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Appraisal of the appropriateness of prescribing in community-dwelling oldest old (aged 80+)

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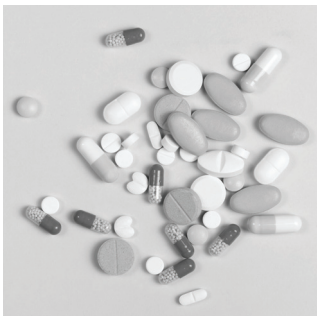
Introduction

Chapter 1: Contents

In the past century, improvements on economic, social and medical scale have led to an increase in life expectancy at birth and to an increased age at death. As people get older, the share of older adults (those aged 65 years, and older) will increase [1]. For most Western countries, the older population is ageing itself, as the share of the oldest old (those aged 80 years, and older) will increase greatly [1].

Ageing of the population is a challenge for health care systems. The higher number of older adults will lead to a higher number of older adults needing medical care. Treatment or prevention of disease will generally include the treatment with medications. Yet, older adults are more sensitive to the effects of medications and are therefore more at risk for medication related problems.

In this introduction, an overview is given on the challenge of ageing, on how medications are prescribed, and on what challenges arise in the rational prescribing process in older adults. Several methods to appraise the medication use are listed, with a specific focus on the formalisation of the assessment of appropriate prescribing using explicit criteria for potentially inappropriate medications.



1.1 The oldest old, and health related problems

Demographics of the oldest old

Ageing is an inevitable and continuous process that affects all organs and organ processes [2]. Ageing affects different aspects of life, including biological, psychological and social changes [3]. Biological changes refer to the gradual deterioration of the body. Decreasing sensory or perceptual processes lead to a decrease in the adaptive capacity to new situations. Social changes concern the altering patterns in the role older adults take up in society [4]. A cut-off based on the calendrical age may not always be the correct indicator for physical and mental age groups, or for determining the retirement age.

There is no consensus on how to define older adults or age groups. In earlier research, the term 'elderly' was used to define older adults, but is no longer indicated due to the pejorative connotation. Old age usually refers to the later part of life, but no universal definition was installed. The term 'oldest old' was introduced 30 years ago [5]. It generally encompasses the oldest age groups in the setting studied. Depending on the inclusion criteria of studies, different age-groups can be used as a result (e.g. 85 years, and older [6, 7]). The MeSH term states 'aged 80 years, and older', and equates it with the term 'oldest old', but not with the term 'elderly'.

In this thesis, we use
'adults, aged 65 years and older' as the definition for old age and older adults
'adults, aged 80 years and older' as the definition for the oldest old.

Currently, older persons (aged 65 years, and over) account for 8.3 % of the world population. This share of older persons is expected to increase to 11.7% by 2030 [8]. Europe (509 million inhabitants) has the highest prevalence of older adults (18.9%), and is expected to age more rapidly in comparison with other continents. Europop2013, and World Population Prospects 2017 indicate that the share of oldest old in Europe (aged 80 years, and over), is to rise from 5.3% to 7.1% in 2030 (equalling 10.900.000 oldest old extra in comparison with today) [9].

For Belgium, there are currently 2.063.000 Belgians aged 65 years and older (18.3% of the population), and 618.593 persons aged 80 and older (5.5% of the population, source: www.bestat.economie.fgov.be). This

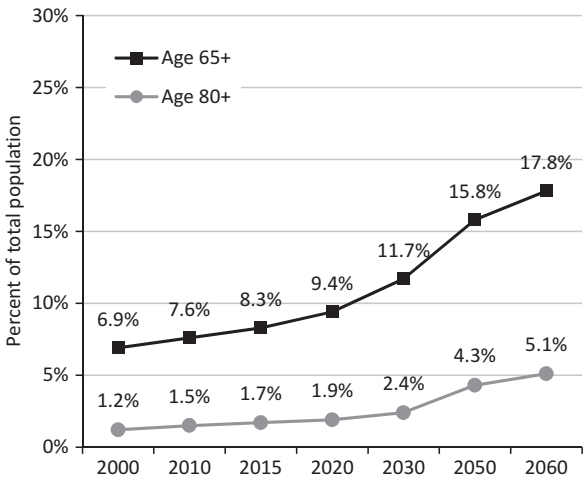


***Figure 1.1**: Demographic evolution of the older global population.*

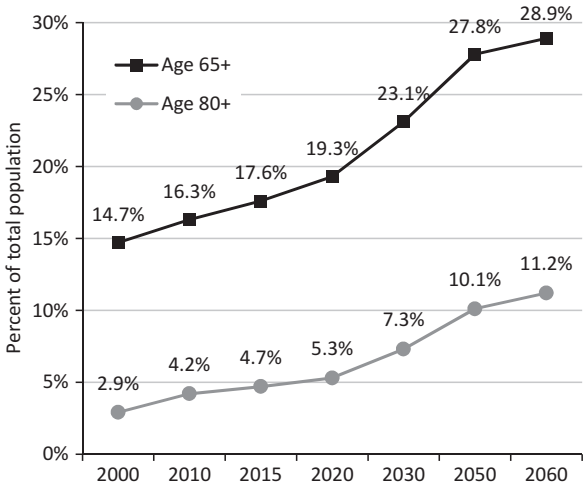


***Figure 1.2:** Demographic evolution of the older population in Europe.*

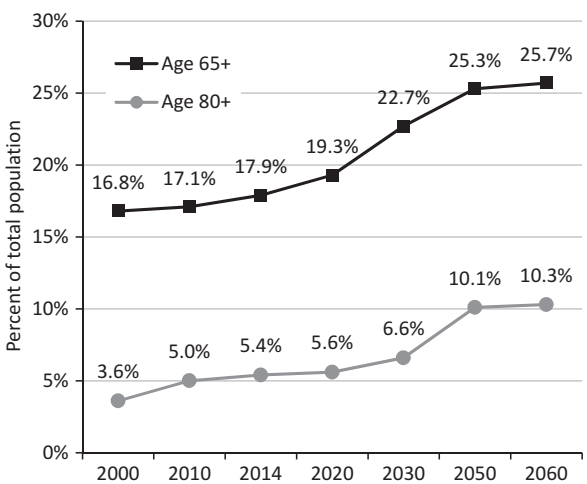


***Figure 1.3:** Demographic evolution of the older population in Belgium*

older population is ageing, as the share of the oldest old (80 years and older) within the older population is expected to increase. Demographic projections suggest that by 2030 around 22.7% of the population will be 65 years and older [10]. The share of the oldest old will rise to 6.6%, equalling approximately 120.000 people extra in comparison with 2014.

Clinical characteristics of the oldest old

Health is defined in numerous ways. According to the World Health Organisation, health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity. For older persons, health or being healthy is more difficult to define. With advancing age, the risk of developing clinical problems will rise. The oldest old are characterised by having **various geriatric problems** [11, 12] (e.g. cognitive, visual, and hearing decline; frailty; or disabilities), and almost all are diagnosed with at least one clinical problem. The prevalence of diabetes, osteoporosis, osteoarthritis, chronic kidney disease and hypertension in the oldest old is higher compared to that of older adults [13]. In contrast, the prevalence of heart failure is lower in the oldest old [13].

The care for older adults is challenging due to the increased risk for a higher level of multimorbidity, disability, or frailty. These concepts are overlapping to some extent, but are distinct concepts [14]. A wide array of assessment methods are available, with varying levels of complexity. Multimorbidity can be measured with either a disease count, but also using more comprehensive methods that incorporate the impact on different body systems. Frailty can be measured by either just the physical skills of older adults, but also more comprehensive methods including the social status, nutritional status, cognition, and the medication intake. Disability usually gives an indication for the level of dependence. It can pertain to the competence to perform activities of daily living, but it also pertains to the social construct of disability.

The level of multimorbidity has been related with several patient-outcomes (e.g. mortality and hospitalisation) [15]. Multimorbidity seems to be an important predictor for mortality, yet studies remain inconclusive. The overall interpretation is limited because of the heterogeneity of assessment methods, or because a less clear definition of disease in the oldest old. Given example, cut-off values for diabetes or hypertension are still debated and are potentially a less clear predictor [16]. In addition, a 'survivor' effect can complicate the interpretation. Some studies describe the decreasing physical abilities (e.g. grip strength, sarcopenia) as a major

predictor for mortality [16].

Ageing will inevitably lead to body changes affecting all body-systems, potentially limiting participation in physical activity or general activities of daily living. Ageing can affect cognitive functioning due to cognitive decline and the occurrence of dementia. A cognitive decline and a higher level of multimorbidity can impact daily life, by hindering possible participation in the community [17, 18]. A lower participation is a social risk factor and can lead to social isolation [19]. At a high age, people encounter personal losses at a higher rate. According to the SHARE data (a European survey of health, ageing, and retirement), most of the community-dwelling oldest old live alone (56%). The remaining either lived with their significant other (27%) or with their relatives (16%, although more in Southern European countries).

Surprisingly, despite increasing risks for developing disease and disability, studies characterise a large part of the oldest old as relatively fit and healthy [7, 11, 16]. And, despite personal losses, the oldest old perceive themselves as relatively happy [20]. Studies on older adults have shown a decreasing trend for doing activities of daily living (ADL or the independence in toileting, eating, mobility …) [21, 22]. Yet, in community-dwelling oldest old, the level of independence was found relatively high [23, 24], with up to 67% managing their activities of daily living with little to no limitations [22]. Possibly, due to a potential 'survivor' effect, only the most resilient or most healthy can live past a very high age.

In Belgium, most of the older adults live at home, even with a relative high level of multimorbidity. According to the Belgian Health Interview Survey, almost half of the older population (48,8%) reported at least one chronic condition, predominantly arthrosis (78.2%), high blood pressure (73.5%) and hyperlipidaemia (70.1%) [25]. In 2011, approximately 120.000 people resided in nursing homes, equalling 5.8% of the Belgian population above 65 years [26]. The federal government aimed to reduce the rate of institutionalisation by broadening the range of home assistance of nursing care at home and other formal care services [27, 28]. Multicomponent home care interventions (including case management, occupational therapy, rehabilitation) aimed to delay the institutionalisation of older adults [29].

Mortality events in 2013 occurred in nearly 61.000 Belgian oldest old, accounting for 56% of all mortality events that year (source: http://statbel.fgov.be/nl/statistieken/cijfers/bevolking/). Most common causes of death were cardiovascular disease (35%), cancer (17%) or respiratory related diseases (12%) [30]. Most common place of death in Belgium is the

hospital (46.9%) and a nursing home (27.2%) [31]

Pharmacokinetics and pharmacodynamics in the oldest old

Pharmacokinetic aspects

Pharmacotherapy in older adults is a complex process, influenced by pharmacokinetic and pharmacodynamic changes when ageing [2, 32–34]. Pharmacokinetic changes describe the processes of a drug in the body over the course of time, namely the absorption, distribution, transformation, and finally clearance of a drug. When ageing, almost all these processes are affected.

- The rate of **absorption** of medications affects the time course and intensity of the initial drug action. Age-related changes in the absorption phase include changes in the gastric acidity and reduced mesenteric blood flow, absorption surface, and transport proteins. The absorption of medications can thus be altered by medications affecting the gastric motility (e.g. anticholinergic drugs), or by medications affecting the gastric pH level (e.g. antacids can delay absorption of psychotropic drugs).
- The medication **distribution** is altered in the older body. As humans age, the mean body mass decreases and the body composition shifts towards a higher body fat mass. As a result, the half-life of lipid-soluble medications (e.g. benzodiazepines) is prolonged, resulting in a higher serum level of hydrophilic medications (e.g. digoxin). Distribution of medications is mediated through albumin or glycoprotein binding. Unbound medication concentrations determine the effect of the medication. Plasma albumin levels tend to decrease when ageing, while glycoprotein tends to increase. A reduction of these proteins (e.g. by ageing, or by malnutrition) might theoretically contribute to medication interactions, although their clinical effect is limited [35].
- A decrease in liver mass and blood flow to the liver leads to an increase in bioavailability of those active medications undergoing first-pass metabolism (e.g. opioids). For some medications, **metabolisation** or enzymatic transformation (predominantly in the liver) is needed in order to have effect. In the case the medications are pro-drugs, decreased first pass metabolism may lead to less active medications (e.g. ACE inhibitors) [2, 33].
- The predominant change in the older body is a decreased **elimination** of a vast array of medications [34]. A decreased liver mass and

decreased blood flow to the liver leads to a lower clearance of active substances that are metabolised by the liver (e.g. propranolol). Most importantly, the decline in renal function affects the elimination of medications, eliminated by the kidney (e.g. antibiotics, digoxin, beta-blockers …). Due to a lower glomerular filtration rate, medications or metabolites can accumulate in the body. The accumulation of medications with a narrow therapeutic margin (e.g. digoxin) can lead to adverse effects [35, 36].

Pharmacodynamic aspects

Pharmacodynamics describe the reaction of the human body to medications. Clinical observations indicate that older adults are **more susceptible** to the effects of medications. Age-related pharmacodynamic changes include a down- or upside regulation of receptors, a different receptor sensitivity, and a reduced homeostatic response in the older body [2]. There is however limited data available on pharmacodynamic differences in very old persons [37], but studies reported a number of drug effects in older adults (predominantly more intense sedative, anticholinergic or extrapyramidal effects).

Most commonly anticoagulants, cardiovascular and psychotropic drugs are linked with altered (usually increased) pharmacodynamic properties. Older persons have a higher risk of bleeding when taking anticoagulants (e.g. warfarin) [38], due to an increased risk of a vitamin K deficit, less coagulation factors in the blood, and a potential interaction between coumarine derivates and for instance NSAIDs. Benzodiazepines can lead to an increased level of sedation in older persons [39], because of a potential accumulation in the body and an associated prolonged duration of effect.

The case of anticholinergics

Medications with anticholinergic effects or anticholinergics have been linked to pharmacodynamic-induced adverse effects, and may depend on age-related pharmacodynamic changes, due to variations in receptor abundance, binding affinity, receptor displacement by other drugs, and physiological factors [40].

Anticholinergics were introduced in the past 50 years, but some were also withdrawn due to increasing evidence of high risks for side effects [41]. Medications with anticholinergic properties interact through competitive antagonism with cholinergic receptors (either nicotinergic or muscarinic) in the human body [42–48], and the effects are more severe

in older adults [43, 49–52].

Based on the location and subtype of muscarinic receptors, different physiological responses are mediated [53]. **Central anticholinergic side effects** include a decreased cognitive functioning in older adults (attention loss, psychomotor speed, working memory, , …) [54, 55], a higher risk for delirium [56], and a 2.8 times increased risk for being hospitalised for confusion or dementia [57]. In addition, a higher exposure to anticholinergics has been associated with altered emotions and behavioural disturbances [58, 59], impaired physical functioning [60–62] and a poorer performance on instrumental activities of daily living [63]. **Peripheral anticholinergic side effects** can also affect older adults and their quality of life. Dry mouth, the most prevalent side-effect, can be bothersome as it can lead to food ingestion problems, speech problems, or increased risks for oral infections due to a decreased saliva flow [64]. Constipation is also a prevalent symptom, that may have a significant impact on the quality of life [65]. Anticholinergics can also affect the eye, leading to dryness and blurred vision [66], and thus increasing the risk for having a fall.

1.2 Medication management, prescribing, and deprescribing

The general practitioner (GP) usually has an important role in the care for older adults, for the first diagnosis of clinical problems and the prescribing of medications. Older adults in Belgium see their GP on average every month, and more than 60% consults a medical specialist yearly [67].

The intake of medications is a daily routine in 51% of all Belgian individuals [25], and the number of prescribed medications is likely to rise with ageing [68]. According to data from the National Institute for Health and Disability (NIHDI, RIZIV in Dutch), 19% of all older adults have polypharmacy (the intake of multiple medications, most commonly defined as five or more). These older adults represent a major cost for the national health care system. The yearly pharmacological reimbursement costs for older patients with polypharmacy are an estimated 420.000.000€ (not including other health care usage) [69].

The oldest old are generally prescribed cardiovascular, nervous system, alimentary or blood(forming) medications [70–72]. The majority (71%) of community-dwelling older adults (in Italy) have at least one cardiovascular medication prescribed, predominantly ACE-inhibitors, diu-

retics, Beta-blocking agents or lipid-modifying agents [71]. Belgian older adults of 75 years and older reported use of predominantly lipid-modifying drugs (35%) and Beta-blocking agents (32%). Nervous system medications predominantly include hypno-sedatives (17% - 43%) [73, 74], and analgesics (45%) [75]. For Belgium, a high use of hypno-sedatives (20%) and antidepressants (12%) among older adults of 75 years and older was noted [25]. Alimentary medications generally include proton-pump inhibitors [76].

Medication management process

The process of setting a diagnosis and choosing appropriate medication in older adults is complex. The World Health Organisation defines the **rational prescribing** of medication as choosing the right medication, for the right patient, for the right indication at the right dosage in the right form and at the right price [77]. It involves not only the choice, but also the decision of optimal dosing and scheduling, informing and educating the patient, and doing the follow-up of the effectiveness of the medications.

Bell proposed a framework, consisting of five main domains, for the evaluation of medication prescriptions (Figure 1.4).

- The first main domain is the act of **prescribing** by clinicians. Clinicians need to assess and fill in the needs for a medication therapy, and the patient's preferences. The combined data input of medication data, patient data and possible drug formulary restrictions yield the output (a prescription). Potential threats for errors during electronic pre-

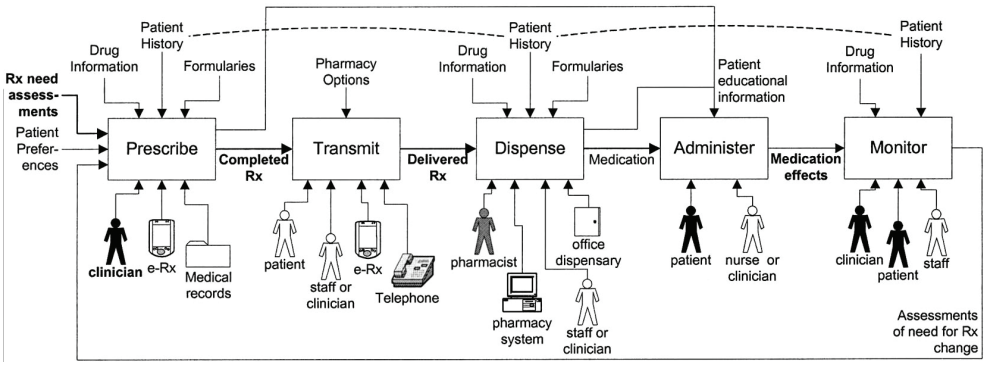


Figure 1.4. *A functional model of the medication management process (source: Bell, Cretin, Marken & Landman, 2004).*

scribing are mistakes during the selection of patients (wrong patient), clinical problems (wrong diagnosis, or not reporting a diagnosis), or medication selection (wrong dosages).

- The second domain is the **transmission** of the prescription. In primary care, patients usually perform this domain themselves, although telephoning or secure emailing of prescriptions by clinicians to pharmacists are possible. Potential threats include transcribing errors.
- The **dispense** activity can be done by clinicians (when medications are available on hand), or by pharmacists. Pharmacists more and more employ electronic systems to store and to access the same information as in the prescribing step. Potential threats include errors in the drug choice, meaning dispensing other medications.
- The **administration** of the medication involves the patient, and sometimes a wide range of other allied health personnel (e.g. nurses in the home or hospital setting). Potential beneficial aspects include the generation of medication administration aids, reminders for renewals, or the consultation of educational material. Potential threats mainly refer to adherence.
- Finally, the **monitoring** involves the patient and a clinician, but can also involve other allied health personnel. Feedback during this step could yield changes in the prescriptions of a patient. Potential beneficial aspects include the generation of alerts when a renewal of a medication was not done, the automated generation of questionnaires to detect adverse effects, or corollary orders (e.g. monitoring tests). Potential threats include the negligence to report adverse effects by the patient or health care professionals or non-adherence to medications.

Electronic systems can aid medication prescribers and dispensers during the whole process. Potential beneficial aspects of electronic systems include safety alerts (based on known allergies, interactions, laboratory tests), formulary alerts (e.g. to improve medication adherence), or the automatic possibility of dosage calculations.

Problems in the medication management

Older adults will have more complex clinical problems for which they may need **multiple medication prescribers**, who are neither geriatricians nor specialists in old age [84]. More medication prescribers can complicate the process of an optimal medication management in the care for poly-medicated older patients with multimorbidity. Medication

prescribers are generally not aware of potentially inappropriate prescribing [85].

Decreased cognitive and physical capabilities linked to ageing can affect the handling of medications (e.g. opening blisters, using an insulin gliding scale) and can lead to a **lower medication adherence** [86]. Educating older adults of the potential risk and benefits of medications and offering tools (e.g. medication boxes, …) can change their health beliefs and can increase adherence [87]. Older adults generally manage their medication intake themselves [88]. The major reason for non-adherence is forgetfulness [89, 90].

Medication errors and drug related problems

There are various definitions for medication errors. One definition is 'a medication error is a failure in the treatment process that may or may not lead to an adverse event' [91]. Errors can be classified according to whether they are mistakes, slips or lapses [92].

Drug Related Problems (DRPs) are defined as all events or circumstances that interfere with the patient experiencing the optimal outcome of pharmaceutical care [93]. The definition of DRPs is sometimes restricted to problematic actual outcomes, but can also include process aspects (e.g. potentially inappropriate prescribing, or distribution errors).

A recent systematic literature study reviewed 20 classification systems, of which seven were selected (overlapping different health care settings, countries, and development methods) for the construction of a new classification system for DRPs [94]. This new comprehensive classification system lists actual or potential DRPs according to two methods; either DRPs resulting from not reaching the treatment goals, or either that a drug treatment causes an undesirable effect [93]. Nine causes of DRPs have been identified, aiming to cover all events during all aspects of pharmacotherapy from the prescribing, the dispensing, monitoring, and to the incorrect usage of a medication (e.g. non-adherence), to even include unexpected effects of medications [93].

DRPs can arise during the prescribing phase in case of contra-indication (e.g. Beta Blocking agents and second or third degree heart block), in the absence of an indication, in case of an inappropriate combination with food/alcohol/other medications (e.g. NSAIDS in combination with warfarin), when an indication is not treated (e.g. no anticoagulant therapy in case of atrial fibrillation), or when a preventive therapy is not started (e.g. not prescribing statins for secondary prevention of cerebrovascular

problems). During the selection of the drug form, DRPs can arise when an inappropriate or suboptimal form is selected (e.g. for older adults, choosing a long-acting hypno-sedative agent). During the dose selection, DRPs can arise when choosing a dose that is either too low or too high. Alternatively, if the dose regimen is too frequent or not frequent enough, or subsequently if the dosage is not adapted to a changed disease state. During the selection of the dosage duration, DRPs can arise when the duration is either too short, or too long. DRPs can also arise during the transmission phase, during the dispensing of medications (e.g. incorrect delivery of medication packages), during the administration (e.g. non-adherence, or incorrect application/usage), or during the monitoring phase (e.g. no follow-up).

For the remainder of this thesis, focus is on DRPs during the prescribing phase.

Older adults are more sensitive to encounter DRPs, due to the pharmacokinetic- and dynamic changes, and the presence of multiple co-morbidities and medications. DRPs are a known risk factor for hospital admissions. DRPs have also been linked with increased risks for mortality [95, 96].

The medication groups most involved in DRPs are psychotropic agents, antiplatelet agents, hypoglycaemic medications and hypnosedatives [97], which are among the highest consumed groups of medications by Belgian older adults [98]. These medication groups can lead to unwanted symptoms such as dehydration, confusion, hallucinations, bleeding and increased risk of falls, and in return, these side effects can lead to the start of a **prescribing cascade** [99]. A prescribing cascade occurs when the adverse effect of medications is misinterpreted as a symptom of a new disorder: e.g. prescribing metoclopramide can induce Parkinson like symptoms (extrapyramidal symptoms) in older adults, for which levodopa can be prescribed [100]. The prescribing of new medications during a prescribing cascade can again lead to another adverse event.

Deprescribing

The medication management process is a cyclical process, where medications are reviewed and can be changed, altered in dosage or duration, or discontinued based on the occurrence of DRPs or on the needs

of the patient.

The actual process of **deprescribing** is little studied. Deprescribing has no official definition, but it generally encompasses the act of discontinuation of medications in favour of more benefits and less risks, in the light of the perceived life expectancy. Studies on deprescribing are heterogeneous in interventions and time, and methodological quality is low [78]. Deprescribing seems difficult to implement, but may be feasible. Scott, Hilmer, Reeve, Potter & Le Couteur have described essential steps for the discontinuation of medications [79, 80]. First, all medications a patient takes should be identified and matched with the indication before starting a new medication. Medication reviewers should answer questions as *why and when* a medication was started, or consider if a medication is part of a prescribing cascade. A second step is to ascertain the overall risk of drug induced harm. Medication reviewers should consider medication related factors (a high number of medications, high-risk medications) and patient related factors (high age, cognitive impairment, non-adherence …) to assess the overall risk for drug-induced harm. Third, the benefits and risks for all medications are to be determined. Additionally, medication reviewers should also consider if the benefit outweighs the risk for non-adherence, the patient's expected life span, and the patient's own expectations. Using this information, the medication reviewer should prioritise the medications for deprescribing according to pragmatic criteria; either greatest harm, least benefit, or medications easiest to discontinue (low risk for rebound effects or withdrawal symptoms), or according to the patient his wishes (most willing to discontinue). Finally a deprescribing plan can be installed to cease medications one at a time, whilst following and monitoring the patient closely for improvement in outcomes or onset of adverse effects.

Current evidence suggests deprescribing is safe and may be beneficial in older adults (65 – 79 years). In the oldest old, the few existing studies indicate that deprescribing does not modify mortality [81, 82]. Intervention techniques adapted to prescribers' beliefs, attitudes, knowledge, skills or behaviour may enable a more successful implementation [83].

1.3 Appraising the appropriateness of prescribing

Context

Researchers are faced with a lack of evidence found in medical sci-

entific literature regarding geriatric pharmacotherapy. Older adults are generally underrepresented in clinical studies, due to methodological challenges; a high non-response due to a high level of multimorbidity, a lower functional status, mental problems, hearing and/or visual problems. As a result, only a few studies have a unique focus on the community-dwelling oldest old [17, 101, 102]. Clinical trials on medication use do not aim to get a representative sample of the population in their studies, and exclude those too old (generally over 65 years), or too sick [103]. Also, most research focused on generating evidence based-treatments of a single medical condition (single disease guidelines), instead of the treatment of patients with multiple conditions [104].

Because of increasing age, age-related changes in pharmacokinetics and pharmacodynamics, co-occurrence of medical problems, and the potential intake of multiple medications, the risk of an adverse drug event can increase [105]. Adverse drug events are common (up to 23%) in older adults, and most (53%) are deemed preventable [105, 106]. Main risk factors for the occurrence of an adverse drug event are a higher number of medications, an impaired renal function, and potentially inappropriate prescribing [107]. The occurrence of an adverse event from correct therapy is possible and part of the normal risk/benefit assessment of therapy. It is an acceptable risk and can be appropriately managed by changes in dosage or active substances. On the contrary, adverse events stemming from inappropriate prescribing are much more problematic, and especially unacceptable, when not appropriately managed.

Rational prescribing by physicians

Following the guidelines from the World Health Organisation (WHO), rational prescribing starts with defining the patient's problem and formulating a working diagnosis. For each patient and their specific problem a therapeutic objective should be stated that is suitable for the patient in terms of effectiveness, safety and preferences. When the treatment is started, information and instructions should be given to the patient, and the treatment should be monitored.

The WHO defined six steps to optimise the process of rational prescribing. It starts (step 1) with defining the problem of the patient and (step 2) selecting the therapeutic objective (e.g. preventive, symptomatic, curative). Then, GPs need to (step 3) assess whether the selected therapy is indicated for the patient, and is as effective, safe, suitable and cheap as possible for an individual patient before prescribing a medication (step 4). Next, the phase of information giving, instruction giving (step 5) is

needed, so patients are knowable of the effects, side-effects, and duration of the therapy. Finally, (step 6) the monitoring of the treatment takes place, so that the treatment can be altered for a better outcome to be more safe or more convenient, or the treatment can be stopped.

Prescribing of medications is linked with every aspect of general practice, including clinical skills, knowledge of epidemiology, the patient, & the therapeutic arsenal.

Pharmaceutical care by pharmacists

Improving the quality of prescribing should not merely be the sole responsibility of medication prescribers. In addition, the role of community-pharmacists could potentially be enhanced (from patient education to guidance in the medication discontinuation). Pharmaceutical care involves the processes when pharmacists cooperate with patients and/or other professionals in the design, implementation, and monitoring of a therapeutic plan in order to yield specific therapeutic outcomes for patients [108].

In other words, pharmacists can aid patients by detecting and preventing potential and actual drug related problems. The basic pharmaceutical care pharmacists can provide is the assessment of a patients' problem, and providing the patient with tailored advice, or medication counselling. Advance pharmaceutical care envelops the individual and patient-centred care for patients with specific medical problems.

Pharmacists have a valuable place in the optimisation of medication therapies in older adults. Pharmacists in the community have the possibility to perform a medication review by screening medications for any DRPs.

Recently, the role of automatic decision support systems during the dispensing phase have been studied, with significant results for the majority of outcomes [109]. Interventions were introduced for pharmacists in the Netherlands to perform a medication review ('*Medicatiebeoordeling*' from the Royal Dutch Pharmacist Association), and also the Belgian Pharmacist Association strives for an optimisation of the medication use [110]. An electronical screening tool was developed recently in belgium, the Ghent Older People's Prescriptions community Pharmacy Screening tool (GheOP^{3}S) [111], that encompasses 83 explicit criteria, suited for an evaluation in community-pharmacies (predominantly medication-only). It is validated [112] and has shown a potential added value for screening the medications in both community-dwelling as nursing home residents [111, 113].

The hospital pharmacist or the pharmacists in nursing homes have the opportunity to closely interact with clinicians, nurses, and patients, and so, to promote the rational prescribing of medications [114]. Hospital pharmacists can perform an expert pharmacist review; the standardised pharmaceutical assessment of older peoples' prescriptions. This method has shown some improvements in the appropriateness of prescribing [115, 116], but it relies on interdisciplinary team work in a well organised clinical environment. Associations with improved clinical outcomes has also not been established [114].

Nurse involvement in pharmaceutical care

Nurses have a predominant role in the administration and monitoring of medications. Nurses can also be instrumental in detecting and reporting medication related problems, and can thus influence the choice of a medication during the prescribing step.

The job expectations of nurses regarding the medication management may not always be clear to them, creating different barriers in medication safety [117]. Nurses' knowledge on psychotropic pharmacology and geriatric pharmacology is low [118, 119]. Nurses perceive their knowledge on these topics most often as subpar, indicating the need for further education [118]. Nurses can influence the prescribing of more (psychotropic) medications when the care burden is too high [120, 121]. Recently, Pharmanurse was created to help nurses in the detection and reporting of adverse drug reactions, using a standardised method for the communication with the prescriber [122]. Pharmanurse supports and facilitates the interdisciplinary medication monitoring process through resident-specific screening lists for adverse drug reactions (ADRs) [123], although the valorisation work needs to be continued.

Multidisciplinary approaches

The first step in multistep multidisciplinary approaches is often the **identification of older adults at risk for an adverse drug reaction** [124]. The inherent difficulty is the differentiation between drug induced symptoms and non-drug related symptoms (so that a prescribing cascade will not take place). There are tools available for the detection of any potential ADRs, and for the detection of patients at risk. These tools include the GerontoNet ADR Risk Score [125] or the Brighton Adverse Drug Reaction Risk Model (BADRI) for the oldest old [126], or more specifically for the anticholinergic and sedative risk estimation, the Drug Burden Index [127].

A second step is the identification of any drug related problems following the medication choice, so that the risk for potentially inappropriate medications is minimised [124]. This can either be done in a **medication review** (multidisciplinary, pharmacist-led, nurse-led, or physician-led), through **educational interventions**, using **tools**, or **using computerised decision support tools**. The PCNE (Pharmaceutical Care Network in Europe) defines a medication review as 'the evaluation of all the patient's medicines with the aim of optimising medicines use and improving health outcomes. This entails detecting drug-related problems and recommending interventions' [128]. The evidence for medication reviews is not convincing in terms of decreasing the number of medications or in clinically relevant endpoints [129]. These interventions are complex, and more research was deemed needed to test the effectiveness and feasibility [129].

Optimizing the pharmacotherapy should encompass all domains of health care, from a better communication between general practitioners and nurses in primary care, to structured medication reviews in the hospital setting. Within the hospital setting, several steps are possible to appraise the medication use and several tools are available that suggest improvements to reduce the clinical impact of DRPs.

The starting point in the prevention of ADRs is the consideration of the medical complexity of the patient before prescribing medications [124]. One option is the integrated medication management, where an unobstructed information flow is possible between all health care professionals, both inside or outside the hospital setting. Another approach is the **Comprehensive Geriatric Assessment (CGA)** [130]. This multidisciplinary consult involves nurses and other allied health personnel. During a CGA, all problems regarding the functioning of older adults are explored, including care dependency and the potential need for support. The aim is to achieve an individualised and integral care plan, that does not limit to pharmacological care. For pharmacotherapeutic adaptations, the quality of life, the life expectancy and patient preferences are taken into account. A CGA may therefore result in an improved quality of prescribing, and a reduction of overall drug-related illnesses [131]. In the CRIME study (CRIteria to assess appropriate Medication use among Elderly complex patients), the effect of CGA showed a 35% risk reduction for serious ADRs, and a significant reduction of potentially inappropriate medications [132].

It must be remembered that none of the approaches above have a clearly shown benefit on the patient's health if applied in isolation [124].

Appraising the appropriateness of geriatric pharmacotherapy must be embedded within a global assessment of the patient's clinical and functional characteristics. The combined knowledge and skills of different actors in the medication management process can prove beneficial for the patient [124].

Defining the appropriateness of prescribing

From a pharmacological perspective, a medication is appropriate if the potential benefit outweighs the potential risk of a medication [133, 134]. Within the pharmacological perspective, several methods have been developed to assess the appropriateness of medications, either by assessing the appropriateness of the number of medications (e.g. polypharmacy), by using tools for the assessment of potentially inappropriate medications (e.g. implicit and explicit screening methods).

Polypharmacy

Definition

One of the key concepts in assessing the medication use of older adults is **polypharmacy.** The term polypharmacy has different definitions. Most commonly, the definition of 'the use of five or more medications' [135] is used, although 'four or more', 'nine or more'[136], or 'more medications than clinically indicated' [137] have been used as well. Following this set of definitions, polypharmacy has a negative connotation, indicating an inappropriate medication use. The concept of 'polypharmacy' can refer to the overuse of excessive, unnecessary, multiple or unindicated medications [138]. It is a multifactorial problem, present in a variety of settings and conditions [139–142].

In this thesis, we use
'the intake of 5 or more chronic medications with systemic effect'
as the definition of polypharmacy

Context of polypharmacy

Comparing studies focusing on polypharmacy is difficult. Apart from the different definitions available, there are also conflicting definitions for the medications included: some studies count the number of tablets ingested, some include topical medications, while others include only

medications with systemic effects.

Prevalences of polypharmacy in older adults ranged between 26 – 58%, with the upper limit of this range noted in older adults admitted to a hospital [143–150]. Large Swedish registry based studies (n = 1.358.486) in persons aged 75 years or older found that 52 – 57% of the population had polypharmacy [143, 151]. In a five year follow-up study of older Finnish people, the prevalence of polypharmacy in the oldest old was 66% [72]. The prevalence of polypharmacy remained stable after five years, only significant changes in the prevalence of excessive polypharmacy (ten or more medications) were found [72]. The prevalence of polypharmacy (five or more medications) in the Belgian population increases steadily with higher age. According to the Belgian Health Survey, approximately a third of people aged 75 years or older had polypharmacy [25]. The PHEBE (Prescribing in homes for the elderly in Belgium) study demonstrated that the medication use in nursing homes may be even higher, where a mean of 7.3 chronic medications was noted, with a predominant high prevalence of psychotropic medication users (79%) [152, 153]. An overview of recent studies reporting polypharmacy in older adults is given in table 1.

