



# Deprescribing of medications at the end of life

Data of older adults living at home or in a nursing home,  
and patients with advanced cancer receiving palliative care

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# Deprescribing van geneesmiddelen aan het einde van het leven

Data van thuiswonende ouderen, bewoners van woonzorgcentra en patiënten met een vergevorderde kanker die palliatief verzorgd worden

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# Table of Contents

List of abbreviations	7
Chapter 1. General Introduction	9
Chapter 2. Scope of this thesis	27
Chapter 3. Methodology used in this dissertation	31
Chapter 4. Associations of potentially inappropriate medication use with four year survival of an inception cohort of nursing home residents	41
Chapter 5. Initiation of advance care planning in newly admitted nursing home residents in Flanders, Belgium: <i>a prospective cohort study</i>	57
Chapter 6. Balancing medication use in nursing home residents with life-limiting disease	73
Chapter 7. Discontinuation of medications at the end of life. A population study in Belgium, based on linked administrative databases	91
Chapter 8. Changes in medication use in a cohort of patients with advanced cancer: <i>the international multicenter prospective European Palliative Care Cancer Symptom (EPCCS) study</i>	111
Chapter 9. Barriers and enablers to deprescribing in people with a life-limiting disease: <i>A systematic review</i>	131
Chapter 10. General discussion and conclusions	153
Summary	177
Samenvatting	183
Curriculum Vitae and List of Publications	189
Dankwoord - Acknowledgements	193



## List of abbreviations

ACE	Angiotensin Converting Enzyme	LLI	Life-limiting illness
ACP	Advance Care Planning	MAC	Medication Advisory Committee
AD	Advance Directive	MAI	Medication Appropriateness Index
ADE	Adverse Drug Event	MDS- CHESS	Minimum Data Set Changes in Health, End-stage disease and Symptoms and Signs score
ADL	Activities of Daily Living (or KATZ-ADL)	MMRI	Minimum Data Set Mortality Rating Index
ADR	Adverse Drug Reaction	MMSE	Mini Mental State Examination
ASA	Acetylsalicylic Acid	NH(s)	Nursing Home(s)
ASCO	American Society of Clinical Oncology	NHP	Nottingham Health Profile
ATC	Anatomical Therapeutic Chemical (classification)	NMDA	N-Methyl-D-Aspartic acid
ASCO	American Society of Clinical Oncology	NSAID	Non-Steroidal Anti-Inflammatory Drug
BPSD	Behavioural and Psychological Symptoms of Dementia	OTC	Over-the-counter
CASP	Critical Appraisal Skills Programme	PIM(s)	Potentially Inappropriate Medication(s)
CENTRAL	Cochrane Register of Controlled Trials	PPI	Proton Pump Inhibitor
COPD	Chronic Obstructive Pulmonary Disease	PRISMA	Preferred Reporting Items for Systematic Reviews and Meta Analysis
CRF	Case Report Form	PRN	Pro Re Nata
DDD	Defined Daily Dose	RCT	Randomized Clinical Trial
DNR	Do Not Resuscitate	RQ	Research Question
EAPC	European Association for Palliative Care	RT	Radiation Therapy
EC	Ethics Committee	SERM	Selective Estrogen Receptor Modulator
EPPCS	European Palliative Care Cancer Symptom	SSRI	Selective Serotonin Reuptake Inhibitor
GDS	Geriatric Depression Scale	START	Screening Tool to Alert to Right Treatment
GHeOP3S	Ghent Older People's Prescriptions community Pharmacy Prescription Screening tool	STOPP	Screening Tool of Older Persons Prescriptions
GP	General Practitioner	STOPPFrail	Screening Tool of Older Persons Prescriptions in Frail Adults with limited life-expectancy
IMA	InterMutualist Agency	WHO	World Health Organization
JBI	Joanna Briggs Institute	WZC	Woonzorgcentrum
KPS	Karnofsky Performance Status Scale		
LLD	Life-limiting disease		







# Chapter 1

## General Introduction

## The ageing population

Lower birth rates and a higher life-expectancy determine the transition to a much older population structure in the European Union (EU). The share of the population aged 65 years and over was approximately 19% in 2016, and is projected to continue to grow in every country of the EU, to nearly 25% in 2030 (Eurostat). In Belgium, the share of people aged 65 and older was 17% in 2016 and is estimated to grow to nearly 25% in 2030 (1). In addition, the older population itself is aging progressively; the share of people aged 85 years and over in Belgium is projected to grow from 2.2% in 2010 to 2.9% in 2030 (2). These extra years are preferably spent in good health (3).

Aging comes with numerous physiological changes, and the risk of chronic disease increases (3). Aging has been associated with multimorbidity, geriatric syndromes and physical and cognitive decline (4). This may result in problems, such as a decrease in quality of life, increasing hospitalizations and health-related costs, an increasing need for long-term care, frailty, and an increased risk of mortality (5-7). Furthermore, multimorbidity often leads to polypharmacy or the concurrent use of five or more chronic medications with systemic effect (8). In its turn, polypharmacy in older adults has been associated with adverse outcomes such as falls, adverse drug events (ADEs), hospitalizations and mortality (9). Moreover, due to pharmacokinetic (the way in which medications move through the body during absorption, distribution, metabolism and excretion) and pharmacodynamic (the effects that medications have on the body) changes older adults are extra susceptible for ADEs (10).

In Flanders, Belgium, extensive home care facilities are available. Thus, nursing homes (NHs) provide care for older adults with multimorbidity and serious functional disabilities – in Activities of Daily Living (ADL) and/or cognitive impairment – and increasing care needs that cannot be met in any other way. Generally, older adults are frail at NH admission, and their health has deteriorated to an extent that long-term survival becomes exceptional (11-13). Validated measuring tools exist to predict mortality or estimate life-expectancy in NH residents (e.g. Minimum Data Set Mortality Rating Index [MMRI] (14)) and in people with multimorbid conditions (e.g. Minimum Data Set Changes in Health, End-stage disease and Symptoms and Signs score [MDS-CHESS] (15)). However, it is difficult, if not impossible, to accurately predict the time of death (16).

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In this dissertation, we define a limited life-expectancy as a life expectancy of less than one year for a person with a life-limiting disease who cannot be treated with the aim of a cure.

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Research has demonstrated that dementia is a life-limiting disease (17), although survival is variable and prognostication in dementia is difficult (18). In Germany, the prevalence of dementia in community dwelling older adults in 2009 was 2.7%, compared to 51.8 % in NH residents, which is about 19-fold higher than in the community (19). Other studies found a prevalence of dementia between 3% and 11% (20-22) in community dwelling older adults, and between 52% and 85% in NH residents (19, 23, 24). Other common diseases associated with a limited life-expectancy in older adults are cardiovascular disease (25-27), chronic obstructive pulmonary disease (COPD) (27, 28), end stage kidney disease (29, 30) and advanced cancer (25). In this context, frailty, solely due to old age, is not considered to be a – life-limiting – disease.

In Belgium, 44% of all registered deaths died of diseases indicative of palliative care needs, including deaths caused by cancer, cardiovascular disease, renal failure, COPD and Alzheimer's disease (31). In this population, 24% died in a long-term care facility (31). Among the older adults dying in NHs, dementia was the most prominent diagnosis, followed by cardiovascular disease, COPD and advanced cancer (32). In Belgium, a larger proportion of people with advanced cancer die in hospitals (51.2%) compared to at home or in a NH (48.8% together) (33).

Given the negative health outcomes associated with life-limiting disease (e.g. hospitalizations, intensive care and emergency room visits) (33), the demand for palliative care provision has increased. Earlier research has demonstrated that advance care planning (ACP) increases referral/use of palliative services, and use of hospice and palliative care and decreases hospitalizations (34-36).

