA≥80% = adherent). A positive outcome was defined as the detection of nonadherence. Furthermore, a Receiver Operating Characteristic (ROC) curve was created to determine the 'goodness' of the test through area under the curve (AUC) calculation. AUCs between 0.5 and 0.7 are considered low, AUCs between 0.7 and 0.9 moderate and AUCs ≥ 0.9 high[28]. In addition, the ROC curve was used to detect the optimal cut-off threshold for the MARS-5 scale. The optimal threshold for the scale is the test score for which the ratio of the number of actual cases detected by our scale (true positives) to the number of non-cases erroneously labeled as cases (false positives) is the largest[28]. Additionally, we will evaluate if MARS-5- and MRA-scores differ between users of different device types and different maintenance therapy, using an ANOVA-test.

RESULTS

Of the 734 patients enrolled in the PHARMACOP-trial, 613 patients had available MARS-5 scores and complete pharmacy refill records. 121 patients were excluded from the analysis after double-checking MRA-scores ≤60%. Baseline characteristics of this patient sample are presented in Table 3.4.2. The mean scores of the COPD Assessment Test, questioning COPD specific health status, correlate with a medium health status impairment. Furthermore, about 40% of patients experienced some limitation of activity due to breathlessness during daily life (represented by a modified Medical Research Council score ≥2) (Table 3.4.2). No statistically significant differences in baseline characteristics were observed between excluded and included patients, except for gender (P=.037) and smoking status (P=.003). There were more males and less smokers in the included sample, compared to the excluded patients (67,6% vs 59,9% males and 41,0% vs 56,0% smokers, respectively).

Table 3.4.2: Basic Characteristics

Parameter	**Patient sample (n = 613)**
Male Sex, No. (%)	417 (68.0)
Age (y), mean (SD)	68.6 (9.5)
BMI, kg/m², mean (SD)	25.5 (4.1)
Smoking status, No. (%)	
Current smoker	253 (41.3)
Pack-years of current smokers, mean (SD)	40.8 (24.7)
Pack-years of ex-smokers, mean (SD)	46.1 (29.6)
COPD, duration (y), mean (SD)	11.2 (9.3)
COPD management supervised by, No. (%)	
GP only	232 (37.8)
Pneumologist only	74 (12.1)
Both GP and pneumologist	306 (49.9)
Influenza vaccination, No. (%)	499 (81.4)
mMRC score[a, ref:35], No. (%)	
mMRC = 0	161 (26.3)
mMRC = 1	210 (34.3)
mMRC = 2	103 (16.8)
mMRC = 3	80 (13.1)
mMRC = 4	59 (9.6)
CAT score[b, ref: 36], mean (SD)	16.6 (7.6)
History of exacerbations in preceding year	
≥ 1 in preceding yr, No. (%)	335 (54.6)
Moderate exacerbation rate[c], mean	1.0 (1.6)
Severe exacerbation rate[c], mean	0.5 (1.1)
Mean Number of COPD medication, mean (SD)[d]	2.3 (1.0)

***BMI** = Body Mass Index. **COPD** = Chronic Obstructive Pulmonary Disease. **GP** = General practitioner.*

[a] Scores on the modified Medical Research Council dyspnea scale can range from 0 to 4, with a score of 4 indicating that a patient is too breathless to leave the house or becomes breathless when (un)dressing.

[b] CAT: COPD Assessment Test; a higher score indicates a worse health status (range 0-40).

[c] Exacerbation rates are expressed as No./patient-year and calculated based on retrospective self-reported patient data. Exacerbations requiring antibiotics or oral steroids treatment are considered "moderate". Exacerbations requiring an emergency room visit or hospitalization are considered "severe".

[d] All medications classified under R03 in the ATC-classification are considered. This includes both rescue and daily maintenance medication.

Self-reported adherence & Medication Refill Adherence

Scores on the MARS-5 scale ranged from 7 to 25. The mean MARS-5 score was 23.49 (SD = 2.60) with a distribution skewed towards high scores (Figure 3.4.1). The median score was 25 (IQR: 23-25). Scores on the individual questions are reported in Table 3.4.1. The number of patients having a MARS-5 sum score of 25 was 324 (52.9%). Internal consistency of MARS-5 was good, reaching an alpha value of 0.77. Deleting any item would lower overall alpha value, ranging from 0.69 to 0.77. Inter-item correlations ranged from 0.224 to 0.594. Evaluating inter-item correlations, it is clear that in 3 out of four cases, the unintentional item correlates the least with the intentional items (Table 3.4.3).

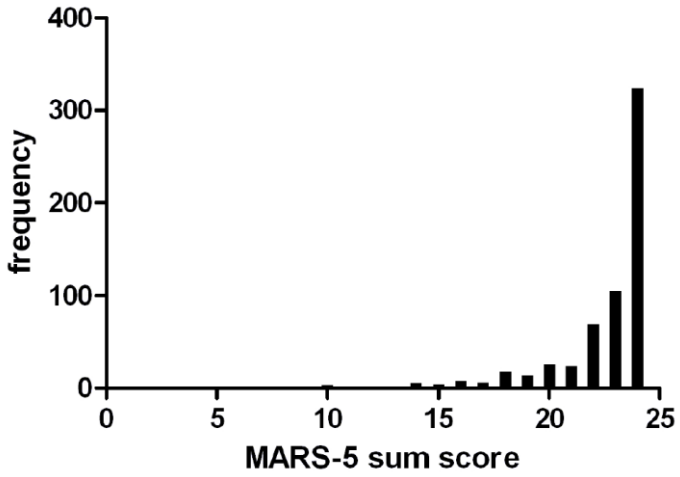

***Figure 3.4.1**: Distribution of the MARS-5 sum scores*

Table 3.4.3: Inter-Item Correlation Matrix for individual items of the MARS-5 questionnaire

Items of MARS-5 questionnaire[a]	Item 1	Item 2	Item 3	Item 4	Item 5
Item 1: "I forget to take my inhalation medication"	1,000	,224	,412	,320	,386
Item 2: "I change the dosage of my inhalation medication"	,224	1,000	,277	,457	,473
Item 3: "I stop taking my inhalation medication for a while"	,412	,277	1,000	,526	,509
Item 4: "I decide to skip one of my inhalation medication dosages"	,320	,457	,526	1,000	,605
Item 5: "I use my inhalation medication less than is prescribed"	,386	,473	,509	,605	1,000

Medication Refill Adherence (MRA-) scores ranged from 8.2% to 120.0%. The overall mean adherence rate calculated from the MRA was 83.4% (SD = 23.8%). The median score was 82.2% (IQR: 66.0%-99.0%). The number of patients that had an MRA-score equaling or exceeding 80% was 386 (63.0%).

There was no significant difference in MRA- (P=.39) or MARS-5 (P=.05) scores between users of different device types. Furthermore, there were no significant between-group differences for MRA- or MARS-5 scores between users of different types of medication (P=.56 and P=.34, respectively). The detailed results are mentioned in the appendices 3.4.1 and 3.4.2).

Accuracy of self-reported adherence

Continuous MARS-5 scores correlated poorly with continuous MRA scores (ρ = 0.103; P=.011). Furthermore, we compared MARS-5 to the reference standard using different thresholds for low adherence (Figure 3.4.2, Appendix 3.4.4 for 2x2 tables). Using a threshold of 25, the MARS-5 had a sensitivity of 53%, specificity of 57% and a positive predictive value of 42%. When lowering the threshold for low adherence stepwise to 20, the instrument achieved a strongly reduced sensitivity of 13%, an increased specificity of 94% but an only moderately increased positive predictive value of 57%.

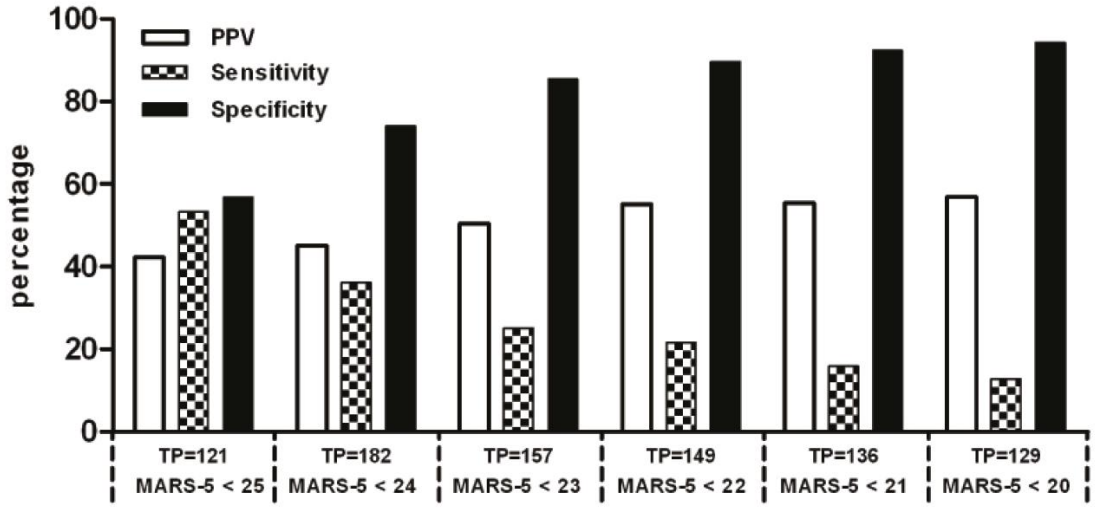

Figure 3.4.2*: The sensitivity, specificity and PPV-values of the MARS-5 sum-score for different thresholds of low adherence compared to the reference standard (i.e. Medication Refill Adherence, MRA)*
MARS-5 *= Medication Adherence Report Scale;* ***TP*** *= True Positives;* ***PPV*** *= Positive Predictive Value*

Plotting a Receiver Operating Characteristic (ROC) curve (Figure 3.4.3), an AUC value of 0.56 was observed (95% Confidence Interval (CI), [0.521-0.616]; P=.005). In accordance to the definition, the optimal threshold would be the value for which the ratio of true positives to false positives (TP/FP) is the highest, but low sensitivity of the test prevented determination of an optimal cut-off threshold. For the current study, we considered a total 393280 drug doses, dispensed to 613 patients over an individually varying period of time (6 months – 1 year).

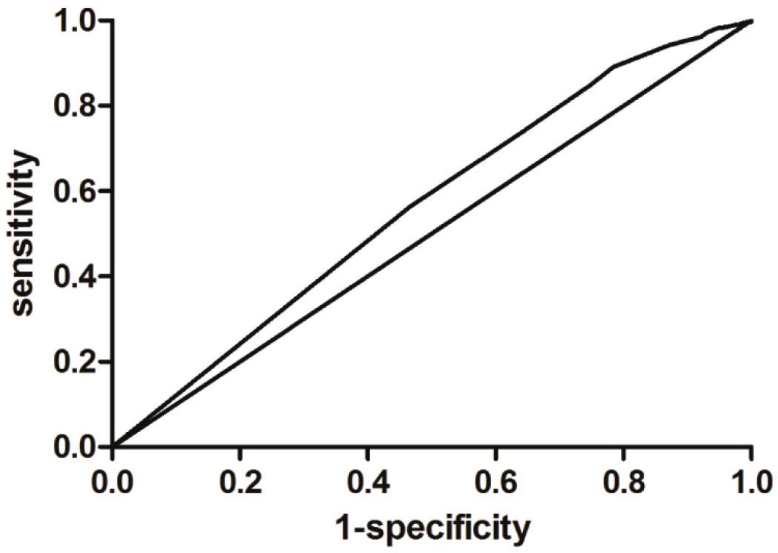

***Figure 3.4.3**: Receiver Operating Characteristic curve (AUC = 0.569; P=.005), evaluating the accuracy of the MARS-5 compared to the reference standard (MRA).*

DISCUSSION

Our main objective was to investigate the accuracy of a self-report measure of adherence, MARS-5, in patients with COPD. MRA was chosen as a reference, since it has been shown to be a very reliable instrument to quantify medication adherence[29-33]. Moreover, it is a non-invasive, objective and inexpensive method to obtain adherence values, especially in large populations[26]. In the present study, MARS-5 showed to have a low sensitivity, specificity and PPV when verified against refill adherence. The MARS-5 questionnaire is therefore inaccurate in identifying nonadherent users of inhalation medication in patients with COPD. In general, the questionnaire overestimated patients' adherence.

Adherence rates, measured in the present study are comparable with previously reported adherence rates for patients with COPD, determined for MRA and MARS-5 respectively[2, 4, 6, 27]. This study also confirms that self-reported adherence to maintenance therapy in COPD is highly skewed towards perfect adherence (Figure 3.4.1)[2]. The MARS-5 was used in a number of primary care studies, but to our knowledge, only two validation studies comparing MARS-5 with pharmacy refill adherence have been performed, presenting inconsistent findings[12, 15]. Menckeberg et al. recruited users of inhaled corticosteroids and found an acceptable correlation between MARS-5 and prescription refill records[12]. However, Van de Steeg et al. found MARS-5 to be inadequate for adherence measurements in users of antihypertensive drugs in a primary care setting[15], which corresponds to our results. This discrepancy could be the result of the question method. In the study of Menckeberg et al., questionnaires were mailed to patients and could be returned without a health-care professional knowing about it. In the study of Van de Steeg et al., as well as in our study, there was a direct contact between patient and health-care professional. The latter could have resulted in giving more socially desirable answers, although it is the most pragmatic approach. In two other reports, MARS-5 was validated against electronic monitoring or serum level determination, again with contradictory results[13, 19].