Polypharmacy is a **major contributing factor for encountering an adverse drug event** [154–157]. A population based study of outpatients showed an 88% increased risk for encountering an ADR for those with a higher medication use compared to those with a low medication use [158, 159]. With more medications prescribed, the risk of encountering potential medication interactions will rise as well. Up to 40% of older adults have potential medication interactions [160, 161], possibly leading to more medication-related hospitalisation [162]. The number of medications was determined as the main contributing factor for ADR related hospitalisations [163]. In a retrospective cohort study, polypharmacy was associated with a four times increased risk for unplanned hospitalisations [164], leading to higher health care costs. Multiple medications can lead to increased health expenditure [165, 166].

Polypharmacy is also associated with a low functional capability. A prospective cohort study demonstrated associations between polypharmacy and a higher care dependency for instrumental activities of daily living (e.g. housekeeping, transportation, …)[167]. Also a poor cognitive status is associated with polypharmacy [168]. In a prospective cohort of community-dwelling older adults, polypharmacy was also associated with an increased risk for falling [169].

Table 1.1. *Overview of recent studies focusing on older adults and polypharmacy.*

Author (year)	Location	N	Kind of prescription	Source of data	Age	% polypharmacy (definition used)
Haider (2005)	Sweden	626 258	Rx	Registry based	75 – 90	57 (≥ 5)
Nobili (2005)	Italy			Administrative database	65 – 95	46 (≥ 5)
Iwata (2006)	Japan	403	Rx	In hospital	≥ 85	27 (≥ 6)
Jyrkka (2006)	Finland	601	Rx + IN	Population based	80 – 84	61 (≥ 5)
Johnell & Klarin (2007)	Sweden	732 228	Rx	Registry based	≥ 85	73 (≥ 5)
Quato (2008)	USA	878	Rx	Population based	75 – 85	37 (≥ 5)
Schuler (2008)	Austria	543	Rx	In hospital	≥ 75	58 (≥ 5)
Moen (2009)	Sweden	348	Rx + OTC	Community-dwelling	65 – 75	26 (≥ 5)
Kim (2011)	Korea	319 185		Claims database	≥ 65	86 (≥ 6)
Herr (2014)	France	2 350	RX + OTC		≥ 70	67 (≥ 5)
Moriarty (2015)	Ireland	133 884	Rx + OTC	Population based	≥ 65	60 (≥ 5)
Charlesworth (2015)	USA	13 869	Rx	Community-dwelling	≥ 65	39 (≥ 5)
Wang (2015)	China	1 562	Rx + IN	Geriatric outpatient clinic	≥ 80	70 (≥ 6)

Rx: Only medications on prescription. IN: If needed medications. OTC: over the counter medications.

Potentially Inappropriate Prescribing

Another strategy is the identification of problematic prescribing, meaning prescribing that could lead to higher risks of adverse events. The act of prescribing medications can thus be considered as a process, and describing the qualitative characteristics of prescribing is the evaluation of a process [170]. Also, the distinction should be made between the problematic choice of a pharmacotherapy and the problematic execution of chosen pharmacotherapy [170]. In the former definition, this concept is related to the potential overuse, underuse or misuse of medications, while the latter is related to (non)adherence, and the monitoring or documenting of pharmacotherapy.

The choice of medications that can lead to actual or potential adverse effects has been of interest since a couple of years. Several methods exist that specifically help clinicians identify **potentially inappropriate medications** (PIMs), defined as medications with no clear evidence-based indication, that carry a high risk of adverse side effects or medications that are not cost-effective [171].

The concepts regarding a problematic choice (underuse, misuse, and overuse) are not clearly defined. Misuse and overuse are related to a suboptimal choice when prescribing medications, while underuse is related to a suboptimal choice for not prescribing a medication.

Underuse

Underuse of medications is an aspect that only recently has been put more in the highlight, and may be understated [172]. This aspect of potentially inappropriate prescribing resolves around the omission of medications that are indicated, unless there is a contraindication [134]. Later, underuse was also defined to medications that have a proven efficacy in patients with a significant life expectancy [171, 173]. Underuse can thus pertain to medications that are not prescribed in case of a present indication, or to non-prescribed prophylactic medication therapies. Prescribing omissions or underuse of medications is seldom the focus of interest in studies, possibly because of the lack of any appropriate tools to assess underuse.

In this thesis, we use
'the absence of prescriptions for medications that are clearly indicated and likely to benefit the patient' as the definition of underuse

Misuse

Misuse generally refers to medications that are prescribed that may potentially lead to Drug Related Problems. It encompasses the use of PIMs, inappropriate dosages, or inappropriate durations [134]. Regarding the choice, it is considered to be misuse of medications when more effective medications or medications with lower risks are available. Next, the dosage (too high, too low) or the dosage scheme (too frequent, not frequent enough) can be suboptimal as well. Finally, it also includes an imbalanced benefit/risk ratio, due to potential interactions (e.g. drug-food, drug-drug, or drug-disease), or known allergies [174].

In this thesis, we use
'the suboptimal choice of an active substance, it's dosage, or its duration' as the definition of misuse.

Overuse

There is no standard definition for the overuse of medication. Some sources pertain to overuse when treatments are given without a medical justification. This approach can be regarded as similar to one of the definitions of polypharmacy (more medications than indicated). According to the MeSH term, overuse indicates the use of a medication in an amount more than as prescribed, pertaining more to the overconsumption in dosages or duration (source: https://www.ncbi.nlm.nih.gov/mesh/2009720).

More recently, the definition of overuse was further refined:

- A medication therapy that is continued, despite lacking indication.
- The use of a combination therapy, where monotherapy might be sufficient.
- Medications in a prescribing cascade, medications that are initiated to counter the side effects of other medications

The definitions for misuse and overuse are sometimes overlapping. The first aspect refers to an incorrect duration, and the second aspect to a suboptimal choice of medications. For the remainder of this thesis, we made the choice to use misuse to refer to a suboptimal choice of active substance, duration or dosage.

1.4 Formalisation of the appraisal of appropriateness of prescribing

Recently, several lists, criteria or tools have been developed to improve patient safety. All these efforts estimate a patient's exposure to potentially inappropriate medications, in order to prevent any medication errors by potentially inappropriate prescribing. These lists, criteria or tools cover the dose-response relationship, drug related side-effects, age factors, …

Purpose and aspects

Their intended purpose can be either the manual application by experts and clinicians in the light of a preparation for a medication chart review or for research purposes. The choice of the most appropriate medication for an individual patient in order to achieve the desired therapeutic outcomes is a major challenge in daily practice.

The appropriateness or inappropriateness of medications can be assessed using implicit (judgement based) and explicit (algorithms based on theory) tools. Explicit tools are criterion based, developed from published reviews, expert opinion, but more often based on consensus [174]. Both implicit and explicit criteria can cover different aspects of potentially inappropriate prescribing, including the choice of a medication, the dosage, the duration, medication duplication, drug-disease interaction, drug-drug interaction, drug-food interaction, overprescribing, underprescribing, cost-effectiveness, non-adherence and the proposal of alternative therapies. Ideally, it should cover all aspects, it should be evidence-based, and it should show significant correlation with clinical outcomes, and finally, it should be applicable beyond research conditions, and thus in clinical practice [174].

Most tools cover the different aspects to some extent. There are numerous tools available, with varying levels of comprehensiveness and complexity [174]. Most are regarded as a useful aid for clinicians to optimise the prescribing of medications, yet **no ideal tool is available** that covers all aspects [174].

Published lists for the appraisal of appropriateness

Implicit criteria

Implicit tools are judgement based, and pertain to the clinical review of a medication chart in individual patients. The most used tool for implicitly assessing the appropriateness of medications is the Medication Appropriateness Index, MAI [175].

The MAI focusses on specific elements of prescribing, covering indication, effectiveness, dose, duration, applicability, potential interactions, duplication, and costs. The MAI has undergone extensive validation and can aid medication reviewers to adjust the medication chart. It is however time consuming and requires extensive patient knowledge and experience [176]. The MAI has not been tested in an electronic version, pos-

sibly since some items require clinical judgement; only some items (e.g. dosage, duration, drug-drug interactions, duplication) can be applied in an electronic application.

Explicit criteria

Explicit criteria were introduced as important, simple, yet effective strategies in reducing potentially medication related problems in older adults [133]. Explicit criteria are more generally applicable in a standardised way, are quick to apply, and more suited for research purposes. Explicit criteria were generated through expert opinion and expert consensus, but are now more and more based on evidence [177]. Explicit criteria have shown potential as electronic applications [178]. The main limitations are the lack of transparency in the development process of the expert panels, and poor interrater reliability [179]. Another main consideration when applying explicit criteria to screen for potentially inappropriate medications is that patient preferences and the whole clinical history of a patient are not taken into account.

Inventory of lists of explicit criteria available

Some lists pertain to medication-only criteria (EU(7)-PIM, ZHAN, Laroche, PRISCUS) [180–183], while others incorporate clinical data (e.g. Beers, ACOVE, BEDNURS, McLeod, …) [97, 184–186]. Some pertain to the misuse of medications only (e.g. STOPP), while others look at potential medication omissions or underuse (e.g. ACOVE, START)[171, 187, 188].

Beers criteria

The Beers criteria are a set of explicit criteria, developed in 1991, with the aim to assess the quality of prescribing in older adults. Since then, it has been updated several times, with the latest update in 2015. It lists medications or medication classes that are to be avoided, to be avoided in case of specific clinical problems, and medications to be used with caution. In the 2015 version, more specific focus was given to a universal applicability of the criteria, and the quality of evidence was added to the criteria.

The Beers criteria are among the oldest criteria available. The main limitation to the Beers criteria is their limited transferability to other medication markets, since it was developed in the United States. Validation of the criteria was done in an American expert panel. There is some evidence that Beers' criteria (1991, 1993 and 2003 criteria) of inappropriate medication use is associated with adverse healthcare impact in commu-

nity-dwelling older adults, although the predictive validity is still questioned [189].

STOPP/START criteria

The **STOPP/START criteria** were developed by geriatricians in the republic of Ireland, as a European counterpart of the American Beers list. These criteria are intended for patients older than 65 years, and address both misuse (STOPP; Screening Tool of Older Person's Prescriptions) and underuse (START; Screening Tool to Alert doctors to the Right Treatment) [171]. They were originally based on expert opinion. In 2014, a revised version has been released, where references are added to the explicit criteria (but not including a strength of recommendation) [187]. The STOPP/START criteria have been validated and show good interrater reliability [190–192]. The STOPP/START criteria have shown a higher sensitivity at detecting potentially inappropriate prescribing in different settings [193]. Underuse and misuse has been linked with an increased risk of ADRs [194] and a subsequent risk for hospitalisation [195]. However, the specificity of the STOPP/START criteria in detecting potentially inappropriate medications that are related to adverse outcomes is yet to be established. Another limitation to the STOPP/START criteria is the number of criteria involved. The length of the lists (81 for STOPP-2, and 34 for START-2) make the manual application time-consuming and requires a high level of familiarity [178]. In most of the studies, clinical pharmacists, physicians or researchers apply explicit criteria in a medication chart review [196]. This is also reflected in research studies, where generally a subset of the criteria is taken [197], possibly due to the (un)availability of medications or clinical data.

Many studies have used the STOPP/START criteria to assess potentially inappropriate medication use in older adults. In community-dwelling older adults, misuse ranged between 20 – 79%, and underuse ranged between 23 – 74% [198, 199], with the upper limit observed in patients entering a nursing home. Most commonly involved STOPP-1 criteria were the long-term prescribing of proton-pump-inhibitors, benzodiazepines or neuroleptics [199–201]. Most commonly involved START-1 criteria involved the omission of calcium/vitamin D in osteoporosis patients, and statin therapy in cardiovascular and diabetes patients [201–203].

Studies generally use a sample of community-dwelling adults, aged 65 and older. The general conclusion is that there is an increasing prevalence of PIMs with more medications [198], a higher level of multimorbidity [198, 204] and a higher age [202, 205, 206]. Studies focussing on

community-dwelling oldest old are in contrast scarce, and even fewer studies look at long-term outcomes [197].

EU(7)-PIM

The **EU(7)-PIM** list was the first attempt to unify other lists of explicit criteria on potentially inappropriate medications. The general basis of the EU(7)-PIM list derives from the earlier developed German PRISCUS list [183], but has now integrated criteria from the Beers list (United States), McLeods (Canada), and Laroche list (France) [133, 182, 186].

The aim was to make a medication-only repository, available for different countries in Europe (the original seven countries included Estonia, the Netherlands, Finland, France, Spain, Sweden and Germany), which can be used for analyses and comparative studies on prescribing patterns throughout Europe, or as a guide in clinical practice. The EU(7)-PIM lists 282 active substances (including seven medication classes), of which some are accompanied with dosage information. An additional strength of this method, is the proposed dosage adjustment for each medication, as well as the option of an alternative medication or therapy [180].

Formalisation of assessment of pharmacodynamic effects: the case of anticholinergics

Anticholinergics are, because of an increased risk for potentially adverse effects, being introduced into lists of potentially inappropriate medications for older adults. Sometimes, they are introduced as medication-only PIMs (Beers, version 2015), and sometimes in combination of clinical problems (e.g. glaucoma, urine retention, … in the STOPP-2 criteria) [187, 207]. In some, a (non-exhaustive) list of active substances is given (Beers, FORTA), and in others, they are referred to as a medication group (without specific enumeration of included medications, e.g. STOPP) [180, 208]. However, the clinical applicability is low since there isn't much agreement, and explicit criteria are often not explicit enough. See table 2 for an overview of anticholinergics mentioned in PIM lists.

Findings of studies suggest the need for methods to identify anticholinergics. Sometimes the anticholinergic activity of commonly used medications is not properly known by prescribers, leading to a risk for concomitantly prescribing anticholinergics [58]. Estimates suggest that 8 to 37% of the older population consume at least one anticholinergic [209–211]. Despite the known side effects, anticholinergics are widely prescribed in older adults. An Italian study found that 14 out of the 25 most prevalently prescribed medications had anticholinergic properties

[212]. The high prevalence of anticholinergic use can be explained that anticholinergics can be both the reason and the result of a prescribing cascade. Cholinesterase inhibitors (e.g. donepezil, rivastigmine) are prescribed more in older adults with dementia, but can cause urge urinary incontinence [213], which can be treated in return with another anticholinergic (e.g. oxybutynin, tolterodine) [214].

Table 1.2. *Overview of anticholinergics mentioned in PIM-tools.*

STOPP-2	
7 explicit criteria	5 explicit criteria listing anticholinergics in combination with clinical problems (including prostatism, urinary retention, delirium, dementia, constipation, glaucoma). 1 explicit criterion listing anticholinergics in a prescribing cascade (e.g. extrapyramidal side-effects of neuroleptic medications) 1 explicit criterion listing the concomitant use of anticholinergics. 2 explicit criteria with specific enumeration of active substances
Beers (2015)	
Mentioned in several tables: medications to avoid, medications to avoid in presence of a clinical problem, and as a separate table of medications with strong anticholinergic properties	1 table depicting medications with strong anticholinergic properties. Specific enumeration of medication classes and active substances: Antihistamines (n=13 active substances), Antiparkinsonian agents (n=2), Skeletal muscle relaxants (n=2), Antidepressants (10), Antipsychotics (n=7), Antiarrhythmic (n=1), Antimuscarinics (n=7), Antispasmodics (n=9), Antiemetic (n=2)
FORTA	
3 medications with anticholinergic properties mentioned.	Doxepin (2 times), olanzapine, biperidene
EU(7)-PIM	
74 medications with anticholinergic properties mentioned. 7 mentioned in the abbreviated version (most common PIMs)	Metoclopramide, oxybutynin, levomepromazine, clozapine, amitriptyline, paroxetine, promethazine, hydroxyzine mentioned in the most common PIMs

Several methods have been developed to quantify the exposure to medications with anticholinergic properties [41, 210, 215–223]. The golden standard to quantify the exposure remains the time consuming and invasive in vivo measurement of anticholinergic activity in blood [224, 225]. Other methods resolve to a theoretical approximation based on the intrinsic potency or by the combination of potency with the dosage in which the medication was prescribed. The anticholinergic potency of medications indicates the activity or affinity at the receptor level.

In this thesis, we use
'the extent to which the patient is exposed to anticholinergics, by an assessment of the number of anticholinergics (and their potency and dosage) on the medication list' as the definition for the anticholinergic exposure

Exposure to several different anticholinergics may cause culminating side-effects [226], perceivable by the patient and resulting in constant bother, and impact on quality of life. Direct questioning of the patient can be used as measure for anticholinergic burden.

In this thesis, we use
'the burden perceived by patients of the (side)-effects of anticholinergics' as the definition for the anticholinergic burden

Critical review of explicit criteria

High quality research is needed for an optimal understanding of the validity of explicit PIM criteria. To date, the clinical relevance and potential of PIM lists has not been fully studied.

The prevalence of potentially inappropriate prescribing has been reported to rise with increasing age, and level of multimorbidity. According to a recent systematic review, the average prevalence of potentially inappropriate prescribing in community-dwelling adults across Europe is 22.6% (with studies ranging between 0 and 98%) [154]. The prevalence of inappropriate prescribing in nursing homes can be even higher, with up to 50% of nursing home residents having at least one potentially inappropriate medication (PIM) [227]. Predisposing factors for potentially inappropriate prescribing is a higher medication use, e.g. polypharmacy, having a depression and being in poor physical or functional health [154].

A systematic review of 12 observational studies and 1 randomised controlled trial examined the evidence of impact of the STOPP/START-1 criteria on clinical outcomes [193]. Patients with potentially inappropriate prescribing (defined by the STOPP-1 criteria) had an 85% increased risk for adverse drug events, but evidence was considered limited. With the addition of three RCTs in a meta-analysis [228], the results remained **inconclusive**, as the researchers were unable to define the relation of the STOPP/START-1 criteria with outcomes mortality and quality of life, pos-

sibly due to bias in the selected randomised controlled trials [229–232], and the heterogeneity of the four RCTs [197].

Little prospective longitudinal research is available. Available longitudinal studies mostly use un-validated explicit criteria from diverse PIM-lists, most commonly derived from the Beers list, and found weak associations with adverse health care impact [189, 233, 234]. In a prospective cohort study in Ireland, the potentially inappropriate medication use (defined by the STOPP/START-1 criteria) in older adults was explored. One of the main findings was that misuse and underuse were independently associated with a higher health care usage (more GP or emergency department visits). Underuse was also associated with functional decline, and a lower quality of life [235]. However, studies could not establish long-term associations with outcomes yet.

Another option is the automatic application in automated health systems. These computerised decision support systems aim to assist clinicians in selecting the correct medication when prescribing, in order to reduce medication errors or increase the appropriateness [124]. This aspect as well has potential limitations, since most decision support systems use different algorithms to identify potentially inappropriate medication use. Also, in order to have maximal benefit, the integration of clinical characteristics with prescribing information should be achieved (e.g. guidance in selecting the dosage based on laboratory testing) [124]. Only recently, studies have been published that looked into the benefit of computerised prescribing systems, and some showed promising results [236]. However, focus until now was focused at certain medications or medication classes (in casu, psychotropic medications).

Explicit criteria are still in development. For a an optimal implementation of explicit criteria, these should be made as specific, explicit and universally adaptable as possible [237].

1.5 Choices made in this thesis

For the course of this manuscript, we made the choice for a specific focus on the domain of appraising the medication use during the prescribing phase in the **drug choice process**. In order to appraise the medication use, we relied on **explicit criteria** for both **misuse and underuse** of medications; namely the **EU(7)-PIM list and STOPP/START-2 criteria.**

The STOPP/START-2 criteria were selected for further exploration chosen because of their focus on misuse and underuse, their clinical focus, and because they are more adapted to the European medication market in comparison with the American based Beers list. The EU(7)-PIM in contrast is relatively new, and has a sole focus on explicit criteria for misuse, without the need for clinical data. It is based on the German PRISCUS list, which was based in return on the Beers list [180]. Of these two PIM lists, we explored explicit criteria that are suitable for the appraisal of data in **automated analysis, for future benchmarking (to facilitate internal medical audit) and for individual per-patient feedback purposes.**

We decided also to **further develop the assessment of pharmacodynamics interactions** among **anticholinergics.** Although several lists of explicit criteria contain criteria on anticholinergics, their operationalisation is poorly developed, and do not provide the basic elements for a proper application in automated analyses.

Chapter 2

Scope of this thesis

Chapter 2: Contents

2.1 Rationale for engaging this thesis

The main goal in this thesis is to appraise the appropriateness of prescribing of medications in the oldest population. We focused therefore on polypharmacy in older adults and on potentially inappropriate medication use, in terms of underuse and misuse. We limited ourselves to explicit criteria from European lists for appraising potentially inappropriate medications with a recent update.

The clinical relevance and validity of lists of explicit criteria for assessing potentially inappropriate medication use is still debated. Currently, not a single list has been described as the golden standard to use. In this thesis, we focused on two European lists of explicit criteria, namely the STOPP/START-2 (focusing on misuse and underuse) and the EU(7)-PIM list (focusing on misuse). We used explicit criteria from these lists that were suitable for automatic application in order to describe the prevalence of polypharmacy, underuse, and misuse, and to explore the possible relationship with outcomes (mortality, hospitalisation, and institutionalisation).

The automatic electronic analysis of the medication use is hardly studied. Our secondary goal is to explore its validity, by exploring whether the possible relationship with outcomes is maintained in the light of present limitations (use of secondary data, semantic interoperability, use of a subset of explicit criteria of START/STOPP-2, …).

Explicit criteria are not always explicit. Anticholinergics are widely prescribed in older adults, yet are known to cause unwanted and potentially severe anticholinergic symptoms. Explicit criteria on anticholinergics do not enumerate on the specific medications or active substances involved, limiting the universal application of explicit criteria regarding anticholinergics. In a tertiary goal, we explore possible adjustments to the identification of anticholinergics and possible adjustments to explicit criteria in PIM lists.

The population of interest here are the oldest old (aged 80+). Only recently, longitudinal studies are undertaken to gain more insights in the clinical, and functional profile of this under-represented but growing age segment. In pharmacological research, the community-dwelling oldest old are seldom the focus of interest. Most research involves either nursing home residents, or hospitalised patients.

In this thesis, our main interest is on the oldest old, still living at home

and participating in the community. We use data from the Belfrail study, an observational longitudinal cohort study of community-dwelling older adults (aged 80, and older).

2.2 Source of the data used in this thesis

To reach our goals, we used data from the Belfrail study, an observational longitudinal cohort study. The Belfrail cohort study was designed to acquire a better understanding of the epidemiology and pathophysiology of chronic disease in the community-dwelling oldest old, and in the relationship between chronic disease, frailty and disability in a multisystem approach [238]. General practitioners (GPs) were responsible for the selection of patients (November 2008 – September 2009). At baseline, personal, clinical, functional and medication data were collected. The GPs recorded the clinical status and the chronic medication use from their medication records. Clinical research assistants collected functional data using standardised tests (questionnaires and examinations). All patients were followed for five years, for which the GP was responsible to collect outcome data (date of death, date of first unplanned hospitalisation, date of moving into a nursing home).

The original goals of the Belfrail study were not intended for the appraisal of the medication use. The results of our thesis are based on the clinical problems in the Belfrail database (consisting of codified diagnoses, and multimorbidity measures, used for other research purposes) and on the codified medication data (codification in the ATC classification, done by our research group). The medications of patients were recorded in a data-entry programme, based on the Belgian medication market. All medications were translated into the Anatomical Therapeutic Chemical (ATC) classification (WHO ATC/DDD index, version 2013).

Table 2.1. *Overview of data collected in the Belfrail study.*

Personal data included age, date of birth, level of education, marital status, living status, receiving nursing care, alcohol consumption (during one week), place of living, ethnical status, and work history.
Clinical data included active and past clinical problems.
Functional data included care dependency (Katz Activities of Daily Living, ADL; Instrumental ADL, IADL), physical activity (LASA Physical Activity Questionnaire, LAPAQ; Barthel Index, and performance-based tests), cognitive impairment (Mini Mental State Examination, MMSE), depressive symptoms (Geriatric Depression Scale, GDS-15), the sense of coherence, and the level of frailty (Groningen Frailty Indicator, GFI). Additionally, the Clinical Research Assistants recorded biometry, grip strength, blood pressure, vision and hearing test, and did a risk estimation for falls (Tinetti test).
Medication data were recorded by the GPs from their patient records. They recorded all current chronic medications that were prescribed using the brand or generic name, the dosage, and the frequency of administration.
Follow-up data were collected using an extensive follow-up questionnaire for the GPs, and a new assessment of the functional profile (Barthel, ADL, MMSE, GDS-15, …). GPs had to report back on the health status, the date of death, the date of institutionalisation, and the date of a first unplanned hospitalisation.

2.3 Research questions

The specific research questions for this thesis were as followed:

1. What is the prevalence of polypharmacy in the community-dwelling oldest old (aged 80 years, and over) in Belgium, and what patient-related factors attribute to a higher medication intake?
   More specifically:
   - How many and which medications do the oldest old community-dwelling in Belgium take?
   - What is the distribution of therapeutic medication subgroups?
   - Are personal/clinical/functional characteristics of patients related to polypharmacy?

2. Is there a relationship between polypharmacy and health related outcomes (hospitalisation, institutionalisation, and mortality) in the community-dwelling oldest old?
   More specifically:
   - Is there a relationship between polypharmacy (the number of medications, the prevalence of polypharmacy, or the presence of specific medication groups) and outcomes (hospitalisation, institutionalisation, and mortality)?
   - Is the relationship, apart from a higher level of multimorbidity, influenced by personal/clinical/functional patient-related factors?

3. Which medications mentioned in international lists of explicit criteria of (in)appropriate prescribing are applicable to the Belgian therapeutic arsenal?
   More specifically:
   - Which medications singled out by the international lists are available in Belgium?
   - Which medications have a meaningful prevalence of use in the oldest old?

4. What is the prevalence of use of potentially inappropriate medications (PIMs) in the community-dwelling oldest old, and is there a relationship between potentially inappropriate prescribing (misuse and underuse) and hospitalisation and mortality?
   More specifically:
   - What is the prevalence of automated explicit criteria of PIMs for misuse (STOPP-2 or the EU(7)-PIM list), and PIMs for underuse (START-2)?
   - With regard to the application of a limited set of explicit criteria generated in automated analysis, is there a relationship between PIMs for misuse and underuse and outcomes (hospitalisation and mortality)?

5. Can an automated tool be developed that quantifies the anticholinergic exposure in old age?
   More specifically
   - What are the anticholinergic medications in Belgium and the Netherlands?
   - How can the anticholinergic exposure be quantified, taking potency and the dosage spectrum of medications into account?

6. What is the prevalence of the anticholinergic use in the community-dwelling oldest old (aged 80 years, and older), and is there a relationship of the anticholinergic exposure with hospitalisation and mortality.
   More specifically
   - How many and which anticholinergic medications do the oldest old community-dwelling in Belgium take?
   - Are personal/clinical/functional characteristics of patients related to anticholinergic exposure?
   - Is there a relationship between the anticholinergic intake (either potency, dosage or total anticholinergic exposure) and outcomes (hospitalisation, and mortality)?

In addition to these research questions, we will review the results of our studies for our secondary goal. In the discussion, we review whether the automatic electronic appraisal of potentially inappropriate medication use is feasible, informative, or valid as an adjunct-strategy to expert medication chart review, in the light of present limitations.

Chapter 3

Polypharmacy in a Belgian cohort of community-dwelling oldest old (80+)

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Chapter 3: Contents

3.1 Abstract

Objectives: Polypharmacy is highly prevalent among older people (65+), but little is known on the medication use of the oldest old (80+). This study explores the medication use of the Belgian community-dwelling oldest old in relation to their demographic, clinical and functional characteristics.

Methods: Baseline data was used from the BELFRAIL study; a prospective, observational population-based cohort of Belgian community-dwelling patients (80+). General practitioners recorded clinical problems and medications. Medications were coded by the Anatomic Therapeutic Chemical classification.

Results: Participants' (n = 503) mean age was 84.4 years (range 80–102) and 61.2% was female. Median chronic medication use was 5 (range 0–16). Polypharmacy (≥5 medications) was high (57.7%), with excessive polypharmacy (≥10 medications) in 9.1%. Most commonly used medication group were antithrombotics, but also benzodiazepines and antidepressants were frequently consumed. Demographics related to polypharmacy (univariate analysis) were female gender, low education and moderate alcohol use.

Age, care dependency and cognitive impairment showed no association with polypharmacy. In multivariate analysis, the predominant association with polypharmacy was found for multimorbidity (OR 1.78, 95% CI 1.5–2.1), followed by depression (OR 3.7, 95% CI 4.4–9.7) and physical activity (OR 0.8, 95% CI 0.7–0.9).

Conclusions: Polypharmacy was high among Belgian community-dwelling oldest old (80+). Determinants of polypharmacy were interrelated, but dominated by multimorbidity. On top of the burden of multimorbidity, polypharmacy was independently associated with less physical activity, and with depressive symptoms.

3.2 Introduction

In highly developed countries, the number of oldest old (80+ years) is increasing. For Belgium, the oldest old represent 5.4% of the population in 2014 and their number is expected to rise to 6.6% of the population in 2030 [10, 239]. Recent government initiatives expanded formal nursing and care services at home, encouraging older people to stay at home [27, 240]. In this shifted primary care focus, general practitioners (GPs) are considered as key players.

Ageing is associated with the development of multiple chronic diseases or multimorbidity, accumulating over time [241]. Multimorbidity can mandate the necessity for multiple medications [242]. It has a major impact on the choice, dose and frequency of medication prescribing [243, 244]. Additionally, multimorbidity increases the risk of polypharmacy, and associated drug related problems in older patients. These drug related problems are associated with increased morbidity, mortality and a higher use of healthcare services [106, 245]. Therefore, medication prescribing in the oldest old (80+) is regarded as a challenge in primary care [246].

Although the oldest subpopulation (80+) is growing, and is characterised by more multimorbidity, their medication use remain understudied. Several studies in younger (65+) population have linked polypharmacy separately with demographic characteristics [246], multimorbidity [247], clinical outcomes [248], and health status [168]. Yet, these conclusions cannot be extended to the oldest old (80+) living in the community [72, 168, 246, 249–251]. Bahat et al. (2013) postulate that the oldest old were survivors of comorbidities and polypharmacy effects [247], yet no study has linked the functional profile, multimorbidity and polypharmacy of the oldest old. Using general practitioners as primary source, this study aims to explore the medication use and particularly polypharmacy of the community-dwelling oldest old (80+) in relation to their demographic, clinical and functional characteristics.

3.3 Methods

The Belfrail-MED cohort

This study uses baseline data from the Belfrail study, a prospective, observational population-based cohort study. The Belfrail cohort was selected using GPs from three Belgian regions. For a full methodological description, see Vaes et al. 2010 [252]. For this study, all non-institutionalised patients with medication records available were included, yielding the Belfrail-MED cohort (n=503). Of those, we explored the chronic medication use, in relation to demographic, clinical and functional characteristics at baseline.

Sampling

Selection of participants was done by 36 GPs, between November 2008 and September 2009 (see Vaes et al., 2010). Eligible participants were at least 80 years old and able to visit their GP. Exclusion criteria were: known presence of severe dementia (Mini Mental State Examination <15/30), in need of acute medical care or palliative care.

Data collection

Data collection was done by GPs (structured data collection and clinical examination) and by clinical research assistants (standardised tests: questionnaires and examinations). GPs recorded **demographic characteristics** and listed all **chronic medications** as prescribed by the GP). Medication data included product name, active substance, and prescribed daily dose.

First, a structured questionnaire was used. GPs assessed clinical problems and comorbidities collecting data of the clinical chart of patients. The clinical problems were encoded by two independent researchers [14]. **Multimorbidity** was measured using the Cumulative Illness Rating Scale (CIRS, see Box 2.1) [253]. The CIRS categorises these problems within 14 body systems and counts the body systems affected by at least one chronic active disease [254], yielding a range from 0 to 14[14].

Functional data included care dependency, physical activity, cognitive impairment, and depressive symptoms. Care dependency was measured using **activities of daily living** (ADL KATZ-scale)[255], **physical activity** using the LASA Physical Activity Questionnaire (LAPAQ) [256, 257].

Cognitive status was assessed with the Mini Mental State Examination (MMSE) [258], adjusted for age and education according to Crum [259]. **Depressive symptoms** were assessed using the Geriatric Depression Scale-15 (GDS-15) [260, 261]. For identification of risk factors to polypharmacy, we used the diagnosis of depression (as categorised by the treating GP) rather than the GDS-15. GPs have, due to the long term follow-up and more frequent visits, an understanding of the mental status of their patients. For a full overview on the ranges, direction and established cut-offs of each test, see Table 3.1.

Table 3.1. *Standardised tests and scales used in the Belfrail-MED cohort.*

Test	Topic	Subtopics	Range*
CIRS Cumulative Illness Rating Scale	Medical problems in primary care, measurement of multimorbidity	Scores based on gravity of co-occurring medical conditions.	[0-14] 0 (no pathologies)
ADL KATZ scale	Activities of daily living	Continence, nutrition, feeding, personal hygiene, toileting, and mobility.	[6-30] 6 (functional independence)
LAPAQ LASA Physical Activity Scale	Physical activity during 2 weeks	Light and heavy household activities and sports	[0-∞[0 (physically inactiveness)
MMSE Mini Mental State Examination	Cognitive status	Orientation in time, space, memory, comprehension and constructive praxis	[0-30] 0 (severe cognitive impairment) Cut-offs conform Crum[259]
GDS-15 Geriatric Depression Scale	Late-life depressive symptoms in primary care[260]	Functional and mood symptoms	[0-15] 0 (lowest probability of depressive symptoms) ≥ 5: moderate to high risk

*Range legend: [..] shows the range of the standardised tests and scales.
Italic writing indicates the meaning of lowest scores.
Normal writing indicates established and validated cut-offs.

Data handling

Medications were recorded using the brand or generic name in a data-entry program, based on the official register of medications on the market from the Belgian Centre for Pharmaceutical Information. The medication was translated into the Anatomical Therapeutic Chemical (ATC) classification (WHO ATC/DDD index, version 2013). Focus was on anatomical main groups (first ATC level) and therapeutic subgroups (second ATC level).

For the operationalisation of a high medication use, polypharmacy

was defined as a daily medication intake of ≥5 medications[242], and excessive polypharmacy as the daily medication intake of ≥ 10 [149]. Duplicate therapy was defined as concomitant use of ≥ 2 agents within therapeutic subgroups (second ATC level).

Statistical analysis

For all variables, there was less than 5% missing data [252]. Data were inserted by a data manager, and data verification and quality control was enhanced by trained researchers. Data analysis was performed with IBM Statistical Package of Social Sciences 21.0 (SPSS Inc., Chicago, IL, USA). *T*-tests and χ^2 tests were used for comparing means and percentages respectively, and non-parametric tests in case of skewed data. Relationships between skewed data were tested using Spearman rank correlations. A significance level of $p < 0.05$ was used.

Multivariate logistic risk profiles for polypharmacy were analysed using the variables, which were significant in univariate analysis. In the endeavour to search for variables, other than clinical characteristics in relation to polypharmacy, two models were constructed. One with the most prevalent (≥10%) clinical problems and one model with the CIRS, as a summarising indicator with continuous properties for multimorbidity.

Physical activity (LAPAQ) scores were divided in deciles to create semi-quantitative data (highest decile indicating the most physically active). For care dependency (KATZ ADL) four groups were created, based on the observed distribution. The models were corrected for age, plus all significant demographic characteristics. The 'Enter' method was used. Each item was carefully weighed until a steady Nagelkerke R^2 was reached.

Ethical approval

The study protocol was approved by the Biomedical Ethics Committee of the Medical School of the Université Catholique de Louvain (UCL), Brussels (B40320084685, on 27/10/2008) and later by the Ethics committee of Ghent University Hospital (B670201421408, on 26/06/2014). All respondents provided informed consent.