## Advance care planning for older adults with multimorbidity and life-limiting disease

Internationally advance care planning (ACP) is defined as 'enabling individuals to define goals and preferences for future medical treatment and care, to discuss these goals and preferences with family and healthcare providers, and to record and review these preferences if appropriate' (36).

ACP has been associated with a decrease in hospitalizations and use of resources, lower levels of unwanted life-sustaining treatments, increasing patient and family satisfaction with care, an increasing number of residents dying in their NH instead of in hospital, and increasing compliance with patients' end-of-life care wishes (35-39). ACP in a palliative care setting should consider preferences for pain and other symptom management, cultural, emotional and spiritual support, and personal care (40).

Traditionally, ACP was mainly focused on having treatment choices on paper as a preparation for the incapacity of patients. Currently, more emphasis is being put on the process of communication and interaction rather than on completing a legal document such as an advance directive (AD) (41).

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In this dissertation, 'ACP' is used as an umbrella term and includes all forms of ACP, regulated by law or not. ACP is an essential component of palliative care, and includes end-of-life decisions such as alleviation of pain and other symptoms, palliative sedation, do not resuscitate (DNR) decisions etc.

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ACP is particularly relevant in older adults, a group of people with increased risk of multimorbidity, geriatric syndromes and physical and cognitive decline (4), which can lead to an admission to a NH. Hence, the NH can be considered as a relevant setting for ACP.

Currently, two forms of ACP occur together in Flemish NHs. Firstly, patient driven ACP, which may, but need not to be documented (e.g. in an AD), and can include nomination of a proxy decision maker. Both possibilities are provided by the law. Several structured forms in accordance with current legislation are offered by a number of organizations, such as health insurance organizations. Secondly, physician driven ACP by means of written general practitioner's (GP) orders, which are medical decisions documented in the medical file in accordance with the institution's protocol. These orders should be discussed with the resident, his family members and other healthcare professionals (42-44). These orders include DNR and do-not-intubate orders, alleviation of pain and other symptoms, etc. (44).

## The growing importance of palliative care and the shift from curative to palliative care

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The World Health Organization (WHO) defined palliative care as 'an approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual (45).

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Important goals of palliative care are symptom management, decision making and assisting patients with ACP (46). Traditionally, palliative care was considered for patients with cancer. Palliative care is not the same as end-of-life or terminal care: palliative care is appropriate at any stage of life-limiting disease and is not limited

to the period of imminent death. In this context, palliative care can be provided together with life-prolonging treatments such as chemotherapy and radiation therapy in cancer patients (47, 48). Randomized controlled trials examining the effect of an early palliative care intervention delivered together with oncology care found a better quality of life (49-51), less depressive symptoms, and less intensive care at the end of life (51) in the intervention group.

Currently, more attention is being paid to integration of palliative care in normal care for non-malignant diseases such as chronic heart failure (52), COPD (53), end stage kidney disease (30, 54), dementia (18), and progressive neurological diseases (55). Moreover, research has demonstrated that the highest prevalence of palliative care needs occurs in NHs and at home (56).

Care goals and treatment targets for people with life-limiting disease should shift from cure to care and from quantity to quality of life. Given that symptom burden usually increases at the end of life, the focus of – palliative - care should be on symptom management. Pain is one of the most frequent and serious symptoms (57). In this context, medication use is an important aspect of quality palliative care.

### Medication use as an important aspect of quality palliative care

Shifting care goals and treatment targets from quantity to quality of life should be reflected in medication use. Treatment of symptom burden is crucial to preserve and support quality of life. Hence, the focus of medication use in palliative care should be on treatment of symptoms which are currently undertreated and on prevention of additional harm due to medication use, i.e. by limiting the burden of side-effects of too toxic or too much medication (drug burden). For people with limited life-expectancy, the medical focus on long-term profit changes entirely into a focus on the different aspects of comfort of the individual. In this context, all medications for primary and secondary prevention are questionable, while restrictions regarding addiction (e.g. to opioids) are irrelevant when short-term benefit and comfort have absolute priority.

The WHO developed a model list of essential medicine for a basic healthcare system and for priority diseases, including a chapter on appropriate medications for pain and palliative care, that can be used to guide clinicians in prescribing and to prevent underuse of medications that are clearly indicated and likely to benefit people in this situation (58). This list was based on a list of the most common symptoms in palliative care, such as pain, dyspnea, constipation, nausea, vomiting, etc.

(59), and contains medications for pain (e.g. paracetamol, ibuprofen, morphine) and other symptoms (e.g. haloperidol, metoclopramide, lactulose) (58). Recently, consensus criteria for prescription of drugs that are most likely adequate for people aged 75 years and older with an estimated life-expectancy of less than three months were developed, comprising mainly medications for symptom management (60). Research has demonstrated that medications for symptom relief increase at the end of life (61). Analgesics, psycholeptics and drugs for functional gastro-intestinal disorders are most frequently prescribed and increase towards death (62-64). Most medications used in palliative care are on-label, i.e. these medications' formulation, strength and routes of administration are registered and approved by their Marketing Authorization (e.g. by the European Medicines Agency in Europe or the Food and Drugs Administration in the United States) for specific indications (populations and disease) (65, 66). However, off-label use of medications – medications used for indications different from the approved indication, in different dose or administration route, or in a different population - to relieve symptom burden in palliative care is common, particularly to treat delirium and dyspnoea (67). Earlier research has demonstrated that between 7 % and 35% of medications are prescribed off-label in palliative care (67, 68). The medication most frequently used off-label is haloperidol with strong level evidence to treat terminal delirium and insomnia and with moderate level evidence for anxiety and nausea and vomiting (67). It is important to note that, although off-label prescribing may have benefits, it can lead to an increase in adverse drug events (ADEs) (65). Preferably, off-label prescribing should be supported by high-level evidence, and obtaining informed consent from the patient is strongly recommended (65).

Polypharmacy is highly prevalent in palliative care (69). Earlier studies have demonstrated that people with a life-limiting disease use a mean number of medications between 7 and 11. The prevalence of polypharmacy – or the concomitant use of 5 or more chronic medications with systemic effect (8) – in this population varies between 25% and 84%, and the prevalence of excessive polypharmacy ( $\geq 10$ ) between 28% and 69% (70-72). Polypharmacy and inappropriate medication use have been associated with negative health-related outcomes, such as hospitalizations, falls, drug-related problems, and decreased quality of life (73, 74). The use of over-the-counter (OTC) medications, such as analgesics, vitamins, laxatives etc., adds to the burden of polypharmacy. Earlier research has demonstrated that 64% of healthy older adults and 70% of patients with a history of cardiovascular disease use at least one OTC medication (75, 76). These patients received more prescribed medications compared to non-users (75), which increased the risk of polypharmacy and associated negative health-related outcomes. Moreover, as death approaches, changes in

pharmacodynamics and pharmacokinetics occur due to altered metabolism, organ dysfunction and weight loss (69). Hence, people with life-limiting disease are extra susceptible for these negative health-related outcomes. Nevertheless, no indications were found for the increasing or decreasing use of OTC medication in relation to time before death.

However, it is important to note that polypharmacy can be judicious at the end of life, when medications that are indicated and likely to benefit the patient are prescribed in order to support and preserve quality of life. Decision making factors that should be considered to avoid inappropriate medication use at the end of life are time until benefit, remaining life-expectancy, care goals in accordance with patient preferences, treatment targets, numbers needed to treat, numbers needed to harm and adverse drug reactions (77).