Low agreement between both measures could have many reasons. Firstly, both measures lead to conceptually different scores. MRA results represent the availability of medication to a patient, where MARS-5 questions behavioral problems with adherence[22, 26]. Classification as (non)adherent is thus based on different characteristics. It should be noted that Morisky et al. originally designed the MARS-5 to facilitate identification of problems and barriers for good adherence rather than to quantify adherence[22]. Therefore, self-reported adherence assessed by MARS-5 could be informative for identifying reasons for nonadherence in routine clinical practice. This type of information cannot be obtained through other measures of adherence. MARS-5 still has some shortcomings as a detection method for qualitative information on nonadherence, e.g. its limited ability to distinguish between intentional and unintentional nonadherence[10]. The differentiation between intentional an unintentional nonadherence is however essential since both types require a distinct handling-

approach[34]. However limited, using MARS-5 could hereby be of help. Indeed, as displayed in Table 3.4.3, item 1, questioning unintentional nonadherence, correlates the least with the other items, questioning intentional nonadherence. Secondly, pharmacy refill adherence reflects both unintentional and intentional nonadherence. Self-report, on the other hand, tends to underestimate unintentional nonadherence in a more distinct way than intentional nonadherence, since patients are simply unaware of it[10, 14]. Therefore, overall lower adherence values, measured through pharmacy refill adherence compared to self-report, could confirm presence of unintentional nonadherence in our study population. Finally, both measures represent adherence in a different time-frame. Pharmacy refill adherence covers adherence throughout a certain period in time (here: up to one year prior to enrollment in the trial), while the self-report measure only inquired about adherence at the time the questionnaire was completed, without specifying any recall period.

The main limitations of this study are related to the use of MRA as a reference measure of adherence. Refill records provide only an estimate of the medication availability, rather than medication consumption, since calculations usually assume that patients start taking the drug on the day of dispensing, use the drug as prescribed, and consume all medications obtained. Furthermore, using pharmacy refill adherence requires a complete refill database and the prescribed dosage has to be available[26]. If drugs were supplied in another pharmacy, adherence values could be underestimated. However, in this trial, we maximized validity of the refill adherence by only including patients that explicitly stated they filled their prescriptions exclusively at the recruiting pharmacy and by double-checking all MRA-scores ≤60%. We acknowledge that exclusion of 121 patients (16.5%) after double-checking MRA-scores ≤60%, is a high amount, however we feel confident this had no influence on the results of the analysis.

In conclusion, we evaluated the accuracy of a widely used method for assessing adherence to drug treatment in clinical practice, self-report using MARS-5, and demonstrated that it is not useful for identifying nonadherent use of inhalation medication in patients with COPD. The results of this study emphasize the necessity to validate questionnaires in a specific setting before using them as instruments within a trial. Moreover, caution is needed when comparing adherence values resulting from different measuring methods. We advise authors using MARS-5 in their research to specify the goal: to qualify or to quantify adherence. Both types of information on adherence could particularly be of interest, depending on the objectives of the study.

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AUTHOR CONTRIBUTIONS:
Tommelein had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Conception and design: Tommelein, Mehuys, Brusselle, Boussery
Analysis and interpretation of the data: Tommelein, Brusselle
Drafting of the article: Tommelein
Critical revision of the article for important intellectual content: Tommelein, Mehuys, Boussery
Final approval of the article: Tommelein, Mehuys, Boussery
Statistical expertise: Tommelein, Brusselle
Administrative, technical, or material support: Van Tongelen
Study supervision: Boussery

FUNDING:
None

POTENTIAL CONFLICT OF INTEREST*:*
All authors have completed and submitted the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare the following: Dr Brusselle reported to have received a grant from GlaxoSmithKline; is a member of the board for Astra-Zenica, Boehringer-Ingelheim, GlaxoSmithKline and Novartis; has received payment for lectures at Astra-Zenica, Boehringer-Ingelheim, Chiesi, GlaxoSmithKline, MerckSharp&Dohme, Novartis, Pfizer and UCB. No other disclosures were reported.

REFERENCES

1. *Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Available at: http://www.goldcopd.org/, Global Initiative for chronic Obstructive Lung Disease 2011.*
2. *George J, Kong DCM, Thoman R, Stewart K. Factors associated with medication nonadherence in patients with COPD. Chest 2005;128(5):3198-204. 10.1378/chest.128.5.3198*
3. *VanderSchaaf K, Olson KL, Billups S, Hartsfield CL, Rice M. Self-reported inhaler use in patients with chronic obstructive pulmonary disease. Respir Med 2010;104(1):99-106. 10.1016/j.rmed.2009.07.003*
4. *Agh T, Inotai A, Meszaros A. Factors Associated with Medication Adherence in Patients with Chronic Obstructive Pulmonary Disease. Respiration 2011;82(4):328-34. 10.1159/000324453*
5. *Bourbeau J, Bartlett SJ. Patient adherence in COPD. Thorax 2008;63(9):831-8. 10.1136/thx.2007.086041*
6. *Vestbo J, Anderson JA, Calverley PMA, et al. Adherence to inhaled therapy, mortality and hospital admission in COPD. Thorax 2009;64(11):939-43. 10.1136/thx.2009.113662*
7. *Toy EL, Beaulieu NU, McHale JM, et al. Treatment of COPD: Relationships between daily dosing frequency, adherence, resource use, and costs. Respir Med 2011;105(3):435-41. 10.1016/j.rmed.2010.09.006*
8. *Butler RJ, Davis TK, Johnson WG, Gardner HH. Effects of Nonadherence With Prescription Drugs Among Older Adults. Am J Manag Care 2011;17(2):153-60.*
9. *Osterberg L, Blaschke T. Adherence to medication. The New England journal of medicine 2005;353(5):487-97. Epub 2005/08/05. DOI 10.1056/NEJMra050100*
10. *Garfield S, Clifford S, Eliasson L, Barber N, Willson A. Suitability of measures of self-reported medication adherence for routine clinical use: A systematic review. BMC Med Res Methodol 2011;11. 10.1186/1471-2288-11-149*
11. *NICE Clinical Guideline 76: Medicines adherence. National Institute for Health and Clinical Excellence 2009.*
12. *Menckeberg TT, Bouvy ML, Bracke M, et al. A comparison of prescription refill adherence and patients' report to identify non-adherence with inhaled corticosteroids. Pharmacoepidemiol Drug Saf 2007;16:S235-S6. 10.1002/pds*
13. *Jonsdottir H, Opjordsmoen S, Birkenaes AB, et al. Medication Adherence in Outpatients With Severe Mental Disorders Relation Between Self-Reports and Serum Level. J Clin Psychopharmacol 2010;30(2):169-75. 10.1097/JCP.0b013e3181d2191e*
14. *Guenette L, Moisan J, Preville M, Boyer R. Measures of adherence based on self-report exhibited poor agreement with those based on pharmacy records. J Clin Epidemiol 2005;58(9):924-33. 10.1016/j.jclinepi.2005.02.002*
15. *van de Steeg N, Sielk M, Pentzek M, Bakx C, Altiner A. Drug-adherence questionnaires not valid for patients taking blood-pressure-lowering drugs in a primary health care setting. J Eval Clin Pract 2009;15(3):468-72. 10.1111/j.1365-2753.2008.01038.x*
16. *Krousel-Wood M, Islam T, Webber LS, Re RN, Morisky DE, Muntner P. New Medication Adherence Scale Versus Pharmacy Fill Rates in Seniors With Hypertension. Am J Manag Care 2009;15(1):59-66.*
17. *Shalansky SJ, Levy AR, Ignaszewski AP. Self-reported Morisky score for identifying nonadherence with cardiovascular medications. Ann Pharmacother 2004;38(9):1363-8. 10.1345/aph.1E071*
18. *George CF, Peveler RC, Heiliger S, Thompson C. Compliance with tricyclic antidepressants: the value of four different methods of assessment. Br J Clin Pharmacol 2000;50(2):166-71. 10.1046/j.1365-2125.2000.00244.x*
19. *Butler JA, Peveler RC, Roderick P, Horne R, Mason JC. Measuring compliance with drug regimens after renal transplantation: Comparison of self-report and clinician rating with electronic monitoring. Transplantation 2004;77(5):786-9. 10.1097/01.tp.0000110412.20050.36*
20. *de Oliveira-Filho AD, Morisky DE, Neves SJ, Costa FA, de Lyra DPJ. The 8-item Morisky Medication Adherence Scale: Validation of a Brazilian-Portuguese version in hypertensive adults. Research in social & administrative pharmacy : RSAP 2013. Epub 2013/11/26. DOI 10.1016/j.sapharm.2013.10.006*
21. *Lee WY, Ahn J, Kim JH, et al. Reliability and validity of a self-reported measure of medication adherence in patients with type 2 diabetes mellitus in Korea. The Journal of international medical research 2013;41(4):1098-110. Epub 2013/07/19. DOI 10.1177/0300060513484433*
22. *Morisky DE, Green LW, Levine DM. Concurrent and predictive validity of a self-reported measure of medication adherence. Med Care 1986;24(1):67-74. 10.1097/00005650-198601000-00007*
23. *Menckeberg TT, Bouvy ML, Bracke M, et al. Beliefs about medicines predict refill adherence to inhaled corticosteroids. J Psychosomat Res 2008;64(1):47-54. 10.1016/j.jpsychores.2007.07.016*
24. *Tommelein E, Mehuys E, Van Hees T, et al. Effectiveness Of PHARMAceutical Care For Patients with COPD (PHARMACOP): a Randomized Controlled Trial. Br J Clin Pharmacol 2013;Accepted for publication.*
25. *Mahler C, Hermann K, Horne R, et al. Assessing reported adherence to pharmacological treatment recommendations. Translation and evaluation of the Medication Adherence Report Scale (MARS) in Germany. J Eval Clin Pract 2010;16(3):574-9. 10.1111/j.1365-2753.2009.01169.x*
26. *Hess LM, Raebel MA, Conner DA, Malone DC. Measurement of adherence in pharmacy administrative databases: A proposal for standard definitions and preferred measures. Ann Pharmacother 2006;40(7-8):1280-8. 10.1345/aph.1H018*
27. *Mehuys E, Boussery K, Adriaens E, et al. COPD Management in Primary Care: An Observational, Community Pharmacy-Based Study. Ann Pharmacother 2010;44(2):257-66. 10.1345/aph.1M481*
28. *Streiner DNG. Health measurement scales: a practical guide to their development and use, 2008.*
29. *Choo PW, Rand CS, Inui TS, et al. Validation of patient reports, automated pharmacy records, and pill counts with electronic monitoring of adherence to antihypertensive therapy. Med Care 1999;37(9):846-57. 10.1097/00005650-199909000-00002*
30. *Steiner JF, Prochazka AV. The assessment of refill compliance using pharmacy records: Methods, validity, and applications. J Clin Epidemiol 1997;50(1):105-16. 10.1016/s0895-4356(96)00268-5*
31. *Farley J, Hines S, Musk A, Ferrus S, Tepper V. Assessment of adherence to antiviral therapy in HIV-infected children using the medication event monitoring system, pharmacy refill, provider assessment, caregiver self-report, and appointment keeping. Jaids 2003;33(2):211-8. 10.1097/00126334-200306010-00016*
32. *Grymonpre R, Cheang M, Fraser M, Metge C, Sitar DS. Validity of a prescription claims database to estimate medication adherence in older persons. Med Care 2006;44(5):471-7. 10.1097/01.mlr.0000207817.32496.cb*
33. *Hansen RA, Kim MM, Song LP, Tu WZ, Wu JW, Murray MD. Comparison of Methods to Assess Medication Adherence and Classify Nonadherence. Ann Pharmacother 2009;43(3):413-22. 10.1345/aph.1L496*

34. Lareau SC, Yawn BP. Improving adherence with inhaler therapy in COPD. International journal of chronic obstructive pulmonary disease 2010;5:401-6. Epub 2010/12/31. DOI 10.2147/copd.s14715
35. Bestall JC, Paul EA, Garrod R, Garnham R, Jones PW, Wedzicha JA. Usefulness of the Medical Research Council (MRC) dyspnoea scale as a measure of disability in patients with chronic obstructive pulmonary disease. Thorax 1999;54(7):581-6.
36. Jones PW, Brusselle G, Dal Negro RW, et al. Properties of the COPD assessment test in a cross-sectional European study. Eur Resp J 2011;38(1):29-35. 10.1183/09031936.00177210