3.4 Results

Table 3.2 presents demographic, clinical, and functional characteristics of the community dwelling oldest old (80+). Participants' mean age was 84.4 years (range 80.0 – 101.8) and 61.2% was female. The majority had a lower level of education (≤8 years, 69.2%). Moderate alcohol use (≥1 daily unit) was present in 32.5% (including 9.3% of the population who drank more than 2 daily units). Median level of multimorbidity was 4 (CIRS, range 1-9) with hypertension (70.4%), osteoarthritis (57.1%) and hyperlipidaemia (44.1%) as predominant clinical problems.

Table 3.2. *Demographics, clinical, and functional characteristics of the study population (n=503) in the Belfrail-MED cohort.*

Demographic	**% (n=503)**
Mean age in years ± SD* (range)	*84.4* ± 3.6 (80 - 102)
Gender (% female)	61.2
Living alone	43.3
Nursing care at home	36.8
Moderate alcohol use (≥1 unit a day)	32.5
Low education (≤8 years)	69.2
Clinical[1]	**%**
Mean multimorbidity[2] ± SD* (range)	*3.8* ± 1.6 (1 – 9)
Hypertension	70.4
Osteoarthritis	57.1
Hyperlipidaemia	44.1
Heart Failure (NYHA[3] > 0)	38.4
Obesity (BMI > 30kg/m^2)	27.9
Osteoporosis	20.9
Diabetes	18.9
Post myocardial infarction / post stroke	17.7
COPD / asthma	13.1
Depression	12.7
Chronic renal failure	11.1
Functional	**Median (IQR*)**
Activities of daily living, ADL	6 (6 - 8)
Physical activity, LAPAQ	70 (30 – 102)
Mental status, MMSE	28 (26 – 29)
Depressive symptoms, GDS-15	2 (1 – 4)

[1] Clinical problems with prevalence above 10% are listed.

[2] Multimorbidity was defined by the CIRS

[3] New York Heart Association (NYHA) functional classification of heart failure

* SD: standard deviation, IQR: Inter quartile range

With regard to activities of daily living, the median ADL was 6 (IQR 6-8), with 9.1% identified as care dependent (ADL>13). The majority was physically active. The median LAPAQ was 70, equivalent of daily walking two hours (IQR 30 – 120). In the lowest decile (most physically inactive) LAPAQ scores did not exceed 3, or equivalently no more than 45 minutes of physical activity in the past two weeks. Cognitive impairment was present in 14.7% (median MMSE 28, IQR 26-29).

General medication use

A total of 2730 chronic medications were recorded, with a mean of 5.4 medications (range 0-16) per patient. Less than 1% used no medication. Polypharmacy (≥5 medications) was present in 57.7 %, and excessive polypharmacy (≥10 medications) in 9.1 %. Just 0.8% of the population had no chronic medications.

Cardiovascular medication was most commonly used (86.3%), then haematological medication (56.1%) and nervous system medication (54.5%, see Table 3.3). At therapeutic subgroup level, antithrombotic medication was most prescribed (54.5%, see Figure 3.1), predominantly

Table 3.3. *Chronic medication use and use of anatomical main groups (1st ATC level).*

Chronic medication use		**%**
Mean medication use (range)		*5.4* (0-16)
Polypharmacy (≥ 5 medications)		57.7
Excessive polypharmacy (≥ 10 medications)		9.1
ATC anatomical main groups		**%**
C	Cardiovascular	86.3
B	Blood and blood forming	56.1
N	Nervous system	54.5
A	Alimentary tract and metabolism	50.1
M	Musculo-skeletal system	23.5
R	Respiratory system	15.9
H	Systemic hormonal preparations	11.7
G	Genito-urinary system and sex hormones	10.3
L	Antineoplastic and immunomodulating agents	3.6
S	Sensory organs	3.4
J	Anti-infectives	2.0
D	Dermatologicals	0.6

acetylsalicylic acid (34.6%), and vitamin K antagonists (10.3%). Use of benzodiazepines (35.6%) and antidepressant (16.1%) was high, with a concomitant use of 12.3% and 12.2% respectively. Chronic antipsychotic, anti-dementia medication and laxative use was low (less than 5%).

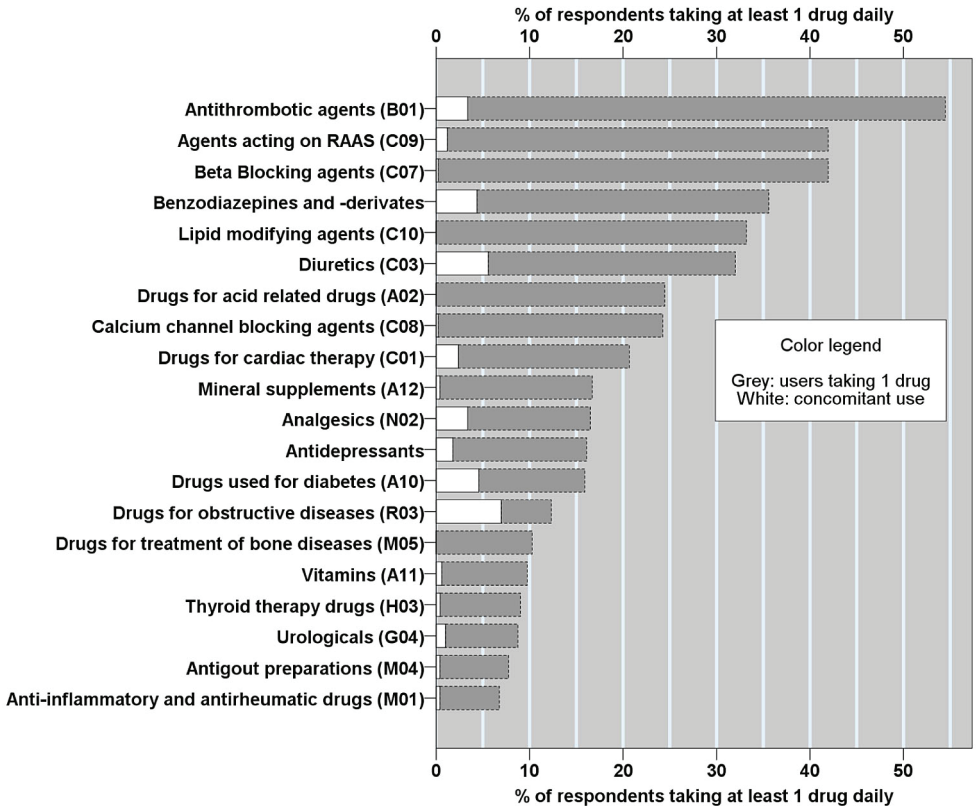

Figure 3.1. *Therapeutic subgroup medication (2nd ATC level), commonly used in the oldest old.*

Characteristics related to polypharmacy in univariate analysis

Demographic factors associated with polypharmacy were female gender (OR 1.6, 95% CI 1.1 – 2.3), and low level of education (≤8 years, OR 1.5, 95% CI 1.0 – 2.2, see Table 3.4). Age was not linearly associated with polypharmacy. The mean medication use per 5 years age category was 5.4 (80-84 years), 5.6 (85-89), 5.0 (90-94) and 4.5 (95+). Clinical problems were, with exception of obesity, all positively associated with polypharmacy.

In terms of functional characteristics, more physical activity had a negative association with polypharmacy (OR 0.9, 95% CI 0.8 – 0.9). Neither cognitive impairment (MMSE) nor care dependency (Katz ADL) showed an association. Moderate alcohol use (≥1 unit daily, OR 0.6, 95% CI 0.4 – 0.9) was negatively associated with polypharmacy.

Table 3.4. *Univariate analysis of demographic, clinical and functional characteristics factors of the Belfrail-MED cohort (n=503) in relation to polypharmacy.*

	Polypharmacy use?			
	Yes n=279	No n=194		Univariate odds ratio
Demographic characteristics	%	%	p-value	(95% C.I.)
Mean age (in years)	*84.5*	*84.3*	*0.536*	*1.02 (0.97 – 1.07)*
Female gender	65.9	54.9	0.005	1.58 (1.10 – 2.28)
Moderate alcohol use	29.3	39.8	0.019	0.63 (0.43 – 0.93)
Low education (≤8 years)	73.7	64.9	0.035	1.52 (1.03 – 2.23)
Clinical				
Mean comorbidity, CIRS	*4.3*	*3.0*	*<0.001*	*1.82 (1.56 – 2.10)*
Hypertension	76.2	62.7	0.004	1.90 (1.29 – 2.80)
Osteoarthritis	62.7	52.2	0.019	1.54 (1.07 – 2.21)
Hyperlipidaemia	56.3	29.9	<0.001	3.02 (2.07 – 4.42)
Heart Failure	47.2	26.3	<0.001	2.51 (1.71 – 3.68)
Osteoporosis	29.7	14.1	<0.001	2.58 (1.61 – 4.12)
Obesity	29.8	26.9	0.481	1.15 (0.78 – 1.72)
Diabetes	26.0	9.5	<0.001	3.35 (1.97 – 5.69)
Post myocardial infarction, post stroke	24.7	10.3	<0.001	2.86 (1.67 – 4.89)
COPD/Asthma	24.7	10.3	<0.001	1.90 (1.09 – 3.31)
Depression	18.1	5.7	<0.001	3.26 (1.73 – 6.14)
Chronic renal failure	16.5	4.3	<0.001	4.36 (2.09 – 9.12)
Functional (mean score)				
Care dependency[1]	*8.2*	*8.1*	*0.901*	*1.00 (0.97 – 1.04)*
Physical activity[2]	*56.6*	*81.7*	*<0.001*	*0.85 (0.79 – 0.90)*
Cognitive impairment[3]	*26.7*	*26.8*	*0.699*	*0.99 (0.94 – 1.05)*

[1] According to the ADL

[2] Physical activity was expressed using the LAPAQ. Test scores were divided into deciles for univariate analysis (most physically active meaning highest decile)

[3] According to the adjusted MMSE

Preliminary analyses

Collinearity was checked (see Table 3.5). Respondents with higher multimorbidity were more care dependent, more inactive or showed more depressive symptoms. Patients with more depressive symptoms showed lower physical activity and more cognitive impairment.

Multivariate analysis for the risk of polypharmacy

Two multivariate logistic regression models were performed (see Table 3.6), with correction for significant demographic characteristics (female gender, alcohol use and the level of education) and for age. The first model constructed around the level of multimorbidity (CIRS) explained 30.3% (Nagelkerke R^2, p<.001) of the variance. Apart from this clinical characteristic, only physical activity was withheld, showing a negative association. There was 77% more chance for having polypharmacy for every higher level of multimorbidity (CIRS, OR 1.8, 95% CI 0.5 – 2.1), and every higher decile of physical activity was associated with a 17% decreased chance of having polypharmacy (LAPAQ, OR 0.8, 95% CI 0.8 – 0.9).

In a second model, individual comorbidities were analysed instead of multimorbidity. This model explained 39.6% (Nagelkerke R^2, p<.001). Physical activity had the strongest (negative) association (LAPAQ OR 0.8, 95% CI 0.7 – 0.9) , followed by hyperlipidaemia (OR 3.4, 95% CI 2.0 – 5.9) and depression (OR 3.7, 95% CI 1.4 – 9.7). In this second model, every higher decile of physical activity was associated with a 22% decreased chance of having polypharmacy, and people with depression were 3.7 times more likely to have polypharmacy.

Table 3.5. *Correlation matrix taken between multimorbidity, functional characteristics, and the number of medications.*

		CIRS	ADL	LAPAQ	GDS-15	MMSE
Multimorbidity	**CIRS**	–				
Activities of daily life	**ADL**	.35**	–			
Physical activity	**LAPAQ**	-.23**	-.25**	–		
Depressive symptoms	**GDS–15**	.21**	.26**	-.38**	–	
Cognitive impairment	**MMSE**	-.11*	-.18**	.22**	-.30**	–
Number of medications taken		.47**	.23**	-.29**	.28**	-.09

All variables are expressed as continuous variables.

* Significant correlation at the p<0.05 level ** Significant correlation at the p<0.001 level

Table 3.6. *Multivariate logistic regression models for the association with polypharmacy (≥5 medications).*

	Multivariate odds ratio (95% C.I.)
Model 1	
Multimorbidity (CIRS) [1]	1.77 (1.49 – 2.10)
Physical activity (LAPAQ) [2]	0.83 (0.76 – 0.90)
Nagelkerke R^2	0.303
Model 2	
Hyperlipidaemia	3.42 (1.98 – 5.91)
Osteoporosis	2.02 (1.03 – 3.93)
Diabetes	2.71 (1.23 – 5.98)
Post myocardial infarction, post stroke	3.09 (1.45 – 6.57)
COPD/Asthma	2.86 (1.32 – 6.19)
Depression	3.73 (1.43 – 9.73)
Chronic renal failure	3.44 (1.23 – 9.66)
Physical activity (LAPAQ) [2]	0.78 (0.71 – 0.87)
Nagelkerke R^2	0.396

* The models were corrected for age, gender, alcohol use, level of education.

1 Multimorbidity was expressed using the CIRS.

2 Physical activity was expressed using the LAPAQ. Test scores were divided into deciles in multivariate analysis (most physically active meaning highest decile).

3.5 Discussion

To the best of our knowledge, this is the first study exploring medication use in the community-dwelling oldest old, attempting to unravel the complex interactions between demographic, clinical, and functional characteristics of polypharmacy. Although the oldest subpopulation (80+) is growing, and is characterised by more multimorbidity, they remain underrepresented in scientific literature. This population is encouraged to stay at home for as long as possible, underlying the importance of GPs as key players in primary care for this population.

In this sample of community-dwelling older adults, where those with severe dementia were excluded, we found a relatively high proportion of healthy and active people aged 80 or more. Although the high proportion of healthy or active older people, polypharmacy was present in the majority, yet still less than in long-term care residents[152, 153]. The medication use did not increase in this age group with advancing age as well. Cardiovascular (particularly antithrombotic medication) and nervous system medication were most used, similar to findings by others[246]. Antidepressant, and benzodiazepines (+ derivates) use was high, with

substantial concomitant use within these groups.

This study aimed to search for all patient related risk factors. No linear association was found with age, as medication use decreased in late-life. This could be explained by a possible survivor-effect or possible deprescribing in the oldest old. The most dominant relationship was found for multimorbidity, indicated by the positive associations with most prevalent clinical problems. Apart from the obvious relationship between clinical characteristics, physical activity and depressive symptoms were the only other characteristics associated with polypharmacy. Depressive symptoms (GDS-15) and the diagnosis of depression were both positively associated with polypharmacy. Only physical activity (LAPAQ) was negatively associated, either suggesting a protective effect for polypharmacy or it is a result of low medication use.

Strengths and limitations

The oldest old are an underrepresented segment of the population in scientific literature. Using validated and standardised tests, a complete picture was obtained of the demographic, clinical, and functional status in the oldest old still living at home. GPs, whom older Belgians regularly visit, collected most data [67, 262]. To the best of our knowledge, this study is the first to give a complete overview of patient-related characteristics (personal, clinical, and functional) in association with polypharmacy, as a dedicated sample of this particular age group, is given. The independent associations of physical activity, and depression with polypharmacy are important for further research.

Because of the cross-sectional design, causality could not be investigated. This study was limited to an analysis of patient-related characteristics associated with polypharmacy. Neither did we focus on prescriber characteristics, since a high medication use is also shaped by physician prescribing preferences (medication knowledge, experiences, peer influence of prescribers, monitoring methods, attitude to deprescribing, and patterns of reactions to complaints). In this study only chronic medication was registered, excluding over-the-counter drugs and *pro re nata* drugs (defined as medication that should be taken when circumstances arise, or as needed).

Another limitation is the absence of a distinction between appropriate and inappropriate medication prescribing. Our aim was to gain insights in patient related characteristics explaining a higher medication

use in older adults, expressed by polypharmacy. This term is often used to describe the prescription of too many medications, but does not distinguish whether each medication has been prescribed appropriately or not. The results of this study must be interpreted with caution, as it is possible that in a number of patients with polypharmacy, all medicines prescribed are appropriate.

Comparison with existing literature

The medication use of community-dwelling oldest old is high, but lower than the medication use of older adults in nursing homes. The mean chronic medication intake of the oldest old was 5.4, compared to a mean of 7.6 medications of a cross-sectional sample of residents of 76 nursing homes in Belgium[152]. The prevalence of excessive polypharmacy (more than 10) in community-dwelling older adults was 9.1%, considerably lower than nursing home residents, where one in three nursing is prescribed at least 10 medications. The medication intake differed as well. Nervous system drugs were less prescribed in the community-dwelling cohort, particularly the use of antipsychotics was clearly lower (2.4% versus 32.9% in 2005, or 26.2% in 2011)[153, 263]. Laxatives were also much less prescribed (4.4% versus 49.8% of nursing home residents).

As found in other studies [72, 153], we found a late life decrease in medication use. Women were more likely to have polypharmacy than men, as was also indicated by others [149, 246, 264]. The observed association between polypharmacy and multimorbidity is obvious and plausible, and consistent with existing literature [265, 266]. Depression was also identified as an independent risk factor of polypharmacy before[149].

Physical activity showed independently a possible protective influence on polypharmacy independently. The correlation between activity and health in older persons is well known [267, 268]. We also found a negative association with moderate alcohol use and polypharmacy. Others found that older people attending social activities are more likely alcohol users [269]. This leads us to the assumption that moderate alcohol use among the oldest old is a proxy for a healthy, social, and active life. Sicker older people with more medications could participate less in social activities and thus drink less alcohol.

Implications for research

The quest for risk factors of polypharmacy is a complex endeavour. More longitudinal research is needed to delineate the consequences on mortality or other major life events (hospitalisation, institutionalisation) of polypharmacy and medication use over time, incorporating physician prescribing preferences. Follow-up research should include the level of (in)appropriateness of prescribing. Both primary care and long-term care settings are to be compared more intensively, in order to gain insights in changing medication patterns across settings. Interventional research is needed to establish whether active management of physical inactivity or adequate treatment of depression may reduce polypharmacy.

3.6 Conclusion

Polypharmacy was high among Belgian community-dwelling oldest old (80+). Determinants of polypharmacy were interrelated, but dominated by multimorbidity. On top of the burden of multimorbidity, polypharmacy was independently associated with less physical activity, and with more depressive symptoms.

Chapter 4

Mortality, hospitalisation, institutionalisation in community-dwelling oldest old: *The impact of medication*

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Chapter 4: Contents

4.1 Abstract

Background: High drug use and associated adverse outcomes are common in older adults. This study investigates association of medication use with mortality, hospitalisation, and institutionalisation in a cohort of community-dwelling oldest old (aged 80 and over).

Methods: Baseline data included socio-demographic, clinical, and functional characteristics, and prescribed medications. Medications were coded by the Anatomic Therapeutic Chemical classification. Survival analysis was performed at 18 months after inclusion using Kaplan-Meier, and multivariate analysis with Cox regression to control for covariates.

Results: Patients' (n=503) mean age was 84.4 years (range 80 – 102), and 61.2% was female. The median medication use was 5 (0 – 16). The mortality, hospitalisation, and institutionalisation rate were 8.9%, 31.0%, and 6.4% respectively. The mortality and hospitalisation group had a higher level of multimorbidity and weaker functional profile. Adjusted multivariate models showed an 11% increased hospitalisation rate for every additional medication taken. No association was found between high medication use and mortality, nor with institutionalisation. A higher association for mortality was observed among verapamil/diltiazem users, hospitalisation was higher among users of verapamil/diltiazem, loop diuretics and respiratory agents. Institutionalisation was higher among benzodiazepines users.

Conclusion: In the community-dwelling oldest old (aged 80 and over), high medication use was clearly associated with hospitalisation, independent of multimorbidity. The association with mortality was clear in univariate, but not in multivariate analysis. No association with institutionalisation was found. The appropriateness of the high medication use should be further studied in relation to mortality, hospitalisation, and institutionalisation for this specific age group.

4.2 Introduction

The oldest old (defined as individuals aged 80 and over) are characterised by a high level of multimorbidity, resulting in possible high medication intake [241, 242]. In this age group, medications are prescribed even though the benefit-risk profile is not always fully understood [270, 271]. Age related changes in pharmacokinetics and –dynamics alter the sensitivity for the therapeutic effects and often increase the side effects.

High medication use and polypharmacy (defined as the daily intake of five medications or more [135]), increases the risk of inappropriate prescribing (including overuse, underuse and misuse), drug interactions, and adverse effects in older adults [272, 273]. This can again contribute to drug related problems (DRPs) [274, 275]. DRPs alter the expected bonus of medications on their health into a possible risk. Due to a worsening clinical or functional profile of those aged 80 and more, DRPs will become more prevalent, and potentially impede with the beneficial influence of medications on their health [276].

Both the beneficial and harmful effects of medication on outcomes have been explored in younger populations (aged 65 and over). In this age group, high medication use has been associated with hospitalisation, mortality, and increased health care costs [277, 278]. In Belgium, medication related hospital admissions account for 20.9% of all hospitalisations in adults aged 65 years and over[96].

However, studies exploring the medication use in relation to relevant outcomes in the oldest old (aged 80 and over) are limited, as well as studies exploring the specific role of medications and their effect on outcomes. Studies either failed to disentangle the independent role of medications, due to the strong interrelationship with multimorbidity [279, 280], or studies focussed primarily on the appropriateness of prescribing [281, 282]. Therefore, this study aims to explore the association of medication use (number of medications, polypharmacy, specific medication groups) in the community-dwelling oldest old (aged 80 and over) with mortality, hospitalisation, and institutionalisation during a follow-up period of 18 months, and taking into account the role of multimorbidity, and demographic, clinical, and functional characteristics.

4.3 Methods

This study uses data of the Belfrail-cohort [252], a prospective, observational population-based cohort study. In summary, eligible patients were adults aged 80 years and older, without known dementia, and not in acute or palliative care. Inclusion of patients was done by general practitioners [252]. For this study, all community-dwelling patients with medication records available were selected, yielding the Belfrail-MED cohort (n=503).

Baseline data

General practitioners and clinical research assistants collected the data (structured questionnaire, clinical examination, and standardised tests). Baseline data collection consisted of socio-demographic, clinical, and functional data described in the baseline study of the Belfrail-MED cohort [283].

Socio-demographic data included age, gender, level of education, level of education, whether they lived alone, or received nursing care at home.

Clinical characteristics were collected from the standardised medical history and the list of current clinical problems. Multimorbidity was operationalised using the Cumulative Illness Rating Scale (CIRS) [253]. The CIRS measures the chronic medical illness burden while taking into consideration the severity of chronic diseases (Hudon, Fortin, and Soubhi 2007). The CIRS counts the number of 14 body systems affected with moderate disability, morbidity or extremely severe disease (severity score at least 3) [254] (possible range: 0 to 14) [14].

Functional characteristics included Activities of Daily Living (ADL, derived from the KATZ scale), physical activity (LASA Physical Activity Questionnaire, LAPAQ), cognitive status (Mini Mental State Examination, MMSE, adjusted for age and level of education) [259], and fall risk (Tinetti).

Medication data included all chronic medications at baseline. The brand name, active substance, and the prescribed daily dose were recorded by the general practitioners.

Follow-up data

Follow-up data was collected using standardised questionnaires, filled in by the general practitioners. The original follow-up period was 5

years. For this study, we defined a cut-off at 18 months, because in longer follow-up periods, associations with baseline characteristics are expected to fade away. Patients who died, who were institutionalised, or were hospitalised during the 18 months follow-up period were considered as 'events'.

The data on mortality included date and cause of death. Data on hospitalisation (defined as unplanned hospital stays lasting longer than 1 day) included the date of the first hospital stay. Institutionalisation was defined as entering the nursing home for permanent stay. The date of entering a nursing home was recorded.

Medication handling

All drugs were recorded by brand or compound name. They were entered into a data program based on the official register of medications on the Belgian market (source: https://www.ehealth.fgov.be). The medication was translated into the Anatomical Therapeutic Chemical classification (WHO ATC/DDD 2013) [284].

For the analysis of the medication use in association with the outcomes, we used three models: the number of medications, polypharmacy, and medication subclasses. Polypharmacy was defined as the chronic intake of ≥5 medications [2]. For the medication subclasses, we analysed the first (main anatomical groups) and second ATC level (therapeutical main groups). Subsequently, we analysed medications at the third ATC level (therapeutic subgroup) or lower for medications or medication groups that are specifically mentioned in Potential Inappropriate Medication (PIM) lists (BEERS, STOPP/START)[133, 187]. Additionally, we created a dichotomous variable including all medications with anticholinergic properties, according to the study of Duran et al. (2010) [215].

Functional data handling

The KATZ ADL-scale and the LAPAQ scores were divided into smaller groups to determine those with the highest care dependency, and those with the lowest physical activity respectively.

The KATZ ADL-scale (range 6 – 30) has six domains (bathing, clothing, toileting, transferring, continence, and feeding), and a higher domain or overall score signifies being more care dependent. We identified those care independent (KATZ ADL score 6, scoring 1 at all six domains), the somewhat care dependent (KATZ ADL scores 7 - 12), and those most care dependent (scoring 13 and more).

The raw LAPAQ scores (range 0 - ∞) were divided into quartiles. The lowest quartile was identified as those with the lowest physical activity.

Finally, the MMSE was used for identification of cognitive impairment, with a cut-off adapted to the age and level of education of the respondents [259].

Statistical analysis

SPSS 21.0 (Statistical Package for Social Sciences, SPSS Inc., Chicago, IL, USA) was used for statistical analysis.

For descriptive statistics means, medians or proportions were used. Comparison of continuous data was done using t-tests or non-parametric tests in case of skewed data. Analysis of categorical variables was done using chi^2 tests.

The Kaplan-Meier method was used to estimate survival. For the assessment for the difference of survival between the groups with and without polypharmacy, the log-rank test was used. The censor date was set at 18 months after inclusion, and time to event was calculated for the three outcomes. For the calculation of the observation periods for both hospitalisation, and institutionalisation, censoring was done for deaths. The date of death was then regarded as the end of the observation period. For all others, censoring was set at 18 months after inclusion. The mean time to death, first hospitalisation or institutionalisation was calculated.

A Cox proportional hazard models was used to calculate univariate and adjusted multivariate Hazard Ratios (HRs). Two multivariate models were constructed, one using the number of medications as the continuous independent variable, and the other using therapeutic medication subclasses. To study the specific role of medications, all models were adjusted for multimorbidity, and additional confounding demographic variables.

Ethical considerations

The study protocol was approved by the Biomedical Ethics Committee of the Medical School of the Université catholique de Louvain (UCL), Brussels (B40320084685, on 27/10/2008) and later by the Ethics Committee of Ghent University Hospital (B670201421408, on 26/06/2014). All patients provided informed consent.

4.4 Results

Description of the study population

An overview of the socio-demographic, functional, and clinical characteristics and the medication use of the participants are provided in Table 4.1. The mean age was 84.4 years (range 80 – 102), 61.2% was female. The median level of multimorbidity (defined by CIRS) was 4 (range 1 – 9), with hypertension as the most prominent clinical problem. The mean number of medications was 5.4 (range 0 – 16) and polypharmacy

Table 4.1. *Demographical, clinical, and functional characteristics, and medication use at baseline (n= 503).*

Demographical	**%**
Mean age in years (range)	*84.4* (80 - 102)
Gender (% female)	61.2
Living alone	43.3
Low education (≤8 years)	69.2
Clinical[1]	**%**
Median multimorbidity[2] (range)	*4* (1 – 9)
Hypertension	70.4
Osteoarthritis	57.1
Hyperlipidaemia	44.1
Heart Failure (NYHA > 0)	38.4
Diabetes	18.9
Post infarct / post stroke	17.7
COPD / asthma	13.1
Chronic renal failure	11.1
Functional	**Median (IQR range)**
Activities of daily living, ADL	6 (6 - 8)
Physical activity, LAPAQ	70 (30 – 102)
Mental status, MMSE	28 (26 – 29)
Medication use[3]	**%**
Median number of medication (range)	*5* (0-16)
Polypharmacy (≥5 drugs daily)	57.7
ATC C - Cardiovascular	86.3
ATC B - Blood and blood forming	56.1
ATC N - Nervous system	54.5
ATC A - Alimentary tract and metabolism	50.1
ATC M - Musculo-skeletal system	23.5
ATC R - Respiratory system	15.9
ATC H - Systemic hormonal preparations	11.7
ATC G - Genito-urinary system and sex hormones	10.3

(≥5 medications) was present in 57.7% of the population. Cardiovascular, haematological, and nervous system drugs were most used.

Mortality

The mortality rate was 8.9% (n=45) at 18 months. Most prominent causes of death were cardiovascular and/or cerebrovascular events (48.9% of deaths), followed by cancer (20.0%), respiratory problems (13.3%), and general deterioration (6.7%).

The deceased patients were older, and received more nursing care at home. They also had a higher mean level of multimorbidity (CIRS). Within the separate clinical problems, only chronic renal failure was significantly associated with higher mortality. All the functional characteristics were associated with higher mortality (see Table 4.2).

The survival rate 18 months after inclusion differed significantly between those with polypharmacy and those without (93% versus 88% respectively, p=0.049).

In univariate analysis, mortality was significantly associated with high medication use. At medication subclass level, mortality was higher in those taking high-ceiling or loop diuretics, selective calcium channel blockers with a direct cardiovascular effect, predominantly verapamil/diltiazem use , antidepressants, and anticholinergics, see Table 4.3.

In multivariate analysis, no association with mortality was found for the number of medications (Hazard Ratio 1.05, 95% CI 0.94 – 1.18), after correction for multimorbidity, age, and gender. At medication subclass level, selective calcium channel blockers, predominantly verapamil/diltiazem, were associated with increased mortality (HR 2.84, 95% CI 1.10 – 7.36), see Table 4.4. The additional introduction of specific clinical problems (heart failure) into the model, yielded similar results.

Hospitalisation

The hospitalisation rate in the Belfrail-MED cohort was 31.0% (n=156). Those hospitalised received more nursing care at home, had a higher level of multimorbidity, and had more clinical problems. They showed a weaker functional profile, were more care dependent, less physically active, more cognitively impaired, and had a higher risk of falling (see Table 4.2).

The hospitalisation rate after 18 months differed significantly between those with polypharmacy and those without (75% vs 63%, p=0.001).

In univariate analysis, hospitalisation was significantly associated with

Table 4.2. *Socio-demographic, clinical, and functional characteristics associated with mortality, first hospitalisation, and institutionalisation after a follow-up of 18 months.*

	Dead?				Hospitalised?				Institutionalised?			
	Yes N=45	No N=458	P value	Hazard Ratio*	Yes N=156	No N=347	P value	Hazard Ratio	Yes N=32	No N=471	P value	Hazard Ratio
Event rate (%)	**8.9**	**91.1**			**31.0**	**69.0**			**6.4**	**93.6**		
Socio-demographic	%	%		HR (95% CI)	%	%		HR (95% CI)	%	%		HR (95% CI)
Mean age	*85.7*	*84.3*	*.016*	*1.09 (1.01 – 1.16)*	*84.9*	*84.2*	*.058*	*1.04 (0.998 – 1.08)*	*86.7*	*84.1*	*<.001*	*1.15 (1.10 – 1.21)*
Female gender	60.0	61.4	.859	0.94 (0.52 – 1.70)	59.0	62.2	.486	0.89 (0.65 – 1.22)	73.2	59.3	.025	1.78 (1.05 – 3.01)
Low education (≤8 years)	65.9	70.4	.533	0.83 (0.45 – 1.55)	70.1	70.0	.971	1.03 (0.73 – 1.45)	70.4	70.0	.936	1.02 (0.62 – 1.70)
Living alone	46.7	43.0	.637	1.15 (0.64 – 2.07)	44.2	42.9	.787	1.06 (0.77 – 1.46)	60.6	40.5	.002	2.06 (1.28 – 3.32)
Clinical												
Mean comorbidity, CIRS	*4.6*	*3.7*	*<.001*	*1.36 (1.15 – 1.59)*	*4.3*	*3.6*	*<.001*	*1.25 (1.14 – 1.36)*	*3.9*	*3.8*	*.496*	*1.08 (0.94 – 1.24)*
Hypertension	73.3	70.2	.664	1.60 (0.60 – 2.24)	71.8	69.9	.674	1.09 (0.77 – 1.54)	73.2	70.1	.587	1.17 (0.69 – 1.98)
Osteoarthritis	61.4	57.9	.657	1.15 (0.63 – 2.10)	59.7	57.5	.644	1.11 (0.81 – 1.53)	58.0	58.3	.965	1.00 (0.62 – 1.61)
Hyperlipidaemia	44.2	45.4	.877	0.95 (0.52 – 1.73)	47.4	44.4	.539	1.08 (0.79 – 1.49)	36.8	46.7	.127	0.68 (0.41 – 1.10)
Heart Failure	46.7	37.6	.230	1.44 (0.80 – 2.58)	46.8	34.6	.009	1.56 (1.14 – 2.14)	42.3	37.7	.468	1.20 (0.75 – 1.92)
Diabetes	29.5	18.0	.062	1.85 (0.97 – 3.54)	24.0	16.8	.056	1.48 (1.02 – 2.14)	5.6	21.2	.002	0.26 (0.10 – 0.73)
Post MI / post CVA	29.3	17.8	.073	1.80 (0.92 – 3.51)	22.8	17.1	.145	1.32 (0.89 – 1.95)	21.7	18.3	.501	1.28 (0.72 – 2.27)
COPD/Asthma	24.4	13.9	.070	1.92 (0.94 – 3.92)	21.4	11.9	.007	1.80 (1.21 – 2.68)	13.0	15.1	.657	0.90 (0.45 – 1.81)
Depression	20.9	12.1	.099	1.88 (0.90 – 3.92)	20.9	9.3	<.001	1.97 (1.34 – 2.91)	18.6	11.9	.125	1.66 (0.91 – 3.03)
Chronic renal failure	25.0	10.1	.003	2.79 (1.41 – 5.53)	16.1	9.4	.031	1.74 (1.12 – 2.69)	13.4	11.1	.574	1.30 (0.65 – 2.63)
Functional												
Most care dependent[1]	25.0	7.8	<.001	3.42 (1.73 – 6.76)	14.6	7.0	.007	2.04 (1.30 – 3.20)	18.8	8.6	.057	1.45 (0.70 – 3.04)
Lowest physical active[2]	44.4	23.2	.002	2.48 (1.38 – 4.49)	31.6	22.3	.028	1.51 (1.07 – 2.12)	36.6	23.2	.016	1.88 (1.16 – 3.05)
Cognitive impairment	30.2	13.8	.004	2.54 (1.32 – 4.86)	22.3	12.2	.004	1.81 (1.23 – 2.67)	24.3	13.7	.023	2.05 (1.19 – 3.54)
Fall risk – Tinetti	45.5	20.0	<.001	3.13 (1.73 – 5.66)	36.0	16.3	<.001	2.45 (1.76 – 3.43)	45.7	18.4	<.001	3.60 (2.25 – 5.76)

[1] Highest care dependency was defined as respondents scoring ≥ 13 (9.1%) on the KATZ ADL scale.

[2] Lowest physical active was defined as the quartile with the lowest raw score on the LAPAQ.

[3] Cognitive impairment was defined using the MMSE, adjusted for age and level of education.

Table 4.3. Medication use associated with mortality, first hospitalisation, and institutionalisation at 18 months.