At the end of life, medications for symptom treatment are often combined with medications to treat life-limiting disease and co-morbidities, and medications for long-term prevention (72). Symptom burden usually increases at the end of life, and so do medications for symptom relief (61). Consequently, when previously prescribed medications are continued as before, this can lead to a variety of problems. First, by adding medications or increasing the dose of previously prescribed medications, polypharmacy, drug burden and, consequently, the risk of drug-related problems, such as adverse drug reactions (ADRs), and drug-drug interactions increase (78, 79). Second, due to the cumulative effect of medications and particularly to the increasing use of medications for symptom relief, the anticholinergic load at the end of life increases (80). This results in a variety of adverse effects (e.g. constipation, dizziness, confusion) and is related to negative health outcomes such as increased risk of falls and higher mortality rates (81). Third, when these adverse effects are wrongly attributed to disease progression and deterioration, cascade prescribing may add to the existing drug burden. Fourth, chronic medication which may have been appropriate in the past may become inappropriate at the time of transition to palliative care e.g. due to absence of clinical indication or clinically significant drug-disease/comorbidity interactions (82). Fifth, medications for long-term prevention become futile because they lack short-term benefit and interact with medications for symptom relief (83).

Many medications used at the end of life can be considered as futile or potentially inappropriate. Medications for long-term prevention (e.g. statins) lack short-term benefit, cause adverse drug reactions (e.g. muscle damage in cachectic patients at the end of life), and drug-drug interactions with medications for symptom relief. Earlier studies found no significant harm and no effects on mortality if these medications (e.g. anti-hypertensives, statins) are discontinued at the end of life (83,

84). Medications for comorbid conditions should be weighed carefully, e.g. blood pressure control and HbA1c is less strict for people with cachexia at the end of life, because this can lead to hypotension and hypoglycaemia (85, 86).

Numerous tools have been developed to identify potentially inappropriate medications (PIMs) in older adults with a normal life-expectancy (e.g. STOPP (87), Beers (88)). However, some medications considered to be 'inappropriate' in the general older population may be used appropriately for symptom relief in a palliative care setting (e.g. short-acting benzo's, tricyclic antidepressants) and vice versa (e.g. folic acid, vitamin D). Thus, these criteria require adaptation in order to be applicable in palliative care (89). Recently, these tools were expanded with specific criteria for people with multimorbid disease (e.g. LESSCHRON (90)), and/or limited life-expectancy (consensus criteria (60), STOPPFrail (91)).

All these tools and criteria aim to guide prescribers in not initiating and/or not continuing PIMs for older adults with normal (e.g. STOPP (87)) and limited life-expectancy (e.g. STOPPFrail (91)) in clinical practice. However, the appraisal of appropriateness of the medications involved is based on evidence from literature search and clinical experience, followed by Delphi consensus methodology. Robust evidence for their (in)appropriateness from randomized clinical trials (RCTs), the classic experimental design for estimating treatment effects, is missing, mainly due to ethical and practical concerns about randomization. Consequently, the effects of discontinuation of PIMs and deprescribing of medications at the end of life are difficult to measure.

## Deprescribing for people with a life-limiting disease

In literature, deprescribing is defined as 'the systematic process of withdrawal of an inappropriate medication, supervised by a healthcare professional, with the goal of identifying and discontinuing drugs in instances in which existing or potential harms outweigh existing or potential benefits within the context of individual patients' care goals, current level of functioning, life-expectancy, values, and preferences' (92). Scott et al. (2015) propose a 5-step deprescribing protocol: (1) ascertain all medications the patient is currently taking and their indications, (2) consider overall risk of medication-induced harm in individual patients in determining the required intensity of deprescribing, (3) assess each medication for its eligibility to be discontinued or determine the risk-benefit ratio of each medication, (4) prioritize medications for discontinuation in accordance with their risk-benefit profile, and (5) implement and monitor medication discontinuation regimen (92). The following terms for stopping or tapering medications are used interchangeably in literature:



discontinuation, withdrawal, cessation and deprescribing.

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In this thesis, we use the term 'discontinuation' in the context of tapering or stopping PIMs in older adults with normal life-expectancy. The term 'deprescribing' is used for tapering or stopping medications that have become futile or potentially inappropriate in the explicit context of a life-limiting disease, because death is imminent. As mentioned in the section about medication use in palliative care, medications considered as PIMs in older adults with normal-life-expectancy may be used appropriately for symptom relief (including off-label use) in a palliative care setting and vice versa, although some overlap is possible depending on the tool used. In the studies in this dissertation, we used the STOPPFrail criteria to appraise the appropriateness of medications (91). These criteria contain medications considered as PIMs for frail older adults with limited life-expectancy that are not always inappropriate when death is imminent (e.g. neuroleptic antipsychotics, proton pump inhibitors), as well as medications that are inappropriate in both situations (e.g. lipid modifying agents, multivitamin combinations). In this thesis, tapering medications was only taken into account to determine if medications suitable for deprescribing were actually deprescribed in chapter 6. In the other chapters regarding deprescribing, only stopping of medications was taken into account.

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Since the medical focus on long-term profit changes entirely into a focus on the different aspects of comfort of the individual, all medications for primary and secondary prevention are eligible for deprescribing. However, earlier studies have demonstrated that the use of these medications is still very high at the end of life, particularly for anti-hypertensives (36%-72%), anti-thrombotics (33%-61%), and osteoporosis medications (23%-33%) (25, 61, 93, 94). On the contrary, the use of lipid modifying agents (approximately 20%) is much lower at the end of life compared to other preventive medications (61, 94). Kutner et al. found that these medications, particularly statins, can be safely and effectively deprescribed when used for primary or secondary prevention (84).

In an end-of-life context, deprescribing can be considered as a medical end-of-life decision, and should be embedded in ACP. In this situation, the risk-benefit ratio of every medication should be weighed carefully, and in accordance with the values and preferences of the individual patient and his family.

Since 2017, international clinical practice deprescribing guidelines have been developed based on the highest level of evidence available for proton pump inhibitors, anti-hyperglycaemic agents, benzodiazepines and Z-drugs, antipsychotics, and cholinesterase inhibitors and memantine (95). However, not all recommendations are based on high level evidence.

## Barriers/enablers to deprescribing

### Prescriber and other healthcare professional-related barriers /enablers to deprescribing

Generally, clinical practice guidelines are known by physicians, but these guidelines focus on a one disease model, and not on multimorbid patients or advanced cancer patients with limited life-expectancy. Furthermore, older adults are usually excluded from clinical trials examining the effect of medications. Hence, physicians feel uncertain about applying these evidence-based guidelines to an older patient with multimorbidity (96). Moreover, recommendations made in these guidelines only involve prescribing of a specific medication for treatment of a specific disease, and not when or in what circumstances this medication can be safely and effectively tapered or stopped. Physicians perceive tapering or stopping a medication that is recommended in a clinical practice guideline or initially prescribed by another – hospital – physician as difficult, particularly when no evidence-based recommendations for deprescribing are available (97, 98). Furthermore, physicians have a genuine fear of patients experiencing deterioration in their health shortly after deprescribing one or more medications, and fear of repercussions should deterioration in the patient's health occur (96-99). Other barriers to deprescribing acknowledged by physicians are time constraints, (changes in) organization of care, patient expectations, fear that deprescribing might be misinterpreted by the patient and his family as 'giving up', etc (99, 100).

The duty to do what is right for the patient, open communication with the patient and his family, interdisciplinary collaboration and communication, and organizational support were perceived as facilitators to deprescribing (98, 99, 101, 102).