APPENDIX 3.4.1: ADHERENCE SCORES FOR DIFFERENT TYPES OF INHALERS

Appendix Table 3.4.1: Adherence scores for different types of inhalers

Evaluated type of inhaler		**MRA**	**MARS**
Handihaler	Mean	82,1%	23,8
	N	255	255
	Std. Deviation	20,6%	2,1
Pressurized metered dose inhaler	Mean	88,2%	22,9
	N	80	80
	Std. Deviation	27,1%	3,1
Aerolizer	Mean	82,2%	22,7
	N	9	9
	Std. Deviation	31,0%	4,4
Diskus	Mean	83,2%	23,6
	N	158	158
	Std. Deviation	24,6%	2,7
Turbohaler	Mean	83,1%	23,2
	N	111	111
	Std. Deviation	26,0%	2,9
Total	Mean	83,4%	23,5
	N	613	613
	Std. Deviation	23,8%	2,6

APPENDIX 3.4.2: ADHERENCE SCORES FOR DIFFERENT TYPES OF MEDICATION

Appendix Table 3.4.2: Adherence scores for different types of medication			
Type of medication		**MRA**	**MARS**
ICS	Mean	90,5%	23,1
	N	11	11
	Std. Deviation	20,2%	2,8
LAAC	Mean	82,1%	23,8
	N	254	254
	Std. Deviation	20,6%	2,1
LABA	Mean	87,5%	23,3
	N	16	16
	Std. Deviation	27,9%	3,5
LABA+ICS	Mean	82,8%	23,4
	N	320	320
	Std. Deviation	25,5%	2,8
Total	Mean	82,8%	23,5
	N	601	601
	Std. Deviation	23,5%	2,6
SABA: *Short-Acting Beta$_2$-Agonists,* ***LABA:*** *Long-Acting Beta$_2$-Agonists,* ***SAAC:*** *Short-Acting AntiCholinergics,* ***LAAC:*** *Long-Acting AntiCholinergics,* ***ICS:*** *Inhalation CorticoSteroids*			

APPENDIX 3.4.3: DECISION TREE FOR DETERMINING PRINCIPAL MAINTENANCE THERAPY

When a patient is prescribed more than one inhaled drug, we will only calculate a medication adherence score for the principal maintenance therapy. This principal therapy can be determined based on following scheme.

Appendix Table 3.4.3
1. If the patients takes a LAAC or LABA, combined with ICS or not, this is the drug that will be chosen for further evaluation, if not, go to 2
2. If the patients takes a LAAC and a LABA, the drug with the lowest baseline score will be chosen for further evaluation, if not, go to 3
3. If the patient does not take a LAAC or LABA, the ICS monotherapy will be chosen for further evaluation, if not, go to 4
4. If the patient does not take a LAAC, LABA or ICS, the SAAC or SABA will be chosen for further evaluation.
LAAC: long-acting anticholinergs; SAAC: short-acting anticholinergs; LABA: long-acting β_2-mimetics; SABA: short-acting β_2-mimetics; ICS: inhaled corticosteroids;

APPENDIX 3.4.4: DICHOTOMIZED MEDICATION ADHERENCE REPORT SCALE (MARS-5) (CUT-OFF = VARIABLE) AND MEDICATION REFILL ADHERENCE (MRA) (CUT-OFF ≥80%)

Appendix Table 3.4.4: Dichotomized Medication Adherence Report Scale (MARS-5) (cut-off = variable) and Medication Refill Adherence (MRA) (cut-off ≥80%)

		MRA	
		<80%	≥80%
MARS-5	<25	121	218
	=25	106	168
MARS-5	<24	82	284
	≥24	145	102
MARS-5	<23	57	58
	≥23	170	328
MARS-5	<22	49	42
	≥22	178	344
MARS-5	<21	36	29
	≥21	191	357
MARS-5	<20	29	22
	≥20	198	364

Chapter 4

General Conclusion

The main goal of this doctoral thesis was to develop and evaluate pharmaceutical care interventions in chronic care. Therefore, we focused on A) older patients with polypharmacy and B) on patients with chronic obstructive pulmonary disease (COPD) as an example of chronic disease.

A) To optimize pharmaceutical care for older patients with polypharmacy, we first needed to get a general image of the problem of potentially inappropriate prescribing (PIP). In a systematic literature review, summarizing 82 sample screenings, we determined that the prevalence of PIP in community dwelling (CD) older people across Europe is 22.6% (CI: 19.2– 26.7%; Range: 0.0 – 98.0%). Furthermore, risk factors most often positively associated with PIP prevalence were polypharmacy, poor functional status and depression. Drug classes most often involved in PIP were anxiolytics (ATC-code: N05B), antidepressants (N06A) and non-steroidal anti-inflammatory and anti-rheumatic products (M01A).

Subsequently, we developed a screening tool to systematically detect PIPs in the community pharmacy practice. This was achieved through a RAND/UCLA process (11 participants) with a round zero meeting, a literature review, a first written evaluation round and a second face-to-face evaluation round. An additional round on feasibility in the contemporary community pharmacy resulted in the Ghent Older People's Prescriptions community Pharmacy Screening (GheOP³S-)tool, a list of 83 PIP-items.

To validate the newly developed GheOP³S-tool, the medication record of 60 patients (≥70 years and ≥5 chronic drugs) admitted to the acute geriatric ward at the Sint-Vincentius hospital (Deinze, Belgium) was screened. Of all 250 PIP-items detected by the GheOP³S-tool, clinical relevance was scored 'serious' for 182 items (73%) and 'significant' for 67 items (26%). Proposed alternative treatment plans were accepted for 79% of the PIP-items (n=198). For 9 patients (15%), the hospitalization was considered related to a PIP, detected with the GheOP³S-tool. The adapted Medication Appropriateness Index detected 536 items, of which 145 were incorporated in 131 PIP-items, detected by the GheOP³S-tool. One-hundred and nineteen PIP-items were additionally detected by the GheOP³S-tool.

We executed two observational studies, including 1016 community-dwelling (CD) (i.e. primary care setting) and 400 institutionalized (INS) (i.e. long-term care setting) older adults with polypharmacy, recruited from 204 community pharmacies and 10 nursing homes, respectively. Evaluating PIP prevalence with the GheOP³S-tool detected a median of 3 PIP-items per person (IQR = 2-5) in CD patients, compared to a median of 4 (IQR=2-6) for INS patients. Most prevalent PIPs were long-term use of benzodiazepines (CD: 50%; INS: 58%), no Ca/VitD suppletion with elevated osteoporotic risk (CD: 54%; INS: 54%) and long-term use of antidepressant agents (CD: 21%; INS: 42%).

B) In the second part of the thesis, we developed the Pharmaceutical Care for patients with chronic Obstructive Pulmonary disease intervention (PHARMACOP-intervention). This intervention focused on improving inhalation technique and adherence to maintenance therapy. To evaluate the effectiveness of the PHARMACOP-intervention, we conducted a single-blind 3-month RCT in 170 community pharmacies in Belgium, enrolling patients prescribed daily COPD medication, aged ≥50 years, and with a smoking history ≥10 pack-years. We compared the intervention group to a usual care control group. Results showed that at the end of the trial, the inhalation technique score (Mean estimated difference [Δ], 13.5%; 95% Confidence Interval [CI], 10.8-16.1; P<.0001) and the medication adherence (Δ, 8.51%; 95%CI, 4.63-12.4; P<.0001) of the intervention patients were significantly higher than of patients in the control group. Furthermore, a significantly lower hospitalization rate was observed in the intervention group, compared to the control group (9 vs. 35; Rate Ratio, 0.28; 95%CI, 0.12-0.64; P=.003). The PHARMACOP-study therefore proved to be effective in primary care.

Nevertheless, the PHARMACOP-intervention protocol is not yet fully implemented in Belgian community pharmacies. In >70% of 80 researched pharmacies, 4/7 protocol items for first prescriptions and 3/5 protocol items for follow-up prescriptions were already routinely implemented. For first and follow-up prescriptions, respectively 39 (49%) and 34 pharmacists (43%) stated they would need to spend at least 5 minutes extra to offer optimal patient counselling. Evaluating pharmacists' perspectives on the implementation of this protocol in daily practice, main reported barriers were lack of time (80%), no integration in pharmacy software (61%) and too much administrative burden (58%).

To evaluate a patient's medication adherence in a straightforward way, an easy but specific tool is needed. We showed that the Medication Adherence Report Scale (MARS-5) was not valid as self-report measure of adherence to inhalation medication, using the medication refill adherence (MRA) as reference. Although the internal consistency of the MARS-5 was high (α=0.77), the scores correlated poorly with MRA scores (ρ=0.10; p=.011). When lowering adherence threshold stepwise from 25 to 20, MARS-5 did not reach sufficient sensitivity (53% to 13%), specificity (57% to 94%) and positive predictive value (42% to 57%) to detect nonadherers, compared to dichotomized MRA. ROC-curve plotting resulted in an area under the curve value of only 0.56 (95% CI, [0.521-0.616]; p=.005).

Chapter 5

Broader International Context

Relevance

Future Perspectives

1. BROADER INTERNATIONAL CONTEXT

1.1. Pharmaceutical Care in general

In Europe, the implementation of pharmaceutical care as a core task of the community pharmacist appears to be an evolving, non-parallel process. As discussed in a systematic review quantifying provided pharmaceutical care tasks across Europe, it is clear that different aspects of pharmaceutical care are implemented to various degrees in different countries[1]. However, some general conclusions can be drawn. On the one hand, community pharmacists scored high on more traditional areas of practice, such as verification of patient understanding or patient record screening. On the other hand, community pharmacists scored low on the area of direct patient care. This could be explained by the fact that these activities tend to be more demanding and time-consuming[1].

In countries outside Europe, e.g. in the United States or Canada, pharmaceutical care services such as patient counselling or cognitive services are already well established in daily community pharmacy practice[2-4]. These include for example the provision of in-store education seminars, performance of specific disease trainings (e.g. diabetes, asthma etc.), and in-store monitoring and screening. As well, a number of these services are remunerated and/or reimbursed[2 3 5].

1.2. Medication Review for Older Patients with polypharmacy

Pharmacist associations from multiple countries have introduced guidelines on medication review[6]. Some of them are rather conceptual, such as the document from the Royal Pharmaceutical Society[6], describing four guiding principles. Others, such as the guideline 'Medicatiebeoordeling' from the Dutch Pharmacists Association (KNMP) mention the very specific steps that should be taken to execute a medication review (patient interview, pharmacotherapeutical analysis, set-up treatment plan, confirm treatment plan and follow-up)[7] (Figure 5.1).

Figure 5.1*: Front covers of medication review guidelines from diverse pharmacy associations. From left to right: Royal Pharmacist Association (UK), Koninklijke Nederlandse Maatschappij ter bevordering der Pharmacie (The Netherlands) and Pharmaceutical Society of Australia (Australia).*

The recently published systematic review of Bulajeva et al[8] further provides us with detailed data about the implementation of medication review in Europe. Thirty-two countries were asked to provide information, of which 25 did. Sixteen reported having established medication review procedures in general (Table 5.1), and 13 declared having established procedures for the community setting in specific. Nine of those 13 countries reported having type I procedures (69%) and 11 reported having a procedure for type II procedures (85%). Only 6 countries reported having type III medication review procedures (46%)[1].

Table 5.1: General information about medication review procedures specified by country (Adopted from Bulajeva et al.[8])

Country	Community setting			Hospital setting	Nursing home setting
	Type I	Type II	Type III		
Bulgaria	x	x		x	
Croatia	x	x	x		
Czech Republic	x	x		x	
Denmark	x	x	x	x	x
Finland	x	x	x	x	x
France				x	
Hungary	x			x	
Iceland				x	
Latvia				x	
The Netherlands	x	x	x	x	x
Norway		x			
Portugal		x		x	
Spain			x	x	x
Sweden	x	x	x	x	x
Switzerland	x	x		x	
United Kingdom		x		x	x

These results show that the implementation of medication review procedures that originate from the community pharmacy is becoming common in European healthcare. Nevertheless, there is still a lot of room for improvement.

1.3. Chronic Disease Counselling in the Community Pharmacy

Chronic disease counselling has been introduced in community pharmacies across Europe, the USA, Canada or Australia[4].

Basic pharmaceutical care includes general medication counselling that is medication centred. This includes providing the patient with information about the drug (name, drug class, storage conditions, cost), the drug use (indication, expected benefit, directions for use, duration of therapy) and – if necessary – non-pharmacologic advice (self-management, self-monitoring)[4 9]. The proportion of patients receiving this counselling varies widely, ranging from 8% to 80%[4]. Furthermore, studies have shown that verbal counselling was far more present for new prescriptions, compared to counselling for repeat prescriptions[4 10].

Next to the more general and medication centred counselling in basic pharmaceutical care, there also exist advanced counselling services (i.e. cognitive pharmacy services) that are individually adapted and patient-centred[5 9]. For example, the New Medicines Service (NMS) provides support for people with long-term conditions that are prescribed a new medicine. The goal of the NMS is to improve medicine adherence[11]. Other services include the Appliance Use Review, the Smoking Cessation Service and the Inhaler Technique Assessment Service (Table 5.2)[12].