	Dead				Hospitalised				Institutionalised			
	Yes	No	P	Hazard Ratio*	Yes	No	P	Hazard Ratio	Yes	No	P	Hazard Ratio
	N=45	N=458	value		N=156	N=347	value		N=32	N=471	value	
Event rate (%)	**8.9**	**91.1**			**31.0**	**69.0**			**6.4**	**93.6**		
	%	%		HR (95% CI)	%	%		HR (95% CI)	%	%		HR (95% CI)
Mean number of medications	*6.4*	*5.3*	*0.033*	*1.12 (1.02 – 1.22)*	*6.3*	*5.0*	*<0.001*	*1.14 (1.05 – 1.20)*	*5.5*	*5.4*	*0.842*	*1.02 (0.94 – 1.10)*
Polypharmacy (≥5 drugs)	71.1	56.3	0.056	1.87 (0.98 – 3.56)	67.3	46.7	0.003	1.69 (1.21 – 2.36)	59.2	57.4	0.782	1.11 (0.69 – 1.78)
At least 1 psychotropic drug	55.6	41.0	0.060	1.73 (0.96 – 3.12)	50.0	38.9	0.020	1.44 (1.05 – 1.97)	56.3	40.0	0.010	1.85 (1.16 – 2.96)
At least 3 cardiovascular drugs	20.0	16.4	0.534	1.26 (0.61 – 2.61)	21.8	14.4	0.040	1.56 (1.06 – 2.28)	18.3	16.4	0.695	1.13 (0.62 – 206)
At least 1 anticholinergic drug	38.6	19.8	0.004	2.40 (1.31 – 4.40)	30.3	17.4	0.001	1.82 (1.29 – 2.56)	22.5	21.3	0.809	1.14 (0.65 – 1.98)
A02 – acid related drugs	31.1	23.8	0.276	1.42 (0.76 – 2.67)	28.2	22.8	0.189	1.22 (0.86 – 1.73)	23.9	24.5	0.914	0.98 (0.57 – 1.69)
A10 – antidiabetic drugs	24.4	15.1	0.101	1.76 (0.89 – 3.47)	17.9	15.0	0.401	1.22 (0.81 – 1.84)	4.2	17.8	0.004	0.24 (0.08 – 0.76)
A12 – Mineral supplements	17.8	16.6	0.839	1.10 (0.51 – 2.35)	23.1	13.8	0.010	1.63 (1.13 – 2.37)	16.9	16.7	0.961	1.00 (0.54 – 1.87)
B01 – antithrombotic agents	51.1	54.8	0.635	0.88 (0.49 – 1.58)	53.8	54.8	0.850	0.98 (0.71 – 1.34)	52.1	54.9	0.666	0.90 (0.57 – 1.44)
C01 – cardiac therapy medication	24.4	20.3	0.513	1.25 (0.63 – 2.47)	25.0	18.7	0.108	1.36 (0.95 – 1.96)	19.7	20.8	0.830	0.95 (0.53 – 1.71)
C03 – Diuretics	46.7	30.6	0.027	1.92 (1.07 – 3.50)	44.2	26.5	<0.001	1.96 (1.43 – 2.68)	39.4	30.8	0.148	1.50 (0.93 – 2.42)
C03CA – Loop diuretics	34.1	15.6	0.002	2.61 (1.40 – 4.86)	29.7	11.6	<0.001	2.61 (1.85 – 3.69)	22.5	16.4	0.202	1.57 (0.90 – 2.74)
C07 – Beta Blocking agents	35.6	42.6	0.362	0.75 (0.41 – 1.38)	37.8	43.8	0.208	0.81 (0.58 – 1.11)	39.4	42.4	0.644	0.86 (0.53 – 1.38)
C08 – Calcium Channel blockers	26.7	24.0	0.692	1.14 (0.59 – 2.21)	24.4	24.2	0.971	1.03 (0.71 – 1.48)	23.9	24.3	0.947	0.96 (0.56 – 1.66)
C08D – Selective Ca channel blockers	11.4	3.3	0.009	3.49 (1.38 – 8.86)	7.7	2.3	0.004	2.49 (1.38 – 4.49)	5.6	3.7	0.451	1.66 (0.61 – 4.56)
C09 – agents acting on RAAS	44.4	41.7	0.722	1.12 (0.62 – 2.01)	42.9	41.5	0.760	1.10 (0.80 – 1.51)	32.4	43.5	0.078	0.67 (0.41 – 1.09)
C10 – Lipid modifying agents	28.9	33.6	0.520	0.81 (0.42 – 1.54)	32.7	33.4	0.871	0.97 (0.70 – 1.36)	28.2	36.0	0.331	0.77 (0.46 – 1.30)
Benzodiazepines [1]	40.0	35.2	0.517	1.21 (0.66 – 2.19)	37.8	34.6	0.483	1.11 (0.81 – 1.54)	49.3	33.3	0.009	1.80 (1.13 – 2.87)
Antidepressants [2]	26.7	15.1	0.043	2.00 (1.03 – 3.86)	23.1	13.0	0.004	1.73 (1.19 – 2.51)	14.1	16.4	0.617	0.92 (0.47 – 1.80)
R03 – medication for obstructive airway diseases	17.8	11.8	0.244	1.29 (0.94 – 1.78)	21.8	8.1	<0.001	2.41 (1.64 – 3.52)	15.5	11.8	0.381	1.36 (0.71 – 2.58)

* Hazard Ratios are calculated using Cox regression analysis (univariate analysis)

[1] Benzodiazepines are defined as ATC classes N05BA, N05CD, N05CF.

[2] Antidepressants are defined as ATC classes N06AA, N06AB, N06AG, and N06AX.

high medication use (see Table 4.3). Hospitalisation was significantly associated with the use of mineral supplements, loop diuretics, verapamil/diltiazem, antidepressants, drugs for obstructive airway diseases, and anticholinergic agents, see Table 4.3.

In multivariate analysis, hospitalisation was significantly associated with high medication use (HR 1.11, 95% CI 1.03 – 1.18). For every additional medication taken at baseline, there was an 11% increased hospitalisation rate. At medication subclass level, hospitalisation was also associated with the use of verapamil/diltiazem (HR 2.14, 95% CI 1.10 – 4.16), loop diuretics (HR 2.24, 95% CI 1.48 – 3.40), and medications used in obstructive airway diseases (HR 1.76, 95% CI 1.12 – 2.79), see Table 4.4. The additional introduction of specific clinical problems (heart failure, COPD/Asthma) into the model, yielded similar results.

Institutionalisation

The institutionalisation rate after 18 months was 6.4% (n=32). Those entering a nursing home were older, female, lived alone, and received more nursing care at home. Their level of multimorbidity was equal to those who remained at home. Having diabetes or using medications for diabetes had a negative association with institutionalisation. The institutionalised were less physically active, more cognitively impaired, had a high risk of falling, but were not more care dependent (see Table 4.2).

There was no difference in institutionalisation rate 18 months after inclusion among those with polypharmacy and those without (94% vs 93%, p=0.654, see Figure 4.1).

In univariate analysis, institutionalisation was not associated with high medication use. Increased institutionalisation was associated with the use of at least 1 psychotropic medication, predominantly due to a higher benzodiazepine use, see Table 4.3.

Multivariate analysis showed no associations with high medication use (HR 1.00, 95% CI 0.90 – 1.09). At medication subclass level, institutionalisation was only associated with the use of benzodiazepines (HR 1.62, 95% CI 1.01 – 2.60), see Table 4.4.

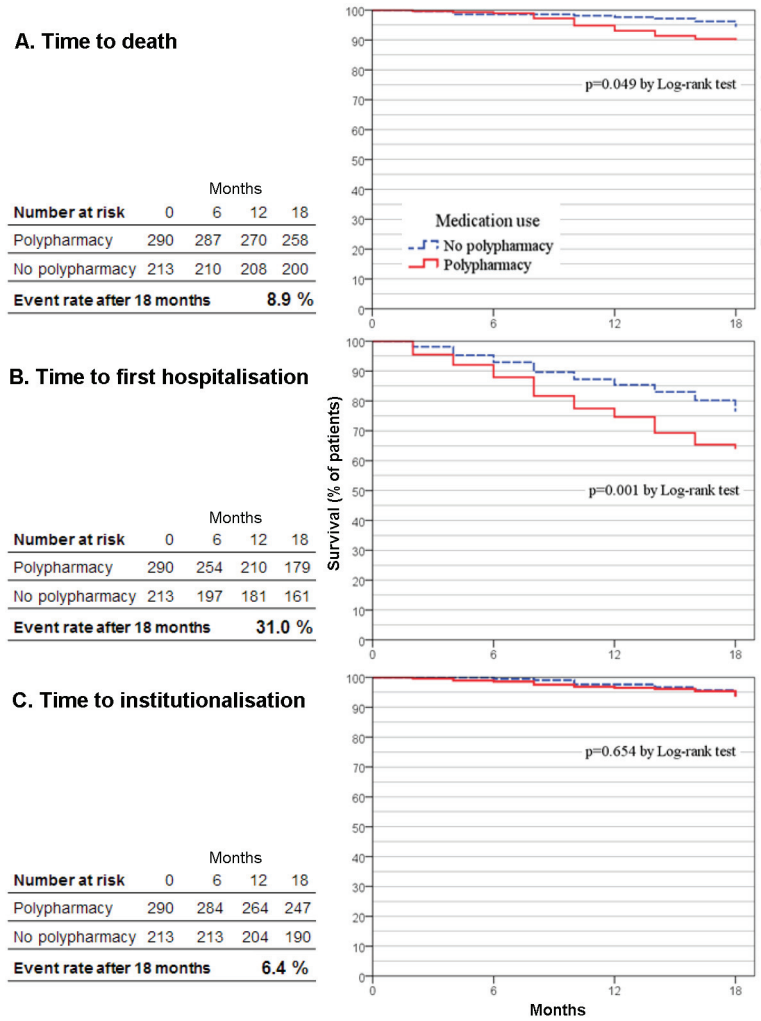

Figure 4.1. *Kaplan-Meier Survival analysis of time to death (**A**), time to the first hospitalisation (**B**), and to institutionalisation (**C**) for patients having polypharmacy (≥5 medications) and patients without polypharmacy.*

Table 4.4. *Multivariate analysis of medication use in association with mortality (9.3%), hospitalisation (31.0%), and institutionalisation (6.4%) after 18 months in a cohort of oldest old, aged 80 and over.*

		Mortality	Hospitalisation	Institutionalisation
Model 1	Number of medications	1.05 (0.94 – 1.18)	1.11 (1.03 – 1.18)	1.00 (0.90 – 1.09)
Model 2	C08D – Selective Calcium channel blockers	2.84 (1.10 – 7.36)	2.14 (1.10 – 4.16)	-
	C03CA - Loop diuretics	-	2.24 (1.48 – 3.40)	-
	R03 - Agents in obstructive airway diseases	-	1.76 (1.12 – 2.79)	-
	Benzodiazepines[1]	-	-	1.62 (1.01 – 2.60)

The models were adjusted for age, gender, and for multimorbidity (using the CIRS).
[1] Benzodiazepines are defined as ATC classes N05BA, N05CD, N05CF.

4.5 Discussion

This study explored association of high chronic medication use with three different outcomes (mortality, hospitalisation, and institutionalisation) during an 18 months observation period in a cohort of community-dwelling oldest old, defined as persons aged 80 years and over.

Main finding of this study

To the best of our knowledge, this is the first longitudinal study investigating these associations in a cohort of community-dwelling oldest old. Our main finding is that in this oldest old cohort, every additional medication used at baseline did increase the rate of hospitalisation with 11% after an observation period of 18 months

At the level of specific medication groups in multivariate analysis, the use of verapamil/diltiazem showed associations with increased mortality. The use of verapamil/diltiazem, loop diuretics and asthma/COPD-medications were independently associated with higher hospitalisation rate. Finally, benzodiazepines were associated with higher institutionalisation rate.

What this study adds

The major strengths of this study are the longitudinal design, and the

exclusive cohort of oldest old (aged 80 and over), and the multivariate analysis, adjusted for multimorbidity. This study provides new information in this specific subpopulation, where little is known on medication related outcomes [285].

Limitations of the study

Limitations are the observational nature, not allowing causal interference. We had data on chronic baseline medication use, but no data on over-the-counter drugs or *pro re nata* drugs (medication that is taken when needed, or if the situation arises).

What is already known

Medication is given to treat or prevent disease, with the aim to lower the risk of mortality, and hospitalisation. The beneficial effect of medications can be jeopardised by the increasing presence of drug related problems with increasing higher medication use. In younger populations (aged 65 and over) the association of polypharmacy with hospitalisation and mortality is more clear [286–288]. In the oldest old (aged 80 and over), the association with hospitalisation remained, but there was no association found with mortality for the number of medications.

One may speculate why in the oldest old (aged 80 and over), high medication use, was not clearly associated with mortality. Only looking at the number of medications may be too crude to address the complex relationship with mortality, as it does not take into account the role of inappropriate medications or the role of not-used medications (either by not prescribing, or by deprescribing). It is possible that patients with high medication use are well treated in a well-balanced therapy with little excess risk of mortality [244], as well as those with a low medication use miss beneficial, necessary medications. In following studies, we will address the role of inappropriate medications, and inappropriate prescribing by both looking at misused and underused medications.

The observed association between institutionalisation and cognitive impairment and use of benzodiazepines suggests that cognitive problems, but not the level of multimorbidity and care dependency, is the dominating reason for older adults to move from home care to the nursing home [289]. The puzzling association with anti-diabetic drugs might be explained by the focused and continuous home care provided for older community-dwelling diabetes patients in Belgium [290].

In our univariate analysis, all aspects of functional profile in the oldest

old were strongly associated with mortality, hospitalisation, and institutionalisation. Other findings also suggest that more functionally active oldest old benefit in terms of reduced mortality or hospitalisation risks [291]. However we could not confirm this association in multivariate analysis, after the introduction of multimorbidity.

4.6 Conclusion

In the community-dwelling oldest old (aged 80 and over), high medication use, independent of multimorbidity, was clearly associated with hospitalisation The association with mortality was present in univariate analysis, but not in multivariate. There was no association with institutionalisation. The appropriateness of the high medication use should be further studied in relation to mortality, hospitalisation, and institutionalisation for this specific age group aged 80 and over.

Chapter 5

Availability and actual use in the Belgian market of potentially inappropriate medications (PIMs) from the EU(7)-PIM list

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Inappropriate prescribing puts older adults (≥ 65 years) at risk for adverse drug reactions [183]. Recently, a European list of Potentially Inappropriate Medications (PIMs) was developed; the EU(7)-PIM list [292]. Experts from the seven participating countries (EE, NL, FI, ES, FR, SE, DE) screened their medication market for PIMs, using existing lists of explicit criteria [133, 182, 183, 186]. The experts developed the EU(7)-PIM list using a two-round Delphi panel. See Box 5.1 for more details on the development and content.

Our first aim was to check the Belgian market on the availability of potentially inappropriate medications as listed in the EU(7)-PIM list. Second, we studied the actual use of PIM products in a cohort of oldest old (≥80 years).

To check the availability, we cross-referenced the official register of medications in Belgium (coded in ATC) to the EU(7)-PIM list. Of the 275 active substances in the EU(7)-PIM list, 157 were available in Belgium. Of those, 139 products were only available on prescription. The seven medication classes in the EU(7)-PIM list contain a total of 60 active substances in the ATC classification, of which 21 were available in Belgium (three antacid combinations and complexes, five proton-pump inhibitors, two iron supplements, four estrogens, and seven triptanes). The medication classes of antacids containing aluminium compounds, and quinine and derivates, were not available in Belgium as registered medications.

To check the actual use of PIM products, we used the Belfrail-MED cohort of 503 Belgian community-dwelling oldest old (≥ 80 years, range 80 – 102 years) [252, 283]. See Box 5.2 for more background on the Belfrail-MED cohort. For this, all prescribed, chronic medications with systemic action in this population were recorded, coded into ATC, and cross-referenced to the EU(7)-PIM list. In the oldest old, the mean number of medications was 5.4 (range 0 – 16). Of the possible 157 PIM-products in Belgium, 77 were identified in this cohort. All 5 available medication classes were identified as well. In this cohort, 72,8% of patients took at least one PIM-product. Lorazepam was the most prescribed PIM product (10.7% of patients), and proton pump inhibitors the most prescribed medication class (17.3% of patients).

While scanning the Belgian medication market, we identified a few other potentially inappropriate medications, not considered in the EU(7)-PIM list, because possibly not available in the participating countries. See Box 5.3 for possible additions to the EU(7)-PIM list.

Also, PIM-products available in combination products should be discussed. For instance, loperamide (A07DA03) is listed as a PIM-product,

but the combination of loperamide in the same dose with simethicone (A07DA53) is not. For the Belgian situation, there are 61 combinations containing a PIM-product.

We encourage other European countries, not (yet) participating in the EU(7)-PIM list, to repeat this exercise, to gain insights in remaining overlaps or gaps of PIMs available in each national medication market. We urge the authors of the EU(7)-PIM list to (1) explicitly list all active substances in the medication classes, and (2) to address the problem of combinations containing PIMs. Also, (3) a procedure must be considered for the evaluation of additional potentially inappropriate active substances, which are not in the EU(7)-PIM list but used in substantial quantities in other European countries.

Box 5.1. *Additional information on the development and content of the EU(7)-PIM list.*

The EU(7)-PIM list is based on the German PRISCUS list of potentially inappropriate medications. Additionally, explicit criteria from other existing PIM lists were selected from the Beers (US), McLeods (CA) and Laroche (FR). For the content validation of each criterion, a two-round Delphi panel was constructed with experts from seven different countries (EE, NL, FI, ES, FR, SE, DE). All invited experts were selected on their experience in geriatric prescribing. The experts (n=27) evaluated each criterion on the appropriateness of medications, dose adjustments in older adults, and gave suggestions for alternative (mostly medication) therapies. Eight experts suggested additional criteria to be added to the EU(7)-PIM list. Finally, twelve experts completed a brief final survey to decide upon issues requiring further consensus.

The EU(7)-PIM list contains 282 criteria; 275 active substances and 7 broad medication classes (defined in the Anatomical Therapeutic Chemical (ATC) classification, yet without explicit enumeration of active substances within the medication classes). Criteria were predominantly medication-oriented, limited to information on the nature of the active substance, and occasionally on duration or dosage, but not on clinical data.

Box 5.2. *Additional information on the Belfrail-MED cohort of oldest old (≥80 years).*

The Belfrail-MED cohort (n=503) originated from the Belfrail study, a prospective, observational population-based cohort study. General practitioners from three Belgian regions were responsible for the selection of patients. Eligible participants were at least 80 years old and had to be able to visit their GP. Further inclusion criteria were being non-institutionalised, and having a medication record available. Exclusion criteria were: known presence of severe dementia (Mini Mental State Examination <15/30), in need of acute care or being in palliative care. The general practitioners were also responsible for recording the chronic medication use (medication being used for longer than 3 months and without known stop date).

The study protocol was approved by the Biomedical Ethics Committee of the Medical School of the Université catholique de Louvain (UCL), Brussels (B40320084685, on 27/10/2008) and later by the Ethics committee of Ghent University Hospital (B670201421408, on 26/06/2014). All respondents provided informed consent.

Box 5.3. *Possible obsolete medications in Belgium, but not on the EU(7)-PIM list.*

The following products have been considered obsolete in Belgium by the drug information centre (BCFI):

- Complex painkiller combinations (e.g. paracetamol + aspirine + caffeine)
- nasal sprays or throat pastilles with antibiotics
- Combined cough preparations with an antitussivum, mucolyticum or expectorans (and possibly antipyretica, H1-antihistaminica, anticholinergica, bronchodilating agents, or sympathicomimetic agents)
- Tilefrine (Effortil®)
- Metamizol (Novalgine®)
- Nefopam (Acupan®)
- Telithromycine (Ketek®)
- Oral Lysate of bacteria (Broncho-vaxom® and Uro-vaxom®)

Note: Some of the products may only be obsolete, but not specifically harmful for elderly.

Note: Metamizol is considered obsolete in Belgium (and Finland[292]). In the EU(7)-PIM list it is only listed as inappropriate if not used in adequate doses (as suggested by the Spanish experts in the Delphi panel).

Chapter 6

Too many, too few, or too unsafe? Impact of inappropriate prescribing on mortality and hospitalisation in a cohort of community-dwelling oldest old

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Chapter 6: Contents

6.1 Abstract

Aims: Little is known about the impact of Inappropriate Prescribing (IP) in community-dwelling adults, aged 80 and older. The prevalence at baseline (November 2008 – September 2009) and impact of IP (misuse, and underuse) after 18 months on mortality, and hospitalisation in a cohort of community-dwelling adults, aged 80 and older (n=503) was studied.

Methods: Screening Tool of Older People's Prescriptions (STOPP, misuse) and Screening Tool to Alert to Right Treatment (START, underuse) criteria were cross-referenced and linked to the medication use (in Anatomical Therapeutic Chemical-coding) and clinical problems. Survival analysis until death or first hospitalisation was performed at 18 months after inclusion using Kaplan-Meier, with Cox regression to control for covariates.

Results: Mean age was 84.4 years (range 80 – 102). Mean number of medications prescribed was 5 (range 0 – 16). Polypharmacy (≥5 medications, 58%), underuse (67%), and misuse (56%) were high. Underuse and misuse coexisted in 40%, and were absent in 17% of the population. A higher number of prescribed medications was correlated with more misused medications (r_s=.51, p<.001), and underused medications (r_s=.26, p<.001).

Mortality and hospitalisation rate were 8.9%, and 31.0% respectively. After adjustment for number of medications and misused medications, there was an increased risk of mortality (HR 1.39; 95%CI 1.10 – 1.76), and hospitalisation (HR 1.26; 95%CI 1.10 – 1.45) for every additional underused medication. Associations with misuse were less clear.

Conclusion: IP (polypharmacy, underuse and misuse) was highly prevalent in adults, aged 80 and older. Surprisingly, underuse and not misuse, had strong associations with mortality and hospitalisation.

6.2 Introduction

Appropriate prescribing of medications is a major challenge in the care for older adults. Older adults are more sensitive to the effects of medications, and have a higher prevalence of comorbidities [293]. Hence, older adults will have a higher medication intake, potentially putting them at risk for adverse drug events [183], increased morbidity, health care utilisation, and mortality [177]. Yet, polypharmacy cannot be equated with Inappropriate Prescribing (IP). IP is possible in polypharmacy, yet not every person with polypharmacy will have IP [265].

Prescribing can be potentially inappropriate if the potential benefits are outweighed by the harms, if there is evidence for an equal or more effective, yet lower-risk alternative [36, 184] or if omission of potentially beneficial medications is present [294]. Tools were developed to identify inappropriate prescribing in older adults, focussing on polypharmacy, underuse, and misuse [174]. Most of these tools consist of lists of explicit criteria of potentially inappropriate medications, often without clinical data required. Some criteria address underuse instances, always requiring clinical data [133, 182, 187], and are designed to alert clinicians when to drop or add a medication in individual patients.

The clinical relevance of screening tools for inappropriate prescribing based on these explicit criteria is not yet fully explored. Most studies were cross-sectional. Gaps in evidence remain, as data from prospective long-term cohort studies are scarce [195, 230, 231, 295]. Moreover, the oldest old (aged 80, and over) have been rarely studied as a separate group in primary care settings [85, 205, 296]. Finally, polypharmacy, underuse, and misuse, although part of the definition of inappropriate prescribing, are seldom concomitantly studied [154].

This study aims to explore the prevalence of inappropriate prescribing (misuse and underuse) in a prospective cohort of community-dwelling oldest old (aged 80, and over), and to explore associations with mortality, and hospitalisation after 18 months.

6.3 Methods

The Belfrail-MED cohort [252, 283] was used (n=503), consisting of Belgian community-dwelling patients aged 80, and over. All subjects were primary care patients, recruited by their own general practitioner. Patients were selected between November 2008 and September 2009. Exclusion criteria were known dementia, and in palliative care.

The general practitioners (GPs) were responsible for the collection of baseline (demographic, clinical, and medication data) and follow-up data (date and cause of death, date of the first hospitalisation). Clinical research assistants were responsible to collect data from the patients, using clinical examinations (e.g. blood pressure, …), and standardised scales (to measure physical activity, activities of daily living…). GPs used their medical records.

Medication handling

The general practitioner recorded all chronic medications at baseline, using the generic name. All chronic medications were codified entered into the Anatomical Therapeutic Chemical Classification (WHO ATC/DDD 2013) [284], based on the official register of medications on the Belgian market (source: https://www.ehealth.fgov.be).

Polypharmacy was defined as the daily intake of 5 medications or more [135].

Assessing inappropriate prescribing

Inappropriate prescribing was operationalised by the computerised application of criteria for misuse and underuse. For misuse, we applied the clinically oriented Screening Tool for Older Person's Prescriptions (STOPP-2 criteria). For underuse, we applied the Screening Tool to Alert doctors to Right Treatment (START-2). These criteria are suitable for use in European countries [297], have been applied and validated in several studies [171, 190, 193], and were recently updated [187].

To assess the prevalence and impact of inappropriate prescribing, the STOPP/START–2 criteria were cross-referenced and linked to the baseline medications and clinical problems.

This was not possible for all criteria, as only a subset of the STOPP/START–2 criteria could be applied (see Figure 6.1). For the START criteria, 13 out of 34 criteria could be used for our analysis, and for the STOPP

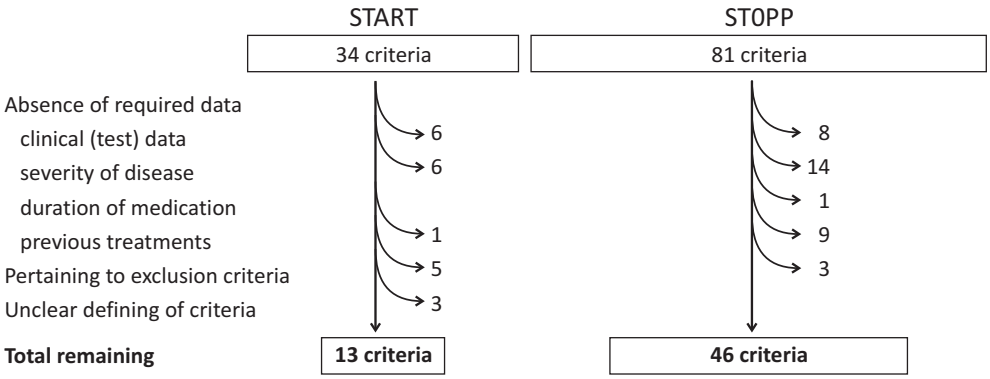

Figure 6.1. *Flowchart for the rationale for exclusion of STOPP/START criteria.*

criteria, 46 out of 81. Reasons to omit criteria included the absence of data in our database required by the criteria: (1) clinical test results, (2) severity of disease data, (3) short duration of medication, and (4) criteria on rank ordering of first choice medications. Other reasons to omit criteria were the unclear definition of clinical problems. Criteria pertaining to diseases excluded in our cohort (e.g. dementia) could also not be applied. Additionally for the STOPP criteria, we omitted one extra criterion because of possible duplication in scoring: criterion 32 (benzodiazepines for ≥ 4 weeks) and 74 (benzodiazepines could increase the risk of fall incidents) were considered too similar. For further analysis, only the former was taken into account.

Outcome parameters

Follow-up data was collected using standardised questionnaires, filled in by the general practitioners. Data collection on mortality included date and cause of death. Data on hospitalisation included the date of the first unplanned hospital stay (longer than 1 day). The full follow-up period of the Belfrail-study was 5 years [252], but to observe direct associations with baseline medication use, a shorter follow-up period was used, setting a cut-off at 18 months after inclusion in the cohort. All further analyses used the 18 months cut-off, although we provided in the text data on the one-year-survival rate for future and external comparisons.

Statistical analysis

SPSS 21.0 (Statistical Package for Social Sciences, SPSS Inc., Chicago,

IL, USA) was used for analysis.

For all variables, there was less than 5% missing data [252]. Normally distributed continuous variables were expressed as means and standard deviations. All skewed variables were expressed using the medians, and interquartile ranges. Categorical data was expressed using numbers and percentages. Both underuse and misuse were divided into three categories; no (0), low (1 – 2), and high (3 or more) underuse or misuse of medications. Relationships between skewed data were tested using Spearman rank correlations.

The Kaplan-Meier method was used to estimate the survival rate, with the log-rank test verifying the differences in survival time between groups. All deceased or hospitalised patients during the 18 months follow-up period were considered as 'events'. For hospitalisation, additional censoring was done for patients who have died.

Cox proportional hazard models were used to calculate univariate and multivariate Hazard Ratios for associations with mortality, and hospitalisation. In univariate analysis, we first tested the associations with inappropriate prescribing, expressed as a continuous variable. Second, we used the above described categories of underuse and misuse (no, low, and high), to explore the associations with possible trends in higher mortality and hospitalisation rates, for higher categories of underuse or misuse.

Lastly, we tested the interaction between underuse and misuse, by multiplying the number of underused and misused medications of each individual. The statistical significance of each interaction term was evaluated by the likelihood ratio test, comparing nested models with or without inclusion of the interaction term.

A similar exercise was repeated in the multivariate models for both the continuous and categorical variables for underuse and misuse. Now, underuse and misuse (continuous and categorical) were corrected for the number of medications taken at baseline. Additionally, underuse was corrected for misuse, and misuse for underuse.

Ethical approval

The study protocol was approved by the Biomedical Ethics Committee of the Medical School of the Université Catholique de Louvain (UCL), Brussels (B40320084685, on 27/10/2008) and later by the Ethics committee of Ghent University Hospital (B670201421408, on 26/06/2014). All respondents provided informed consent.

6.4 Results

The patients in the Belfrail-MED cohort (n=503) had a mean age of 84.4 years (range 80 - 102), and 61.2% were female. Hypertension was the most common clinical problem, followed by osteoarthritis, and hyperlipidaemia (see Table 6.1).

The mean number of medications was 5.4 (range 0 – 16). Cardiovascular (86.3%), haematological (54.5%), and nervous system drugs (54.5%) were most used.

Prevalence of inappropriate prescribing

Polypharmacy (≥5 medications) was present in 57.7% of the population. Using the START 2 criteria, underuse was identified in 67.0% of the population (range 0 – 5), and using the STOPP 2 criteria, misuse was iden-

Table 6.1. *Demographics and clinical characteristics of the study population (n=503).*

Demographic	**% (Total n = 503)**
Median age in years (range)	83.9 (80 - 102)
Gender (% female)	61.2
Living alone	43.3
Nursing care at home	36.8
Low education (≤ 8 years)	69.2
Clinical[1]	**%**
Hypertension	70.4
Osteoarthritis	57.1
Hyperlipidaemia	44.1
Heart Failure (NYHA[2]> 0)	38.4
Obesity (BMI > 30kg/m^2)	27.9
Osteoporosis	20.9
Diabetes	18.9
Post myocardial infarction / post stroke	17.7
COPD / asthma	13.1
Depression	12.7
Chronic renal failure	11.1

[1]Clinical problems with prevalence above 10% are listed.

[2]New York Heart Association (NYHA) functional classification of heart failure

tified in 56.1% (range 0 – 6).

In 17.1% of the population, no underuse or misuse was found. Only underuse was present in 26.8%, and only misuse in 15.9%. The combination of underuse with misuse was present in 40.2% of the population (of which 31.4% had polypharmacy, and 8.7% low medication use).

The most prevalent criterion for underuse was the absence of an Angiotensin Converter Enzyme Inhibitor in patients with systolic heart failure (26%), and the absence of an antiplatelet therapy in patients with documented coronary, or cerebral or peripheral vascular disease (24%). The most prevalent criterion for misuse (35%) was the intake of benzodiazepines for longer than 4 weeks (see Table 6.2 for the prevalence of other criteria).

Association of inappropriate prescribing with the amount of medications taken

The Spearman rank correlation between the number of medications taken, underuse, and misuse is shown in Table 6.3. The number of medications showed a high positive correlation with misuse (rs 0.51, $p<.001$), and with underuse (rs 0.26, $p<.001$). Moreover, there was also a statistically significant correlation between underuse and misuse, in the positive direction (rs 0.19, $p<.001$).

Survival analysis of inappropriate prescribing on mortality, and hospitalisation

The mortality rate after18 months was 8.9% (n=45), and the hospitalisation rate 31% (n=156). Causes of death included cardiovascular and/or cerebrovascular related events (48.9% of deaths), cancer (20.0%),respiratory related events (13.3%), or general deterioration (6.7%).

The survival analysis showed a significant difference between different categories of underuse for both mortality, and hospitalisation (log rank $p<.001$). The survival rates for mortality after 18 months for those with no, low (1 – 2), and high underuse (3 or more) were respectively 97%, 96%, and 88% (see Figure 6.2). The survival rates for hospitalisation after 1 year were respectively 85%, 81%, and 59% (see Figure 6.3).

For misuse, no significant difference was found for both outcomes.

Table 6.2. *Most identified STOPP/START–2 criteria.*

Inappropriate prescribing	Most identified	% of the population (n=503)
Underuse	Angiotensin Converting Enzyme (ACE) inhibitor with systolic heart failure and/or documented coronary artery disease	26.2
	Antiplatelet therapy (aspirin or clopidogrel or prasugrel or ticagrelor) with a documented history of coronary, cerebral or peripheral vascular disease.	24.3
	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	14.9
	Regular inhaled 2 agonist or antimuscarinic bronchodilator (e.g. ipratropium, tiotropium) for mild to moderate asthma or COPD.	10.5
	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).*	9.1
Misuse	Benzodiazepines for ≥ 4 weeks	35.2
	Any duplicate drug class prescription e.g. two concurrent NSAIDs, SSRIs, loop diuretics, ACE inhibitors, anticoagulants	12.5
	Antimuscarinic drugs with dementia, or chronic cognitive impairment or narrow-angle glaucoma, or chronic prostatism**	10.7
	Use of regular (as distinct from PRN) opioids without concomitant laxative (risk of severe constipation)	7.8
	Concomitant use of two or more drugs with antimuscarinic/ anticholinergic properties	3.4

* Only the clinical indicator osteoporosis could be used. Fragility fractures and Bone Mineral Density scores were not available. **The clinical indicator dementia was an exclusion criteria for this cohort.