### Patient and family-related barriers/enablers to deprescribing

Patient barriers and enablers to deprescribing are strongly related to their attitude and beliefs regarding medications (103). When patients perceive improvement of their condition after initiation of a medication or hope for future benefits they are unlikely to be willing to have this medication deprescribed (103). On the contrary, when patients feel that the medication is no longer necessary, question continued use, or dislike medications (e.g. due to the related costs), they are more willing to have their medications deprescribed (103). Other barriers to deprescribing perceived by patients are lack of physician time and support that is necessary to taper or stop medications, experience of withdrawal symptoms, pressure from family, fear of return of previous condition or withdrawal symptoms, etc. (103).

On the other hand, physician support and a positive patient-physician relationship positively influences the patient's willingness to deprescribing (103, 104).

## Rationale for undertaking of this research

In summary, the existing evidence regarding deprescribing of medications at the end of life is weak:

The term 'deprescribing' is relatively new, particularly in palliative care.

- Earlier research on deprescribing is limited to older adults with a normal life-expectancy (87, 88), multimorbid patients (90), and frail older adults with a life-expectancy of 12 months or less (91). Only a few studies on deprescribing have been conducted in palliative care or end-of-life care (84, 85, 93, 94).
- Existing clinical practice guidelines on prescribing of specific medications focus on a one disease model, and not on multimorbid patients or patients with advanced cancer receiving palliative care. Recommendations made in these guidelines only involve prescribing of a specific medication for treatment of a specific disease, and not when or in what circumstances this medication can be safely and effectively tapered or stopped (96).
- Research on which medications can be safely and effectively deprescribed and the effects of deprescribing on health-related outcomes such as quality of life, hospitalization and mortality in an end-of-life context is still at the very beginning.
- Existing tools and criteria for the appraisal of the appropriateness of medications (e.g. STOPPFrail (91)) are not entirely transferable to an end-of-life context, and are based on evidence from literature and clinical experience, followed by Delphi consensus methodology. Robust evidence from RCTs is missing.
- Existing clinical practice deprescribing guidelines (95) are based on the highest level of available evidence. However, not all recommendations are based on high level evidence.

Hence, we need a thorough approach to study these aspects into depth.

Two urgent needs for guidance regarding safe and effective deprescribing of medications at the end of life occur. First, we need pharmacological guidance to determine which medications can be safely and effectively deprescribed in order to develop a list of medications suitable for deprescribing for people with limited life-expectancy. Second, behavioural guidance is necessary to explore how to deprescribe medications in this situation.

The development and implementation of a sustainable multifaceted deprescri-

bing intervention in clinical practice may improve appropriate medication use, decrease drug burden, preserve and support quality of life and prevent negative health outcomes in people with advanced disease and limited life-expectancy in clinical practice. The studies in this dissertation provide evidence to guide the development of such a deprescribing intervention.

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## Chapter 2

Scope of this thesis

## Research aim

The overall aim of this research is to develop the prerequisites for an intervention to support the initiation of deprescribing in clinical practice for people with advanced disease and limited life-expectancy. In this dissertation, we describe the current situation regarding medication use in general, and polypharmacy and potentially inappropriate medication (PIM) use in particular, in nursing home (NH) residents with a normal life-expectancy and NH residents with life-limiting diseases in Flanders, in the Belgian population aged 75 years and older at time of death, and in patients with advanced cancer receiving palliative care. We explore relationships between these aspects and socio-demographics, survival, hospitalization, mortality, and initiation of advance care planning (ACP), to gather information regarding the context of deprescribing in Flanders, Belgium and 11 other countries in Europe and beyond. Subsequently, we examine whether PIMs are actually discontinued and medications suitable for deprescribing are actually deprescribed in Flanders, Belgium and internationally and if yes, we determine the prevalence of discontinuation of PIMs and deprescribing. Finally, we explore barriers and enablers to deprescribing in people with a life-limiting disease. This information is crucial to find out which preconditions should be fulfilled to allow for the development of a sustainable multifaceted deprescribing intervention.

## Research questions

1. What is the prevalence of polypharmacy and potentially inappropriate medication use according to the STOPPFrail criteria in an inception cohort of newly admitted nursing home residents in Flanders and is there a relationship with the length of survival?
2. Is there a relationship between deprescribing and initiation of advance care planning in a cohort of newly admitted nursing home residents in Flanders?
3. Is there deprescribing at the end of life in nursing home residents with life-limiting diseases in Flanders and what is the prevalence of deprescribing?
4. Is there discontinuation of potentially inappropriate medications according to the STOPPFrail criteria in the year before the end of life in the full population of deceased aged 75 or older at time of death, in 2012, in Belgium, and what is the prevalence of discontinuation of potentially inappropriate medications?
5. Is there deprescribing in patients with advanced cancer receiving palliative care in 12 countries in Europe and beyond, and what is the prevalence of deprescribing?

6. What are the factors that facilitate and/or hinder (enablers/barriers) deprescribing in people with a life-limiting disease?

## Outline of this dissertation

Following this general introduction and scope, chapter 3 contains a description of the methodology – description of data sources and data analyses - used in this dissertation. Chapters 4 to 9 of this dissertation are based on scientific articles that have been published. All of these chapters can be read independently. Each chapter addresses one research question. Chapter 4 to 6 are three field studies performed in NHs in Flanders, chapter 7 is a large population study of all deceased in 2012 in Belgium aged 75 or older at time of death, and chapter 8 is a large international cohort study in different healthcare settings providing palliative care. In chapter 4 the prevalence of polypharmacy and PIM use are examined in an inception cohort of newly admitted NH residents in Flanders, Belgium. Kaplan Meier and Cox regression analyses were performed to explore the relationship with length of survival and mortality. In chapter 5, the relationship between initiation of ACP in newly admitted NH residents in Flanders, Belgium and two examples of good practice for people with limited life-expectancy, an increasing use of analgesics (1) and a decreasing use of lipid modifying agents (2), is explored. Chapter 6 is a field study, containing an analyses of medication use in relation to time before death, deprescribing of medications suitable for deprescribing, and new initiation of PIMs at the end of life, in NH residents with life-limiting diseases in Flanders, Belgium. Chapter 7 is a population study in Belgium, using linked administrative databases, containing the same analyses as the field study in chapter 6. Chapter 8 is an international multicentre cohort study containing a trend analyses of medication use at the end of life for patients with advanced cancer receiving palliative care in 30 palliative care services in 12 countries. Chapter 9 is a systematic review exploring the factors that hinder or facilitate deprescribing of medications for people with a life-limiting disease. Finally, this dissertation contains a summary of the main findings and a discussion of the results, including methodological strengths and limitations, and implications for clinical practice, policy and research. At the end of this dissertation you can find a summary of the main findings and conclusions in English and in Dutch.

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## Chapter 3

Methodology used in this dissertation

## Description of the population

**T**wo different populations were studied in this research: NH residents and patients with advanced cancer receiving palliative care.

Generally, nursing home residents are older adults with multimorbidity, geriatric syndromes and serious functional disabilities – in ADL and/or cognitive impairment – and increasing care needs that cannot be met in any other way (e.g. by home care). Most older adults are frail at NH admission and their health has deteriorated to an extent that long-term survival becomes exceptional (1-3). Earlier research has demonstrated that between 52% and 85% of NH residents have dementia (4-6), which is the most prominent diagnosis in those dying in NHs. Furthermore, multimorbidity often leads to polypharmacy (7). Polypharmacy in older adults has been associated with adverse outcomes such as ADEs (7). Moreover, due to pharmacokinetic and pharmacodynamic changes, the presence of multiple comorbidities and medications, older adults are extra susceptible for ADEs.