[1] For definitions regarding type of medication review: see Chapter 1, Table 1.3

Table 5.2: Examples of remunerated advanced counselling services in community pharmacies in other European countries[5 11-15]

	Target group	Goal	Method
New Medicines Service (UK)	People with long-term conditions newly prescribed a medicine for asthma, COPD, diabetes type 2 and hypertension or are newly prescribed antiplatelet/ anticoagulant therapy)	To improve medication adherence	Structured patient interview to supplement and reinforce information provided by the GP to help patients make informed choices about their care. Additionally, the pharmacists links the use of newly prescribed medicines to lifestyle changes or other non-drug interventions to promote well-being and promote health in people with long term conditions.
Appliance Use Review (UK)	Patients with an appliance[1]	To improve the patient's knowledge and use of their appliance	Structured patient interview to establish the way the patient uses the appliance and the patient's experience of such use. Identifying, discussing and assisting in the resolution of poor or ineffective use of the appliance by the patient. Advising the patient on the safe and appropriate storage and disposal of the appliance.
Smoking cessation service (Scotland)	Current smokers, older than 12 years	To provide extended access to smoking cessation support, including the provision of patient centred behavioural support and evidence-based pharmacotherapy	Counselling sessions (multiple appointments). In-depth interviews. Written and verbal counselling on nicotine replacement therapy.
Medicine Use Review (UK)	Patients on multiple medicines, particularly those receiving medicines for long term conditions	To improve medication adherence	Structured patient interview in which the patient's actual use, understanding and experience of taking their medicines is established. Identifying, discussing and resolving poor or ineffective use of their medicines. Identifying side effects and drug interactions that may affect adherence. Improving the clinical and cost effectiveness of prescribed medicines and reducing medicine wastage.
Inhaler Technique Assessment Service (Denmark)	Patients with asthma or chronic obstructive pulmonary disease	To improve inhalation technique	Ten-minute interactive counselling session during which pharmacy staff assesses the inhalation technique of individual asthma patients at the pharmacy counter, and correct any errors.
Polymedication Check (Switzerland)	Patients with 4 or more chronic drugs	To improve medication adherence	A session in which all current problems with the pharmacotherapy are discusses, medication adherence is assessed and addressed and when needed, a pill box up to three months is offered.
Medicatie-beoordeling (The Netherlands)	Patients with polypharmacy	To improve quality of prescribing	A medication review is performed by the pharmacist. This includes a pharmacotherapeutic anamnesis with the patient, a pharmacotherapeutic analysis by the pharmacist, a physician-pharmacist consultation and a pharmacist-patient follow-up consultation.

[1]Appliances include: catheter, laryngectomy or tracheostomy, anal irrigation system, vacuum pump or constrictor ring for erectile dysfunction, wound drainage pouch, incontinence appliance or stoma.

2. RELEVANCE

2.1. General

Scientific research is performed to elucidate how the world is functioning. The acquired knowledge can consequently be used to develop or optimize various sectors of society such as industry, education, governmental practices, the health system or social cohesion. This potential value of research is called 'societal relevance'. Where academic value of research is mainly determined by the impact factor of the journal in which it is published or the number of citations, societal relevance finds it value in the implementation in (national) guidelines and practice settings as well as in the (cost-)effectiveness of the researched interventions[16].

2.2. Implementation of cognitive pharmacy services in Belgian guidelines

In Belgium, the Royal Decree issued in 2009, clearly outlines good pharmaceutical practices of the community pharmacists, including pharmaceutical care aspects and cognitive pharmacy services (*See also General Introduction, section 1.3*)[9].

Accordingly, the Belgian Pharmacist Association (APB) defined three action points in their guidelines. These would be the action points where the community pharmacist should focus on in the future: optimization of chronic medication start-up, optimization of medication adherence and medication review. The APB subsequently merges all services serving these three action points under the umbrella term 'Good Medicine Use services'[17].

To achieve these action points, the APB has already established the 'Counselling New Medication' service. This service is currently remunerated for newly diagnosed asthma patients starting inhaled corticosteroids. The service includes a counselling session during first dispensing and a follow-up counselling session during first refill. Both counselling sessions comprise of an evaluation of asthma control using the Asthma Control Test as well as an elaborate demonstration of and education about the inhalation technique. Furthermore, potential issues regarding medication adherence are discussed when deemed necessary. Belgian community pharmacists that execute this service receive a remuneration of €20 per session.

Additionally, a 'Counselling Polypharmacy Patients' service has been developed and will be piloted in 2016. This service includes a medication review by the community pharmacist, comprising of a structured patient interview, a pharmacotherapeutic analysis, an adherence improving intervention when deemed necessary and a pharmacist-physician consultation to discuss the findings of the review process. In collaboration with the APB, researchers of two Belgian Universities will evaluate the effectiveness of this new service on both clinical and patient related outcomes.

2.3. Implementation of cognitive pharmacy services in Belgian ambulant practice

According to Belgian research evaluating pharmaceutical care practices of 623 Belgian community pharmacists, the extent to which pharmaceutical care is provided in general is sufficient, however with a large room for improvement[1 18]. For example, about one fifth of community pharmacists clearly state that they do not check for DRPs.

Focusing on the 'Counselling New Medication' service, it appears that the implementation of the sessions is limited, however slightly increasing. In 2015, 21 262 first-dispensing counselling sessions were declared, compared to 16 913 in 2014. Follow-up counselling appears to be more difficult to organize, as only for 1593 and 1491 patients a session was declared, in 2015 and 2014 respectively (Figure 5.2)[19].

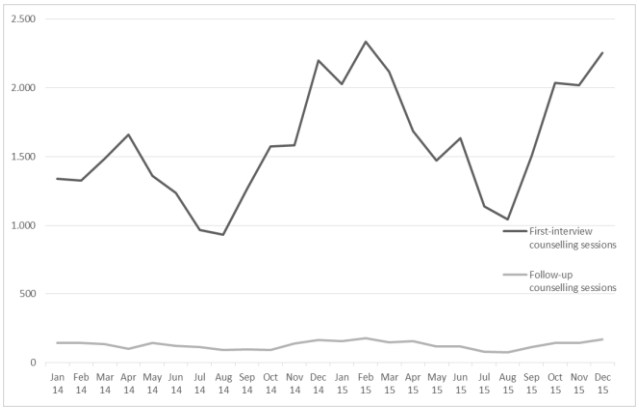

***Figure 5.2**: Monthly declarations of 'Counselling New Medication' services*

In September 2014, the National Institute for Health and Disability Insurance (NIHDI) introduced the Collaborative approach to Optimise Medication use for Older people in Nursing homes (COME-ON) project. As in Belgium, medication for nursing homes is dispensed through community pharmacies and patients withhold their GP while transitioning to a nursing home, this also considers the first-line setting. The purpose of this study was to evaluate the effect of a complex, multifaceted intervention, including multidisciplinary case conferences on appropriateness use of medicines for older people in Belgian nursing homes. Up to now, a multicentre cluster controlled trial has been set up in 63 Belgian nursing homes (30 intervention; 33 control). In each of these nursing homes, 35 residents were selected for participation. Three-monthly multidisciplinary case conferences between nurse, general practitioner and pharmacist were conducted on a resident level. Case conferences facilitated structured medication reviews in order to optimize the resident's medication profile. Education and training, through e-learning and on-site sessions, were provided. The primary outcome compared the number of PIPs and PPOs per resident between groups. Secondary outcomes included outcomes of case conferences, costs and facilitators/barriers for implementation of the intervention[20]. The results of this study are currently being analysed.

2.4. Improving implementation in practice: Strategies for patient counselling

Strategies to improve the implementation of the 'Counselling New Medication' service include expanding the service to other diseases, e.g. COPD, diabetes, hypertension, etc[21]. Furthermore, instead of only counselling the *start-up* of chronic therapy, the service could also be expanded to counselling *chronic* therapy on a regular basis[21]. Indeed, scientific evidence supports counselling of chronic therapy. The randomized controlled Pharmaceutical Care for Asthma Control and Improvement (PHARMACI)-trial for example, included chronic asthma patient, randomly assigning them to a usual pharmacist care control group or to an intervention group. This intervention group received protocol-based care mainly focusing on inhalation technique and medication adherence. The PHARMACI-trial showed an improvement in inhalation technique and medication adherence in the intervention group. Additionally, asthma control for uncontrolled patients improved and the use of reliever medication and frequency of night-time awakenings diminished[22]. Another trial, the PHARMaceutical Care for patients with COPD (PHARMACOP)-trial, was a single-blind 3-month randomized controlled trial researching the effectiveness of pharmaceutical care for patients with COPD (*see Chapter 3 Part 2*). This trial also recruited patients with chronic COPD and demonstrated an improved inhalation technique and medication adherence along with a decrease in hospitalization rates for patients with COPD[23]. Moreover, the intervention appeared to have a cost-saving effect[24].

However, community pharmacists can not only play an important role in respiratory diseases. As well for patients with diabetes or hypertension, randomized controlled trials showed that long-term counselling by community pharmacists can significantly improve disease control[25 26]. Significant reductions in blood glucose, HbA1c and systolic blood pressure in the intervention group as compared with control groups were for example found[25 26]. Therefore, it can be concluded that counselling sessions delivered in a community pharmacy setting, in collaboration with patients and physicians can improve the achievement of targets. This suggests that redesigning the patient pathway to include interventions by community pharmacists may be beneficial.

2.5. Improving implementation in practice: Strategies for medication review

2.5.1. Developing the medication review process as a complex intervention

The ultimate goal of medication review is to improve appropriateness of prescribing and to improve patient centred outcomes. It is unlikely that one single intervention will be able to achieve this. Multiple research indeed confirms that more integrated approaches are needed to effectuate a significant change in prescribing behaviour and consequently reduce the burden of PIP[27 28]. Considering medication review, in fact, multiple actors in healthcare are involved. Therefore, the development of such a service could be done according to the canvas of a 'complex intervention' (Figure 5.3)[29].

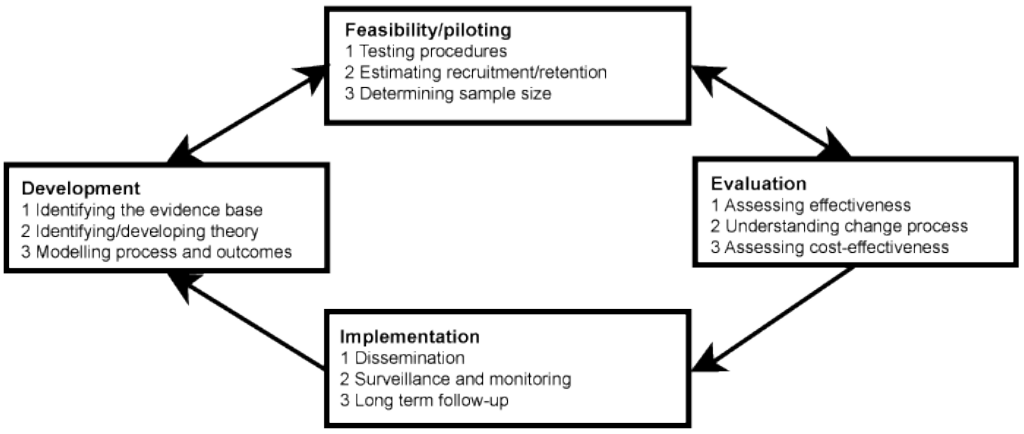

***Figure 5.3**: Key elements of the development and evaluation process of a complex intervention. Adopted from Craig et a[29]l.*

According to the canvas of complex interventions[29], the first issue would be the identification of the evidence for a medication review by community pharmacists. This is discussed in the introduction section (*See section 2.1: 'Medication review for older patients with polypharmacy'*). Subsequently, appropriate rationales and theories supporting each part of the intervention should be evaluated to yield a first intervention proposal.

Concerning the performance of a medication review in community pharmacies, our proposed intervention consists of a straightforward protocol to execute a multidisciplinary medication review, initiated from the community pharmacy. It contains the following steps: (1) a pharmacotherapeutic anamnesis combined with a digital screening of the patient's medication with the GheOP³S-tool, yielding a list of *potentially* inappropriate pharmacotherapy; (2) a multidisciplinary consultation, where these *potential* issues could be discussed and lead to an eventual list of *actual* inappropriate pharmacotherapy; (3) a consultation with the patient, after which a final treatment plan with action points for each healthcare provider of the multidisciplinary team could be set up; (4) communication of the final action points to all healthcare providers that are part of the multidisciplinary care team through a secure electronic platform.

2.5.2. (Dis)advantages of using the GheOP³S-tool as part of the complex intervention

Using the GheOP³S-tool as a backbone for performing medication reviews has multiple advantages. During the developmental process, it was taken into account that clinical or laboratory data are mostly not available for community pharmacists. As clinical data are not needed to apply the tool to the medication history, the pharmacists can initiate the medication review process based on the dispensing data in the community pharmacy. Additionally, the GheOP³S-tool is explicit and therefore very straightforward and quick to apply, limiting the time-burden of the process, a much cited barrier[30] [31].