Table 6.3. *Description of the medication use, and level of inappropriate prescribing.*

Description of the medication use		**Mean (range)**
Medication use		5.4 (0 – 16)
Underuse		1.2 (0 – 5)
Misuse		0.9 (0 – 6)
		%
Polypharmacy (≥5 drugs daily)		57.7
ATC C - Cardiovascular		86.3
ATC B - Blood and blood forming		56.1
ATC N - Nervous system		54.5
ATC A - Alimentary tract and metabolism		50.1
ATC M - Musculo-skeletal system		23.5
ATC R - Respiratory system		15.9
ATC H - Systemic hormonal preparations		11.7
ATC G - Genito-urinary system and sex hormones		10.3
Inappropriate prescribing	**Underuse, %**	**Misuse, %**
0	33.0	43.9
1 – 2	52.7	46.7
3 or more	14.3	9.3
Combinations	**Low medication use (0 – 4), %**	**Polypharmacy (5 or more), %**
No misuse or underuse	12.5	4.6
Only underuse	15.3	11.5
Only misuse	5.8	10.1
Underuse, and misuse	8.7	31.4
Correlations[1]		**rs (p-value)**
Underuse * Misuse		.19 (<.001)
Underuse * Number of medications		.26 (<.001)
Misuse * Number of medications		.51 (<.001)

[1]All variables are expressed as continuous variables

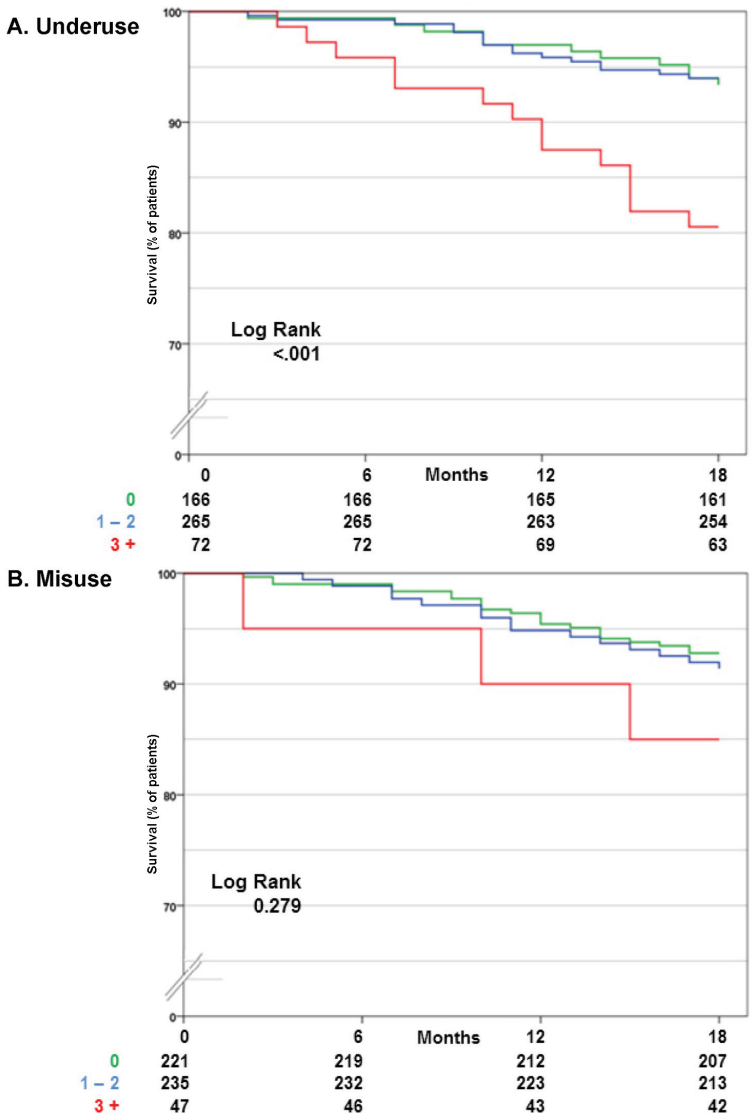

Figure 6.2. *Kaplan-Meier Survival analysis of time to death for groups of underuse (**A**), and groups of misuse (**B**).*

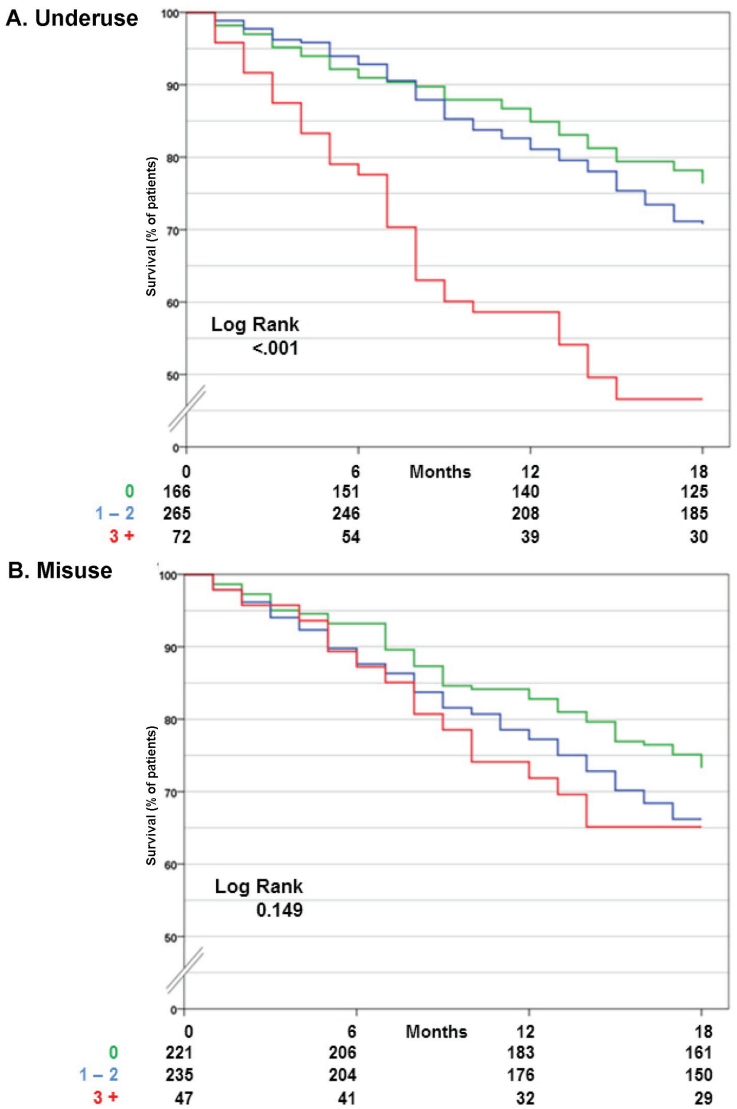

Figure 6.3. *Kaplan-Meier Survival analysis of time to first hospitalisation for groups of underuse (**A**), and groups of misuse (**B**).*

Univariate analysis for the impact of inappropriate prescribing

In our previous analysis of polypharmacy, we observed a significant association of the number of medications with mortality, and with hospitalisation [298] (in univariate analysis e.d.). Here, we also looked concomitantly at the additional effects of underuse and misuse (see Table 6.4). For mortality, underuse expressed as a continuous variable, showed an increased risk (HR 1.43, 95% CI 1.15 – 1.78). In categorical analysis, patients with high underuse (3 or more) had a 3.3 fold significantly increased risk for mortality, compared to those with no underuse. Misuse did not show a significant association with mortality.

For hospitalisation, underuse expressed as a continuous variable showed an increased risk as well (HR 1.35, 95% CI 1.19 – 1.54). In categorical analysis, patients with high underuse (3 or more) had a 2.8 fold significantly increased risk for being hospitalised, compared to those with no underuse. Misuse, yet only when expressed by the continuous variable, showed an increased risk for hospitalisation (HR 1.20, 95% CI 1.06 – 1.36), but not for mortality.

Table 6.4. *Univariate Cox regression analysis of mortality (8.9%) and hospitalisation (31.0%) in association with inappropriate prescribing in a cohort of oldest old (n=503).*

			Mortality	Hospitalisation
Continuous		**Range**	**HR (95% CI)**	**HR (95% CI)**
Number of mediations		0 - 21	1.12 (1.02 – 1.22)	1.14 (1.08 – 1.20)
Underuse		0 – 5	1.43 (1.15 – 1.78)	1.35 (1.19 – 1.54)
Misuse		0 – 6	1.16 (0.92 – 1.47)	1.20 (1.06 – 1.36)
Interaction effects				
Underuse*misuse		0 – 24	1.07 (1.00 – 1.15)	1.08 (1.04 – 1.12)
Categorical	**Cut-offs**	**N**		
Underuse	0	166	1	1
	1-2	265	.89 (.43 – 1.86)	1.17 (.81 – 1.71)
	3 or more	72	3.33 (1.58 – 7.04)	2.79 (1.79 – 4.34)
Misuse	0	221	1	1
	1-2	235	1.52 (0.80 – 2.90)	1.33 (0.95 – 1.86)
	3 or more	47	1.95 (0.76 -5.03)	1.49 (0.87 – 2.55)

The associations of inappropriate prescribing was first tested, using the continuous variables for underuse and misuse. Using categorical analysis, trends were explored for a higher risk for mortality or hospitalisation with a higher degree of underuse, or misuse

The interaction effect (multiplying underuse with misuse, range 0 - 24) was significant as well, for both mortality (HR 1.07, 95% CI 1.00 – 1.15, p=0.044) and hospitalisation (HR 1.08, 95% CI 1.04 – 1.12).

Multivariate analysis for the impact of inappropriate prescribing

The results of the multivariate analysis are shown in Table 6.5. After correction for the number of medications and for the number of misused medications, underuse (expressed continuously and categorically) showed significant increased risks for mortality and hospitalisation. For every additional underused medication at baseline we observed a 39% increased risk for mortality, and a 26% increased risk for hospitalisation after 18 months. Compared to those with no underuse, those with high underuse (3 or more) showed a 2.9 fold increased risk for mortality, and a 2.1 fold risk for hospitalisation.

Misuse, after controlling for the number of medications and underuse, did not show significant associations with both mortality, and hospitalisation.

Table 6.5. *Multivariate Cox regression analysis of mortality (8.9%) and hospitalisation (31.0%) in association with inappropriate prescribing in a cohort of oldest old (n=503).*

			Mortality	Hospitalisation
Continuous	**Range**		**HR (95% CI)**	**HR (95% CI)**
Underuse	0 – 5		1.39 (1.10 – 1.76) [1]	1.26 (1.10 – 1.45) [1]
Misuse	0 – 5		0.93 (0.69 – 1.24) [2]	0.98 (0.84 – 1.14) [2]
Categorical		**N**		
Underuse	0	166	1	1
	1 – 2	265	0.88 (0.41 – 1.90)	1.04 (0.71 – 1.53)
	3+	72	2.91 (1.28 – 6.61) [1]	2.08 (1.29 – 3.36) [1]
Misuse	0	221	1	1
	1 – 2	235	1.16 (0.58 – 2.34)	0.96 (0.67 – 1.38)
	3+	47	1.07 (0.36 – 3.17) [2]	0.74 (0.41 – 1.36) [2]

The associations of inappropriate prescribing was first tested, using the continuous variables for underuse and misuse. Using categorical analysis, trends were explored for a higher risk for mortality or hospitalisation with a higher degree of underuse, or misuse.

[1]Underuse was corrected for the number of medications, and for the number of misused medications.

[2]Misuse was corrected for the number of medications, and for the number of underused medications.

6.5 Discussion

To the best of our knowledge, this study is the first prospective longitudinal cohort study of community-dwelling older adults, aged 80 and more, exploring the associations of inappropriate prescribing with mortality and hospitalisation, using a computerised version of the STOPP/START–2 criteria.

Main findings

First, we observed a high prevalence of polypharmacy (58%), concurrent with a high prevalence of underuse (67%), and misuse (56%). The combination of polypharmacy, underuse and misuse was present in 31% of the population. Only in 9% of the population, no polypharmacy, no underuse and no misuse was observed.

Second, the Spearman rank correlations suggest that the number of medications was positively correlated with the number of misused medications, and also with the number of underused medications.

Lastly, our main finding is that every additional underused medication was associated with a relative increase in mortality rate of 36%, and in hospitalisation rate of 26% after 18 months, independent of the number of medications taken, and of the number of misused medications.

Limitations of this study

Results of this observational study do not allow infer causal relations. The relation between inappropriate prescribing and mortality and hospitalisation was established out of the proof of a (chronic) inappropriate medication intake throughout the study period. Also, the results cannot be generalised beyond the population of cognitive fit community-dwelling older persons.

The negative results need to be interpreted with caution, especially the absence of associations with misuse, as the sample sise may have resulted in underpowered statistical analysis for this aspect. Additionally, we did not use the full STOPP/START–2 criteria, only those that were applicable in our database, and suitable for the computerised evaluation. Also, other authors have made partial use of the STOPP/START criteria for pragmatic reasons [299]. However, the criteria applied in this study matched with the most prevalent criteria in other studies [154, 172, 187,

196, 229, 300]. Nevertheless, the true prevalence of inappropriate prescribing could have been underestimated in this study. To check this issue for misuse, we repeated the same analysis with the medication-only EU(7)-PIM list [292], also focussing on misuse. Again, only in univariate analysis, we observed only a limited association of misuse with hospitalisation, and not with mortality. All associations of misuse disappeared after entering the number of medications and underuse into the multivariate model.

In our database of prescriptions, over the counter drugs were not included, also possibly underestimating the prevalence of misuse.

Comparison with other findings

In our study, there was a high prevalence of polypharmacy (58%), underuse (67%), and misuse (56%). Interpretation and comparison of the prevalence of inappropriate prescribing must be done with caution, since most studies either used younger aged populations, or used the STOPP/START–1 criteria. In other studies, underuse ranged between 23 – 58% [85, 187, 198, 301, 302], and misuse ranged 21-60% [85, 198, 205, 302, 303]. For underuse, our results were over the upper limit of this range, and the results for misuse were close to upper limit of the range.

Cross-sectional studies focussing on younger age groups, and using the Beers [304–306] or STOPP/START–1 [196] criteria, have shown higher prevalence of inappropriate prescribing in those that were hospitalised. Associations with mortality have been observed as well, although only in older hip fracture patients [234].

Comparison with the scarce existing longitudinal cohort studies is difficult, as these studies focussed on younger adults (65, and over), on those in nursing homes, or studied other outcomes such as adverse drug events, economic costs, or geriatric syndromes (falls) [195, 230, 231].

The impact of underuse has also been observed in another cohort, focussing on cardiovascular patients (aged 50 – 74 years) [295, 307, 308].

Implications for research

This study clearly indicated that higher underuse was associated with higher mortality and with higher hospitalisation rate. As this observational study allows no causal inference, we can only formulate hypotheses for further research.

The results of this study suggests that the underuse of medications, next to polypharmacy, is strongly associated with outcomes. An explana-

tion could be the reluctance of general practitioners to prescribe additional medications in patients with a high multimorbidity and polypharmacy [309, 310], or of a possible aversion of patients for new therapies. The lack of clear evidence of some pharmacotherapies in the oldest age groups may explain reluctance of general practitioners to adhere to general treatment recommendations in this age group [311]. However, most of the START criteria are evidence-based and should not be overridden.

In addition, deprescribing or not starting medications , might be caused by a perception of futility in the face of approaching death in this population. In case this clinical perception is true, this could lead to a higher morbidity in the group of those with underuse, making mortality more the cause rather than the consequence of underuse. However, it should be remembered that this cohort was limited to community-dwelling active and cognitively fit oldest old, not in palliative care. Another hypothesis could be that substandard prescribing in older adults is a physician trait [312], and an instrumental variable that leads to a combination of polypharmacy, underuse, misuse, and higher mortality/ hospitalisation.

Applicability of the STOPP/START criteria in a particular patient has until now most often based on the human judgement of a clinical pharmacologist (or similar). Our study indicates that the electronical application of the STOPP/START–2 criteria is feasible, but that further specification of clinical problems and medication groups in the light of computerisation is needed [178]. Large scale application on big data will need substantial progress in semantic interoperability of clinical data in heterogeneous electronic health records [178, 313, 314].

Implications for practice

The interpretation and transferability of the results to other care settings or other patients must be done with caution. The Belfrail-MED cohort excluded those in nursing homes, those with known dementia and those in palliative care. These community-dwelling oldest old patients can be considered as the most active and healthy in this age segment.

The findings of our study are in favour of using the STOPP/START–2 criteria in clinical practice, or for education purposes of clinicians. They are adapted to European medication markets, and can detect underuse.

Using a cut-off for polypharmacy, with a simple arbitrary point (e.g. ≥ 5 medications) or as a sole indicator for quality is problematic. Polypharmacy can be a risk for worse outcomes, even when all prescribed medica-

tions are justified. In this study, underuse of medications that should have been prescribed for a specific indication may also be hazardous. Our present and previous results indicate that a more patient-tailored approach is needed to solve this dilemma [298]. The discussion on too much medication, or too unsafe needs more differentiation, and a clear assessment of misuse and underuse using full knowledge on the patient, his/her comorbidities, and his/her medications. Computerisation of the analysis of medication lists should be considered as a facilitator of the data collection process and the medication chart review, but not as a substitute for assessment of the pharmacological therapy of an individual patient.

6.6 Conclusion

Inappropriate prescribing (polypharmacy, underuse and misuse) was highly prevalent in community-dwelling adults, aged 80 and older. Underuse and misuse were highly correlated and coexisted in almost half of the population. Surprisingly, underuse, and not misuse, had strong associations with mortality and hospitalisation, even when controlling for polypharmacy and misuse. Incentives towards patient-tailored appropriate prescribing in older adults are needed, taking the number of medications, underuse and misuse into account.

Chapter 7

A novel scale linking potency and dosage to estimate anticholinergic exposure in older adults: *the Muscarinic Acetylcholinergic Receptor ANTagonist Exposure (MARANTE) scale*

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Chapter 7: Contents

7.1 Abstract

Background: Quantification of the anticholinergic exposure insufficiently or imprecisely incorporates dosage information, leading to inaccurate estimations.

Aim: To construct a novel scale, including potency and dosage for the quantification of the anticholinergic exposure in older adults.

Methods: Potency information was retrieved from a previous systematic review. The dosage range for each drug was delineated in minimal, maintenance, and maximal dosage for adults and older adults. Dosage information was collected from authorative sources and reviewed in an expert panel. The Muscarinic Acetylcholinergic Receptor ANTagonist Exposure (MARANTE) scale was tested for clinimetric properties using cohorts of community-dwelling older adults and nursing home residents.

Results: After 3 data collection rounds, data for the dosage ranges remained incomplete for 32 active substances. Remaining gaps were filled in, and 11 dosage adjustments were proposed during the expert panel meeting. We chose the values {0; 1; 2) for the categories of potency and {0; 0.5; 1; 1.5; 2) for the levels of dosage ranges, showing good clinimetric properties.

Forty-one anticholinergic drugs were prescribed in the two cohorts. Most (61%) were low potency anticholinergics, used for depression (19%, e.g. citalopram).

There were 31.8% (median MARANTE 1.5, IQR 1.5 – 2.5) and 37.6% (median 2, IQR 1.5 – 2.5) anticholinergic users in the community-dwelling cohort and nursing home cohort respectively.

Conclusion: The MARANTE scale combines potency with the dosage spectrum, to quantify the anticholinergic exposure in older adults. An open feedback system on the list of anticholinergic and proposed anticholinergic potency and dosage values is advised.

7.2 Introduction

Anticholinergics are a group of drugs that competitively inhibit the muscarinic or nicotinergic receptors in both the central nervous system (CNS) and in peripheral tissues, resulting in an inhibition of the acetylcholine (Ach) pathways [42, 43, 46, 47, 61, 315]. Apart from the pure anticholinergics, active substances with anticholinergic properties are used in a variety of diseases and symptoms (including depression, psychosis, Parkinson's disease, allergy, pain, urinary incontinence, etc.[43, 48, 315]. Some anticholinergic drugs are used therapeutically for their anticholinergic properties, while others have other primary mechanisms of action for their intended therapeutic goal, and only additionally anticholinergic properties. Therefore these drugs and their adverse effects are not always recognised as anticholinergic [43]. Depending on the receptors affected, several adverse effects are possible. Common muscarinic central adverse events include dizziness, nervousness, delirium and hallucination [43, 48–50, 61] while the peripheral adverse events include dry mouth, constipation, blurred vision and urinary retention. Impact on nicotinic receptors might be responsible for long term negative effect on cognition [316, 317].

Older adults (65 years or older) consume anticholinergics more than younger patients despite the fact that they are more sensitive to the effects of these drugs [43, 49, 61]. Age-related changes in pharmacokinetics lead a changed permeability of the blood-brain-barrier, and a decreased clearance, resulting in a higher serum and brain concentration [49, 246, 318, 319]. Moreover, changes in pharmacodynamics may further augment the risk of adverse events, as the cholinergic activity is reduced because of a decrease in the number and binding affinity of receptors, homeostatic mechanisms tend to fail, and signal transduction is diminished [320–326]. Additionally, older adults often have multimorbidity [49, 246, 318, 319], resulting in concurrent use of multiple drugs (i.e. polypharmacy) [49, 50, 61, 246], of which a number might produce anticholinergic effects.

Turheim stated that designing a general formula for dose adjustment in older adults is almost impossible [320–322], because of the additional complexity of interpersonal variation, and increasing prevalence of renal and hepatic failure. Nevertheless, a number of tools have been developed to assess the intensity of the exposure to anticholinergic drugs,

and to estimate and manage the risk of anticholinergic adverse events in older adults. On the one hand, one of these tools is the determination of serum anticholinergic activity (SAA), in serum samples of individual patients [43, 61]. However, this is a time-consuming, invasive, expensive method, making it a less ideal method for clinical applications [43, 61]. On the other hand, Anticholinergic Risk Scales (ARS) identify anticholinergics and quantify the exposure by categorising them on potency [41, 210, 215–223]. Evidence suggest that higher potency scores can lead to an impaired cognitive and physical functioning [217, 319, 327] and an increased risk of falling, leading to increased hospitalisation or mortality rates [48, 328, 329]. A limitation to these ARS, is the variation in the number of included drugs (sometimes because of differences in availability of anticholinergics in the countries where the scales were developed) and the accuracy of determination of anticholinergic properties. Moreover, the daily dosage is generally not taken into account [215]. The anticholinergic exposure cannot be thoroughly evaluated without precise dosage information [51].

In an attempt to simplify and standardise the evaluation of intrinsic potency, and to avoid inconsistencies in assigning drugs with anticholinergic properties, two systematic reviews were recently published [215, 330]. These reviews combine active substances with anticholinergic activity in an international standardised list, based on the integration of the results of previous developed ARSs. However, Salahudeen et al. lists all anticholinergics from the ARSs, without transparent enumeration on the level of evidence of the anticholinergic properties [330]. Both reviews categorised the intrinsic potency of each anticholinergic on the list into categories (Salahudeen in a 4-point scale, and Durán in a 3-point scale). The authors of both systematic reviews both refrained explicitly from addressing the issue of dosage in their publications.

Until now, there is no method that combines both potency and the whole spectrum of dosage information of anticholinergic drugs, adapted for use in older adults (65 years, and older). This study therefore aims (1) to delineate the daily dosage spectrum, by setting four dosage ranges (low, moderate, high and very high) for active substances with anticholinergic properties identified in Durán's list (2); to create a novel scale, the Muscarinic Acetylcholinergic Receptor ANTagonist Exposure scale (MARANTE), by choosing cut-off values for the dosage ranges of each anticholinergic drug, and (3) to construct and test clinimetric properties [331] and the distribution of scores on the MARANTE scale in two cohorts of older patients in Belgium (one cohort of community-dwelling oldest

old (aged 80 years or more) [283] and one cohort of nursing home residents [332].

7.3 Methods

Delineating the dosage spectrum of anticholinergics

The MARANTE scale is based on the anticholinergic potency of drugs, and on the daily dosage patients take of a drug. The daily dosage is the summation of all doses during the interval of a day, and a dose is the amount taken at one administration moment (expressed in mg). To organise our search for information for dosage instructions, we determined dosage concepts for younger adults (18 to 65 years), and for older adults (65 years and older). For means of this study, only the dosage concepts of older adults (indicated with the term 'geriatric') will be given in the results section, but we will give a comparison on the availability of data between younger and older adults.

- The (Geriatric) Minimal Effective Dose: **(G)MinEV**
- The (Geriatric) Maintenance Dose: **(G)MainD**
- the (Geriatric) Maximal Effective Dose: **(G)MaxEV**

When collecting dosage information, it was expected to find multiple values for the same concept. For the (G)MinEV and (G)MainD, when sources contradict each other, a range was used (indicated by a lower and upper limit, or the lowest and highest value found for that concept respectively), or either a pin-point value. For the (G)MaxEV, a pin-point value was given, since little variation was expected.

The values of the three dose concepts determined four dose ranges: low, moderate, high, and very high. For use in the calculation of the MARANTE scale, the lowest dose (e.g. the lower limit in the range mentioned) was used to indicate the cut-offs. The dosage concepts, and the dosage ranges are graphically presented in Figure 7.1.

- **Low**: *Higher than zero* (0 mg) and *less* than the (G)MinEV;
- **Moderate**: *Equal or higher than* the (G)MinEV, but *lower than* the (G) MainD
- **High:** *Equal or higher than* the (G)MainD, but *lower than* the (G)MaxEV
- **Very high:** *Equal or higher than* the (G)MaxEV.

We limited our ambition to find dosage ranges for the subset of all active substances with anticholinergic properties, defined in the systematic review of Durán et al. [333], and all anticholinergics that were observed

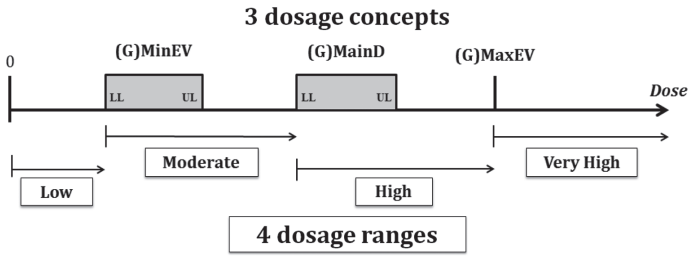


Figure 7.1. *Graphical representation of the dosage concepts, and the dosage ranges used in the calculation of the MARANTE scale.*

in the medication lists of two Belgian cohorts of older adults. All information was collected for use of the daily dosage (meaning irrespective of the number of administration moments in one day).

To define dosage ranges for all selected active substances, information on the dosage concepts was collected in three rounds from authorative sources. All steps of data gathering were collected and documented in a transparent way.

In a first round, we collected dosage information for the main indication only from international reference sources. To determine the main indication, we consulted the World Health Organisation (WHO) Collaborating Centre for Drug Statistics Methodology (http://www.whocc.no/atc_ddd_index/). As international reference sources, we used the Drug Bank (www.drugbank.ca), Micromedex (http://www.micromedexsolutions.com/); the Dutch website of Farmacotherapeutisch Kompas (FK; http://www.farmacotherapeutischkompas.nl/), the Belgian drug reference book BCFI (http://www.bcfi.be/), and the British handbook Martindale [334].

In case the information in these reference sources was insufficient or inconsistent, in the second round we retrieved new information from the European Public Assessment Report (EPAR) and the Summary of Product Characteristics (SmPC) [335].

When neither of these documents contained decisive information, we consulted in a third round the Geriatric Formulary from the Dutch Expertise Centre of Pharmacotherapy in Old Persons, Utrecht University (NL) (http://www.ephor.nl/eng) [336].

We organised an expert panel to discuss the remaining missing information and discrepancies. Six experts (a neurologist, a psychiatrist, an old age psychiatrist, a geriatrician/clinical pharmacologist, and two general practitioners/clinical pharmacologists) were invited based on their expertise and experience on drug use in older patients. Prior to this ex-

pert panel, the experts had to fill in all remaining gaps in dosage values based on their experience. During the expert panel, the experts cleared any discrepancies (overlapping dosage ranges, or non-specific recommendations for dosage adjustments) through consensus. Finally, the experts also critically reviewed and controlled the remaining dosages of the remaining active substances in older adults for which data was available in the literature, to ensure uniformity. If no concrete dosage adjustment could be proposed for older adults, it was decided to take half of the dosage of younger adults. In the light of changed pharmacokinetics and pharmacodynamics in the body of an older person (e.g. a decreased renal function), or from their own clinical experience, experts could propose additional dosage adjustments which were discussed in the panel.

Creating the MARANTE scale

The MARANTE scale is intended to provide a clinical estimate of the exposure of an individual patient to anticholinergics. In later stages, it is intended to be used in the automated analysis of medication lists of older adults to create alerts for the drug prescribers.

Prerequisites are the correct identification of anticholinergics, the correct classification of their potency, as proposed by Durán et al. (2013), and the observation of the daily dosage, to determine its place in the four dosage ranges, as described above and illustrated in Figure 7.1. For each anticholinergic drug identified on a medication list, an anticholinergic load will be calculated by multiplying the potency value with the dosage range value.

The anticholinergic loads of all the anticholinergics on the medication list (with indicating the number of drugs) are then summated to a score on the MARANTE scale, reflecting the intensity of exposure to all anticholinergics on the drug list, and thus deemed to be indicative of the risk of anticholinergic adverse events.

$$\text{MARANTE} = \sum_{1 \to n}^{n} (p_n \times d_n)$$

The two categories of potency, as proposed by Durán et al. (2013) are low and high potency. We empirically checked the value sets of {1,2} and {1,3}. To quantify the dosage ranges (low to very high), we empirically checked approaches {0.5, 1, 1.5, 2}, {1,2, 3, 4}, and {1, 2, 4, 8}.

Exploring the clinimetric properties of the MARANTE scale

We explored the prevalence of anticholinergic drugs, and the distribution of the MARANTE scale in two cohorts of older patients in Belgium, either community-dwelling (Belfrail-MED cohort) or nursing home residents (Ageing@NH cohort). The cohorts were selected because of availability of data, and the expected high prevalence of anticholinergic users.

The mean age of the Belfrail-MED cohort was 84.4 years [283]. Furthermore, the majority of the population was female (61.2%) and used more than five drugs daily (57.7%). The study protocol for the BELFRAIL cohort was approved by the Biomedical Ethics Committee of the Medical School of the Université Catholique de Louvain (UCL), Brussels (B40320084685, on 27/10/2008) and later by the Ethics committee of Ghent University Hospital (B670201421408, on 26/06/2014). The secondary use of the dataset of this protocol was covered by this approval.

The second cohort used was a cohort of nursing home residents, derived from the Ageing at a Nursing Home (Ageing@NH) cohort, a longitudinal study of newly-admitted nursing home residents. The selection of residents was done between September and December 2013, and the cohort was followed for 2 years. At baseline, their mean age was 84.2 years and 65.4% was female. For means of this study, the medication data of the surviving residents during the second follow-up year was used (n=755). The study protocol for the ageing@NH cohort was approved by the ethics committee of the Antwerp University Hospital Belgium (EC-number 13/43/420)[332].

Clinimetric evaluation

We studied the clinimetric properties of the MARANTE scale by examining the histograms and skewness of the distribution of scores on the MARANTE scale (using The Kolmogorov-Smirnov test (K-S)). We examined different values sets for potency and dosage ranges For potency either {1 or 2} and {1,2 or 3}. For dosage ranges either {0.5, 1, 1.5 or 2}, and {1,2, 3, 4} or {1, 2, 4, 8}. Selection was based on the analysis of the histograms of scoring results in two large cohorts (see earlier). Value sets leading to distributions, with empty values, overly broad or multimodal distributions were not selected.

All statistics were performed using SPSS (IBM SPSS Statistics 22).

7.4 Results

Description of the selected anticholinergics

Of the 100 active substances of the systematic review of Durán et al (2013), 71 were available on the medication markets in Belgium (n=63) and the Netherlands (n=64).

Of the 71 active substances available in Belgium and the Netherlands, 41 were actively prescribed in the two cohorts used. Some of these active substances were available in different routes of administration (e.g. aerosol therapy or nebulation in ipratropium), or in combination with other active substances (e.g. fixed dose combinations including codeine), or as a purified enantiomer of an active substance in Durán's list (e.g. citalopram and the S-enantiomer escitalopram). Of the 41 substances, 25 (61 %) were classified as low potency and 16 (39%) were high potency anticholinergics. The main indications for which these formulations with anticholinergic properties were used included depression (18.8%, predominantly citalopram, escitalopram, amitriptyline, nortriptyline), pain (17.4%, predominantly fentanyl, tramadol, morphine), and obstructive airway diseases (15.9%, predominantly ipratropium, and theophylline).

Results from the dosage information collection

After the first round of the dosage information collection, only 3 active substances out of Durán's list could be matched with all dosage reference points. For the others, precise values for these concepts were not available, and recommendations for dosage adjustments in older adults were absent or unspecific.

After the second and third round, 6 more active substances had all dosage reference points filled in. This means that the remaining 32 active substances had incomplete data for one or more dosage ranges. For the adults concepts, we missed values for 17% of the concepts, and for older adults, we missed 55%. These gaps were than discussed in the expert panel.

After the expert panel, all drugs were matched with all dosage reference values. Also, all overlaps in dosages were clarified. Only for citalopram, there was overlap between the ranges of the minimal effective dose and the maintenance dose. These ranges were concatenated and given the value of "low". Other adaptations were proposed in the dosage ranges for older adults for drugs cleared by the kidney (e.g. cimeti-

dine, tolterodine, …), where the dose ranges were lowered beyond the doses retrieved from the authorative sources. For 11drugs (e.g. triazolam, levomepromazine) the dosages of the geriatric minimal effective value were lowered, because the experts felt that the dosages retrieved from authorative sources were still too high, based on their clinical experience with older adults.

The experts indicated that their decisions were made for use in the context of common clinical practice, but not of palliative care, since the focus of care is different. For this reason, they made suggestions for oxycodone to lower the dosages. For fentanyl, they suggested to only include the parenteral forms into the scoring for the anticholinergic exposure, as the intramuscular injection or intravenous solution are more used in anaesthesia or palliative care. The changes made by the experts are listed in Appendix **1**.

The basic data for defining the dosage ranges for each of the identified anticholinergic drugs is given in Table 7.1.

Table 7.1. *Representation of all decisions taken in the expert panel, per drug , for adults and older adults separately.*

Active substance	Gaps in adult doses	Expert Decision	Gaps / dose adaptations in literature	Expert Decision
Amitriptyline		MainD lowered (150 to 100 mg)		GMaxEV lowered (150 mg to 75 mg)
Clozapine		MinEV increased (12,5 to 50mg)	No change	Lower dose required! GMinEV=10 mg GMainD=25 mg GMaxEV=100 mg
Diphenhydramine	No MinEV MainD= 75 – 300 mg	MinEV=75mg MainD= 100mg	Lower in older persons	Lower even further than ½ ! GMinEV=25 mg GMainD=50 mg GMaxEV=75 mg
Doxepin				GMaxEV lowered (150 mg to 100 mg)
Hydroxyzine	No MinEV	Lower doses. MinEV = 1/3 MainD	Only GMaxEV. ½ adult dosage	HDR
Levomepromazine	No MainD / MaxEV	MainD=2*MinEV MaxEV=4*MinEV	½ adult dosage	Lower even further than ½ ! GminEV= 5 mg GMainD= 10 mg GMaxEV= 25 mg
Tizanidine			½ adult dosage	Accepted
Nortriptyline			GMainD missing	GMainD=50mg
Tolterodine	No MinEV/MaxEV	MinEV = ½ MainD MaxEV = 2*MainD	½ adult dosage	Accepted
Ipratropium (bromide)			No change	Accepted
Promethazine	No MinEV/MaxEV MainD= 15 – 150 mg	MinEV=15 mg Maind=50 mg MaxEV= 150 mg	½ adult dosage	Alterations: GMinEV=10 mg GMainD=25 mg GMaxEV=50 mg
Amantadine			GMainD=GMaxEV (100mg) No GMinEV	Lower even further: GMainD=75 mg (not 100) GMaxEV=100 mg (not 200)
Clonazepam			½ adult dosage	accepted
Oxycodone				Omit from this list, only in palliative settings

Active substance	Gaps in adult doses	Expert Decision	Gaps / dose adaptations in literature	Expert Decision
Fentanyl				Only consider transdermal, other for palliative settings only
Olanzapine			Only GMinEV (5mg)	GMinEV lowered to 2,5 mg GMainD=2*GMinEV GMaxEV=4*GMinEV
Paroxetine	No MainD	MainD=40 mg	½ adult dosage	Accepted, only MaxEV set to 30mg (not 25mg)
Oxybutinin			No GMaxEV	GMaxEV=20mg
Cimetidine	No MaxEV	MaxEV= 2*MainD	No changes	HDR
Ranitidine			No changes	HDR
Theophylline	No MaxEV	MaxEV= 2*MainD	HDR	accepted
Triazolam	No MinEV MainD=0,125mg MaxEV=0,5mg	MinEV=0,125 mg MainD=0,25 mg MaxEV=0,5 mg	No changes	HDR
Cetirizine			HDR	Accepted
Levocetirizine	Only MainD (5 mg)	½ cetirizine dose	No changes	½ adult dose
Citalopram	MinEV=MainD (20mg)	Accept	GMinEV=GMainD (10mg)	Accepted
Escitalopram			½ citalopram dosages	Accepted
Domperidone	No MinEV	MinEV=10mg MainD=20mg	No changes	Accepted
Haloperidol	MainD=1 – 15 mg	MainD=5mg	HDR	Lower GMaxEV even further (10 to 5 mg)
Loperamide	No MinEV MainD=2 – 12mg	MinEV=4 mg MainD=2*MinEV MaxEV lowered (16 to 12mg)	No changes	GMinEV lowered to 2 mg GMainD lowered to 4 mg
Mirtazapine		MaxEV further lowered (450 to 60 mg)	No changes	½ adult dose
Risperidone			GMainD=1-4 mg GMaxEV=2-4 mg	GMainD=2 mg GMaxEV=4 mg
Trazodone			GMainD = GMaxEV (300mg)	GMinEV further lowered (100 to 50 mg) GMainD=100 mg GMaxEV=150 mg

Legend: HDR: Half adult Dose Required in older patients, according to the expert panel.