Patients with cancer are people of all ages, including young adults. Multimorbidity and polypharmacy are less prominent, depending on the patient's age and general health before he/she was diagnosed with cancer. The population we studied were patients with advanced cancer receiving palliative care. In this situation, symptom burden usually increases, and symptom management becomes crucial to support and preserve quality of life. Thus, medications for symptom relief are added to the medication chart. When previously prescribed medications such as cancer therapy, medications to treat co-morbidities and medications for long-term prevention, are continued as before, this often leads to polypharmacy and increased drug burden at the end of life. Consequently, the risk of ADEs increases (8, 9). Moreover, pharmacokinetic and pharmacodynamic changes occur due to altered metabolism, organ dysfunction, and weight loss at the end of life (10). Therefore, these people are also extra susceptible for ADEs.

## Description of data sources

To address the research questions of this dissertation, quantitative analyses and a systematic review were performed.

Quantitative analyses were performed to examine the current situation regarding discontinuation of PIMs and deprescribing for people with advanced disease and limited life-expectancy, using four different datasets. For chapters 4 and 5, data from the Ageing@NH cohort study examining the general health of newly admitted NH



residents in Flanders were used (research question [RQ] 1 and 2). For chapter 6, data from a cross-sectional study examining symptom burden and medication use in NH residents with life-limiting diseases were used (RQ 3). For chapter 7, data were analysed from linked administrative databases containing healthcare data on the full population aged 75 and older at time of death, deceased in 2012 in Belgium (RQ 4). For chapter 8, data from the international multicentre prospective European Palliative Care Cancer Symptom study were used (RQ 5).

In chapter 9, a systematic review about the barriers and enablers to deprescribing was conducted in accordance with the methodology of the Cochrane Handbook of Systematic Reviews of Interventions (RQ 6) (11).

### The Ageing@NursingHome (Ageing@NH) study

The Ageing@NH study is a prospective cohort study examining the general health of newly admitted NH residents in Flanders, Belgium. The primary aim of this study was to assemble a cohort of newly admitted NH residents to assess their physical and cognitive status at NH admission and its evolution at follow-up one and two years later. From September 2013 until January 2014, all new residents of participating NHs in Flanders, the Dutch speaking part of Belgium, were included consecutively. Baseline data were collected two to four months after NH admission, during the period between December 2013 and March 2014. The same residents were invited to participate after one and two years for follow-up assessment, provided that they were still alive and still resided in a participating NH. After three years, an additional follow-up for mortality was performed, without any further data collection. Residents were interviewed using a structured questionnaire and validated measuring tools for ability to perform ADL independently (Katz index in Activities of Daily Living (KATZ-ADL)) (12), cognitive status (Mini Mental State Examination (MMSE)) (13), quality of life (Nottingham Health Profile (NHP)) (14), depressive feelings (Geriatric Depression Scale (GDS-8)) (15), and six month mortality risk (MMRI) (16). These data were completed with administrative data, data from the nursing chart and a copy of the medication chart. In case of dementia, the proxy decision maker (at admission) or the responsible nurse (year1&2) was interviewed.

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, the current version of each year of data entering). Focus was on anatomical main groups (first ATC level) and therapeutic subgroups (second ATC level).

ACP was not the main objective of this study, but the available data on ACP were

used to explore the relationship with medication use. Therefore, content and quality of ACP were not examined, but we explored the timing of any form of ACP initiation. Hence, chapter 5 is not a study of the prevalence of normative ACP, but an empiric approach of the practices in the field of ACP, and also the absence of ACP, in the NH setting.

## Cross-sectional study examining symptom burden and medication use in NH residents with life-limiting disease

The primary aim of this cross-sectional study was to describe symptom burden and medication use in NH residents with life-limiting disease. A convenience sample of ten NHs in Flanders, the Dutch speaking part of Belgium, were included in this study.

Residents were eligible for inclusion if aged  $\geq 65$ , Dutch speaking, able to answer questions adequately according to the responsible nurse, having a life-expectancy of  $\leq 12$  months, and suffering from one of the following life-limiting diseases: end stage organ failure, advanced cancer or dementia. Residents with a life expectancy of  $< 1$  month were excluded for ethical reasons.

Residents diagnosed with dementia who were capable to adequately answer questions (MMSE  $\geq 18$ ) were interviewed themselves. Residents diagnosed with dementia for whom this was not the case were included if their informal caregiver was aged  $\geq 16$ , and visited them at least twice a month, then the informal caregiver was questioned instead of the resident himself. Residents who were incapable to answer questions adequately due to dementia, deafness, aphasia or other reasons and for whom no informal caregiver was available were excluded. Socio-demographic data, data on physical and mental health, life-expectancy, medication use and self-reported symptom burden were collected using a structured questionnaire and validated measuring tools for ability to perform ADL independently (KATZ-ADL) (12), cognitive status (MMSE) (13), and six month mortality risk (MMRI) (16).

Medication use was based on a copy of the resident's full medication chart, and was evaluated two times: (t2) at the time of data collection and (t1) three to six months before. 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 ATC classification (WHO ATC/DDD index).

Medications considered to be suitable for deprescribing were selected based on scientific evidence (17-19) and expert opinions, and cross-referenced and linked to the medications at t1 and t2. Deprescribing was defined as stopping or lowering the dose of the selected medications between t1 and t2, on the individual level. Initia-

tion of new medication at the end of life was defined as initiation between t1 and t2 of a specific medication that was not used at t1. Appraisal of the appropriateness of the initiated medications was determined with explicit criteria of PIM using the STOPPFrail criteria (20). The STOPPFrail criteria were cross-referenced and linked to the medications at t1 and t2.

## Linked administrative databases

We used an integrated database consisting of death certificate data, census data and fiscal data obtained from Statistics Belgium, healthcare claims data of the seven healthcare insurers in Belgium from the InterMutualistic Agency's (IMA), and data from the Belgian Cancer Registry for all deceased in 2012 in Belgium. This integrated database covers approximately 99% of the full population who died in 2012. All separate databases were linked in a secure and ethically responsible manner to guarantee anonymity of the deceased (21).

We used – in hospital and community – pharmacy dispensing data to determine PIM use. We selected PIMs available on the Belgian market and listed on the STOPPFrail list of explicit criteria for PIM use in frail older adults with limited life-expectancy, for which no specific patient-level clinical information was needed to determine inappropriateness (20). Based on experts' opinions and the available evidence, we categorized these PIMs into three groups: medications for long-term prevention, medications for which chronic use is inappropriate, and (outdated) medications for which a safer alternative exists. For every selected PIM, the corresponding ATC-code was selected from the IMA database for further analyses.

## The European Palliative Care Cancer Symptom (EPCCS) study

The EPCCS study is an international multicentre prospective cohort study in which palliative care services in 24 hospitals, 4 hospices, 1 NH, and 1 palliative care home-care service participated, representing the following countries: Australia, Belgium, Canada, Denmark, Georgia, Germany, Italy, Norway, Portugal, Spain, Switzerland, and the United Kingdom. The primary aim of the EPCCS study was to extend the knowledge about and gain new insight in the prevalence and development of the most frequent cancer related symptoms during the course of disease. A single web-based survey on palliative care organization, services and academics was completed in 2010 by participating centers before any patients were included, in order to describe the organization and delivery of palliative care at specific centers across Europe and beyond. Patient's medical data were collected using a case report form (CRF) to be completed by the healthcare providers at baseline as well as follow-up.