As well, an extra document with supporting information provides the community pharmacist with substantial background information and possible alternative treatment plans which empowers the community pharmacists to initiate follow-up interdisciplinary communication. This extended document is currently available in Dutch and French via the GheOP³S-tool's website[32].

There are however also some disadvantages. First, as with all explicit screening tools, there exists a risk that community pharmacists will oversimplify prescribing and fall into a black/white vision. However, we believe that when educational training sessions expressively emphasize that a lot of different factors drive prescribing and there can be a justified reason to deviate from standard guidelines, this can be prevented. Second, medication review is an ongoing process. All members of the healthcare team must realize that after determination of the final action points, actual implementation only gets started. Therefore, counselling the patients in medication changes, monitoring them and performing regular follow-up consultations will be necessary.

2.5.3. Piloting and evaluating the complex intervention

The proposed intervention should first be piloted and the feasibility has to be assessed. To do so, a mixture of qualitative and quantitative methods will be necessary to understand barriers to participation and to estimate response rates. Depending on the results, a number of studies may be required to progressively refine the design before embarking on a full-scale evaluation (Figure 3). The effectiveness is preferably assessed through an experimental, randomised design[29].

2.5.4. Nationwide implementation in routine practice

When the effectiveness of the proposed complex intervention is evaluated positively, the intervention is to be implemented in routine practice in healthcare. It has been recognized that passive strategies to do so are ineffective[29]. Instead, a number of facilitators should be actively pursued and established in different levels in healthcare. We discuss here possibilities for the governmental level, the informatics level and the healthcare providers' level.

2.5.4.1. The governmental level

Governments could give incentives to perform medication screening in the ambulatory setting by providing a remuneration for this service. Adequate remuneration seems to be necessary to allow initial investments but appears not to be the only trigger to provide new services[30]. Moreover, pharmacists state that time and resource burdens are not problematic if a remuneration is adequate[30] [31]. Additionally, a clear legal outline of the specific role of each healthcare provider in the medication review process could empower each one of them to take up their tasks[33-35].

The community pharmacist could act as the initiator of the process after which a consultation in local multidisciplinary teams takes place. It is especially this involvement of community pharmacists into local multidisciplinary teams that appears to be problematic[8 35]. For example, of the 16 European countries where procedures for medication review in the community are established, communication with physicians is only part of the medication review procedure in 5 of them (31%)[8]. In order to enhance interprofessional collaborations, governments could support the organization of local interdisciplinary conferences[33]. Therefore, in Belgium, the NIHDI recently granted financial support to the organisation of local small-group multidisciplinary consultations that implement recognized quality improving projects[36].

2.5.4.2. The informatics level

Both limited time and difficult communication are often mentioned as barriers to implement medication review[33 37]. These are two issues that informatics or software companies could easily tackle. First, informatics and software companies could be of major help in facilitating interprofessional communication by developing communication channels that are secure and easy to use[33].

Second, automatizing the screening of medication lists or medication histories, including clinical support systems could enhance the implementation of this intervention strategy as this would limit the time needed to perform the review. Considering the GheOP³S-tool in specific, this tool could be fully automatized in the future, restricting the time spent to the interpretation of the detected PIP's relevance.

2.5.4.3. The healthcare providers' level

Healthcare providers should be educated about medication reviews and their potential role in the process. This includes recognizing each healthcare provider's role and responsibility while none claiming a position of superiority. In research on medication review however, not all community pharmacists consider this an essential part of their job[35]. On the other hand, physicians are not always willing to cede certain responsibilities and therefore do not accept other health care providers as vital members of the healthcare team[33]. It is however important that each healthcare provider feels confident providing care for older adults (i.e. prescribing for older adults, evaluating pharmacotherapy of older adults, etc.). Therefore, specific courses on geriatric pharmacotherapy should be organized[37].

Indeed, external support helps both community pharmacists and prescribers to improve their service-management skills. For pharmacists, educational interventions showed to significantly shorten the time spent on the medication review[30] while for prescribers, educational interventions showed to improve prescribing compentences[38]. Moreover, pharmacists not receiving external training often lacked confidence to submit recommendations to prescribers[30].

Therefore, the two largest post-academic training institutes for pharmacists in Belgium, IPSA and SSPF[2], already recognize the value of good external support for performing a medication review using the GheOP³S-tool. During the 2016 training cycle, both institutes organize classes to teach community pharmacists about the process of a medication review and how to work with the GheOP³S-tool[39 40].

2.6. (Cost-)effectiveness of cognitive pharmacy services

Cognitive pharmacy services in general range in complexity from emergency contraception counselling to minor ailments schemes and clinical medication review[12]. Also, the remunerations for these services are highly variable. Systematic reviews consider them however to have a net cost benefit, with estimated returns on investment ranging from $1.30 to $26 per dollar spent[12 41 42].

The (cost-)effectiveness of medication reviewing in specific has been evaluated in a both a narrative and systematic way[43-45]. The reviews were however challenging because of variations in the nature of the populations studied, the outcome data measured and the evaluation criteria used[43]. Furthermore, performed interventions were often inadequately described or varied widely. There is nevertheless some consistency in concluding that falls and hospitalizations might be reduced with modest cost savings[43-45]. Also, significant results favouring pharmacists' intervention were found for specific health outcomes such as blood pressure, blood glucose control, etc[45]. No studies reported a benefit in terms of mortality, mental capacity or activities of daily living[43 44]. It can be concluded that clinical medication review is probably of value and may be cost-effective.

Evaluating the effect of counselling patients in the community pharmacy appears to have the same drawbacks. The interventions and outcomes measured varied broadly[42 46]. Specifically focusing on counselling patients with COPD in the community pharmacy, a cost-effectiveness analysis of the PHARMACOP-trial discussed in Chapter 3 Part 2 was executed, showing that the average overall costs per patient for the PHARMACOP intervention and usual care were €2,221 and €2,448, respectively within the 1-year time horizon. This reflects cost savings of €227 for the PHARMACOP intervention per patient with COPD per year[24].

[2] IPSA (Instituut voor Permanente Studie voor Apothekers) is the Flemish post-academic training institute. SSPF (Société Scientifique des Pharmaciens Francophones) represents the Wallonian counterpart.

3. FUTURE PERSPECTIVES

3.1. Academic perspectives

On an academic level, several follow-up studies are planned to be executed. First, the performance of a medication screening with the GheOP³S-tool will be tested in a controlled trial including older patients with polypharmacy, admitted to the acute geriatric ward of the general hospital in Oudenaarde, Belgium. In this controlled trial, a medication screening with the GheOP³S-tool will be compared to a medication screening with the STOPP/START-criteria[47] and to a control group, receiving usual care. The primary outcome of the trial will the appropriateness of prescribing, however also patient-related outcomes, such as patient satisfaction and self-rated health, will be assessed.

Second, an additional screening will be performed on the data from the GheOP³S-tool validation study reported in Chapter 2 Part 3. This additional screening will apply the GheOP³S-tool's addendum considering dose adjustments in renal impairment to the medication history of all 60 included patients. Subsequently, the study will evaluate whether providing community pharmacists with estimated glomerular filtration rates would yield to additional detection of PIP with high clinical relevance. During this study, a dose adjustment recommendation for each drug incorporated in the GheOP³S-tool addendum will be composed. This recommendation will be based on guidelines about dose adjustment in impaired renal function, collected from the 'Renal Drug Handbook'[48], the 'Doseringsadviezen voor geneesmiddelen' by the KNMP[49], and the considered Summaries of Product Characteristics.

Third, based on the results from studies already performed with the GheOP³S-tool, the content of the GheOP³S-tool will be further optimized. Zooming in on the data from the comparison with the adapted Medication Appropriateness Index (*See Chapter 2 Part 3*), we will be able to detect which items are systematically missed. These will be consequently be added to the tool. On the contrary, items with very low prevalence rates will be omitted. Additionally, new drugs are marketed since the development of the tool and new evidence about the use of already marketed drugs in older patients is surging. This new information will as well be integrated in the GheOP³S-tool.

Notwithstanding the fact that already a number of barriers and facilitators to the implementation of medication review are known, we want to research whether there exist additional issues specific for the Belgian setting. Therefore, we will perform semi-structured interviews with both general practitioners and community pharmacists separately regarding their view on medication review through multidisciplinary healthcare teams. The interviews will question current practices regarding medication review, perceived needs, concerns and prerequisites for medication review, role specification in the medication review process and willingness to perform medication review.

3.2 Future discussion topics

3.2.1 Future opportunities for the community pharmacist's profession

As the professional tasks of the community pharmacist grow broader, it might be interesting to consider pharmacy specialties in line with physician specialities. A number of interesting areas of expertise include geriatric pharmacy, paediatric pharmacy or pregnancy/lactation pharmacy (Table 5.3). This is an interesting strategy as a lot pharmacotherapeutic aspects differ between these patient groups, e.g. benefit/risk ratios, preferred administration routes, dosing schedules, evidence, etc. These specialized pharmacists can consequently be consulted by other pharmacists but also by other healthcare professionals such as physicians when they encounter unsolvable problems with their patients. Consultant pharmacists already exist in the UK and their specialties include anticoagulation, respiratory medication, mental health, community healthcare, older people's care etc[50].

On the other hand, pharmacy specialties could exist based on tasks of the community-pharmacist. These tasks could for example include pharmacist-reviewers, counselling pharmacists, compounding pharmacists and pharmacist specializes in Individual Medication Preparation (IMP) (Table 5.3).

It is however clear that such specialties need specific training. During the last decades the master's program to become a pharmacist has already changed significantly to better align education and practice[51-54]. Up to the early 21st century, the pharmacy program was centered around classes about chemistry and compounding. Since 2010 classes about communication, practical use of drugs and (advanced) pharmaceutical care related classes were gradually introduced. Additionally, since January 2015 post-academic training for pharmacist has become obligatory[55]. However, there is still some room for improvement, as multidisciplinary care becomes more and more important, it is absolutely necessary that all courses for healthcare professionals and postacademic trainings introduce multidisciplinary classes.

Table 5.3: Suggestions for pharmacy specialties

Specialties based on specific target groups		
Pharmacy specialty	Target group	Specific tasks
Geriatric pharmacist	Geriatric patients	Evaluating risk/benefit ratios
Paediatric pharmacist	Paediatric patients	Developing specific dosing schedules and administration routes
Oncologic pharmacist	Patients with cancer	Evaluating pharmacotherapeutic treatment of oncologic drugs and their side-effects
Pregnancy/lactation pharmacist	Pregnant or lactating women	Evaluating risk/benefit ratios for mother and child
Specialties based on specific pharmacy tasks		
Pharmacy specialty	Target group	Specific tasks
Pharmacist-reviewer	Patients with polypharmacy	Reviewing the pharmacotherapeutic regimen
Counselling pharmacist	Patients with chronic disease	Organizing and performing of specific counselling sessions in the community-pharmacy
Compounding pharmacist	Patients in need of specific administration routes or not commercially available preparations	Offer advice about or being responsible for the preparation of difficult compounding strategies or administration routes.
IMP pharmacist	Patients with complicated medication schemata	Reviewing the pharmacotherapeutic regimen in the light of optimal medication schemes for robotic unit dispensing

IMP: *Individual Medication Preparation*

3.2.2 Challenges and possibilities for routine implementation of pharmaceutical care

Large routine implementation of pharmaceutical care remains to date a major challenge and the data in this doctoral thesis support this statement (*see Chapter 2 Part 4 and Chapter 3 part 3*). There exist some cultural challenges to face to significantly change mentality.

3.2.2.1 Scale optimization or Organization optimization

At the beginning of 2015, Belgium had 4,950 pharmacies, or one per 2,150 inhabitants. This is one of the densest networks in Europe. In comparison, The Netherlands count 1981 pharmacies, or one per 8,481 inhabitants. To ensure adequate, effective and regular supply of medicines in all regions of the country, new pharmacies may only be opened based on demographic or geographic criteria according to a restrictive law. The introduction of this law slowed down the growth of the number of pharmacies, but did not prevent that there exist a large number of small, local pharmacies, often with only one pharmacist present. Some actors consider these small, local pharmacies unable to qualitatively deliver pharmaceutical care to the patient. However, these local pharmacies could be supported in time-management and reorganization of their tasks so they are enabled to deliver high quality pharmaceutical care and the accessibility to the patients is retained, which is a major strength of Belgian health care.