Table 7.2. *Active substances with anticholinergic properties (n= 41) identified in drug lists of older adults in Belgium, with corresponding ATC, route of administration, potency, and dosage ranges for younger adults, and for older persons.*

Drug	ATC	Main indication		Potency	DDD	GMinEV (LL)	GMainD (LL)	GMaxEV
Other forms / Comb.								
Amitriptyline	N06AA09	Depression	P.O.	2	75	25	50	75
+psycholeptics	N06CA01		P.O.	2	75	25	50	75
Clomipramine	N06AA04	Depression	P.O.	2	100	10	30	75
Clozapine	N05AH02	Psychosis	P.O.	2	300	10	25	100
Diphenhydramine	R06AA02	Motion sickness / allergy	P.O.	2	200	25	50	75
Comb.	R06AA52		P.O.	2		25	50	75
Doxepin	N06AA12	Depression	P.O.	2	100	10	50	100
Hydroxyzine	N05BB01	Anxiety	P.O.	2	75	12.5	37.5	50
Comb.	N05BB51		P.O.	2		12.5	37.5	50
Imipramine	N06AA02	Depression	P.O.	2	100	10	30	100
Levomepromazine	N05AA02	Psychosis	P.O.	2	300	5	10	25
Com.	R06AD52			2		5	10	25
Nortriptyline	N06AA10	Depression	P.O.	2	75	25	50	75
Tizanidine	M03BX02	Muscle pain	P.O.	2		1	3	12
Oxybutynin	G04BD04	Urinary freq. / incontinence	P.O.	2	15	5	15	20
Tolterodine	G04BD07	Urinary freq. / incontinence	P.O.	2	4	1	2	3
Trihexyphenidyl	N04AA01	Parkinson	P.O.	2	10	0.5	3	7.5
Ipratropium (bromide)	R03BB01	Obstructive airway diseases	Inhal.Aer	2	0.12	0.25	0.75	2
			Inhal. Sol.	2		0.06	0.12	0.24
+ Fenoterol	R03AL01			2		0.06	0.12	0.24
+ Salbutamol	R03AL02			2		0.5	1.5	2
Promethazine	R06AD02	Motion sickness and allergy	P.O.	2		10	25	50
Comb.	R06AD52			2		10	25	50
Amantadine	N04BB01	Parkinson	P.O.	1		50	75	100
Clonazepam	N03AE01	Epilepsy	P.O.	1	8	0.5	0.75	10
Diazepam	N05BA01	Anxiety	P.O.	1	10	2.5	5	15
Fentanyl	N02AB03	Pain	Nasal	1	1.2	0.3	0.6	1.6
Fluoxetine	N06AB03	Depression	P.O.	1	20	10	20	60
+ psycholeptics	N06CA03			1		10	20	60
Olanzapine	N05AH03	Psychosis	P.O.	1	10	2.5	5	10
Oxycodone	N02AA05	Pain	P.O.	1		10	20	40
Paroxetine	N06AB05	Depression	P.O.	1	20	10	20	30
Cimetidine	A02BA01	Peptic ulcers	P.O.	1	800	200	400	800
Comb.	A02BA51			1		200	400	800

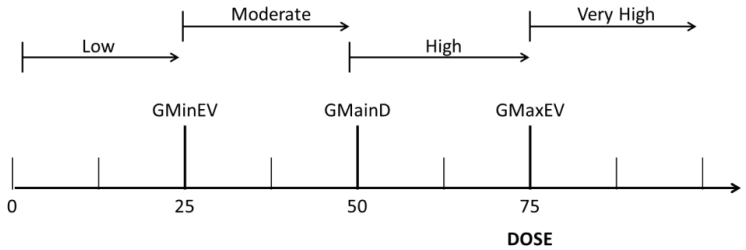
Drug	ATC	Main indication		Potency	DDD	GMinEV (LL)	GMainD (LL)	GMaxEV
Other forms / Comb.								
Quetiapine (fumarate)*	N05AH04	Psychosis	P.O.	1	400	25	75	375
Ranitidine	A02BA02	Peptic ulcers	P.O.	1	300	150	300	600
Theophylline	R03DA04	Obstr. airway diseases	P.O.	1	400	150	200	300
+ adrenergics	R03DB04			1		150	200	300
Comb. excl. psycholeptics	R03DA54			1		150	200	300
Comb. incl. psycholeptics	R03DA74			1		150	200	300
Triazolam	N05CD05	Insomnia	P.O.	1	0.25	0,0625	0,125	0,25
Carbamazepine	N03AF01	Epilepsy	P.O.	1	1000	100	800	1200
Cetirizine	R06AE07	Allergy	P.O.	1	10	2,5	5	10
Levocetirizine	R06AE09			1		1,25	2,5	5
Citalopram	N06AB04	Depression	P.O.	1	20	10	20	20
Escitalopram	N06AB10					5	10	10
Codeine	R05DA04	Coughing	P.O.	1	100	7,5	45	120
Comb. excl. Psycholeptics	N02AA59	Pain		1		15	120	240
Codeine, Comb. with psycholeptics	N02AA79	Pain		1		15	120	240
Dihydrocodeine	N02AA08	Pain		1		15	120	240
Dihydrocodeine, comb.	N02AA58	Pain		1		15	120	240
Domperidone	A03FA03	G.I. disorders	P.O.	1	30	10	20	30
Dosulepin	N06AA16	Depression	P.O.	1	150	50	75	112,5
Haloperidol	N05AD01	Psychosis	P.O.	1	8	0,5	2,5	5
Loperamide	A07DA03	Acute diarrhoea	P.O.	1	10	2	4	12
Loperamide oxide	A07DA05			1		2	4	12
Comb.	A07DA53			1		2	4	12
Mirtazapine	N06AX11	Depression	P.O.	1	30	7,5	15	30
Morphine	N02AA01	Pain	P.O.	1	100	5	15	30
Apomorphine	G04BE07			1		5	15	30
Ethylmorphine	R05DA01			1		2,5	5	100
+ antispasmodics	N02AG01			1		5	15	30
Comb.	N02AA51			1		5	15	30
Nicomorphine	N02AA04			1		5	15	20
Risperidone	N05AX08	Psychosis	P.O.	1	5	1	2	4
Tramadol	N02AX02	Pain	P.O.	1	300	25	50	300
Comb.	N02AX52			1		25	50	300
Trazodone	N06AX05	Depression	P.O.	1	300	50	100	150

Table legend: Comb.: Combinations, P.O.: Per Os, oral drug, Inhal. Aer.: Inhalation Aerosol, LL: Lower limit.

Example: Patient (82 years) takes on a daily basis Amitriptyline 25 mg for the treatment of neuropathic pain, and Trihexyphenidyl 5 mg for the treatment of Parkinson's disease.

Amitriptyline

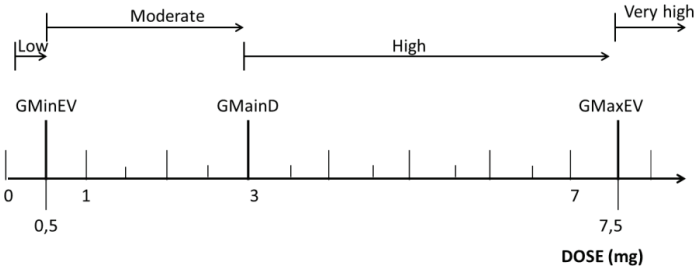
Potency: Amitriptyline is classified as a high potency anticholinergic.
This would receive a potency score of 2.
Dosing: 25mg falls in the moderate category: equal or higher than the GMinEV.
This dosage would receive a scoring of 1.



The anticholinergic load for Amitriptyline 25 mg: 2 x 1 = **2**

Trihexyphenidyl

Potency: Trihexyphenidyl is classified as a high potency anticholinergic.
This would receive a potency score of 2.
Dosing: 5mg falls in the high category: equal or higher than the GMainD.
This dosage would receive a scoring of 1,5.



The anticholinergic load for trihexyphenidyl 5 mg: 2 x 1.5 = **3**

MARANTE scale: The finale score on the MARANTE scale equals the sum of all individual anticholinergic loads: **2 + 3 = 5.**

Figure 7.2. *Example of the calculation of scores on the MARANTE scale.*

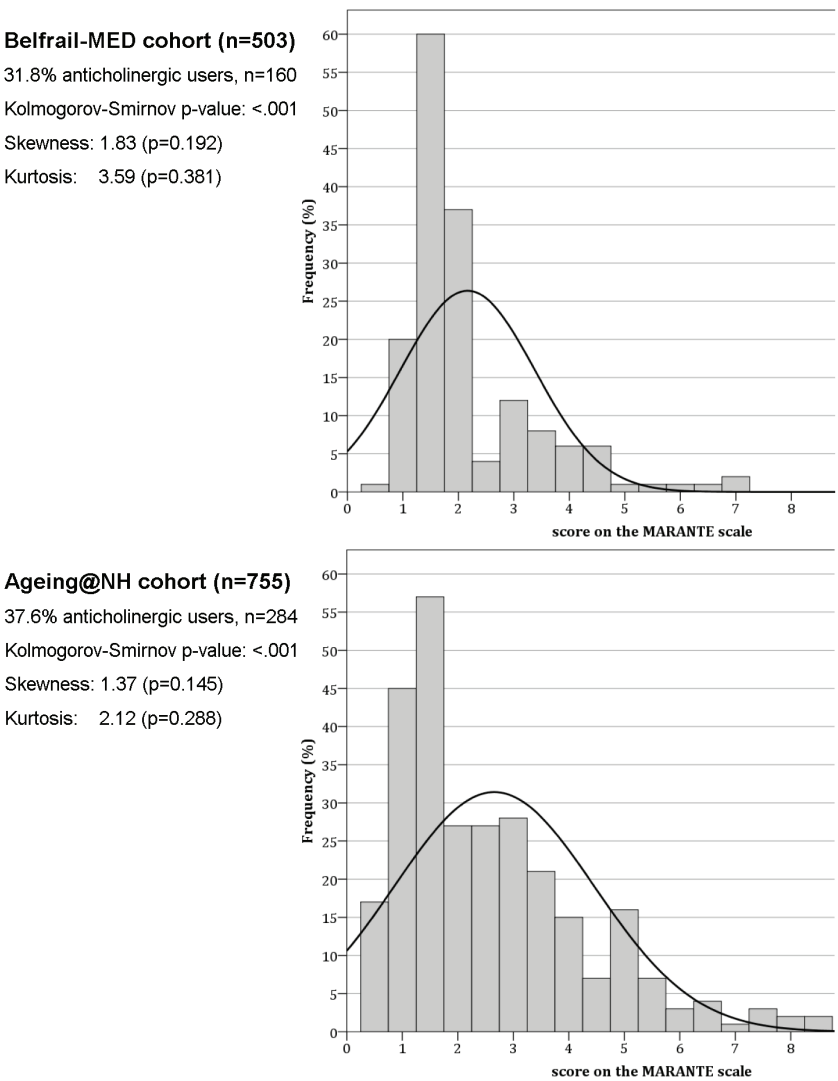


Figure 7.3. *Histograms of the distribution of the scores on the MARANTE scale in the Belfrail-MED cohort (n=503) and the Ageing@NH cohort (n=755). Only those taking anticholinergics are shown (n=160, and n= 284).*

Clinimetric properties analysis

Histograms were used to demonstrate the clinimetric properties of several approximations for the calculations of the MARANTE scale, examining different values for both potency (either {1,2} and {1,3}), and dosage ranges (either {0.5, 1, 1.5, 2}, {1,2, 3, 4}, or {1, 2, 4, 8}). All models resulted in a positively skewed distribution of the scores on the MARANTE scale in both cohorts (with Kolmogorov-Smirnov test at the $p<0.001$ level, except for the combination of the {1,2} and {1,2, 3, 4} value set).

The potency value set {1,3} was disregarded, as this approach yielded empty cells, and a multimodal histogram.

The dosage value set {1, 2, 4, 8} created a multimodal histogram as well, with a broad dispersion of scores in both cohorts. In addition, it overemphasises the weight of the dosage versus potency. Therefore, this value set was disregarded.

Finally, we selected the {0.5, 1, 1.5, 2} over the {1,2, 3, 4} dosage value set, as we wanted to treat the potency and the dosage value equipotent. So, for the calculation of the scores on the MARANTE scale, we decided to use the {1,2} value set for potency, and the {0.5, 1, 1.5, 2} value set for dosage.

In the Belfrail-MED cohort, we observed a prevalence of 31.8 % users of anticholinergics with a median score of 1.5 (IQR 1.5 – 2.5, range 0 - 7). In the Ageing@NH cohort, the prevalence of anticholinergic users was higher: 63.5% users of anticholinergics with a median score of 2 (IQR 1.5 – 3.5, range 0 – 10.5), probably due to a higher intake of drugs and more specifically of psychotropic drugs. The final histograms for both cohorts are presented in Figure 7.3. An example of the calculation of scores on the MARANTE scale is given in Figure 7.2.

7.5 Discussion

Main findings

In the present study, we developed a score to quantify the anticholinergic exposure in individual patients. This MARANTE scale is designed for older adults (aged 65 years, and over), and combines both potency and the full spectrum of dosage ranges of anticholinergic drugs. It provides an instrument for large scale surveillance of the risk of exposure to the class of anticholinergics, which are widely used by older adults and are

known to cause a high risk of adverse events [48, 337].

The search for detailed dosage information proved to be a laborious task, with only limited information available on dose adaptations in older adults. The sources were often non-specific, inconclusive, and without specific recommendations for dosage adjustments in the older adults.

Strengths & limitations

Strengths of the MARANTE scale are the introduction of four dosage ranges, based on 3 cut-off points, which lowers the chance of over- or underestimation of the true anticholinergic exposure. Furthermore, dosage information for almost half of the currently used anticholinergic drugs was completed.

We only completed the dosage information for a pragmatic sample of 41 active substances (out of the 100 anticholinergics, currently used internationally) which might be seen as a limitation. However, this work needs to be completed for all the 100 anticholinergic drugs identified on the list of Durán et al. (2013) and for any newly developed active substance with anticholinergic properties. In this endeavour, we strive to collect dosage values for all remaining active substances in the following year. Next, we would like to invite the scientific community with an interest in anticholinergics, to review our findings, in order to fine-tune the MARANTE scale. For this, we have created an online collaboration platform (found at: https://secureramit.ugent.be/marante/).

The starting point of this article was the systematic review of Anticholinergic Risk Scales, performed by Durán et al. (2013) [215]. The Durán's list may not have included active substances with anticholinergic properties, currently prescribed in significant numbers in some countries [338], or active substances recently brought onto the market. Therefore, it is advisable that the list will be reviewed with regard to systemic anticholinergic effects and usage/ registration throughout the world. In addition, one may critique the simplified classification into low and high potency.

Variable inter-individual effect of anticholinergics might be another difficulty [320–322]. This is not taken into account, as the MARANTE scale is designed for application in larger samples. Review at patient level must be done with caution, since individual variability in both pharmacokinetics and pharmacodynamics is quite possible. The MARANTE scale is an approximation of the degree of exposure to anticholinergic drugs, and not an approximation of the patient's body to the drugs.

Lastly, although the expert panel cleared out many inconsistencies and gaps, further evidence is needed for the confirmation of the dosage

ranges of the reviewed drugs.

Comparison with other studies

Only Carnahan et al (2006) and the Drug Burden Index [319] incorporated the dosage of drugs into the quantification of the anticholinergic burden. Yet, Carnahan et al. (2006) uses only the maximal effective dosage as a reference point, possibly underestimating the true anticholinergic burden [216]. In contrast, the Drug Burden Index standardises the actual daily dose of each drug for this minimal effective value [319], potentially overestimating the true anticholinergic burden.

Additionally, the Drug Burden Index also includes drugs with dubious anticholinergic properties, treats all drugs as equipotent, and uses dosage reference points that were set for dosages in young adults [43].

Implications for further research

In a next step, the clinical implications of the MARANTE scale need to be investigated. Anticholinergics have been considered as potentially inappropriate [187, 207], and are widely regarded as to be used with caution in older persons. The relationship of anticholinergic exposure (either solely based on the potency of medications, or in combination with one dosage reference point) remain inconclusive, given different designs and Anticholinergic Risk Scales used [54, 329, 339–341]. We will investigate the clinical relevance of the MARANTE scale, by searching for associations with mortality and hospitalisation in the Belfrail-MED cohort.

Clinical studies are needed to test the association between the MARANTE scale as a measure of anticholinergic exposure, and the observed intensity of anticholinergic burden, that might affect the quality of life in older patients. In explorative observational studies of the association between anticholinergic exposure and hard outcomes (e.g. hospitalisation, mortality), the impact of the added precision and power of the MARANTE scale can be explored [342]. Additionally, it is important to replicate this present study and all above suggested studies in a population of younger adults.

Implications for practice

By combining both potency and dosage information to calculate exposure, an extra dimension was created. This novel MARANTE scale can aid practicing physicians in prescribing and reviewing patient's drug lists, by implementation in medical software. The overview of all dosage adjustments in older patients can serve as a reference documents for pre-

scribing in older adults. Also, prescribers can have better judgements of a patient's exposure for possible anticholinergic exposure, to evaluate the patient's response to anticholinergics.

To help prescribers, drug reference book committees, regulatory agencies, as well as the pharmaceutical industry should actively exchange knowledge on dose adjustments for older adults, to assure safer prescribing.

Automated tools, based on the MARANTE scale could facilitate early recognition and monitoring of anticholinergic burden, and make more feasible the application of explicit criteria of inappropriate prescribing, as mentioned in STOPP-START, the Beers List, the EU(7)-PIM list [180, 187, 207].

International cooperation is needed to constantly evaluate, adapt and update the basic information behind a tool, such as the MARANTE scale. Transparent management of modifications, trough interactive web-based involvement of the global scientific community, could guaranty both editorial independence, and state-of-the-art quality of information. Implementation in point-of-care evidence-based information systems is crucial.

Chapter 8

Anticholinergic exposure in a cohort of adults aged 80 and over. Associations of the MARANTE scale with mortality and hospitalisation

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Chapter 8: Contents

8.1 Abstract

Background: Anticholinergics are frequently prescribed in older adults, and can lead to adverse drug events. The novel MARANTE (Muscarinic Acetylcholinergic Receptor ANTagonist Exposure) scale measures the anticholinergic exposure by incorporating potency and dosages of each medication into its calculations.

Aims: To assess prevalence and intensity of the anticholinergic exposure in a longitudinal cohort study of community-dwelling patients aged 80, and over (n=503), and to study the impact on mortality and hospitalisation.

Methods: Chronic medication use at baseline (November 2008 - September 2009) was entered and codified with the Anatomical Therapeutic Chemical classification. Time-to-event analysis until first hospitalisation or death was performed at 18 months after inclusion, using Kaplan-Meier curves. Cox regression was performed to control for covariates.

Results: Mean age was 84 years (range 80 – 102), and mean number of medications was 5 (range 0 – 16). Prevalence of anticholinergic use was 31.8%; with 9% taking ≥2 anticholinergics (range 0 – 4). Main indications for anticholinergics were depression, pain & gastric dysfunction. Female gender, the level of multimorbidity, and the number of medications were associated with anticholinergic use.

Mortality and hospitalisation rate were 8.9%, and 31.0% respectively. After adjustment for the level of multimorbidity and medication intake, multivariable analysis showed increased risks for mortality (HR 2.3, 95%CI 1.07 – 4.78) and hospitalisation (HR 1.7; 95%CI 1.13 – 2.59) in those with high anticholinergic exposure.

Conclusion: The longitudinal study among Belgian community-dwelling oldest old demonstrated great anticholinergic exposure, which was associated with increased risk of mortality and hospitalisation after 18 months.

8.2 Introduction

Medications with anticholinergic properties (anticholinergics)block the effect of acetylcholine on the muscarinic and nicotinergic receptors in central or peripheral organ systems, inhibiting the acetylcholine-mediated response [42, 43, 46, 47, 61, 315]. Anticholinergics are widely prescribed in older patients [43, 49, 61] for several indications (including depression, psychosis, allergy, …). Often prescribers don't perceive the prescribed drug as an anticholinergic [343].

On top of the higher level of comorbidities and the higher overall medication intake, older persons become more sensitive to the side-effects of anticholinergics due to a decreased elimination of medications, as well as an increased permeability of the blood-brain barrier [49, 246, 318, 319]. Inhibition of acetylcholinergic mediated muscle contraction can lead to peripheral side effects, which include blurred vision, urine retention, or constipation. Competitive binding to muscarinic brain receptors can lead to central nervous symptoms, which include dizziness, hallucinations, or confusion. These side effects can again in the long term lead to the appearance of delirium [276], impaired cognitive function[59], an increased number of falls[344] and hospital readmission risk [345]. Usage of anticholinergics has been linked to an increased risk for mortality and hospitalisation [329, 346].

Only scoring the anticholinergic potency of medications to quantify the anticholinergic exposure is deemed too simplistic, as it should also incorporate the dose-relationship [339]. In the past decades, several Anticholinergic Risk Scales (ARS) have been created to measure the anticholinergic burden in older patients. All these tools list medications with anticholinergic properties and quantify the intrinsic burden of each medication[41, 209, 216, 218–221], but there is a significant variation on included drugs[215]. Dosage is only taken into account in two of them. The ARS by Carnahan et al. uses the maximal effective dosage, and it does not take dosage adjustments for older persons into account [216]. The Drug Burden Index (DBI) calculates the anticholinergic burden using only the minimal effective value of medications. However, the anticholinergic nature of the medications listed in the DBI is unclear[43]; the DBI does not incorporate the anticholinergic potency of medications, and finally the minimal effective value of medications was determined for a younger population.

Results from studies using one dosage reference point did not vali-

date whether a higher anticholinergic exposure is related to mortality or hospitalisation, neither in the short nor the long term [341, 344, 347, 348]. Therefore, this study aims (1) to determine accurately the point-prevalence and the intensity of the anticholinergic exposure using the Muscarinic Acetylcholinergic Receptor ANTagonist Exposure through the MARANTE scale in a prospective cohort of oldest old primary care patients (aged 80, and over), and (2) to investigate associations with mortality and first hospitalisation during an observation period of 18 months.

8.3 Methods

Sample

We used the Belfrail-MED cohort [252, 283] of 503 Belgian community-dwelling primary care patients aged 80, and over. All subjects were recruited by their own general practitioner between November 2008 and September 2009. Exclusion criteria were known dementia, and being treated in palliative care.

Data collection

Baseline data included personal, clinical, functional, and medication data, and was collected by trained investigators and general practitioners (GPs). The trained investigators conducted structured questionnaires, and standardised tests to collect personal (age, gender, living situation, …) and functional data (physical activity, activities of daily living, and cognitive impairment). GPs did clinical examinations, and used their medical records, to collect medication information and clinical data (current and past clinical problems, in order to assess the level of multimorbidity). For a full background on the data collection, and construction of the level of multimorbidity (Cumulative Illness Rating Scale, CIRS), see previous publications [14, 238].

The GPs recorded all chronic medications at baseline. Chronic medications were defined as entries on the medication list without a stop date. All chronic medications with systemic effect were codified into the Anatomical Therapeutic Chemical classification (WHO ATC/DDD 2013) [284], based on the official register of medications on the Belgian market.

Clinical and functional data handling

For a full background on the clinical and functional data handling, we refer to the original Belfrail-MED article [252, 283].

To measure the level of multimorbidity the Cumulative Illness Rating Scale (CIRS) was used [253]. The CIRS measures the chronic medical illness burden while taking into consideration the severity of chronic diseases [254]. For the construction of the CIRS, all current and past medical problems were used. Out of 14 body systems, every body system affected with severe disease was counted, to a possible range of 14 [14, 254].

To measure the physical activity, the LASA Physical Activity Questionnaire (LAPAQ) was used [256]. For our calculations, we divided the raw LAPAQ scores (range 0 - ∞) into quartiles, to identify the lowest scoring quartile as those with the lowest physical activity .

Activities of Daily Living (ADL) were derived from the KATZ scale, which measures the care dependency in six domains: bathing, clothing, toileting, transferring, continence, and feeding [255]. For our calculations, we divided the raw KATZ ADL scores (range 6 – 30), to identify those most care dependent (scoring 13 and more).

To identify cognitive impairment, we relied on the Mini-Mental State Examination (MMSE) [258]. A cut-off adapted to the age and level of education of the respondents was used to identify cognitive impairment [259].

Assessing anticholinergic exposure

To evaluate anticholinergic exposure, we used the MARANTE scale, based on the systematic review by Durán et al. (2013)[349] and a methodological study by Klamer & Wauters [350]. Duran listed 100 active substances with anticholinergic properties originating from 7 anticholinergic risk scales (ARSs), and categorised them according to their anticholinergic potency (low or high) [349]. In Klamer & Wauters' study, for 41 active substances (increasing to 69 when counting variations of routes of administration, pharmaceutical forms, or combination products) 3 dosage reference values were identified. All reference values were based on information from authorative sources, and then validated and completed by an expert panel.

Calculating the anticholinergic exposure

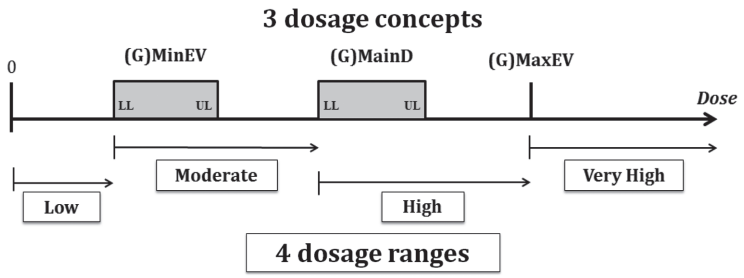
The MARANTE scale is the summation of all anticholinergic loads in a patient's medication list. The anticholinergic load is calculated by mul-

tiplying the values of potency and daily dosage of each medication. Patients not taking anticholinergics receive a score of 0. A complete overview of the calculation of the score on the MARANTE scale is given in Box 8.1.

Potency

For potency, we used the distinction between a low and high anticholinergic potency as suggested in Duran's list and the Klamer & Wauters study [350], with a value of 1 for low potency, and 2 for high potency anticholinergics.

Box 8.1. *Schematic overview of the construction of the MARANTE Scale.*



1. Anticholinergic dosage terms and value scoring (per medication)
2. Anticholinergic load for one medication
   potency × dosage score = (p × d)
3. Value scoring of the MARANTE scale
   Sum of all anticholinergic loads for n medications

Box legend: LL: Lower limit UL: Upper Limit. GMinV: Minimal geriatric effective value. GMainD: Maintenance geriatric dosage. GMaxEV: Maximal effective geriatric dosing.

Dosage

For dosage, we determined the daily dosage per anticholinergic from the posology instructions in the medication list. The daily dosage equals the sum quantities of all doses given to a patient of a specific medication during the course of 1 day.

This daily dosage is compared to the reference values (set in Kramer & Wauters et al., 2016), and based on the pharmacological concepts: minimal geriatric effective value (GMinEV), maintenance geriatric dosage (GMainD), and maximum geriatric effective value (GMaxEV). These refer-

ence points permit to accord values for very low, low, high and very high daily dosage ranges.

- A dosage higher than 0mg, and below GMinEV received a dosage score of 0.5.
- A dosage equal/higher than GMinEV and below the maintenance geriatric dosage (GMainD) was scored 1.
- Equal/above GMainD and below the maximal effective geriatric dosing (GMaxEV) was scored 1.5,
- All dosages equal/above GMaxEV received a dosage score 2.

Follow-up data

Follow-up data included data on mortality (date and cause of death), and hospitalisation (date of the first hospitalisation) during an observation period of 18 months. . A hospitalisation was defined as an unplanned hospital stay, lasting longer than one day. Index date was the date of baseline assessment.

Statistical analysis

All statistical analyses were done using SPSS 21.0 (Statistical Package for Social Sciences, SPSS Inc., Chicago, IL, USA). For all variables, there was less than 5% missing data [252].

Descriptive statistics include means, and standard deviations or range for normally distributed data, and medians with interquartile range for skewed data. Categorical data was expressed using numbers and percentages.

After calculation of all the scores of the MARANTE scale, the results were categorised in low and high anticholinergic exposure, based on the median of the distribution (lower to, and above of the median). For each patient, we also calculated separately the sum of the values for potency, and the sum of values for the dosage, to explore the impact of the two elements of the MARANTE scale.

Time-to-event analysis was estimated using the Kaplan-Meier method, with the log-rank test verifying differences in time-to-event between groups (no vs low, low vs high, and no vs high anticholinergic exposure). A follow-up period of 18 months after inclusion was used to observe direct associations of mortality and unplanned hospitalisation with the baseline anticholinergic exposure of patients. Death or unplanned first hospitalisation were considered as events. For hospitalisation, additional censoring was applied for patients who died. All relations between an-

ticholinergic exposure and outcomes were based on the baseline medication intake without proof of a continuous (chronic) anticholinergic intake throughout the study period.

Univariable and multivariable analyses were done to calculate Hazard Ratios for the associations with mortality and hospitalisation. The MARANTE scale was used in univariable and multivariable analysis as a continuous variable, but also as categorical variable. Categories dividing no, low, and high exposure were formed based on the distribution of the scores on the MARANTE scale. Categorical analysis was performed to observe trends in associations between anticholinergic exposure and outcomes. In the multivariable analysis, we corrected the associations with outcomes, for the number of medications taken at baseline, and with the level of multimorbidity. The level of multimorbidity (CIRS, as a continuous variable) was chosen, because of the dominating association over other patient characteristics (for more background, see the original Belfrail-MED paper [283])

Ethical approval

The study protocol was approved by the Biomedical Ethics Committee of the Medical School of the Université catholique de Louvain (UCL), Brussels (B40320084685, on 27/10/2008) and later by the Ethics committee of Ghent University Hospital (B670201421408, on 26/06/2014). All participants provided informed consent.

8.4 Results

Description of the population

The mean age of patients in the Belfrail-MED cohort (n=503) was 84.4 years (range 80 - 102). The majority was female (61%), and had a low level of education (≤ 8 years, 69%).

The median level of multimorbidity, expressed by the CIRS, was 4 (range 1 - 9). The most common clinical problems were hypertension (70.4%), osteoarthritis (57.1%), hyperlipidaemia (44.1%), and heart failure (38.4%)

The mean number of chronic medications prescribed was 5.4 (range 0 – 16). Prescribing of 5 or more medications was present in 57.7%, and in 0.8% there was no chronic medication use. Predominant main anatomi-

Table 8.1. *Personal, clinical, and functional characteristics, and the general medication use of the study population (n=503).*

Personal	**%**
Mean age in years (range)	*84.4 (80 - 102)*
Gender (% female)	61.2
Low education (≤ 8 years)	69.2
Living alone	43.3
Clinical[1]	
Median level of Multimorbidity (range)	*4 (IQR 3 - 5)*
Hypertension	70.4
Osteoarthritis	57.1
Hyperlipidaemia	44.1
Heart Failure (NYHA[2]> 0)	38.4
Obesity (BMI > 30kg/m^2)	27.9
Osteoporosis	20.9
Functional	**Median (IQR*)**
Activities of daily living, ADL	6 (6 - 8)
Physical activity, LAPAQ	70 (30 – 102)
Mental status, MMSE	28 (26 – 29)
Medication use	
Mean number of chronic medications	*5.4 (range 0 – 16)*
Patients with polypharmacy (5 or more)	57.7
Most prevalent prescribed medication subclasses (>15%)	
Antithrombotic agents	54.5
Beta blocking agents	41.9
Medications acting on RAAS	41.9
Benzodiazepines and Z-drugs	35.6
Lipid modifying medications	33.2
Diuretics	32.0
Drugs for acid related disorders	24.5
Calcium channel blockers	24.3
Cardiac therapy medications	20.7
Mineral supplements	16.7
Analgesics	16.5
Antidepressants	16.1
Medications used in diabetes	15.9

[1]Clinical problems with prevalence above 20% are listed.

[2]New York Heart Association (NYHA) functional classification of heart failure

*IQR: Inter quartile range

cal medication classes (1st ATC level) were cardiovascular medications (in 86.3% of the population), followed by blood regulating medications (56.1%), and nervous system medications (54.5%). The most prescribed therapeutic subgroup (2nd ATC level) were antithrombotic medications (54.5%). All personal and clinical characteristics, as well as the description of the general medication use of the study population are given in Table 8.1.

Description of the anticholinergic use

In this population of community-dwelling oldest old, 68.2% had no medications with anticholinergic properties prescribed on a chronic basis; 23% were taking 1 anticholinergic; 7.0% 2; , 1.2% 3, and 0.6% taking 4 anticholinergics.

In total, 217 prescriptions of medication with anticholinergic properties were identified. Most often these anticholinergic prescriptions were of low potency (80.0%). The dosages in which anticholinergics were prescribed were rarely considered too low (1.8% below GMinEV), yet often high (51.5% above GMainD) or very high (17.1%, above GMaxEV).

Medications with anticholinergic effects (n=217) were predominantly ATC N (nervous system medications) for the treatment of depression (35.0%, predominantly escitalopram, trazodone, and citalopram), or for pain (18.4%, predominantly tramadol). Other predominantly prescribed medications in ATC A (alimentary medications) were for the treatment of gastrointestinal disorders/peptic ulcers (20.7%; predominantly ranitidine and domperidon). Anticholinergics in ATC R (respiratory agents), were for treatment of asthma (8.8%), or ATC G (genito-urinary medications), for the treatment of urinary problems (5.5%).

Description of the anticholinergic exposure

The scores on the MARANTE Scale ranged between 0 – 7. Based on the distribution of the MARANTE, two equal groups were created. One low exposure group (MARANTE 0.5 – 1.5, 16.1%), and a high exposure group (MARANTE ≥ 2, 15.7%). As a consequence, to be categorised into the high exposure group it would sufficient to take one high potency anticholinergic at a low dose (above GMinEV), or a low potency at a very high dose (above GMaxEV). To be categorised into the low exposure group, a high potency could only be taken at the lowest dose (below GMinEV), or a low potency at a dose lower than the GMaxEV, or the combinations of maximum three low potency anticholinergics at the lowest doses.

Table 8.2. *Description of anticholinergic use in the study population (n=503).*

General description		**n=503**	**%**
Anticholinergics use			31.8 %
Range of number of Anticholinergics			0 – 4
Range of potency scores			0 – 5
Range of dosage scores			0 – 6
Range of scores on the MARANTE scale			0 – 7
Details of anticholinergics		**n=217**	**%**
Potency	Low		80.0
	High		20.0
Dosage	Below GMinEV (very low)		1.8
	Above GMinEV (low)		30.0
	Above GMainD (high)		51.5
	Above GMaxEV (very high)		17.1
Most prevalent anticholinergics (>2%)			
A02BA02	Ranitidin		14.7
N02AX02	Tramadol		10.1
N06AB10	Escitalopram		8.8
R03AL01	Ipratropium bromide* (+ Fenoterol)		7.4
N06AX05	Trazodone		7.4
A03AF03	Domperidone		5.5
N02AX52	Tramadol (combination products)		5.5
N06AB04	Citalopram		4.6
G04BD04	Oxybutinin*		4.1
N06AA09	Amitriptyline*		3.7
N06AX11	Mirtazapine		3.7
N06AB05	Paroxetine		3.7
Anticholinergic Exposure (MARANTE) categories		**n=503**	**%**
No	0		68.2
Low	0,5 – 1.5		16.1
High	≥ 2		15.7

Medications market with an * are high potency anticholinergics

Table 8.3. *Univariable analysis of personal, clinical, functional characteristics and medication use of the Belfrail-MED cohort (n=503) in relation to anticholinergic use.*

	Anticholinergic use?		p-value	Univariable odds ratio (95% C.I.)
	Yes n=160	No n=343		
Personal	%	%		
Mean age (in years)	84.5	84.4	.718	
Female gender	68.1	58.0	.030	1.55 (1.04 – 2.30)
Living alone	44.4	42.9	.749	
Low education (≤8 years)	78.0	66.3	.008	1.80 (1.16 – 2.79)
Clinical				
Mean comorbidity, CIRS	*4.2*	*3.6*	*<.001*	*1.28 (1.14 – 1.44)*
Hypertension	65.0	73.1	.064	
Osteoarthritis	69.6	52.8	<.001	2.05 (1.37 – 3.06)
Hyperlipidaemia	46.8	44.6	.639	
Heart Failure	40.6	37.3	.477	
Osteoporosis	32.4	18.9	.001	2.39 (1.52 – 3.75)
Obesity	30.4	27.8	.548	
Diabetes	18.9	19.1	.959	
Post myocardial infarction, post stroke	20.6	17.9	.472	
COPD/Asthma	19.4	12.5	.045	1.68 (1.01 – 2.83)
Depression	26.6	6.5	<.001	5.22 (2.99 – 9.12)
Chronic renal failure	16.8	8.9	.011	2.06 (1.17 – 3.61
Functional				
Most care dependent (ADL) [1]	6.3	10.7	.120	
Most physical inactive (LAPAQ) [2]	34.8	20.6	.001	2.05 (1.34 – 3.12)
Cognitive impairment (MMSE) [3]	15.9	14.9	.774	
Medication related				
Number of medications (0 – 16)	7.2	4.6	<.001	1.39 (1.29 – 1.51)
Polypharmacy users	78.8	47.8	<.001	4.05 (2.62 – 4.24)

[1] Highest care dependency was defined as respondents scoring ≥ 13 (9.1%) on the KATZ ADL scale.