This CRF consisted of a brief set of medical and treatment-related variables (e.g. medication use), a four-item version of the mini mental state examination (MMSE) (22) and the Karnofsky Performance Status Scale (23). A retrospective recording of date of death was performed in February 2014, six months after inclusion of the last patient. Patient self-reported data were collected at each patient encounter using a patient-CRF, consisting of socio-demographic items (e.g. age, gender) and questions about common cancer-related symptoms (24). All patients were followed every four (three to five) weeks for at least three months or until death. All data were collected longitudinally between April 2011 and October 2013 (25).

The original goals of the EPCCS study were not intended for the analyses and appraisal of medication use. The recording of date of death allowed us to analyse medication data retrospectively, using death as the index date. Data on medication were based on dichotomous questions (use: yes/no) for cancer treatment (radiation therapy and anti-tumour medication) and 19 other therapeutic groups. Data collection on medication was simplified regarding the number of medication groups and the method of questioning to make it comprehensible for all healthcare professionals responsible for filling in the questionnaire. We grouped medication into four main categories, based on the opinion of experts: cancer therapy, medication specific for cancer-related symptom relief, medication for other symptom relief, and medication for long-term prevention (25).

## Data analyses

To analyse the data used in this dissertation, a number of statistical methods were used consistently across chapter 4 to 6 and in chapter 8. All analyses for these chapters were performed using IBM Statistical Package for the Social Sciences (SPSS 23.0, IBM Corporation USA). A significance level of  $p < 0.05$  was set.

Differences in means between groups were calculated with t-tests (2 groups) or One-way ANOVA (> 2 groups), and differences in discontinuous outcomes with Pearson's Chi-square tests. For paired measurements, differences in means within the same group were calculated with paired samples t-test, and differences in discontinuous outcomes with McNemar (2 measurements) or Cochran's Q (> 2 measurements) tests.

In chapter 4, the Kaplan Meier method was used to estimate survival and log-rank tests were used for subgroup analyses. A Cox proportional hazards model was developed to examine associations between polypharmacy, PIM use and mortality.

In chapter 5, logistic regression analyses were used to analyse associations between different socio-demographic and other independent variables on our chosen

outcomes. Associations of these independent variables with the evolution in time of our chosen outcomes were explored using Cochran-Mantel-Haenszel and McNemar tests.

In chapter 6, associations between our chosen continuous outcomes were examined using Pearson correlations.

In chapter 8, data were analysed retrospectively using death as the index date. To explore changes in medication use in relation to time before death, we used ANOVA for trend in the continuous outcome and Cochran Armitage test for trend in the discontinuous outcomes. Associations of chosen independent variables with trend of our chosen outcomes were explored using Cochran-Mantel-Haenszel and McNemar tests.

Chapter 7 is a population study including the whole population aged 75 and older who died in 2012. Thus, it was not necessary to calculate p-values. A logistic regression model was used to examine the factors which were independently associated with our chosen outcome. All statistical analyses were performed using Statistical Analysis Software (SAS®) 9.4 and SAS® Enterprise Guide 7.1 (SAS® Institute Inc., North Carolina, USA).

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## Chapter 4

# Associations of potentially inappropriate medication use with four year survival of an inception cohort of nursing home residents

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## Abstract

**Background:** Survival in older adults has a high variability. The possible association of length of survival with potentially inappropriate medication (PIM) use remains unclear.

**Aim:** To examine the four-year survival rate, the prevalence of polypharmacy and PIM use at admission, and the association between the two, in an inception cohort of newly admitted nursing home residents

**Methods:** Data were used from ageing@NH, a prospective observational cohort study in nursing homes. Residents (n = 613) were followed for four years after admission or until death. PIM use was measured at admission, using STOPPfrail. The Kaplan-Meier method was used to estimate survival, using log-rank tests for subgroup analyses. Cox regression analyses was used to explore associations with PIM use and polypharmacy, corrected for covariates

**Results:** Mean age was 84, 65% were females. After one, two, three and four years the survival rates were respectively 79%, 60.5%, 47% and 36%. At admission, 47% had polypharmacy and 40% excessive polypharmacy, 11% did not use any PIMs, and respectively 28%, 29%, and 32% used one, two and three or more PIMs. No difference in survival was found between polypharmacy and no polypharmacy, and PIM use and no PIM use at admission. Neither polypharmacy nor PIM use at admission were associated with mortality.

**Conclusion:** Residents survived a relatively short time after NH admission. Polypharmacy and PIM use at admission were relatively high in this cohort, although neither was associated with mortality.

## Introduction

Survival in older adults differs in length, and has been associated with different factors, such as multimorbidity, physical and cognitive decline, and frailty (Huang et al., 2017; Kamo et al., 2017; Koroukian et al., 2016; Rizzuto, Melis, Angleman, Qiu, & Marengoni, 2017). The association of polypharmacy and potentially inappropriate medication (PIM) use with mortality is also debated. Previous studies on this item have concentrated at one time point, but the association of polypharmacy and PIM use with the longitudinal evolution of survival remains unclear (Bo et al., 2018; Muhlack, Hoppe, Weberpals, Brenner, & Schottker, 2017; Schlesinger, Weiss, Nenaydenko, Adunsky, & Beloosesky, 2016). This study focusses on four year survival and its association with polypharmacy and PIM use according to the STOPPfrail criteria (Screening Tool of Older Persons Prescriptions in Frail older adults with limited life-expectancy) (Lavan, Gallagher, Parsons, & O'Mahony, 2017). The study population is an inception cohort of newly admitted nursing home (NH) residents: a group of older adults, included after their first admission in a NH, and followed thereafter (Elsevier glossary of methodological terms, 2018).

Generally, NH residents are a frail population with a high prevalence of multimorbidity, high care dependency, and dementia (Holmes & Sachs, 2017; Kojima, 2015). Furthermore, multimorbidity is commonly treated with high levels of medications and also PIMs (Davies & O'Mahony, 2015; Lavan et al., 2017; Vetrano et al., 2013). PIM use has been studied extensively in older adults with a normal life-expectancy. Numerous implicit (e.g. MAI (Samsa et al., 1994)) and explicit tools (e.g. STOPP/START (O'Mahony et al., 2015)) have been developed to guide clinicians with discontinuation of these PIMs. Depending on the tool used, between 24% and 95% of NH residents are exposed to PIMs (Morin, Laroche, Texier, & Johnell, 2016; Sevilla-Sanchez, Molist-Brunet, Amblas-Novellas, Espauella-Panicot, & Codina-Jane, 2017). PIM use has been associated with adverse outcomes such as falls, adverse drug events, hospitalizations and mortality in older adults with a normal life expectancy (Fried et al., 2014). However, these tools do not take the frailty and limited life-expectancy of most NH residents into account. Only recently, specific – STOPPfrail – criteria were developed for this population (Lavan et al., 2017).

The main care goal in a frail population with limited life-expectancy should be preservation of quality of life. In this context, it is crucial to prevent negative medication-related outcomes, i.e. by identifying and discontinuing PIMs. Furthermore, to ensure appropriate care by NH staff with expertise regarding the areas of care that are most needed, it is vital to get an insight in the average survival time after NH admission, and its associated factors. This information is also important for policy

makers and NH managers to estimate future long-term care needs and the related costs, and to determine the policy regarding waiting lists.

The aim of this study is to examine, in an inception cohort of newly admitted NH residents, the four-year survival rate, the prevalence of polypharmacy and PIM use according to the STOPPFrail criteria at NH admission, and the association between the two, corrected for covariates.

## Materials and methods

This study uses data of the ageing@NH cohort study, examining the general health of NH residents at admission and during their four-year stay in the NH or stay until death. Two other articles reporting on data of this study were published earlier (Ivanova et al., 2018; Paque, Goossens, Elseviers, Van Bogaert, & Dilles, 2017). More information on methods can be found there.