3.2.2.3 Improved communication between healthcare professionals

Communication between healthcare professionals is essential to guarantee optimal treatment for the patients. From the research in this thesis it is clear that there is a need for enhanced (willingness for) communication between community pharmacists and GPs. The Belgian deontological code clearly describes an obligation to collaborate, citing that *"The community pharmacist loyally exchanges data with other health care professionals that are useful of necessary for the patient's interest"* (Article 57, Code Farmaceutische Plichtenleer). Furthermore, the NIHDI stimulates better first-line collaboration practices by granting financial support to the organisation of local small-group multidisciplinary consultations that implement recognized quality improving programss[36]. However, to achieve optimal first-line collaborations, it is as well warranted that all concerned healthcare professions are considered as equals. A number of items could be tackled herein, e.g. the fact that only physicians are reimbursed by the NIHDI for attending postacademic classes, that some healthcare professionals do not recognize shared-decision making and that patients often rely on the advice of only one health care professional because of cultural traditions. Raising awareness with both healthcare professionals and patients could be a major support to change this mentality.

4. REFERENCES

1. *Hughes CM, Hawwa AF, Scullin C, et al. Provision of pharmaceutical care by community pharmacists: a comparison across Europe. Pharm World Sci 2010;**32**(4):472-87.*
2. *Christensen DB, Farris KB. Pharmaceutical care in community pharmacies: practice and research in the US. The Annals of pharmacotherapy 2006;**40**(7-8):1400-6.*
3. *Jones EJ, Mackinnon NJ, Tsuyuki RT. Pharmaceutical care in community pharmacies: practice and research in Canada. The Annals of pharmacotherapy 2005;**39**(9):1527-33.*
4. *Puspitasari HP, Aslani P, Krass I. A review of counseling practices on prescription medicines in community pharmacies. Research in social & administrative pharmacy : RSAP 2009;**5**(3):197-210.*
5. *Pharmaceutical Services Negotiating Committee. Advanced Services. Secondary Advanced Services 2016. http://psnc.org.uk/services-commissioning/advanced-services/.*
6. *Royal Pharmaceutical Society. Helping patients to make the most of medicines: Good practice guidance for healthcare professionals in England, May 2013.*
7. *Koninklijke Nederlandse Maatschappij ter bevordering der Pharmacie K. KNMP-richtlijn: Medicatiebeoordeling, 2013.*
8. *Bulajeva A, Labberton L, Leikola S, et al. Medication review practices in European countries. Research in social & administrative pharmacy : RSAP 2014.*
9. *Royal Decree. Belgisch Staatsblad, 21st January 2009.*
10. *Pronk MC, Blom LT, Jonkers R, et al. Patient oriented activities in Dutch community pharmacy: diffusion of innovations. Pharm World Sci 2002;**24**(4):154-61.*
11. *Boyd M, Waring J, Barber N, et al. Protocol for the New Medicine Service Study: a randomized controlled trial and economic evaluation with qualitative appraisal comparing the effectiveness and cost effectiveness of the New Medicine Service in community pharmacies in England. Trials 2013;**14**:411.*
12. *Houle SKD, Grindrod KA, Chatterley T, et al. Paying pharmacists for patient care: A systematic review of remunerated pharmacy clinical care services. Canadian pharmacists journal : CPJ = Revue des pharmaciens du Canada : RPC 2014;**147**(4):209-32.*
13. *Scottish Government. PHS Smoking Cessation Service, 2013.*
14. *Kaae S, Sondergaard B, Haugbolle LS, et al. Sustaining delivery of the first publicly reimbursed cognitive service in Denmark: a cross-case analysis. The International journal of pharmacy practice 2010;**18**(1):21-7.*
15. *PharmaSuisse. Entretien de polymédication. Secondary Entretien de polymédication 2015. http://www.pharmasuisse.org/FR/dienstleistungen/themen/pages/polymedikationscheck.aspx.*
16. *Wilbertz J. Evaluating societal relevance of research: University of Groningen, 2013.*
17. *Algemene Pharmaceutische Bond. Oriëntatienota APB, Personal Communication, 2015.*
18. *Foulon V, De Wulf I. Behavioral Pharmaceutical Care Scale: research on the extent of the implementation of pharmaceutical care in Belgian pharmacies. Journal de Pharmacie de Belgique 2007;**62**(3):85-92.*
19. *Algemene Pharmaceutische Bond. Data betreffende declaraties BNM-ENM, Personal Communication, 2016.*
20. *Anrys P, Strauven G, Boland B, et al. Collaborative approach to Optimise MEdication use for Older people in Nursing homes (COME-ON): study protocol of a cluster controlled trial. Implementation science : IS 2016;**11**:35.*
21. *Universiteit Antwerpen (UA), (UCL) UCdL. Evaluation of a new medicines counselling service for asthma patients in community pharmacies in Belgium. , April 2015.*
22. *Mehuys E, Van Bortel L, De Bolle L, et al. Effectiveness of pharmacist intervention for asthma control improvement. The European respiratory journal 2008;**31**(4):790-9.*
23. *Tommelein E, Mehuys E, Van Hees T, et al. Effectiveness of pharmaceutical care for patients with chronic obstructive pulmonary disease (PHARMACOP): a randomized controlled trial. Br J Clin Pharmacol 2014;**77**(5):756-66.*
24. *van Boven JF, Tommelein E, Boussery K, et al. Improving inhaler adherence in patients with chronic obstructive pulmonary disease: a cost-effectiveness analysis. Respiratory research 2014;**15**:66.*
25. *Ali M, Schifano F, Robinson P, et al. Impact of community pharmacy diabetes monitoring and education programme on diabetes management: a randomized controlled study. Diabetic medicine : a journal of the British Diabetic Association 2012;**29**(9):e326-33.*
26. *McLean DL, McAlister FA, Johnson JA, et al. A randomized trial of the effect of community pharmacist and nurse care on improving blood pressure management in patients with diabetes mellitus: Study of cardiovascular risk intervention by pharmacists–hypertension (scrip-htn). Archives of Internal Medicine 2008;**168**(21):2355-61.*
27. *Kaur S, Mitchell G, Vitetta L, et al. Interventions that can reduce inappropriate prescribing in the elderly: a systematic review. Drugs Aging 2009;**26**(12):1013-28.*
28. *Meid AD, Lampert A, Burnett A, et al. The impact of pharmaceutical care interventions for medication underuse in older people: a systematic review and meta-analysis. Br J Clin Pharmacol 2015.*
29. *Craig P, Dieppe P, Macintyre S, et al. Developing and evaluating complex interventions: the new Medical Research Council guidance. BMJ (Clinical research ed) 2008;**337**.*
30. *Niquille A, Lattmann C, Bugnon O. Medication reviews led by community pharmacists in Switzerland: a qualitative survey to evaluate barriers and facilitators. Pharmacy Practice 2010;**8**(1):35-42.*
31. *Roberts AS, Benrimoj SI, Chen TF, et al. Understanding practice change in community pharmacy: a qualitative study in Australia. Research in social & administrative pharmacy : RSAP 2005;**1**(4):546-64.*
32. *Pharmaceutical Care Unit. Ghent Older People's Prescriptions community Pharmacy Screening tool: Rationales, management plans and additional information. Secondary Ghent Older People's Prescriptions community Pharmacy Screening tool: Rationales, management plans and additional information. 2016. http://www.ugent.be/fw/nl/onderzoek/bioanalyse/farmzorg/tools.htm/gheops.htm.*
33. *Bardet JD, Vo TH, Bedouch P, et al. Physicians and community pharmacists collaboration in primary care: A review of specific models. Research in social & administrative pharmacy : RSAP 2015;**11**(5):602-22.*
34. *Hatah E, Braund R, Duffull SB, et al. General practitioners' views of pharmacists' current and potential contributions to medication review and prescribing in New Zealand. Journal of primary health care 2013;**5**(3):223-33.*
35. *Kelly DV, Bishop L, Young S, et al. Pharmacist and physician views on collaborative practice: Findings from the community pharmaceutical care project. Canadian pharmacists journal : CPJ = Revue des pharmaciens du Canada : RPC 2013;**146**(4):218-26.*

36. National Institute for Health and Disability Insurance (INAMI). Medisch-farmaceutisch overleg. Secondary Medisch-farmaceutisch overleg 2015. http://www.inami.fgov.be/nl/themas/zorgkwaliteit/geneesmiddelen/medisch-farmaceutisch-overleg/Paginas/default.aspx#.Vsc-YEArKW4.
37. Cullinan S, Fleming A, O'Mahony D, et al. Doctors' perspectives on the barriers to appropriate prescribing in older hospitalized patients: a qualitative study. Br J Clin Pharmacol 2015;**79**(5):860-9.
38. Kamarudin G, Penm J, Chaar B, et al. Educational interventions to improve prescribing competency: a systematic review. BMJ open 2013;**3**(8):e003291.
39. Instituut voor Permanente Studie voor Apothekers (IPSA). Cursusoverzicht. Secondary Cursusoverzicht 2016. http://www.ipsa.be/.
40. Société Scientifique des Pharmaciens Francophones (SSPF). Nos Formations - Pharmaciens. Secondary Nos Formations - Pharmaciens 2016. https://www.sspf.be/fr/.
41. Perez A, Doloresco F, Hoffman JM, et al. ACCP: economic evaluations of clinical pharmacy services: 2001-2005. Pharmacotherapy 2009;**29**(1):128.
42. Touchette DR, Doloresco F, Suda KJ, et al. Economic evaluations of clinical pharmacy services: 2006-2010. Pharmacotherapy 2014;**34**(8):771-93.
43. Zermansky AG, Silcock J. Is medication review by primary-care pharmacists for older people cost effective?: a narrative review of the literature, focusing on costs and benefits. PharmacoEconomics 2009;**27**(1):11-24.
44. Chinthammit C, Armstrong EP, Boesen K, et al. Cost-effectiveness of comprehensive medication reviews versus noncomprehensive medication review interventions and subsequent successful medication changes in a Medicare Part D population. Journal of managed care & specialty pharmacy 2015;**21**(5):381-9.
45. Hatah E, Braund R, Tordoff J, et al. A systematic review and meta-analysis of pharmacist-led fee-for-services medication review. Br J Clin Pharmacol 2014;**77**(1):102-15.
46. Van Wijk BL, Klungel OH, Heerdink ER, et al. Effectiveness of interventions by community pharmacists to improve patient adherence to chronic medication: a systematic review. The Annals of pharmacotherapy 2005;**39**(2):319-28.
47. O'Mahony D, O'Sullivan D, Byrne S, et al. STOPP/START criteria for potentially inappropriate prescribing in older people: version 2. Age Ageing 2015;**44**(2):213-8.
48. Ashley C, Currie A. Renal Drug Handbook, 3rd Edition: CRC Press, 2008.
49. Koninklijke Nederlandse Maatschappij ter bevordering der Pharmacie K. Verminderde Nierfunctie - Doseringsadviezen voor geneesmiddelen. Den Haag, 2012.
50. Malson G. The role of the consultant pharmacist in the NHS. Clinical Pharmacist 2015;**9**(7).
51. Ghent University. Master of Science in Pharmaceutical Care. Secondary Master of Science in Pharmaceutical Care 2015-2016. https://oasis.ugent.be/studiekiezer-web/nl/afstudeerrichting/JMFAZO
52. Universiteit Antwerpen. Master of Science in Pharmaceutical Care. Secondary Master of Science in Pharmaceutical Care 2015-2016. https://www.uantwerpen.be/nl/onderwijs/opleidingsaanbod/master-farmaceutische-zorg/profiel/.
53. KU Leuven. Master of Science in Pharmaceutical Care. Secondary Master of Science in Pharmaceutical Care 2015-2016. https://onderwijsaanbod.kuleuven.be/opleidingen/n/SC_50996454.htm.
54. Vrije Universiteit Brussel. Master of Science in Pharmaceutical Care. Secondary Master of Science in Pharmaceutical Care 2015-2016. http://www.vub.ac.be/opleiding/farmaceutische-zorg/programma.
55. Belgisch Staatsblad. Koninklijk Besluit betreffende de permanente vorming van de apothekers van de voor het publiek opengestelde officina's, 31 Juli 2014:56428-30.

Chapter 6

From ‘Summary’ to ‘About the Author’

1. SUMMARY

In **Chapter 1**, we describe that with an increasing complexity of medication use, the role of the community pharmacist as well becomes broader, resulting in more care-related activities. Sound pharmaceutical practices subdivides a pharmacist's tasks into basic and advanced pharmaceutical care. Basic pharmaceutical care is rather general and medication-centred, where advanced pharmaceutical care is individually-adapted and patient-centred, meant for those patients with special pathologies, multi-morbidity or poor medication adherence. However for both types of pharmaceutical care, co-operation with the patient and co-operation with other healthcare professions is needed.

During the last decades, extensive research in the community pharmacy field showed that the involvement of a community pharmacist in patient care can make a difference. Considering pharmaceutical care, multiple programs – both basic and advanced – can be identified across different parts of the world. Such programs range in complexity, but are of value and may be cost-effective.

Optimizing pharmaceutical care in Belgium, especially for chronic care patients and patients with difficult medication schemata, has a great potential to improve treatments and overall cost savings as these groups consume a disproportionate share of health care expenditures. As the number of chronic care patients and patients with difficult medication schemata is increasing, it would be unfortunate that the added value of a community pharmacist's clinical input is not maximally utilized. These patients require surely a patient-centered and multidisciplinary care approach. The ultimate goal is to ensure that these people derive maximum benefits from their drug therapy.