[2] Lowest physical active was defined as the quartile (25.2%) with the lowest raw score on the LAPAQ.

[3] Cognitive impairment was defined using the MMSE, adjusted for age and level of education.

Only significant univariable odds ratios are shown.

The description of the anticholinergic use is given in Table 8.2.

Patient characteristics associated with anticholinergic use

All personal, clinical, functional, and medication characteristics associated with the use of anticholinergics are presented in Table 8.3.

Personal factors associated with anticholinergic use were female gender (OR 1.55, 95% CI 1.04 – 2.30) and low education (OR 1.80, 95% CI 1.16 – 2.79). Age was not associated with anticholinergic use in this cohort of oldest old patients.

Clinical characteristics associated with anticholinergic use included the level of multimorbidity (OR 1.28, 95% CI 1.14 – 1.44), predominantly depression (OR 5.22, 95%CI 2.99 – 9.12).

For the functional characteristics, physical inactivity (OR 2.05, 95% CI 1.34 – 3.12), but neither cognitive impairment nor care dependency, showed associations with anticholinergic use. Both the level of medication use (expressed as a continuous variable), and the dichotomous variable of polypharmacy were strongly associated with anticholinergic use.

Survival analysis of anticholinergic exposure on mortality and hospitalisation

The unadjusted survival analyses of different categories of anticholinergic exposure on mortality and first hospitalisation are given in Graph 1.

The mortality rate after 18 months was 8.9% (n=45). Most common causes of death were cardiovascular and/or cerebrovascular related events (48.9% of deaths), cancer (20.0%),respiratory related events (13.3%), or general deterioration (6.7%). The survival rate was lower among those who had high anticholinergic exposure, as compared to those without. There was only a significant difference in survival percentage between those with no (93.3%)versus those with high (85.0%, p=0.001) anticholinergic exposure.

The Time-to-event analysis showed that the probabilities of having a hospitalisation (31%, n=156) varied among the categories of anticholinergic exposures. Those with high anticholinergic potency (45.7%) had a significantly lower hospitalisation rate than those with no (74.6%, p<0.001) and low anticholinergic exposure (68.2%, p=0.003). There was no difference in survival rates (p=0.626) in those with low and no anticholinergic exposure.

Univariable analysis for the association of the MARANTE scale

Table 8.4. *Univariable analysis of the place of anticholinergic exposure and confounding variables in association with mortality and first hospitalisation.*

Anticholinergic Exposure			**Mortality**	**Hospitalisation**
Continuous	**Range**		**HR (95% CI)**	**HR (95% CI)**
Number of anticholinergics	0 – 4		1.40 (1.02 – 1.93)	1.39 (1.17 – 1.67)
Potency score	0 – 5		1.33 (1.04 – 1,70)	1.32 (1.15 – 1.52)
Dosage score	0 – 6		1.26 (1.01 – 1.58)	1.29 (1.14 – 1.45)
MARANTE scale	0 – 7		1.22 (1.02 – 1.47)	1.25 (1.13 – 1.38)
Categorical	**Cut-off**	**N**		
Taking anticholinergics		160	2.13 (1.19 – 3.82)	1.69 (1.23 – 2.33)
MARANTE scale	0	343	Ref	Ref
	Low (0.5 – 1.5)	81	1.52 (0.68 – 3.39)	1.14 (0.73 – 1.79)
	High (≥ 2)	79	2.77 (1.43 – 5.38)	2.36 (1.63 – 3.42)
Confounding variables				
Continuous	**Range**			
Number of medications	0 - 16		1.12 (1.02 – 1.22)	1.14 (1.08 – 1.20)
Age (years)	80 - 102		1.09 (1.01 – 1.16)	1.04 (0.998 – 1.08)
Categorical				
Female gender			0.94 (.52 – 1.70)	0.89 (0.65 – 1.22)
Low education (≤8 years)			0.83 (.45 – 1.55)	1.03 (0.73 – 1.45)
Living alone			1.15 (.64 – 2.07)	1.06 (0.77 – 1.46)
Multimorbidity[1]			1.36 (1.15 – 1.59)	1.25 (1.14 – 1.36)
Polypharmacy			1.87 (0.98 – 3.56)	1.69 (1.21 – 2.36)

[1] Multimorbidity was expressed using the CIRS.

with mortality and hospitalisation

All univariable associations with mortality, and first hospitalisation are given in Table 8.4.

For mortality and for hospitalisation, the continuous variables for the number of anticholinergics, the potency score, the dosage score and the score on the MARANTE Sale, showed all significant increased risks. The Hazard Ratio for the MARANTE scale had a more narrow confidence interval than the potency and dosage scores for both outcomes, potentially indicating a higher precision. For the low anticholinergic exposure category, no significant increased risks were observed.

Age, the level of multimorbidity (CIRS), and the number of medications were also associated with mortality and hospitalisation.

Those with a high anticholinergic exposure (MARANTE scale ≥2) had a 2.8 fold increased risk for mortality (HR 2.77, 95% CI 1.43 – 5.38) and a 2.4 fold increased risk for hospitalisation (HR 2.36, 95% CI 1.63 – 3.42)

compared to those with no anticholinergic exposure.

Multivariable associations with mortality, and first hospitalisation are given in Table 8.5. Two models are presented, the first was adjusted for the number of medications, and the second for both the number of medications and for the level of multimorbidity.

Associations between the number of anticholinergics, the potency score and dosage score disappeared in the multivariable analysis.

The analysis based on the scores on the MARANTE scale did yield statistically significant and clinically relevant results. For both outcomes, the Hazard Ratio for the MARANTE scale (continuous variable) had more narrow confidence intervals than the potency and dosage scores, potentially indicating higher precision

In the multivariable analysis model, the anticholinergic exposure quantified by the MARANTE scale was categorised, and adjusted for confounding variables. Only–significant associations were found for those with high anticholinergic exposure for both mortality (HR 2.20, 95% CI 1.03 – 4.67) and for first unplanned hospitalisation (HR 1.71, 95% CI 1.13 – 2.59).

Table 8.5. *Multivariable Cox regression analysis of mortality (8.9%) and hospitalisation (31%) in association with the anticholinergic exposure in a cohort of oldest old (n=503).*

		Mortality		Hospitalisation	
	Range	HR (95% CI) MODEL 1	HR (95% CI) MODEL 2	HR (95% CI) MODEL 1	HR (95% CI) MODEL 2
APPROACH 1: Continuous					
Number of anticholinergics	0 – 4	1.18 (0.80 – 1.74)	1.14 (0.77 – 1.67)	1.14 (0.92 – 1.41)	1.12 (0.90 – 1.38)
Potency score	0 – 5	1.17 (0.86 – 1.58)	1.14 (0.84 – 1.55)	1.12 (0.95 – 1.33)	1.12 (0.94 – 1.32)
Dosage score	0 – 6	1.13 (0.86 – 1.47)	1.09 (0.83 – 1.42)	1.13 (0.98 – 1.31)	1.11 (0.96 – 1.28)
MARANTE	0 – 7	1.11 (0.89 – 1.39)	1.09 (0.87 – 1.36)	1.12 (0.99 – 1.26)	1.10 (0.98 – 1.25)
APPROACH 2: Categorical					
MARANTE	**n**	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**
0	343	Ref	Ref	Ref	Ref
Low (0.5 – 1.5)	81	1.35 (0.59 – 3.08)	1.31 (0.57 – 3.02)	0.93 (0.59 – 1.49)	0.93 (0.58 – 1.47)
High (≥ 2)	79	2.26 (1.07 – 4.78)	2.20 (1.03 – 4.67)	1.75 (1.16 – 2.64)	1.71 (1.13 – 2.59)

Two approaches models were used. In the first, associations of anticholinergic exposure with the continuous variable were analysed (e.g. the number of medications, and the continuous MARANTE score). In the second model, we performed categorical analysis to search for trends for a higher risk for mortality or hospitalisation with a higher Anticholinergic exposure.

Two models were used, where model 1 was adjusted for the number of medications (0 – 16), and model 2 was additionally adjusted for the level of multimorbidity (0 – 9).

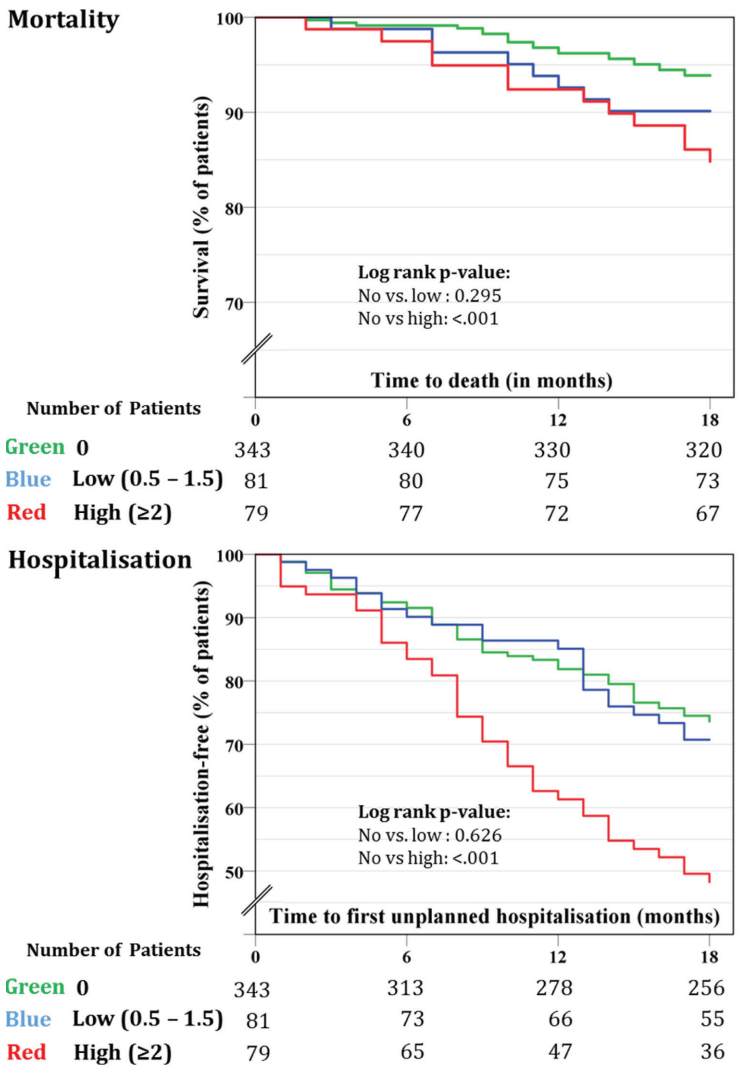


Figure 8.1. *Survival analysis of groups of MARANTE scale (No, Low, and High anticholinergic exposure) for mortality and hospitalisation.*

8.5 Discussion

Main findings

In this longitudinal study, we applied for the first time a new anticholinergic scale based on both potency and the whole dosage spectrum. Our main finding is that the MARANTE scale is a robust and potent approximation for quantifying anticholinergic exposure.

We were able to show that a third of this community-dwelling cohort over oldest old (aged 80 years and older) takes chronically at least one medication with anticholinergic properties. Anticholinergics with low potency (80% of all anticholinergics) were most consumed, yet dosing was considered often high (52%) or very high (17%) in this population.

Based on the median score on the MARANTE scale in subset of patients with anticholinergic exposure, equal groups were created. Those with a high anticholinergic exposure (a score ≥ 2 on the MARANTE scale) showed increased risks for both mortality and hospitalisation in multivariable analysis, controlling for the number of medications and the level of multimorbidity. These patients showed a 2.2fold increased risk for mortality, and a 71% increased risk of being hospitalised during an observation period of 18 months.

Strengths and limitations

We explored the point-prevalence and intensity of the anticholinergic exposure at baseline in a cohort of community dwelling oldest old with a new measurement instrument, taking into account potency and dosage We studied the intensity of the baseline anticholinergic exposure, by looking at associations with mortality, and first unplanned hospitalisation using a prospective cohort during an observation period of 18 months, The observational nature of this study does not permit to ascertain causal relations of the anticholinergic exposure with outcomes. Confounding by indication is possible as anticholinergics are used in patients with multiple diseases, all possibly associated with the outcomes.

In multivariable analysis, taking into account multimorbidity and polypharmacy, simple measures of anticholinergic exposure (number of anticholinergics, sum of values for potency, sum of values for dosage) failed to observe significant results. Only the application of the MARANTE Scale, and the subsequent categorisation in two groups of low and high exposure revealed that high anticholinergic exposure is associated with

mortality and hospitalisation.

Only the chronic medication use was analysed (no *if-needed* or over the counter medications), potentially underestimating the anticholinergic exposure. All associations with mortality or first hospitalisation were based on the baseline chronic medication intake, without control for a continuous chronic anticholinergic intake during the observation period.

It should also be remembered that this cohort was limited to community-dwelling active and cognitively fit oldest old, limiting the transferability and interpretation into other populations.

In this study, only associations with mortality and hospitalisation were analysed. The data collection of the original Belfrail cohort was not intended to look at the symptomatic adverse events of medications (e.g. sedation). All participants were randomly and consecutively selected by their GPs, some degree of prevalent user bias cannot be excluded.

The MARANTE scale is built on the premise of a pure additive effect of different anticholinergic loads, and does not consider possible synergistic or antagonistic effects of medications at the receptor level.

In relation to other findings

With advancing age, the consumption of medications will rise as well, and consequently the intake of anticholinergics will rise [246]. Other studies estimate that up to 51% of the community-dwelling population take medications with anticholinergic properties [212], yet interpretation of this prevalence should be done with caution. Depending on the method used for classifying anticholinergics, the prevalence of anticholinergic use in just one population of older community-dwelling men could range between 13 – 39% [351].

Our findings are in concordance with other studies, searching for associations between patient-characteristics and the use of anticholinergics. The association of anticholinergic use with female gender, age, depression, the number of medications, multimorbidity and with the number of medications have been observed before [340, 352, 353]. In this study, the association with cognitive impairment was absent [49, 218], since older adults without dementia were included in the Belfrail-MED cohort.

Anticholinergics have been considered as potentially inappropriate [187, 207], and are widely regarded as to be used with caution in older persons. However, the definition of medications with anticholinergic properties varies significantly, leading to a multiplicity of lists and explicit criteria, making a direct comparison difficult to perform. In addition, giv-

en different samples used, and different cut-offs for what high anticholinergic exposure is [58], associations with mortality and hospitalisation remain inconclusive, or even contradictory.

Previous publications did not find consistent associations of anticholinergic exposure with mortality or hospitalisation[54, 329, 339–341, 344, 347, 354]. Limiting the results to the oldest old (aged 80, and older), one longitudinal study reported significant associations with mortality [354], while others did not [329, 344, 347]. For hospitalisation, in one publication a significant, yet limited association was found in the oldest old [341].

Our findings suggest an increase in mortality and first unplanned hospitalisation with high anticholinergic exposure. Although associations were absent for a low anticholinergic exposure, the risks were still increased for both outcomes. The clinical relevance of a low anticholinergic exposure must not be disregarded. A low anticholinergic exposure might be associated with other clinical problems (e.g. more anticholinergic side-effects).

Implications for practice

Medication prescribers will need education and assistance to appreciate the importance of these 'invisible' anticholinergic medicines (and the patient contexts in which they are prescribed) and to incorporate calculations of individual patient anticholinergic exposure into their clinical decision-making. This has the potential to reduce patients' anticholinergic exposure and adverse drug events.

Medications with anticholinergic properties are not always known to prescribers [343], nor are anticholinergic side effects recognised. The array of tools and methods available, each using different medications, can lead to confusion in knowing the true anticholinergic properties of medications. The MARANTE scale can aid medication prescribers to recognise those patients with high anticholinergic exposure, and to monitor these patients more systematically for their experienced side-effects.

Past and recent interest on anticholinergics in older adults, understress the importance of a consensus on a unified list of medications with anticholinergic properties, with agreements on their potency and dosages. We therefore invite other researchers in an open discussion at https://secureramit.ugent.be/marante.

A computerised application of the MARANTE scale in older adults can be used to implement particular explicit criteria of inappropriate prescribing in automated systems of decision support and quality assurance,

but it should not be used as a substitute for the clinical assessment of the pharmacological therapy of an individual patient.

Implications for research

This cohort existed of relatively healthy and active older adults (aged 80, and older). It would also be interesting to examine the effects of a high anticholinergic exposure in older adults, aged 65 years and older. Also the associations of a higher anticholinergic exposure with outcomes are to be studied in more frail patients in nursing homes, where there are more patients with dementia, who are more susceptible to the anticholinergic effects [61, 315]. Older adults in nursing homes have a higher medication intake, predominantly a higher psychotropic medications, and possibly a higher anticholinergic exposure [152, 355].

Finally, it is important to relate the anticholinergic exposure to the anticholinergic burden, e.g. the direct burden perceived by patients. Other studies reported associations of anticholinergic exposure with lower quality of life [356], possibly due to a higher prevalence of common anticholinergic adverse effects (sedation, hallucinations, dry mouth, or constipation). Therefore, in a following study, we will investigate associations of anticholinergic exposure (quantified by the MARANTE scale) with the anticholinergic burden.

8.7 Conclusion

In a cohort of community-dwelling oldest old (aged 80, and over), a high prevalence of anticholinergic use was observed, predominantly in high and very high dosages. The novel MARANTE scale provided a robust estimation of the anticholinergic exposure, but further validation is still needed. Those with high anticholinergic exposure showed increased risks for mortality, and hospitalisation.

Chapter 9

General discussion

Chapter 9: Contents

In this manuscript, we aimed to explore and appraise the medication use of Belgian community-dwelling oldest old (aged 80, and over). We used medication data from a population characterised by a high level of multimorbidity and a high medication intake, all obtained from primary research data of a large longitudinal epidemiological cohort study (the Belfrail study).

We appraised the medication use during the prescribing step in the medication management process, focussing on the electronic application of explicit criteria for potential misuse or underuse of medications. Methods for assessing potentially inappropriate medications during the prescribing step, either implicit or explicit, have the potential to aid clinicians. These tools have been predominantly used in research settings, but studies focussing on the oldest old are scarce, certainly in the community-dwelling oldest old. In the following discussion, we will review the findings of our studies, it's limitations and strengths. Finally, we propose implications for practice and research.

9.1 Discussion per research question

Research question 1

What is the prevalence of polypharmacy in the community-dwelling oldest old (aged 80 years, and over) in Belgium, and what patient-related factors attribute to a higher medication intake?

In chapter 3, we aimed to explore the medication use in the community-dwelling oldest old, in an attempt to unravel the complex interactions between the demographic, clinical and functional characteristics of polypharmacy.

Polypharmacy (defined as the intake of 5 or more chronic medications with systemic effect) was high (58%) in Belgian community-dwelling oldest old. The findings from the Belgian Health survey reported a lower prevalence of polypharmacy (around one in three Belgians aged 75 years and older reported having polypharmacy). In comparison with other studies on polypharmacy in older adults, the prevalence of polypharmacy was higher in our study, although the other studies had a younger sample [70, 76, 143, 146, 147, 149, 151, 357–359].

The oldest old generally have the highest mean number of medications. The trend for increasing number of medications with higher age is

not continuous, as we saw a late-life decrease in the number of medications. At medication subclass level, the oldest old used predominantly cardiovascular medications and antithrombotic agents, but there was also a high chronic use of hypno-sedatives and antidepressants. The Belgian Health survey reported that the oldest age group in their survey (those aged 75 years, and older) had a higher use of antacid agents, antithrombotic agents, beta blocking agents, hypno-sedatives, but not diabetes medication, estrogens, thyroid medications, and anti-inflammatory agents [360]. A comparison between the oldest age group in the Belgian Health Survey and the oldest old in the Belfrail showed similar prevalences of individual medication classes, although the Belfrail sample had a higher prevalence of hypno-sedatives and antithrombotic agents [360].

In comparison with older adults in long-term care, some differences were also visible. The medication use was higher in Belgian nursing home residents [152]. Belgian community-dwelling oldest old had less medications, predominantly less psychotropic agents and laxatives. Antipsychotic agents and antidepressants were less prescribed in this cohort, potentially due to the exclusion of patients with dementia in the Belfrail cohort.

The novelty of this study lies in the study of the interrelations between the determinants of polypharmacy, the confirmation of the dominance of multimorbidity as a determinant, and the important relationship with the level of physical activity and depressive symptoms.

Research question 2

Is there a relationship between polypharmacy and health related outcomes (hospitalisation, institutionalisation, and mortality) in the community-dwelling oldest old?

Our results suggest that polypharmacy had clear associations with hospitalisation, but no significant association with mortality was found. The continuous variable (the number of medications) had stronger associations with the outcomes, yet only associations with hospitalisation were significant. Possibly, polypharmacy is too crude to be qualified as an indicator for prescribing quality. For a better understanding, the crude use of polypharmacy (as defined by a cut-off) could only be appraised if it is matched with the level of multimorbidity [265].

At medication subclass level, some medication classes showed increased risks for mortality (selective calcium channel blockers), hospi-

talisation (selective calcium channel blockers, loop diuretics, and agents used for obstructive airway diseases) and institutionalisation (hypnosedative use).

The results suggest that the functional profile was strongly associated with outcomes. Other findings also suggest that functionally active oldest old benefit in terms of reduced mortality or hospitalisation risks [291]. However the dominating association was found with the level of multimorbidity.

The novelty of this study lies in the longitudinal appraisal of exposure and outcome of polypharmacy, and the realisation that even with a simple quantitative definition, clear associations with hard outcomes can be observed.

Research question 3

Which medications mentioned in international lists of explicit criteria of (in)appropriate prescribing are applicable to the Belgian therapeutic arsenal?

The availability of medications mentioned in the EU(7)-PIM list in the Belgian medication market was not overwhelming (157 out of 275 medications were available). In comparison with other countries regarding the availability of PIMs, the Belgian medication market has less PIMs. Potentially because medications that enter the market are reviewed and all evidence (or lack thereof) is listed, and suggestions for the therapeutic arsenal, or suggestions on obsolete medications are regularly handed out to clinicians by the Belgian Centre for Pharmaceutical Information. The applicability of the STOPP/START-2 criteria, purely on the availability of the medications, is higher. For Belgium, only the active substance zaleplon is not available. The STOPP/START-2 criteria mention medication classes rather than individual active substances.

The most consumed medication class mentioned in the EU(7)-PIM are proton pump antagonists. Yet, if all separate benzodiazepines were considered as a medication group, this group would have had a higher prevalence in the oldest old.

The novelty of this study is that the impact of the characteristics of the national therapeutic arsenal on the use of the PIM lists was studied, prior to its application in the country.

Research question 4

What is the prevalence of use of potentially inappropriate medications (PIMs) in the community-dwelling oldest old, and is there a relationship between potentially inappropriate prescribing (misuse and underuse) and hospitalisation and mortality?

There was a high prevalence of underuse (according to START-2) and misuse (according to STOPP-2 and EU(7)-PIM) in the oldest old community-dwelling. Comparing the prospective cohort study of Moriarty et al. on potentially inappropriate medication use in Irish older adults, we saw that the prevalence of misuse was comparable to our findings (57% vs. 56% in our study), yet underuse was less prevalent in the Irish study (42% vs 67%), potentially because of the younger cohort used.

Manuscripts looking at potentially inappropriate medications do not always include underuse of medications [154]. In the few studies available, medication underuse seems relatively common in older adults, either using the AOU index (assessment of underuse index, an implicit method for detecting underuse) or START criteria [188]. Conform our findings, the most prevalently detected START criteria was the potential underuse of anticoagulants, calcium or vitamin D, and statins [154, 361–363]. The underuse of ACE inhibitors was higher in our study. This may be explained by the recent adaptation in the criterion. Example given, in the latest version, more clinical problems were included. In START-1, an ACE inhibitor should be started in case of chronic heart failure. In START-2, an ACE inhibitor could also potentially be started in case of documented coronary artery disease [187, 194].

The high prevalence of underuse in the oldest old is not easy to explain, yet our findings confirm that underuse is common in this age group. Several hypotheses for a high prevalence of underuse can be formulated:

The electronic appraisal of explicit criteria could be less specific than the appraisal during a medication chart review by a researcher or clinician, leading to an overestimation of the actual underuse. No information was available on the rationale for not being prescribed an underused medication.

Underuse could have been the result of a rational prescribing process. Underuse of medications can be desired in the light of an unstable health condition. With patients with limited life-expectancy, not prescribing supposed beneficial or preventive medication therapies can be the intention.

Underuse could have been intended, as the result of limited pharmacotherapeutic evidence in the oldest old. The underrepresentation of older adults in clinical trials can lead to inadequate evidence and knowledge regarding medication therapy in older adults. Medication prescribers might refrain themselves from prescribing medications where the correct benefit-risk assessment of medications in older adults is not known [364].

Underuse could have been unintentional, due to little time available during the medication prescribing process, to unravel complex medication regimes, to apply explicit criteria in daily practice [365], or in case of shared medication responsibility.

With regard to the application of explicit criteria generated on data yielded in primary field research, but not intended for the pharmacological evaluation, only a limited set was transformed into codes for automatic appraisal. Only half of the STOPP-2 criteria and 1/3 of the START-2 criteria could be operationalised, due to lacking data on laboratory tests, sometimes unclear defining of explicit criteria, or because the explicit criteria referred to dementia patients, who were not considered in the Belfrail-Med cohort. It was also not possible to operationalise explicit criteria referring to past medication therapies (e.g. 'if not used before', or 'if not used as a first-line treatment'), as the rationale for prescribing or not prescribing medications was not known. Other manuscripts on potentially inappropriate medication use defined by explicit criteria look for direct associations with adverse effects (e.g. the occurrence of a fall, heart block). In our database, the reason for being hospitalised was not known as well. Despite all these limitations, the subset of explicit criteria for underuse still showed a remarkable positive association with mortality and hospitalisation.

The novelty of this study pertains to the electronic application of explicit criteria as secondary use of a research database, demonstrating co-existence of the different aspects of inappropriate prescribing (polypharmacy, misuse and underuse), and a clear longitudinal relationship with hard outcomes.

Research question 5

Can an automated tool be developed that quantifies the anticholinergic exposure in old age?

Anticholinergics are often mentioned as a group, but specific enu-

meration of this group is difficult. Following the systematic review by Duran and colleagues, the use of anticholinergics in Belgium was investigated. Most common anticholinergics were ranitidine (15%), tramadol (10%), and various antidepressants (citalopram, amitriptyline, …).

The MARANTE scale is specifically designed for geriatric patients, and combines both potency and the full spectrum of the dosage of anticholinergic medications. The MARANTE may prove to be an instrument for large-scale surveillance of the risk of exposure to the class of anticholinergics, which are widely used by older adults and known to cause a heavy burden of adverse events. Strengths of the MARANTE scale include the introduction of four dosage ranges, based on three cut-off points, which lowers the chance of over- or underestimation of the true anticholinergic exposure.

Several formulas have been proposed to calculate dosage adjustments in older adults, and a general formula is still absent [320]. Also, the dose-response relationship is not known. It is however clear that a higher dosage will result in a higher risk for the effect or side-effect of a medication. The most studied method for assessing the anticholinergic exposure is the validated Drug Burden Index (DBI) [62]. The DBI has limitations, as it includes only one reference value for the dosage, and this value varies across national medication guidelines, making international comparison difficult [366]. Finally, similar to the theoretical lists, it assumes a linear additive effect. In the DBI, it is unclear of a doubling in the dosage will lead to a doubling in the response. Therefore, we opted for a scoring system, rather than a dosage-response formula.

The novelty of this study was the in-depth, systematic, and transparent approach to operationalisation of the measurement of a pharmacodynamics interaction, as an explicit criterion of potentially inappropriate prescribing.

Research question 6

What is the prevalence of the anticholinergic use in the community-dwelling oldest old (aged 80 years, and older), and is there a relationship of the anticholinergic exposure with hospitalisation and mortality.

Anticholinergic use was high, with one in three of the oldest old being prescribed a medication with anticholinergic properties. Anticholinergics with low potency (80% of all anticholinergics) were most consumed, yet dosing was considered often high (52%) or very high (17%) in this popu-

lation.

Associations between anticholinergic use with personal/clinical/functional characteristics were investigated in univariate analysis only. Female gender, age, having depressive symptoms, polypharmacy, the number of medications, and multimorbidity were all associations. Only the association with cognitive impairment was absent [49, 218], potentially because of the exclusion of older adults with dementia in the Belfrail-MED cohort.

In multivariate analysis, those with a high anticholinergic exposure (a score≥ 2 on the MARANTE scale) showed increased risks for both mortality and hospitalisation. Similar to the design of the study in chapter 6, associations with intermediate outcomes were not performed. It was not known if common anticholinergic symptoms (e.g. sedation, dry eyes, constipation, …) were the reason for being hospitalised, or for death.

The novelty of this study was the longitudinal observation of the association between an automated and interoperable measure of anticholinergic exposure with hard outcomes.

9.2 Strengths and limitations

Strengths

This thesis has contributed to the understanding of the medication use in the community-dwelling oldest old in Belgium, with an exploration in the appraisal of the appropriateness of the medication use.

The Belfrail-MED cohort included a comprehensive assessment of personal, clinical, functional characteristics, and medication data in a representative cohort of community-dwelling oldest old patients [238], making this a high quality and practice based epidemiological study. The main strength is the longitudinal design of the study. All patients were followed for several years, making it possible to look for associations of the medication use with outcomes.

The Belfrail-MED cohort had a specific focus on the oldest age group. The patients were included in a relevant setting, so that the risk of bias of a temporary situation (e.g. admittance to the emergency department, hospital stays …) was minimalised.

Limitations

The studies presented in this thesis use cross-sectional (chapter 3, 5)

and longitudinal (chapter 4, 6, 8) observational data. The observational nature of the data only allows to look at potential associations, but it does not allow to conclude any causal relations.

All studies presented in this thesis use secondary data. Using secondary data can provide several benefits (accessibility and feasibility to perform longitudinal studies), but also has limitations. The data collected in the Belfrail cohort was not intended for the appraisal of the medication use. In chapter 6, only a subset of all STOPP/START-2 criteria could be used, partly due to missing variables in the dataset. The data were also limited to the community-dwelling oldest old population, which may limit the transferability of our findings to younger populations.

Another important limitation presented in our studies, is that all associations were investigated between the medication use at baseline and hard outcomes happening in a period of time, without accounting for intermediate outcomes (adverse drug effects). The reason for a hospitalisation, or the reason for death were not noted. In order to fully grasp the effect of potentially inappropriate medications, adverse drug reactions should be part of the outcomes.

Although several sets of explicit criteria have been published, most lack evidence. The STOPP/START-2 criteria show promising but not convincing evidence when using the lists as an intervention to reduce drug related problems [228]. Yet, also at the level of explicit criteria, evidence is much needed. Explicit criteria are generally generated through expert consensus. Only recently, in the 2015 updated version of the Beers criteria, explicit criteria were graded according to the strength and quality of evidence. Approximately 48 out of 250 criteria were matched with a high level of evidence [367]. In the STOPP/START-2 criteria, a number of references is given for each criterion, but these are not matched with a level of evidence. The lack of evidence must be remembered in the interpretation of the results presented in this thesis.

In the optimisation of the pharmacotherapy of older adults, there are hardly any simple solutions. As to date, no software-driven interventions have been found reliable or effective for the purpose of minimizing inappropriate prescribing [368]. In the studies presented here, only a limited set could be automated. Electronic applications have the advantage to be straightforward and easy to apply [369], yet for an optimal implementation of explicit criteria, these should be made as specific, explicit and universally adaptable as possible [237]. In chapter 6, only a limited set of explicit criteria in the STOPP/START-2 list could be automated.

The automatic electronic application of explicit criteria using second-

ary data can yield false-positives. The rationale for prescribing, deprescribing or not starting medications was not known in the Belfrail-cohort. Patients might be wrongfully classified as not being prescribed an essential medication (having underuse), because their medication history (e.g. allergic reaction to a medication) was not known.

With all these limitations stated here, it can only be concluded that the automatic electronic application of explicit criteria for appraising the potential inappropriateness of medication cannot replace actual clinical judgement. At most, the automatic application of explicit criteria can be used as a supportive to clinicians and human experts.

9.3 Implications for clinical practice

In the following point, we review future implications for clinical practice.

In this manuscript, focus was on the choice of medications during the prescribing phase in the medication management process. We reviewed one potential adjuvant method (e.g. explicit criteria to appraise potentially inappropriate medications), but other recommendations can be made for the whole medication management process.

Actions can be taken to promote a better coordinated care across different health care settings (during or after a hospital stay, after entering a nursing home) in order to exclude any errors due to miscommunications or uncertain responsibilities (e.g. is it the general practitioner or the medical specialist who reviews the medication list after a hospital stay) [370, 371]. A study has shown that the promotion and optimisation of communications between general practitioners and medical specialists for instance can lead to a better outcome for patients [372].

The validity and informative nature of secondary data for appraising the medication use

The validation process of these explicit criteria is still ongoing. Most explicit criteria were designed in expert meetings, and validated through consensus techniques. Few PIM tools state the level of evidence for each criterion. Almost all explicit criteria are developed through consensus in expert panels, and lack therefore robust evidence. Only in the most recent version of Beers, explicit criteria were reviewed and graded accord-

ing to their level of evidence. Approximately 48 out of 250 criteria had a high level of evidence [367]. For each STOPP/START-2 criterion, a number of references is given, but the criteria are not matched with a level of evidence.

Despite the significant associations found in this thesis, no associations with direct adverse effects were studied. The obtained data did not include the rationale for prescribing, nor for being hospitalised. It must be remembered that of all hospital admissions, only a portion of 10-15% is medication-related, and that in those cases, half of it was deemed preventable [96].

Next, explicit criteria do not cover all aspects of the medication choice. Explicit criteria can be broader, and also include the convenience of medication therapies. For instance the EU(7)-PIM mentions the insulin gliding scale as potentially inappropriate for older adults for its complexity in use, and increased risk for over/under dosing [180].

Another aspect often not mentioned is the cost of certain medications, as this can also be a limiting factor for patients [373]. Future versions of explicit, criteria could include the cost-effectiveness of the selected criteria, and the proposed alternative medication or non-medication therapy. Unfortunately, the evidence on non-pharmacological alternatives is still scant and inconsistent [374, 375].

The feasibility, and validity of automatic electronic appraisal of the medication use

Using secondary data for the appraisal of the medication use, obtained from secondary data from dispensing databases or health care records is possible and can be informative. The application of medication-only explicit criteria is more feasible, and can be highly informative for policy makers to notice the most prevalent medications associated with DRPs. The application of explicit criteria that need medication data ànd clinical data is less obvious. A full application of explicit criteria needs a vast amount of data registration, and not all criteria can be assessed without the clinical information of the patient.

One possible approach is the introduction of national electronic applications or e-Health applications. Electronic applications can aid prescribers by screening the patient, his/her medications and clinical problems for potentially inappropriate medications. Electronic applications have the advantage to be straightforward, stable, and easy to apply [369], yet for an optimal implementation of explicit criteria, these should be made

as specific, explicit and universally adaptable as possible [237]. Now, this is not always the case.

With the findings in our studies, it is feasible to apply a substantial number of the criteria from the STOPP/START-2, and EU(7)-PIM list in an e-Health application. Medication prescribers could be guided towards prescribing safe and balanced medication therapy.

The challenge of underuse in clinical practice

There is growing interest in potentially underused medications. Underuse of medications has been found to be associated with a more frail profile. Example given, preventive cardiovascular medications (antiplatelets or statins) are not always prescribed to more frail older adults, because this is not always considered as a serious co-morbidity [295].