### Study design and study population

A convenience sample of 67 NHs in Flanders, the Dutch speaking part of Belgium, were included in the study. In the participating NHs, all newly admitted residents between September 2013 and December 2013 were invited to participate in the study, if aged  $\geq 65$ , Dutch-speaking and permanently admitted to the NH. All residents were consecutively recruited during the period of four months for the baseline assessment at NH admission. All residents – or their proxy decision maker in case of dementia – had to provide informed consent.

### Procedure

Residents were interviewed one to three months after admission using a structured questionnaire and validated measuring tools for activities of daily living (Katz-ADL) (Katz, Ford, Moskowitz, Jackson, & Jaffe, 1963) and mental health (MMSE) (Cockrell & Folstein, 1988). These baseline data were completed with administrative data (date of birth, admission and date of death), data from the nursing chart, and a copy of the resident's medication chart. In case of dementia, the proxy decision maker was interviewed.

Survival data (alive or death, date of death) were collected during four years after study entry. A follow-up assessment was conducted one and two years after NH admission, but these data were not included in our analyses. We focused on the assessment at NH admission because one of the main aims was to examine if polypharmacy and PIM use at admission were associated with the survival rate after admission.

## Data handling

Medication use was based on a copy of the full medication chart. 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).

Polypharmacy was defined as the use of five or more prescribed chronic medications, and extreme polypharmacy as the use of ten or more. The prevalence of PIMs was measured using the STOPPFrail criteria (Lavan et al., 2017). STOPPFrail is a list of explicit criteria for PIM use, aiming to assist clinicians with deprescribing medications in frail older adults with limited life-expectancy in all healthcare settings. This list was created based on the authors' clinical experience in geriatric pharmacotherapy and literature appraisal. The draft criteria were distributed to a panel of experts for validation by the Delphi technique (Lavan et al., 2017). The STOPPFrail criteria were cross-referenced and linked to the baseline medications. Because the clinical information necessary to interpret their [in]appropriate use was not available in this study, we excluded, based on experts' opinions (RVS and TC), the following medications: anti-platelets, leukotriene antagonists, muscarinic antagonists, diabetic oral agents, ACE inhibitors, angiotensin receptor blockers, and prophylactic antibiotics.

High care dependency was defined as a KATZ-ADL score greater than 17, based on the highest tertile of the frequency distribution at baseline. Residents with an MMSE score lower than 16 out of 30, and a KATZ score for disorientation greater than or equal to 6 out of 8 – showing a daily disorientation in time and place – and who were unable to respond adequately to the questionnaire, were considered to have dementia symptoms. People without dementia, who were living alone before admission and not being directly transferred from hospital to the NH, were considered as social admittance.

## Data analysis

All statistical analyses was done using SPSS 23.0 (IBM Statistics Inc., Chicago, IL). Resident characteristics were explored with descriptive statistics. The Kaplan-Meier method was used to estimate survival, using 31/12/2017 as the censor date for the survivors, and using log-rank tests for subgroup analyses. Residents who moved during the observation period (e.g. to another NH) were excluded from further analyses. A Cox proportional hazards model was developed to examine associations of polypharmacy, PIM use and covariates with mortality. A statistical significance level of  $p < 0.05$  was set.

## Ethical considerations

The study protocol was approved by the ethics committee of the Antwerp University Hospital Belgium (EC-number 13/43/420). The board of directors and the supervising general practitioner (GP) of the NH signed a study agreement. Residents or their legal representative signed an informed consent.

## Results

### Study population

At NH admission, mean age was 84 years, and 65% were females ( $n = 613$ ). The most important reasons for NH admission were physical decline (63%) and increasing care needs (58.5%), followed by cognitive decline (36%), and social admittance (24%). Mean Katz-ADL was 15.6 (range 6–24), 38% were highly care dependent, and 34% had dementia symptoms (Table 4.1).

### Survival rates over four years

Mean survival time after admission was 31 months. One year after NH admission, 79% was still alive. The cumulative survival rates after two, three and four years were respectively 60.5%, 47%, and 36%, with every year a decrease of the yearly mortality (Figure 4.1).

### Medication use and PIM use according to STOPPFrail at NH admission

At admission, participants used a mean of 9 medications, 47% had polypharmacy (5–9 chronic medications), and 40% excessive polypharmacy ( $\geq 10$  chronic medications). Mean number of PIMs was two (range 0–6), 11% did not use any PIMs, and respectively 28%, 29%, and 32% used one, two and three or more PIMs according to the STOPPFrail criteria. The most commonly used PIMs were proton pump inhibitors (PPIs) and H2 receptor antagonists (41%), vitamins (32%), antipsychotics (28%), calcium (28%), and lipid modifying agents (26%) (Table 4.2).

### Associations of four year survival

*With polypharmacy and PIM use.* Survival analyses with Kaplan Meier showed no difference in survival between no polypharmacy, polypharmacy and excessive polypharmacy at admission, neither between PIM use and no PIM use at admission (data not shown). No associations were found between polypharmacy and mortality, and

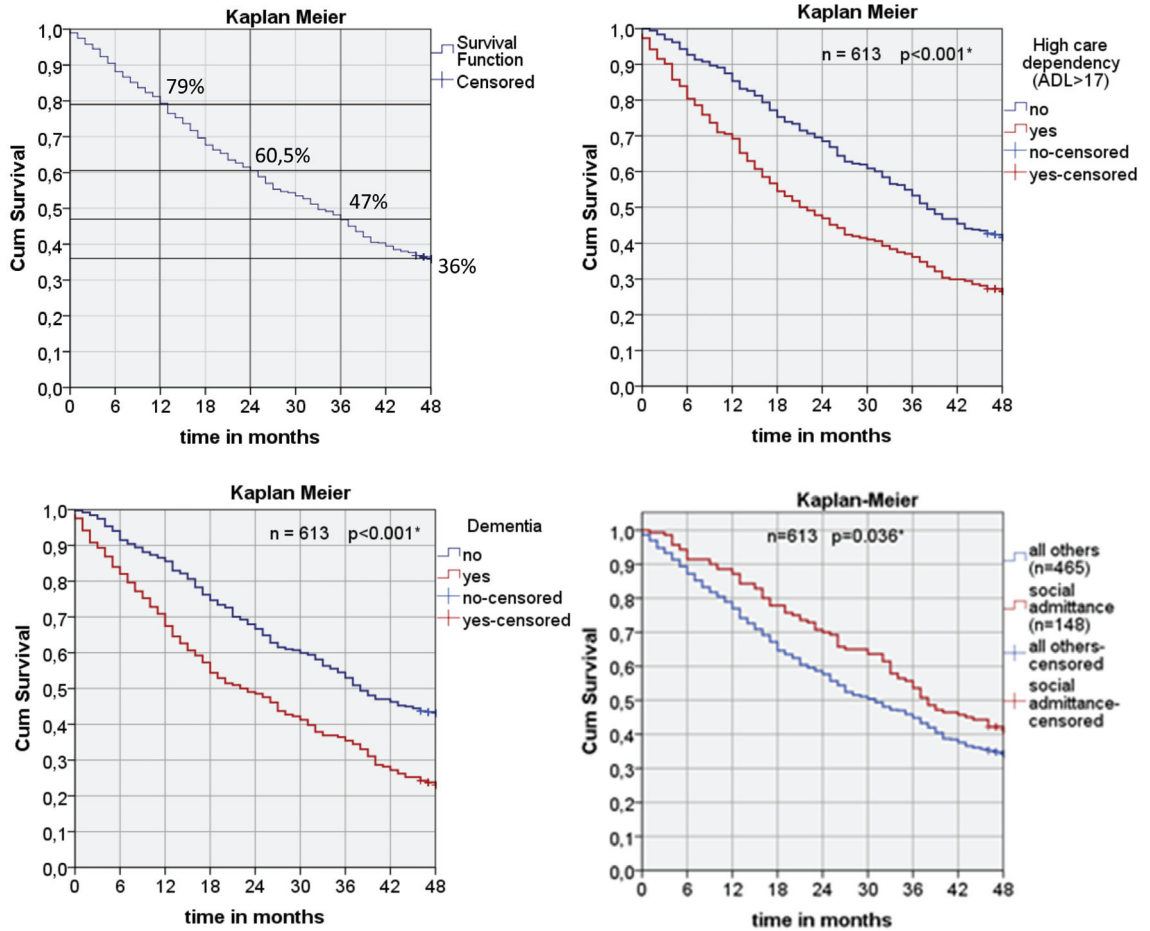
between PIM use and mortality in Cox regression analyses (resp.  $p = 0.150$ ,  $p = 0.901$ ) (Figure 4.2 and Table 4.3).