In this doctoral thesis, we developed and evaluated advanced pharmaceutical care services (i.e. cognitive pharmacy services) for chronic care patients. Therefore, we focused on two patient groups that are increasingly present in ambulatory care and are burdensome for both the patient and the healthcare system. The first patient group included older patients with polypharmacy, and is addressed in **Chapter 2**. The second group targeted in this doctoral thesis considered patients witch Chronic Obstructive Pulmonary Disease (COPD) as an example of chronic disease. This patient group is addressed in **Chapter 3**.

In **Chapter 2 Part 1**, we first performed a systematic literature review to get an insight in the overall prevalence of Potentially Inappropriate Prescribing (PIP) for older community-dwelling patients in Europe. We showed that about one fifth of all community-dwelling older patients had at least one PIP. Additionally, reviewing the drugs and drug classes mainly associated with PIP, we observed that anxiolytics, antidepressants and non-steroidal anti-inflammatory and anti-rheumatic products were mostly involved in PIP. The risk factors most often positively associated with PIP were polypharmacy, poor functional status and depression.

To tackle this issue from the community pharmacy, in **Chapter 2 Part 2,** we developed an advanced pharmaceutical care service that included a medication screening originating from the community pharmacy, based on solely dispensing records. To perform the medication screening, an explicit screening tool containing PIP-items with high clinical relevance for primary care was compiled. The screening tool was as well checked to be feasible in a typical community pharmacy practice. The development of this screening tool resulted in the Ghent Older People's Prescriptions community Pharmacy Screening (GheOP³S-)tool, a list containing 83 PIP-items.

In **Chapter 2 Part 3,** the newly developed GheOP³S-tool was validated using the results of an observational study, performed on acutely hospitalized older patients with polypharmacy. Almost all PIP-items detected with the GheOP³S-tool were considered 'serious' or 'significant' according to the treating geriatrician. Additionally, for 80% of patients, the proposed alternative treatment plan was (partially) accepted. Comparing the GheOP³S-tool to a full clinical medication review, about one third of PIP-items were detected. These results show that using the GheOP³S-tool to systematically screen the medication use of older patients with polypharmacy, could ultimately optimize patient outcomes. This way, community pharmacists initiate a process that – in some cases – requires discussion with the prescribing physicians. Therefore, performing medication screening with the GheOP³S-tool could also further improve interdisciplinary communication and collaboration.

Subsequently, in **Chapter 2 Part 4 and 5,** we evaluated PIP-prevalence according to the GheOP³S-tool, based on two observational studies. The first was executed in about 200 Belgian community pharmacies and included about a thousand ambulatory older patients with polypharmacy. Analogously, a second observational study, included 400 institutionalized patients with polypharmacy from 10 nursing homes in Flanders. PIP prevalence according to the GheOP³S-tool appeared to be high in both ambulatory and institutionalized patients, with at least one detected item in more than 95% of patients. As well, in almost all patients, more than one PIP-item was detected. Most prevalent PIP-items appeared to be long-term use of benzodiazepines, no Ca/VitD supplementation with elevated osteoporotic risk and long-term use of antidepressant agents.

In summary, in **Chapter 2**, we demonstrated that a new tool to screen for PIP in older patients with polypharmacy is very effective to detect potential points for prescribing optimization. Additionally, we showed that the tool detects items that are clinically relevant and that the room for improvement in both ambulatory and institutionalized Belgian older adults with polypharmacy is large.

Subsequently, in **Chapter 3 Part 1** we describe COPD as a disease and possibilities for COPD management optimization. In Belgium, about 2 to 3% of the population has COPD. COPD is irreversible and progressive disease. The pathological changes found in COPD result in physiological abnormalities such as mucus hypersecretion, progressive airway obstruction, air trapping, gas exchange abnormalities, and systemic effects. For patients with COPD however, exacerbations of respiratory symptoms put a significant burden on their quality of life. Exacerbations have a characteristic response with increased inflammation. There is also increased dyspnoea and possible hypoxaemia. COPD puts a significant burden on the patient's health as it is ranked second for Disability-Adjusted Life Years lost. According to the World Health Organization, COPD is the 3th ranked cause of death worldwide. Besides the human burden of COPD, as well the economic burden is high. In the European Union both the indirect and direct costs for the treatment of COPD approximately count for 6% of the total European healthcare budget.

Although COPD can be managed well with both non-pharmacological (e.g. smoking cessation, pulmonary rehabilitation) and pharmacological options (e.g. bronchodilators), adherence to therapy is often suboptimal. Only about half of the COPD population takes his medication as prescribed. Additionally, administration through inhalation devices seems to be problematic for many patients with COPD. About one fifth of patients with COPD make major inhalation errors. Both inhaler mishandling and suboptimal medication adherence are associated with reduced disease control.

In **Chapter 3 Part 2**, we evaluated the results of a Randomized Controlled Trial (RCT) including about 700 patients in Belgium. This RCT researched the effectiveness of a pharmaceutical care intervention, provided by the community pharmacist that focuses on inhalation technique and medication adherence (the PHARMACOP-protocol). This RCT showed that the PHARMACOP-protocol significantly improved inhalation technique and medication adherence. Moreover, the intervention significantly decreased the number of hospitalizations in the intervention group, compared to the control group.

Nevertheless, in **Chapter 3 Part 3**, we observed that the PHARMACOP-protocol is not yet fully implemented in the Belgian community pharmacies. In more than 70% of 80 interviewed pharmacists, only about half of the protocol items for both first and follow-up prescriptions were routinely implemented. Pharmacists additionally reported significant barriers to implementation of this protocol in daily practice, such as lack of time, no integration in pharmacy software and too much administrative burden.

To address medication adherence in the community pharmacy, in **Chapter 3 Part 4**, we observed that a self-report measure of adherence (the Medication Adherence Report Scale – MARS-5) was not valid to identify nonadherent users of inhalation medication among patients with COPD, compared to the medication refill adherence (MRA) as a reference.

In conclusion, in Chapter 3, we demonstrated that a pharmaceutical care intervention improves both medication-related (inhalation technique and medication adherence) and patient-related (hospitalization) outcomes. Currently, a solid base of pharmaceutical care for patients with COPD is already provided by Belgian community pharmacists, however, some additional items (e.g. smoking cessation counselling) should be routinely addressed. Implementing facilitators (i.e. simplify administrative burden, remuneration, software support) could further optimize the current provision of pharmaceutical care for these patients.

2. SAMENVATTING

In **Hoofdstuk 1** beschrijven we dat met de stijgende complexiteit van medicatiegebruik, de rol van de officina-apotheker breder wordt. Dit resulteert in meer zorggerelateerde activiteiten voor de officina-apotheker. De 'Goede Officinale Praktijken' verdeelt de taken van een apotheker in basis en voortgezette farmaceutische zorg. Basis farmaceutische zorg is eerder algemeen en stelt de medicatie centraal in de begeleiding. Voortgezette farmaceutische zorg is daarentegen individueel aangepast en stelt de patiënt centraal. Deze laatste is dan ook vooral bedoeld voor patiënten met speciale pathologieën, multimorbiditeit of slechte therapietrouw. Voor beide types van farmaceutische is hoe dan ook een samenwerking met de patiënt en andere gezondheidszorg medewerkers noodzakelijk.

Gedurende de laatste tientallen jaren, toonde uitgebreid onderzoek vanuit de officina-apotheek aan dat de betrokkenheid van een officina-apotheker in de patiëntzorg een verschil kan betekenen. Wat betreft farmaceutische zorg, kunnen wereldwijd zowel basis als voortgezette programma's geïdentificeerd worden. Dergelijke programma's variëren in complexiteit maar zijn waardevol en mogelijks kosteneffectief.

Het optimaliseren van farmaceutische zorg in België zou veel behandelingen kunnen verbeteren en meer kosten besparen. Dit in het bijzonder voor chronische patiënten en patiënten met moeilijke medicatieschema's. Deze patiënten verbruiken immers een disproportioneel aandeel van de uitgaven in de gezondheidszorg. Aangezien het aantal dergelijke patiënten blijft stijgen, zou het zonde zijn om de meerwaarde van klinische input door de officina-apotheker niet aan te wenden. Deze patiënten verdienen immers een patiëntgerichte en multidisciplinaire aanpak met als uiteindelijk doel maximaal voordeel uit hun farmacotherapie te halen.

In deze doctoraatsthesis ontwikkelden en evalueerden we voortgezette farmaceutische zorg diensten – ook wel "cognitive pharmacy services" genoemd – voor chronische patiënten. We plaatsten onze focus op twee patiëntgroepen die almaar meer aanwezig zijn in de eerstelijnstgezondheidszorg, die een significante last betekenen voor de patiënt en druk zetten op de kosten in de gezondheidszorg. De eerste groep omvat oudere patiënten met polyfarmacie en wordt behandeld in **Hoofdstuk 2**. De tweede groep omvat patiënten met Chronic Obstructive Pulmonary Disease (COPD) als een voorbeeld van een chronische pathologie. Deze groep wordt behandeld in **Hoofdstuk 3**.

In **Hoofdstuk 2 Deel 1** voerden we een systematische review uit om inzicht te krijgen in de algemene prevalentie van mogelijke Geneesmiddel Gebonden Problemen (GGP) voor oudere ambulante patiënten in Europa. We toonden aan dat ongeveer één vijfde van de Europese ambulante oudere patiënten minstens één GGP had. Daarnaast evalueerden we ook de geneesmiddelen en geneesmiddelgroepen die het meest geassocieerd waren met GGPs. Dit bleek vooral om anxiolytica, antidepressiva en niet-steroïdale anti-inflammatoire middelen te gaan. De risicofactoren die het meest geassocieerd waren met GGPs, betroffen polyfarmacie, slechte functionele status en depressie.

Om dit probleem vanuit de officina-apotheek aan te pakken, ontwikkelden we een voortgezette farmaceutische zorg dienst in **Hoofdstuk 2 Deel 2**. Deze dienst omvat een medicatiescreening die opgestart wordt vanuit de officina-apotheek en louter gebaseerd is op aflevergegevens. De medicatiescreening gebeurt op basis van een expliciete screening tool die GGPs bevat met hoge klinische relevantie voor de eerste lijn. Voor alle items die in deze tool opgenomen zijn, werd ook nagegaan of het haalbaar is om erop te screenen in de typische Belgische officina-apotheek praktijk. De ontwikkeling resulteerde in de Ghent Older People's Prescriptions community Pharmacy Screening (GheOP³S-)tool, een lijst van 83 items.

In **Hoofdstuk 2 Deel 3** valideerden we vervolgens de nieuw ontwikkelde GheOP³S-tool. We gebruikten hiervoor de resultaten van een observationele studie, uitgevoerd op 60 acuut gehospitaliseerde oudere patiënten met polyfarmacie. Bijna alle GGPs die bij deze patiënten gedetecteerd werden met de GheOP³S-tool, bleken 'ernstig' of 'significant' volgens de behandelende geriater. Daarenboven werd voor 80% van de items het alternatieve behandelingsschema dat voorgesteld was door de apotheker, (deels) aanvaard. Wanneer de resultaten van de screening met de GheOP³S-tool vergeleken werd met de resultaten van een volledige klinische medicatiereview, bleek dat ongeveer één derde van alle mogelijke problemen reeds gedetecteerd werd. Deze resultaten tonen aan dat de GheOP³S-tool kan gebruikt worden om systematisch het medicatiegebruik van oudere patiënten met polyfarmacie te screenen. Met gebruik van de GheOP³S-tool initiëren officina-apothekers echter wel een proces dat in sommige gevallen overleg vereist met de voorschrijvende arts(en). Op die manier kan het gebruik van de GheOP³S-tool ook nog bijdragen tot interdisciplinaire communicatie en samenwerking.

Vervolgens in **Hoofdstuk 2 Deel 4 en 5**, evalueerden we via twee observationele studies de prevalentie van GGPs in België. De eerste studie werd uitgevoerd in ongeveer 200 Belgische officina-apotheken en includeerde een duizendtal ambulante oudere patiënten met polyfarmacie. Analoog voerden we een tweede observationele studie uit met 400 oudere rusthuisbewoners met polyfarmacie, afkomstig uit 10 Vlaamse rusthuizen. De prevalentie van GGPs bleek in beide settingen hoog te zijn, met minstens één gedetecteerd item in 95% van de patiënten. De meest prevalente GGPs waren het langdurig gebruik van benzodiazepines, geen calcium en vitamine D-supplementen voor patiënten met een verhoogd osteoporoserisico en het langdurig gebruik van antidepressiva.

Samengevat, in **Hoofdstuk 2** ontwikkelden we een nieuwe voortgezette farmaceutische zorg dienst, en toonden we aan dat de nieuwe GheOP³S-tool om te screenen voor GGPs bij oudere patiënten met polyfarmacie zeer effectief is om mogelijke verbeterpunten in het voorschrijfproces te detecteren. Daarenboven toonden we aan dat de tool items detecteert die klinisch relevant zijn en dat de ruimte voor verbetering in zowel de ambulante als rusthuissetting groot is.