For statins, a recent review in the Lancet stated that underuse may be caused by exaggerated claims about side-effect rates, as suggested earlier in the PROSPER study [376]. The risk for myopathy or muscle-related symptoms attributed to statin use is low, and is resolved rapidly if the treatment is stopped. This potential risk does not weigh up to the potential fatal effect of no treatment (e.g. heart attacks, strokes) [377].

A high underuse (50%) of anticoagulants in patients with atrial fibrillation was also reported before [378]. Dalleur et al. concluded that there was no clear clinical rationale for withholding anticoagulant therapy in this indication [378].

The challenge of misuse in primary care

The chronic use of psychotropic agents (benzodiazepines, antidepressants, but not antipsychotics), and the prevalence of duplicate therapies in a substantial part of the community-dwelling oldest old population indicate potential incentives towards an optimisation in pharmacotherapy.

The high use of benzodiazepines in Belgium has been noted before [379, 380], and our findings suggest it is still an actual problem. Benzodiazepine use has been associated with cognitive impairment, cognitive decline, higher risk of falling, and finally increased mortality risks, yet the literature is inconclusive (due to methodological differences including design, outcome, time of follow-up, or sample) [381, 382]. Nonetheless, chronic hypno-sedative use could lead to habituation, impeding their efficacy in the long-term [383], or could lead to dependence (including withdrawal symptoms in case of therapy cessation, e.g. agitation, irri-

tability, headaches, nausea, …)[384], and side-effects inherent to their working mechanism (e.g. sedation, impaired alertness or increased risk of falling) [385]. Discontinuation of benzodiazepines can reduce potential costs (e.g. hospitalisations for fall incidents can cost up to €11426 per patient [386]). Changing misused medications is not an easy task, and is not the sole responsibility of the prescriber. In a Belgian nursing home, a significant drop in prevalence of psychotropic medication users was noted through a transition towards a more patient-centred care model [387]. Patients, nurses and other allied health-personnel were all involved in offering credible and sustainable alternatives to psychotropics.

Anticholinergics can be a problem in older adults, because anticholinergics and their side effects are not always recognised [43], or prescribers don't perceive the prescribed medication as an anticholinergic [343]. Incentives may be needed to raise awareness of these 'hidden' anticholinergics. Medication prescribers and dispensers are less aware that routinely used medications, unintended for their primary indication, can have anticholinergic properties [337]. Some anticholinergic medications are also available as over-the-counter medications (e.g. cetirizine), and can add to the potential risk for a higher anticholinergic exposure [315]. The applicability of the MARANTE in electronic applications used by both medication prescribers and dispensers can be investigated, so it could alert them on the high prevalence of (sometimes unknown) anticholinergics.

The duplication of a medication subclass was present in 13% of the community-dwelling oldest old, similar to earlier findings of hospitalised older adults (9%) or in the British Clinical Practice Research Datalink (11.3%) [195, 388], and hence a drug related problem, that is prevalent and merits attention.

Similarly, the overuse of medications (medications without an indication, a combination therapy where a monotherapy has not been tried before, and medications in a prescribing cascade) can be addressed as well. Recent government initiatives (reduction in the amount of copayment) focused on other examples of overuse, namely the overutilization of proton pump inhibitors, nasal sprays and antibiotics.

The place of explicit criteria for potentially inappropriate medications in the medication management process

Explicit criteria can aid medication prescribers in finding potentially inappropriate medications. The manual application in clinical practice of these sets of explicit criteria is however time-consuming, needs motiva-

tion of the medication prescribers, and needs some knowledge. Short consultation times may not be feasible to perform individual medication chart reviews.

Now, most sets of explicit criteria are used in research and seldom in clinical practice, despite general practitioners' beliefs that explicit criteria are useful, and having an added value [389]. In Norway, general practitioners use the NORGEP (derived from the Beers criteria) in daily practice, and it is also used for the evaluation of the prescribing of medications by GPs across different settings [390].

When the aim is to identify inappropriate medication use in older patients, the STOPP/START-2 criteria are recommended. They are valid, integrate the clinical status of a patient, and most importantly, they also focus on underuse. An added bonus is that the STOPP/START-2 criteria mention only a few medications not on the Belgian medication market. Yet, the STOPP/START-2 are not complete, and have limitations. They are not always explicit, or clear to use, and do not propose alternatives for a potentially inappropriate medication, nor provide a graded level of evidence.

A possible suggestion for clinicians, who want to implement this in daily practice, is the targeted selection of PIMs. This could decrease the number of patients that need to be reviewed, based on age alone, and thus decrease the workload. Example given, clinicians could solely focus on the rational prescribing of cardiovascular medications and hypnosedative medications.

Suggestions for explicit criteria, and the automatic application thereof

Explicit criteria for the detection of potentially inappropriate medications are not often used in clinical practice. More often, the application of these sets in medication review is performed mainly manually, and in the context of research.

Our findings suggest that the automatic application is feasible, but more research into its validity is needed. There were many limitations, including the usage of a subset of explicit criteria, limitations to using data not intended for pharmacological evaluations, limitations to not including direct adverse outcomes or patient' preferences and all that in an automated way. Still, we could find associations between explicit criteria on underuse with mortality and being hospitalised. The validity of our findings needs to be confirmed in other settings, before it can be implemented routinely in clinical practice.

The appraisal of pharmacotherapy cannot rely on the use of explicit criteria only. It must be embedded within a patient's global assessment of his clinical status and his preferences and needs. Explicit criteria can be used as a supplementary to other initiatives to improve the medication management process. Still, due to the non-standardised nature of the algorithms when applying explicit criteria automatically, a direct comparison of studies is difficult. Future incentives can be taken to strive towards an optimal semantic operability of these criteria.

It can be interesting to study the added value of the combination of a medication review, and the use of explicit criteria as a preparation for the medication review. For pragmatic reasons (availability of patients, health care professionals, electronic health records) a parallel-group cluster randomised controlled trial in long-term residential care facilities (nursing homes) could be conducted. The pragmatic cluster trial can be considered as a superiority trial, since an improvement in pharmacotherapy (less potentially inappropriate prescribing) is expected in favour of the intervention group. The intervention could be the automated appraisal of the medication use for potentially inappropriate medications. Nurses conduct monitoring observations for specific medication-related symptoms, and enquire with the patient about his/her preferences regarding medication changes. The report will be discussed in a medication review, held between the general practitioners, nurse, and pharmacist.

9.4 Implications for research

The challenge of deprescribing

Explicit criteria offer the option to clinicians to notice potentially inappropriate medications, but do not offer solutions. In the light of deprescribing potentially inappropriate medications, future PIM tools could introduce guidelines for the discontinuation of pharmacotherapy in older adults. The EU(7)-PIM list handles dose reductions and alternatives to a current potentially inappropriate medication [292].

Recently, the STOPP-2 criteria have been adapted to older adults with limited life-expectancy, the STOPPFrail criteria [391]. It includes 26 explicit criteria, who were included in the list based on consensus of specialists in geriatric medicine. The first two criteria address potential deprescribing in case an indication lacks or in case of poor adherence to medications. The other criteria are similar to the current majority of STOPP criteria, ad-

dressing the discontinuation of medication classes (e.g. proton pump inhibitors, anti-spasmodics …). The STOPPFrail criteria do not include the discontinuation of anticoagulants and antidepressants.

Study suggestions for explicit criteria and anticholinergics

Studies with strong methodological designs are needed to establish causal relationships of potentially inappropriate medications or the anticholinergic exposure with outcomes [337]. The recent meta-analysis on the effectiveness of the START/STOPP criteria did not offer convincing results [228], and similar analyses of other sets of explicit criteria are lacking as well. Explicit criteria need to be studied more using randomised controlled trials using sets of explicit criteria as an intervention, and in relation with direct outcomes.

Now, different sets of explicit criteria emerge, that are mostly embedded into national drug markets. Following the European Science Funds meeting with experts on the development and usage of explicit criteria, forces should be combined to create a comprehensive repository of explicit criteria of potentially inappropriate medications instead of refining or adapting individual sets of PIMs [170]. This repository should combine explicit criteria from already established lists, with frequently used and validated PIM lists as a starting point. The clinical applicability of explicit criteria is often low, mainly because of lack of adaptability to national medication markets, a low suitability for automated electronic assessment, a sometimes-low level of evidence, and the limited access to high-quality medical information in electronic health records. The repository can be used in different settings (either for patients at home, in a hospital or in a nursing home), and for different purposes (for research and clinical research, as a feedback tool for prescribers on a national level, for benchmarking, or for health purposes).

For, anticholinergics, it could be investigated whether the application of the MARANTE could be used as an intervention in patients to reduce the anticholinergic exposure. Another step in the validation of the MARANTE scale, is establishing associations with direct anticholinergic effects. In other words, it could be investigated whether a higher score on the MARANTE scale leads a higher burden of common anticholinergic symptoms (including peripheral effects as dry mouth, dry eyes, constipation, urinary retention, and central effects as confusion, delusions, hallucinations, and sedation). The relationship of anticholinergic exposure with quality of life is also inconclusive. One study (a secondary analysis

of an RCT using a sample of palliative patients) reported a significant association, but did not adjust for other medication effects, or the illness status [392]. Investigating the relationship with the quality of life, could also open up the debate of the potential impact of a reduction of the anticholinergic exposure. A single-blind RCT investigated a pharmacists-led intervention to reduce the anticholinergic exposure in nursing home residents and the impact on the cognitive function and mouth dryness after four to eight weeks [393]. No significant changes were found, possible due to the short follow-up time, the sample, protopathic bias or because dosing of medications was not included in the quantification of the anticholinergic exposure.

This could be investigated in a randomised controlled trial including patients in primary care. For each patient, a medication review will be started where anticholinergics are reviewed on their potency and dosage, in order to reduce the anticholinergic exposure in patients. For the primary outcome, the reduction in proportion of patients with an anticholinergic exposure can be used. Secondary, the link with common anticholinergic symptoms can be investigated, in order to know if anticholinergic exposure is linked with burden. Secondary outcomes may include the number of medication-related symptoms, the level of alertness or sedation, the quality of life, cognitive function, activities of daily living, to even health care usage (hospital admissions).

Specific research options for PIMs and for the MARANTE

More evidence regarding dose adaptations or dose recommendations for older populations is needed, possibly by the inclusion of older people in pharmacological research.

A next step in the implementation for explicit criteria and for the MARANTE scale could be the introduction of alternative medications or discontinuation strategies. For most medications mentioned in explicit criteria, and for most anticholinergics, alternatives can be proposed (e.g. for most antidepressant medications, sertraline has been demonstrated as a safe alternative with no anticholinergic properties) [394, 395], and discontinuation strategies can be offered (e.g. using existing withdrawal guidelines for antipsychotic agents [396].

From the original 100 active substances listed in Durán et al [397], 63 were available in Belgium. Further refining is needed for both national and international use. For Belgium, other anticholinergics that were not included into the systematic review (e.g. pentoxyverine) are to be re-

viewed. Alternatively, dosages could be reviewed for active substances that are processed in the pharmacy. For international usage, the anticholinergics not available in Belgium, need to be reviewed. To allow future collaboration, an electronic platform was created were researchers, clinical, and pharmacological experts are invited to participate, ensuring that the remaining gaps are filled in.

Explicit criteria are not always explicit [237]. One aspect often lacking in all sets of explicit criteria are pharmacodynamic interactions. The risk of bleeding by cumulative effects of different medications is addressed in some list by a considerable number of complex explicit criteria, indicating its clinical importance. Also, there is often not enough specification to address anticholinergic interactions or interactions among medications prolonging QT-interval.

The role of the prescriber

Future research initiatives towards more appropriate prescribing of medications may focus on the role of the GP. A multitude of interdependent intrinsic (beliefs, attitudes, knowledge …) and extrinsic (patient, setting, health system …) factors shape the behaviour of medication prescribers towards the (dis)continuation of potentially inappropriate medications. To empower the role of the GP, barriers (time consumption, comprehensiveness…) and facilitators (as a support in medication reviews) need to be explored for a successful implementation of electronic decision support systems intended for an optimisation of the pharmacotherapy in older adults.

Another possible addition to the current health care practice, is the possible inclusion of geriatricians in the context of an interdisciplinary pharmacotherapeutic evaluation of older adults in primary care. A new, integrated and comprehensive approach to the care (e.g. collaborative care) for older adults can be explored, where age-related problems and disorders in clinical practice are integrated with clinical decision making. The shift towards this paradigm is essential in order to apply appropriate strategies to adequately address pharmacotherapy in vulnerable older patients with multiple chronic diseases and polypharmacy. The evaluation of older adults and their medications should be done in the knowledge of an overall assessment of personal, clinical and functional parameters (e.g. comprehensive geriatric assessment). This assessment based on an interdisciplinary multi-step process integrates the skills of different healthcare providers (doctors, pharmacists, nurses) and is crucial to map-

ping and adequately addressing the medical complexity of this heterogeneous patient group [398].

It is possible, that the focus of care shifts from 'to cure' towards 'to care' in a more goal-oriented care. The focus in goal-oriented care can be the extension of life, but also the sole avoidance of unwanted side-effects [399]. Prescribers can overlook the possibility of other diseases and medications in one patient, leading to more potentially inappropriate medications for that patient [400].

There is some evidence of the added value of multidisciplinary meetings [401–403], but more research is needed within the context of the patient, to ensure an optimal medication therapy [105]. Barriers and facilitators need to be addressed, for different health care settings and for different long-term impact of multidisciplinary meetings needs to be investigated. The automated detection of any potentially inappropriate medications could decrease the requirements placed on the participants in the meetings, and could speed up the process of the review.

Challenges for deprescribing

The evidence for deprescribing medications in patients with a low life expectancy is low [404]. Some studies support evidence for deprescribing in oncological or palliative care [405–413], and one study described an improved quality of life [405]. More high-quality research is needed under which deprescribing yields a maximal benefit in terms of clinical outcomes [78].

- What medications or medication classes are to be considered for deprescribing?
- How to involve the patient in the process of deprescribing? Is deprescribing related to a higher level of adherence, and what are the clinical consequences?
- Is deprescribing of medications safe, or is deprescribing associated with adverse events in both short and long term?
- Are deprescribing programs cost-effective, and can they be routinely applied in clinical settings?

9.5 Implications for health policy

The assessment of the quality of prescribing in old age at a public health level should evolve towards the use of quality indicators. Quality

indicators can be derived, but are not limited to PIMs. A PIM may or may not evolve into a QI, provided additional validation research has been performed [170]. Explicit criteria for assessing PIMs should evolve to the status of a Quality Indicator. In this endeavour, the possibility of record linkage with epidemiological patient registries with more detailed clinical content could be explored.

The validity of polypharmacy as an indicator for appropriate medication use

Polypharmacy has been the subject of various studies, showing associations with potential adverse outcomes. However, polypharmacy should not be equated as a characteristic of care that inevitably leads to adverse outcomes [265].

Polypharmacy can be both appropriate and inappropriate. Evidence undeniably suggest that polypharmacy is often non-desirable, as previous studies have shown associations with encountering adverse drug reactions [414], yet it is an ill-defined term. Too many medications should not automatically be equalled with unsafe medications, despite a high correlation. The accent could shift from a pure crude cut-off for the number of medications towards the clinical indication for each medication. Many older adults have multiple clinical problems, and may benefit from multiple medications.

Addressing the overuse of medications in relation to the clinical problems of the patient, could improve the predictive value for addressing patients at risk for adverse outcomes, hospitalisation or mortality. Again, a full appraisal can only be done with the knowledge of the level of multimorbidity.

Now, polypharmacy and extreme polypharmacy are being used as quality indicators for the care for older adults in nursing homes. Our findings suggest that the usage of these sole quality indicators is crude, can be used to signal out problematic settings, but may not be useful as an alert for individual patients. More elaborate sets of quality indicators and/or explicit criteria are needed to provide practical support for medication review.

Chapter 10

General conclusion

In this thesis, we appraised the medication use of the community-dwelling oldest old (aged 80 years, and older) by the electronic application of explicit criteria for the detection of potentially inappropriate medications (PIMs) during the prescribing phase in the medication management process. We reviewed the applicability and validity of explicit criteria on the Belgian medication market, and we looked into associations with health related outcomes (mortality, hospitalisation, and institutionalisation) using secondary data.

Explicit criteria in the STOPP/START-2 criteria and the EU(7)-PIM list are applicable to the Belgian medication market. The electronic application of explicit criteria is possible and feasible, but requires a vast amount of personal and clinical data of patients. Less than half of the explicit criteria in the STOPP/START-2 criteria could be applied electronically.

There is still further need for validation of explicit criteria, since they are often not specific enough, and can miss pharmacodynamic interactions. In casu, anticholinergics are often ill-defined in lists of PIMs, and dosages are not mentioned. We propose a new method, the MARANTE scale, that quantifies the anticholinergic exposure by the intrinsic potency of medications and by the dosage. The application of the MARANTE scale showed promising results, with clear associations with mortality and hospitalisation, but needs further validation.

Main findings were that community-dwelling oldest old Belgian population were relatively healthy and active, but there was a high prevalence of polypharmacy, underuse, and misuse. In one in three oldest old patients, these concepts were present. Polypharmacy showed no clear associations with long-term hard outcomes, nor did misuse. Surprisingly, underuse of medications had clear associations with mortality, and hospitalisation.

Clinicians must be aware that explicit criteria cover some and not all aspects of the medication management process, that automated use of explicit criteria is possible but requires access to reliable medication and clinical data. The exclusive use of explicit criteria in clinical practice is therefore not possible beyond the scope of a medication review, and can for now only serve as an adjuvant in the preparation of the medication profile.

Summary

The older population is growing globally. Especially in European countries, the number of older adults (65 years, and older) is expected to grow. Also in Belgium, the higher share of older adults will pose a challenge for the health care system. The older population will age itself, as the share of oldest old will grow (those aged 80 years, and over). For Belgium (a western European high-income country with over 11.000.000 inhabitants), an increase of approximately 120.000 adults over 80 years is expected by 2030.

With ageing, the risk for developing more clinical problems will rise (e.g. hypertension, osteo-arthritis, cognitive impairment …). With more clinical problems, more medications will be prescribed. This can be a potential problem, since older adults are more sensitive to medications due to age-related pharmacokinetic and pharmacodynamic- changes. Older persons have a higher risk for encountering certain medication side-effects such as dry mouth, dry eyes, a higher risk for bleeding, a higher risk for a fall, which can affect the quality of life in a patient, but can also have an impact on the health care system (by prescribing more medications to counter these side-effects, or by a higher risk for a hospitalisation).

The overall aim was to extend the knowledge on the pharmacotherapy in the community-dwelling oldest old adults (aged 80 years, and over) so that the quantity and quality of life can be improved by (1) quantifying the actual chronic medication use in terms of prevalence, medications involved, and identifying patient-related risk factors for a higher medication intake. (2) Assessing the appropriateness of the medication use, in terms of prevalence of polypharmacy on the one hand and underuse or misuse on the other hand by using the electronic application of screening tools for potentially inappropriate prescribing to evaluate the predictive validity and the clinical relevance.

Chapter 3 describes the Belfrail-Med cohort (n=503) of Belgian community-dwelling oldest old (aged 80 years, and over), in terms of personal, clinical, and functional characteristics. In this cross-sectional study, a high prevalence of polypharmacy (intake of 5 or more chronic medications) was noted; 58%. There was a high use of hypno-sedative agents and antidepressants. Apart from the dominant association of multimorbidity, a lower physical activity

and more depressive symptoms were also found to be associated with polypharmacy.

In chapter 4, the influence of the medication use on mortality, the first unplanned hospital admission and the transfer to long-term care was analysed. More medications was associated with a hospitalisation, independently from the level of multimorbidity. The association with mortality was only present in univariate analysis, and no association with institutionalisation was found. A deeper look at specific medication groups, showed that a higher use of hypno-sedative agents was associated with entering the long-term care system, and the intake of anticholinergics (see lower) was associated with mortality and hospitalisation, but only in univariate analysis.

In chapter 5 and 6, the (in)appropriateness of medications was assessed using explicit criteria for potentially inappropriate medications. Explicit criteria can aim to assess underuse (when a medication can still be beneficial, but is not prescribed) or misuse (when a medication is prescribed, despite a higher risk for adverse effects). Using the EU(7)-PIM list or STOPP/START-2 criteria, a high prevalence of misuse (56 – 73%) and underuse (67%) was found. The concepts of underuse, misuse and polypharmacy were found to be interrelated. More medications prescribed, meant more misused medications, but also more underused medications. One in three oldest old had a combination of misuse, underuse and polypharmacy. Only in 9%, these three concepts were not found. Surprisingly, only underuse showed associations with mortality and hospitalisation. For each medication that was underused, a 39% increased risk for mortality, and a 26% increased risk for hospitalisation was found.

In chapter 7, a closer look was taken at the role of medications with anticholinergic properties (from now on anticholinergics). Anticholinergic use can cause a plethora of side effects, including dry eyes, dry mouth, urinary retention, constipation, blurry vision, hallucinations, sedation, dizziness, or agitation. Anticholinergics are a hot item, due to the preventable unwanted effects, and the higher risks for cognitive decline, hospitalisation, and mortality. Theoretical lists of anticholinergic medications were constructed. Yet, there is no uniformity on which medications to include, nor on the potency (the affinity at receptor level). In addition, the dosage of medications is not taken into account in most methods.

In chapter 7, the development of the Muscarinic Acetylcholine Receptor ANTagonist Exposure (MARANTE), where potency and dosage is combined, is described. Starting from a systematic review of anticholinergic risk scales, 100 medications were identified. In this systematic review,

these medications are categorised on their potency (strong or weaker affinity at receptor level). From these 100 medications, dosage information was given for all medications actively taken in the Belfrail-Med cohort and in a cohort of newly admitted nursing home residents. The MARANTE scale was tested for its' clinimetric properties in these two cohorts.

In chapter 8, the anticholinergic use is described, and associations of a high anticholinergic use with mortality and hospitalisation were investigated. Anticholinergics were taken by 32% of the population, most commonly agents for depression, pain, or gastrointestinal complaints. In most cases (80%) low potency anticholinergics were prescribed, yet often high (52%) or very high (17%). Those with a high anticholinergic exposure (score of two or higher on the MARANTE scale) had a 2.2 fold increased risk for mortality, and a 71% increased risk for hospitalisation.

This manuscript aimed to give more insights in the oldest old, an underrepresented age cohort in scientific literature, and especially on a crucial aspect of their lives and for their health; their medication use. The results indicate that the medication use of the oldest old can still be improved. The oldest old consume many medications, with a specific high use of hypno-sedatives and antidepressants. The electronic applications for screening for potentially inappropriate medications and the identification of anticholinergics could support medication prescribers, or medication reviewers in choosing the optimal and safe pharmacotherapy in older adults.

Samenvatting

Het aandeel oudere personen neemt wereldwijd toe. Voornamelijk in Europese landen wordt een enorme toename van oudere personen (boven 65 jaar) verwacht. Ook in België wordt een vergrijzingsgolf verwacht, welke een impact zal hebben op de huidige gezondheidszorg. De oudere populatie wordt ook verwacht te verouderen, getuige het groeiende aandeel personen boven 80 jaar. In 2030 wordt verwacht dat er meer dan 120.000 extra personen boven 80 jaar in België zullen zijn.

Door veroudering zal de kans op het krijgen van een ziekte toenemen (bijvoorbeeld hypertensie, artrose, mentale achteruitgang, …), waarvoor geneesmiddelen kunnen voorgeschreven worden. Meer geneesmiddelen bij oudere personen vormt een potentieel probleem. Oudere personen zijn gevoeliger aan de werking en bijwerkingen van geneesmiddelen door allerlei farmacokinetische en –dynamische veranderingen. Oudere personen hebben hierdoor bijvoorbeeld een grotere kans op bepaalde bijwerkingen; droge mond, droge ogen, constipatie, een hoger bloedingsrisico, een hoger risico voor een valincident, wat een impact kan hebben op de kwaliteit van leven van de patiënt, maar ook op de gezondheidszorg (door een hoger aantal hospitalisaties, of door een hoger aantal geneesmiddelen om die bijwerkingen te behandelen).

Deze doctoraatsthesis had als doel de kennis rond farmacotherapie bij oudere thuiswonende personen te verhogen, om indirect de kwaliteit en kwantiteit van leven te verhogen. Dit door (1) het chronische geneesmiddelengebruik in kaart te brengen; de hoeveelheid, de geneesmiddelengroepen die werden voorgeschreven, en patiënt-gerelateerde risicofactoren aan te duiden die geassocieerd zijn met een hoger geneesmiddelengebruik. (2) Het tweede doel betrof het in kaart brengen van potentieel ongeschikte geneesmiddelen (ondergebruik, en verkeerd gebruik), en het beoordelen van het medicatiegebruik door een elektronische toepassing te maken van gevalideerde expliciete criteria, om zo bij te dragen tot de predictieve validiteit en klinische relevantie van deze criteria.

Hoofdstuk 3 vormt de basis voor de verdere hoofdstukken. In dit hoofdstuk wordt het Belfrail-MED cohorte beschreven; een cohorte van 503 thuiswo-

nende oudste ouderen (80 jaar en ouder) in België, met een uitgebreide dataverzameling van persoonlijke, klinische, en functionele karakteristieken. In deze paper werd een hoge prevalentie van polyfarmacie (de inname van vijf of meer chronische geneesmiddelen) aangetoond, namelijk 58%. Een belangrijk aandeel nam ook op chronische basis slaap- en kalmeermiddelen, en antidepressiva in. Naast de dominante factor multimorbiditeit (het tegelijk voorkomen van meerdere ziektebeelden) waren hogere mate van fysieke inactiviteit en depressieve symptomen geassocieerd met polyfarmacie.

In hoofdstuk 4 werd de invloed van het medicatiegebruik op mortaliteit, de eerste ongeplande hospitalisatie, en op de opname in een woonzorg centrum. Meer voorgeschreven medicatie was geassocieerd met hogere risico's tot hospitalisatie, onafhankelijk van de graad van multimorbiditeit. De associatie van een hoger medicatiegebruik met mortaliteit was enkel aanwezig in univariate analyse, en er was geen associatie met een opname in een woonzorgcentrum. Kijkend naar medicatie subklassen, was het gebruik van een slaap- of kalmeermiddel (benzodiazepines en derivaten) geassocieerd met een opname in een woonzorgcentrum, en het nemen van medicatie met anticholinerge eigenschappen (zie later) geassocieerd met mortaliteit en hospitalisatie, hoewel enkel in univariate analyse.

In hoofdstuk 5 en 6 werd de (on)geschiktheid van het geneesmiddelengebruik uitgediept. De geschiktheid van het medicatiegebruik werd beoordeeld aan de hand van expliciete criteria. Expliciete criteria kunnen enerzijds op ondergebruik (wanneer een geneesmiddel niet werd voorgeschreven, hoewel het mogelijks nut kan hebben), of foutief gebruik (wanneer een geneesmiddel meer risico's dan baten heeft) gericht zijn. Aan de hand van de EU(7)-PIM list en STOPP/START-2 criteria werd een hoge prevalentie mogelijks foutieve medicatie was (56 – 73% afhankelijk van de gehanteerde lijst van expliciete criteria), en ondergebruik (67%) gemeten. De drie concepten (ondergebruik, verkeerd gebruik en polyfarmacie) waren ook aan elkaar verwant. Hoe hoger het aantal geneesmiddelen, hoe meer mogelijks foutieve geneesmiddelen een patient had, maar ook hoe meer ondergebruikte geneesmiddelen er waren. Ongeveer een derde van de oudste ouderen (31%) had te veel, te weinig, of mogelijks gevaarlijke geneesmiddelen. Anderzijds had slechts 9% van de oudste ouderen geen enkel van de drie concepten. Het ondergebruik van geneesmiddelen toonde verrassend genoeg associaties met mortaliteit en hospitalisatie. Per geneesmiddel dat mogelijks nuttig was, maar niet werd voorgeschreven bij de start van de studie, was er een 39% ver-

hoogd risico op mortaliteit, en een 26% verhoogd risico voor een opname in een ziekenhuis.

In hoofdstuk 7 werden medicatie met anticholinerge bijwerkingen (vanaf nu anticholinergica) uitgediept. Anticholinergica kunnen tot allerlei bijwerkingen leiden, zoals onder andere droge mond, droge ogen, urineretentie, constipatie, wazig zicht, hallucinaties, sedatie, sufheid, duiseligheid, of verwardheid. Anticholinergica zijn een hot item, omwille van de vele vermijdbare bijwerkingen, maar ook omdat studies verbanden met cognitieve achteruitgang, hospitalisatie of mortaliteit hebben aangetoond. Er werden daarom theoretische lijsten opgemaakt met anticholinerge geneesmiddelen. Echter, er is geen eenduidigheid over wat nu juist een geneesmiddel met anticholinerge werking is, in welk mate een receptor geblokkeerd wordt. Daarenboven wordt het aspect van dosering slechts in geringe mate beoordeeld. Daarvoor werd de Muscarinic Acetylcholine Receptor ANTagonist Exposure (MARANTE) schaal ontwikkeld, waarin de kracht (van affiniteit op receptorniveau) met de dosis van het geneesmiddel wordt gecombineerd. Van 100 geneesmiddelen geïdentificeerd in een systematische review werd vervolgens dosisinformatie gezocht van courant gebruikte geneesmiddelen in enerzijds het Belfrail-MED cohorte en anderzijds in een populatie nieuwe woonzorgcentra bewoners. De klinimetrische eigenschappen van deze nieuwe schaal werden getest in deze twee cohorten.

In hoofdstuk 8 werd het anticholinergica gebruik in kaart gebracht. Medicatie met anticholinerge werking werd door 32% van de populatie genomen, vaak voor de indicatie van depressie, pijn, of gastro-intestinale klachten. In de meeste gevallen (80%) werden geneesmiddelen met een zwakke affiniteit op receptorniveau voorgeschreven. Kijkende naar de dosering, waren de dosissen vaak hoog (52%) of te hoog (17%) voor oudere personen. De MARANTE schaal toonde ook verbanden met mortaliteit en hospitalisatie. Zij met een hoge anticholinerge blootstelling hadden een 2.2 keer verhoogd risico op sterfte, en 70% meer risico op hospitalisatie.

Dit manuscript heeft als doel meer inzicht te brengen in een populatie die weinig bestudeerd is, over een bepaald aspect van hun leven dat hun gezondheid mee bepaalt, maar eveneens weinig onderzocht is. De resultaten van de verschillende studies tonen aan dat het geneesmiddelengebruik mogelijks nog verbeterd kan worden. Er is een aanzienlijk deel van de oudste populatie die te veel geneesmiddelen neemt, met een belangrijke consumptie van slaap-en kalmeermiddelen. De elektronische toepassing voor het herkennen van mogelijkse ongeschikte

geneesmiddelen, of de identificatie van anticholinergica kan medicatie voorschrijvers ondersteunen om een optimaal en veilig geneesmiddelenvoorschrift op te stellen voor oudere personen.

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Curriculum vitae

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Nurse. Doing a PhD in the field of pharmacoepidemiology & clinical pharmacology.

Special interests: Appraising the appropriateness of medications in older adults / Anticholinergic exposure and burden / Nurses' knowledge on psychotropics

Career highlights

PhD in Health Sciences – Ghent University 2014 – 2017

- Teaching pharmacotherapy; rational prescribing of medications
- Guiding master students of Antwerp University.
- Guiding Master after Master students General Practice.
- Invited speaker: appropriateness of medications in older adults.

Nurse – AZ Jan Palfijn Gent 2011 – 2014

- Cardiology / Coronary Care Unit.
- Mentor for nursing students during internships.
- Invited speaker Hogeschool Gent: Actual perspectives in health care.

Education

Master of Science in Nursing and Midwifery
from Ghent University (2009-2011)
Bachelor in Nursing (Hospital Nursing)
from Hogeschool Gent (2006-2009)

Skills

- Expert courses: Pharmacology (Ghent University, master in pharmacy) / Clinical Studies / Pharmaco-epidemiology and drug safety (Utrecht University) / Database Utilization Workshop: Using pharmacoepidemiology (ICPE 2016) / Medical Device Epidemiology (ICPE 2016) / Introduction and Advanced Drug Utilization Research (ICPE 2016) / Educational Sessions EuroDURG 2014
- Transferrable skills: UGent: Leadership, Communication skills, Presentation skills, authentic networking skills. Hogeschool Gent: Mentor skills training

Publications

- Wauters M, Versluys K, Steeman E, Petrovic M. Ontwikkeling en validatie van een kennistest over psychofarmaca voor verpleegkundigen op de afdeling acute geriatrie. Verpleegkunde. 2013;28(4):4–11.
- Wauters M, Elseviers M, Vaes B, Degryse J, Dalleur O, Vander Stichele R, Van Bortel L, Azermai M. Polypharmacy in a Belgian cohort of community-dwelling oldest old (80+). Acta Clin Belg. 2016 Jun;71(3):158–66.
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- Leten L, Azermai M, Wauters M, De Lepeleire J (2017) A qualitative exploration of the chronic use of psychotropic drugs in nursing homes. Tijdschr Gerontol Geriatr. doi: 10.1007/s12439-017-0223-7

Presentations

- Wintermeeting Geriatrie 2012 – Oostende (Belgium). Poster presentation: De ontwikkeling en validatie van een kennistest omtrent psychofarmaca bij verpleegkundigen op de dienst acute geriatrie.
- EuroDURG 2014 – Groningen (The Netherlands). Poster presentation: Drug prescribing patterns in the very old: baseline observation.
- BESPE 2014 – Gent (Belgium). Oral presentation: Het medicatiegebruik van de oudste thuiswonende ouderen: Resultaten uit de BELFRAIL studie.
- Winter meeting 2015 – Oostende (Belgium). Poster presentation: Polypharmacy in a Belgian cohort of community-dwelling oldest old: baseline observations and associated risk factors.
- Research Day Ghent University 2015 – Gent (Belgium). Bullet point presentation: Polypharmacy in a Belgian cohort of community-dwelling oldest old: baseline observations and associated risk factors
- EACPT 2015 – Madrid (Spain). Oral presentation: Polypharmacy in a Belgian cohort of community-dwelling oldest old: Baseline observations and associated risk factors.
- EACPT 2015 – Madrid (Spain). Poster presentation: Impact of Medication use on mortality in community-dwelling oldest old.

- Wintermeeting Geriatrie 2016 – Oostende (Belgium). Oral presentation: Mortality, hospitalisation, institutionalisation in community-dwelling oldest old: The impact of Medication.
- Research Day Ghent University 2016 – Gent (Belgium). Bullet point presentation: Mortality, hospitalisation, Institutionalisation in community-dwelling oldest old: The impact of Medication.
- ICPE 2016 – Dublin (Republic of Ireland). Oral presentation: Too many, too few, or too unsafe? Impact of inappropriate prescribing on mortality, and hospitalisation in community-dwelling adults, aged 80 and older.
- ICPE 2016 – Dublin (Republic of Ireland). Poster presentation: STOPP-2 versus PIM-EU(7): Comparing prevalence, and impact of inappropriate prescribing on mortality and hospitalisation
- Wintermeeting Geriatrie 2017 – Oostende (Belgium). Poster presentation: A novel scale linking potency and dosage to estimate anticholinergic exposure in older adults: the MARANTE scale.
- Wintermeeting Geriatrie 2017 – Oostende (Belgium). Poster presentation: Too many, too few, or too unsafe? Impact of inappropriate prescribing on mortality, and hospitalisation in a cohort of community-dwelling oldest old.
- Wintermeeting Geriatrie 2017 – Oostende (Belgium). Oral presentation: Anticholinergic Exposure in a cohort of adults aged 80 and over. Associations of the MARANTE scale with mortality and hospitalisation
- EuroDURG 2017 – Glasgow (UK). Poster presentation: Electronic assessment of the anticholinergic exposure using the MARANTE scale.
- EuroDURG 2017 – Glasgow (UK). Poster presentation: Anticholinergic exposure in primary care and in long-term care: differences in medications involved and intensity?
- Wintermeeting Geriatrie 2018 – Oostende (Belgium): Anticholinergic exposure in primary care and in long-term care: differences in medications involved an associations with mortality?

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If I have seen further than others,
it is by standing upon the shoulders of giants

Maarten Wauters
22 december 2017