De tweede groep waarop we in deze thesis focussen, betreft patiënten met COPD als voorbeeld van een chronische pathologie. In **Hoofdstuk 3 Deel 1** beschrijven we COPD als ziekte, naast de mogelijkheden voor de optimalisatie van COPD-management. In België lijdt ongeveer 2 à 3% van de bevolking aan COPD. COPD is onomkeerbaar en progressief. De pathologische veranderingen die bij COPD optreden, resulteren in fysiologische abnormaliteiten zoals oversecretie van mucus, progressieve luchtwegobstructie, problemen met gasuitwisseling en andere systemische effecten. Voor patiënten met COPD echter, worden vooral de opstoten van hun respiratoire symptomen als een grote last ervaren. Dergelijke exacerbaties gaan gepaard met een karakteristieke respons van verhoogde inflammatie. Er is ook meer kortademigheid en mogelijke hypoxie. Volgens de World Health Organization, is COPD de derde meest voorkomende doodsoorzaak ter wereld. Naast de gevolgen voor de patiënt zelf, zet COPD ook een grote druk op de economie. In de Europese Unie, worden de directe en indirecte kosten voor de behandeling van COPD geraamd op ongeveer 6% van het totale gezondheidszorgbudget.

Hoewel COPD goed kan behandeld worden met zowel niet-farmacologische als farmacologische maatregelen, is de therapietrouw soms suboptimaal. Slechts ongeveer de helft van de patiënten met COPD neemt zijn therapie zoals voorgeschreven. Daarbovenop blijkt het toedienen van de medicatie via inhalatie voor veel patiënten met COPD problematisch. Zowel het foutief gebruik van de inhalatietoestellen als slechte therapietrouw zijn beide geassocieerd met verminderde ziektecontrole.

In **Hoofdstuk 3 Deel 2** evalueerden we de resultaten van een gerandomiseerde gecontroleerde studie (RCT) die ongeveer 700 Belgische patiënten met COPD includeerde. Deze RCT onderzocht de doeltreffendheid van een voortgezette farmaceutische zorg dienst die focust op inhalatietechniek en therapietrouw (het PHARMACOP-protocol) en voorzien wordt door de officina-apotheker. Deze RCT toonde aan dat het PHARMACOP-protocol de inhalatietechniek en therapietrouw van de interventie patiënten significant verbeterde ten opzichte van de controlegroep. Daarenboven lag het aantal hospitalisaties in de interventiegroep significant lager dan in de controlegroep.

Echter, in **Hoofdstuk 3 Deel 3**, observeerden we dat het PHARMACOP-protocol nog niet volledig geïmplementeerd wordt in Belgische officina-apotheken. Meer dan 70% van de bevraagde apothekers bleek slechts de helft van de items van het protocol routinematig in de apotheek te implementeren. Officina-apothekers vermeldden daarenboven significante barrières om het protocol in de dagdagelijkse praktijk te implementeren zoals tijdsgebrek, geen integratie in de apotheeksoftware en te veel administratieve belasting.

Om therapietrouw in de officina-apotheek aan te kaarten, is ook een valide methode om dit te evalueren noodzakelijk. In **Hoofdstuk 3 Deel 4** toonden we aan dat een zelfrapporteringsmethode voor therapietrouw (i.e. de Medication Adherence Report Scale, MARS-5) niet bruikbaar was om niet-therapietrouwe patiënten met COPD te identificeren. We gebruikten in deze studie de Medication Refill Adherence (MRA) als referentie.

In conclusie, in **Hoofdstuk 3**, toonden we aan dat voorgezette farmaceutische zorg door officina-apothekers zowel medicatiegerelateerde uitkomsten (inhalatietechniek, therapietrouw) als patiëntgerelateerde uitkomsten (hospitalisaties) verbetert. Momenteel wordt reeds een goede basis aan farmaceutische zorg voor patiënten met COPD verstrekt, echter een aantal additionele items zoals begeleiding bij rookstop, zouden routinematig moeten geïmplementeerd worden. Het implementeren van facilitatoren zou verder de huidige provisie van farmaceutische zorg bij deze patiënten kunnen verbeteren. Het betreft dan het versimpelen van de administratieve last, voorzien van remuneratie of ondersteuning via de software.

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3. CURRICULUM VITAE

3.1. Personal Information & Education

Name:	Eline Tommelein
Date of birth:	October 22nd, 1988
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Private address:	Hutsepotstraat 25 0201
	9052 Zwijnaarde
2009 – 2011:	Master of Science in Drug Development
	Ghent University
	Master dissertation: *"Physicochemical characterization and expression efficiency of different liposome:mRNA complexes for mRNA vaccination"*
2006 – 2009:	Bachelor of Science in Pharmaceutical Sciences
	Ghent University
2000 – 2006:	Latin – Mathematics
	Onze-Lieve-Vrouwe College, Oostende

3.2. Publications

3.2.1. Scientific publications in peer-reviewed journals

1. **Effectiveness of pharmaceutical care for patients with chronic obstructive pulmonary disease (PHARMACOP): a randomized controlled trial**
   Tommelein E, Mehuys E, Van Hees T, Adriaens E, Van Bortel L, Christiaens T, Van Tongelen I, Remon JP, Boussery K, Brusselle G
   *British Journal of Clinical Pharmacology 2014; **77**(5): 756-66.*
2. **Accuracy of the Medication Adherence Report Scale (MARS-5) as a quantitative measure of adherence to inhalation medication in patient with COPD**
   Tommelein E, Mehuys E, Van Tongelen I, Brusselle G, Boussery K
   *Annals of Pharmacotherapy 2014; **48**(5):589-95.*
3. **Pharmaceutical Care for patients with COPD in Belgium and views on protocol implementation**
   Tommelein E, Tollenaere K, Mehuys E, Boussery K
   *International Journal of Clinical Pharmacy 2014;**36**(4):697-701*
4. **Improving inhaler adherence in patients with chronic obstructive pulmonary disease: a cost-effectiveness analysis**
   van Boven J, Tommelein E, Boussery K, Mehuys E, Vegter S, Brusselle G, Rutten-van Mölken M, Postma M
   *Respiratory Research 2014; **15**:66*
5. **Older patients' prescriptions screening in the community pharmacy: development of the Ghent Older People's Prescriptions community Pharmacy Screening (GheOP³S-) tool**
   Tommelein E, Petrovic M, Somers A, Mehuys E, Van Der Cammen T, Boussery K
   Journal of Public Health
6. **Potentially inappropriate prescribing in community dwelling older people across Europe: a systematic literature review**
   Tommelein E, Mehuys E, Petrovic M, Somers A, Colin P, Boussery K
   *European Journal of Clinical Pharmacology 2015; **71**(12):1415-27*

3.2.2. Publication in non-peer-reviewed journals

1. **De doeltreffendheid van farmaceutische zorg bij patiënten met COPD: bespreking van de recent gepubliceerde PHARMACOP-studie**
   Tommelein E, Mehuys E, Van Hees T, Adriaens E, Van Bortel L, Christiaens T, Van Tongelen I, Remon JP, Boussery K, Brusselle G
   *Farmaceutisch Tijdschrift Van België 2014; **3**:4-14*
2. **Het optimaliseren van de farmacotherapie bij patiënten met Chronisch Obstructief Longlijden (COPD) in de officina-apotheek: een kosten-effectiviteitsanalyse**
   van Boven J, Tommelein E, Boussery K, Mehuys E, Vegter S, Brusselle G, Rutten-van Mölken M, Postma M
   *Farmaceutisch Tijdschrift Van België 2014; **3**:15-16*

3.3. Conference participations

3.3.1. Oral presentations

- **Second PharmCare Symposium, September 15th, 2012, Brussels, Belgium**
  Effectiveness of pharmaceutical care for patients with COPD (PHARMACOP): A randomized controlled trial
- **ESPACOMP 2012, October 25-27th, 2012, Ghent Belgium**
  Medication Adherence Report Scale (MARS-5) not valid as a quantitative measure of adherence to inhalation medication in patients with COPD.
- **PRISMA Symposium, January 15th 2013, Amersfoort, The Netherlands**
  Doeltreffendheid van farmaceutische zorg bij patiënten met COPD (PHARMACOP): een gerandomiseerde gecontroleerde studie
- **ESPACOMP 2013, November 14-16th, 2013, Budapest, Hungary**
  Pharmaceutical care for patients with COPD (PHARMACOP-trial): focus on adherence outcomes.
- **PRISMA Symposium, May 20th 2014, Amersfoort, The Netherlands**
  Identificatie van mogelijks farmacotherapiegerelateerde problemen (mFTPs) bij geïnstitutionaliseerde ouderen in Vlaanderen adhv de GheOP³S-tool.
- **Third PharmCare Symposium, February 7th, 2015, Zeist, Belgium**
  Screening op mogelijke geneesmiddel gebonden problemen in de officina-apotheek: ontwikkeling en eerste resultaten van de GheOP³S-tool
- **PRISMA Symposium, May 19th 2015, Amersfoort, The Netherlands**
  Screening op mogelijke farmacotherapiegerelateerde problemen in de officina-apotheek: ontwikkeling en eerste resultaten van de GheOP³S-tool
- **39ste Winter Meeting 2016, Belgian society for Geriatrics and Gerontology, February 26th-27th, 2016, Oostende, Belgium**
  Screening for potentially inappropriate prescribing in the community pharmacy: development, validation and first results of the GheOP³S-tool.
- **WONCA Europe conference 2016, June 15th – 18th, 2016, Copenhagen, Denmark**
  Screening for potentially inappropriate prescribing in the community pharmacy: development and first results of the GheOP³S-tool

3.3.2. Poster Presentations

- **ESPACOMP 2012, October 25-27th, 2012, Ghent Belgium, awarded with the poster prize.**
  Beliefs about Medicines Questionnaire (BMQ) could be helpful in predicting (non)adherent behavior in patients with COPD.
- **Second PharmCare Symposium, September 15th, 2012, Brussels, Belgium**
  Begeleiding van COPD-patiënten in de apotheek: Ontwikkeling en implementeerbaarheid van een farmaceutisch zorgprotocol
- **Third PharmCare Symposium, February 7th, 2015, Zeist, Belgium**
  De GheOP³S-tool: haalbaarheid in de dagelijkse praktijk anno 2014

- **75th FIP World Congress of Pharmacy and Pharmaceutical Sciences 2015, September 29th – October 3rd, 2015**

  Screening for potentially inappropriate prescribing in the community pharmacy: development and first results of the GheOP³S-tool.

3.4. Training

- **Klinische Chemie Cyclus**

  (5 modules) 2013, georganiseerd door PAO-farmacie, Utrecht, Nederland.

- **Periodieke Individuele Analyse Farmacotherapie (PIAF-) opleiding Medicatiebeoordeling**

  Achtdaagse opleiding (9/09/2014, 10/09/2014, 07/10/2014, 11/11/2014, 13/01/2015, 10/03/2015, 14/04/2015, 26/05/2015), georganiseerd door PAO-farmacie, Utrecht, Nederland.

- **Frans Voor Apothekers**

  (12u) 2016, georganiseerd door Universitair Centrum voor Talenonderwijs, Universiteit Gent

3.5. Master thesis support

- **Kathleen Tollenaere, 1st Master Pharmaceutical Care (2011-2012).**

  Begeleiding van COPD-patiënten in de apotheek: Ontwikkeling en implementeerbaarheid van een farmaceutisch zorgprotocol.

- **Katrien Van Meirhaeghe, 1st Master Pharmaceutical Care (2012-2013).**

  Adviesverstrekking omtrent geneesmiddel-alcohol interacties in de praktijk.

- **Charlotte Van Damme, 1st Master Pharmaceutical Care (2013-2014).**

  De prevalentie van onoordeelkundig voorschrijven bij ouderen: literatuuronderzoek en een observationele studie bij geïnstitutionaliseerde ouderen.

- **Eva Pattyn, 1st Master Pharmaceutical Care (2013-2014).**

  Screening op onoordeelkundig voorschrijven bij Belgische rusthuisbewoners m.b.v. de GheOP³S-tool: een observationele studie.

- **Kristof Mattelin, 1st Master Pharmaceutical Care (2013-2014).**

  De rol van de apotheker in het reduceren van onoordeelkundig voorschrijven bij rusthuispatiënten: een observationele studie.

- **Eline Christiaen, 1st Master Pharmaceutical Care (2014-2015).**

  QT-prolonging and anticholinergic medication in older Belgian polypharmacy patients.

- **Simon Capiau, 1st Master Pharmaceutical Care (2014-2015).**

  Alcoholgebruik in de thuiswonende oudere populatie & interacties met hun chronische en acute medicatie.

- **Sara Botte, 1st Master Pharmaceutical Care (2015-2016).**

  Anticholinergica en de herkenning van hun bijwerkingen in de officina-apotheek