*With covariates.* Survival rates were lower in residents with high care dependency and dementia symptoms compared to residents who were less care dependent and without dementia symptoms (both  $p < 0.001$ ) (Figure 4.1). Survivors were more hospitalized during the year before admission compared to the deceased ( $p = 0.011$ ) (Table 4.3). In addition, a higher survival rate was associated with social admittance, younger age and female gender ( $p = 0.036$ ,  $p < 0.001$  and  $p = 0.029$  respectively) (Figure 4.1 and Table 4.3).

**Table 4.1.** Basic characteristics of the study population.

	All (n = 613)
Age in yrs mean (SD) [range]	84.02 (6.63) [65–105]
Gender (%):	
female	65.4
male	34.6
Survival in months mean (SD) [range]	30.81 (17.33) [0–48]
Total medication mean (SD)	8.94 (3.92)
Polypharmacy (%):	
No polypharmacy (0–4)	12.3
Polypharmacy (5–9)	47.4
Excessive polypharmacy ( $\geq 10$ )	40.3
Most important reason for admission <sup>a</sup> (%)	
(more than one answer possible):	
physical decline	62.6
increasing care needs	58.5
cognitive decline	36.1
increasing caregiver burden	16.5
other	24.0
Living situation before admission (%):	
alone	61.6
with partner, partner and children or children	35.6
other	2.8
Stay before admission (%):	
hospital	42.9
at home	21.7
other	35.4
Social admittance (%)	24.1
Hospitalization year before admission (%)	68.9
Katz ADL mean (range 6–24)	15.63
High care dependency (ADL > 17) (%)	37.7
MMSE mean (range 0–30)	18.40
Dementia symptoms (%)	34.2

<sup>a</sup> More than one answer possible.



**Figure 4.1.** Survival rates of an inception cohort of newly admitted NH residents and differences in long-term survival according to level of ADL dependency, presence of dementia symptoms and social admittance.

Top left: cumulative survival of newly admitted NH residents: at admission (month 0) everyone is still alive, 12 months after NH admission 79% is still alive, and after 24, 36 and 48 months resp. 60.5%, 47%, and 36% are still alive.

Top right: Difference in survival between residents with high (ADL > 17) and lower care dependency: residents with high care dependency die sooner compared to those with lower care dependency.

Bottom left: Difference in survival between residents with and without dementia symptoms: residents with dementia symptoms die sooner than residents without dementia.

Bottom right: Difference in survival between social admittance and all others: residents without dementia symptoms, living alone before NH admission, and not transferred directly from hospital to the NH live longer compared to the others.



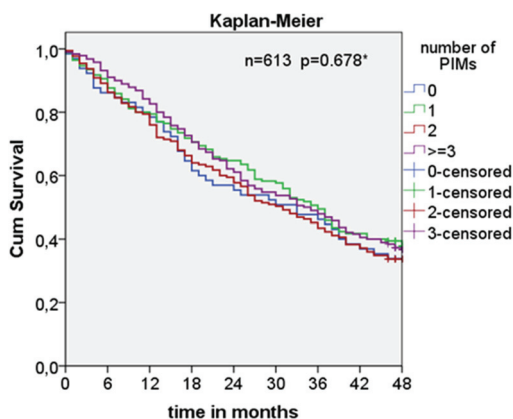
**Table 4.2.** Prevalence of Potentially Inappropriate Medications (PIMs) in frail older adults with limited life-expectancy according to the STOPPFrail criteria (Lavan et al., 2017).

PIM use at admission		n = 613
Number of PIMs mean (SD) [range]		1.94 (1.201) [0–6]
Prevalence of PIM use (%):		
no PIMs		10.6
1 PIM		28.2
2 PIMs		29.4
≥ 3 PIMs		31.8
STOPPFrail criteria (%):		
PPIs and H2 receptor antagonists		40.8
multi-vitamin combination supplements		31.6
neuroleptic antipsychotics		28.0
calcium supplements		27.7
lipid modifying agents		26.3
anti-dementia (incl. memantine)		15.0
5-alpha reductase inhibitors		10.3
long-term oral steroids		4.1
anti-hypertensives (incl. alpha blockers)		3.9
long-term oral NSAIDs		3.8

**Table 4.3.** Mortality and associated characteristics at NH admission, Cox regression.

Mortality n = 613	4-year survivors n = 219	Deceased n = 394	P-value*	Unadjusted HR (95%CI)
Number of PIMs mean	1.94	1.95	0.901	0.99 (0.92–1.04)
PIM use (%):				
0 PIM (reference category)	10.0	10.9	0.682	1
1 PIM	30.6	26.9		1.12 (0.79–1.59)
2 PIMs	26.9	30.7		0.98 (0.76–1.28)
≥ 3 PIMs	32.4	31.5		1.13 (0.87–1.45)
Total medication mean	8.98	8.92	0.855	1.00 (0.98–1.03)
Polypharmacy (> 5) (%)	85.4	89.3	0.150	1.34 (0.97–1.85)
High care dependency (%) (ADL > 17)	27.2	40.0	< 0.001	1.66 (1.36–2.04)
Dementia symptoms (%)	21.0	38.1	< 0.001	1.78 (1.45–2.18)
Hospitalization the year before admission (%)	75.6	65.0	0.011	0.77 (0.61–0.97)
Social admittance (%)	26.9	22.6	0.228	0.77 (0.61–0.99)
Age mean	82.35	85.06	< 0.001	1.03 (1.02–1.05)
Gender: male (%)	27.9	36.5	0.029	1.36 (1.11–1.68)

\*P-value for survivors versus deceased, independent samples t-test to compare means and chi2 to compare percentages.



**Figure 4.2.** Differences in long-term survival according to the number of PIMs used. No differences in survival were found between residents taking no PIMs and residents taking one, two, and three or more PIMs.

## Discussion

### Main findings

One year after NH admission, 79% of the residents were still alive. Only 36% survived for four years. At admission, 47% had polypharmacy and 40% excessive polypharmacy. According to the STOPPFrail criteria, 11% did not use any PIMs, and respectively 28%, 29%, and 32% used one, two and three or more PIMs. Survival did not differ between residents with or without polypharmacy, nor between those who used PIMs and those who did not. Neither polypharmacy nor PIM use were associated with mortality.

### Strengths and limitations

To the best of our knowledge, this is the first study exploring survival in a large inception cohort of NH residents, who were included in the study at NH admission, and followed for four years. This study provided extensive data on the general health and medication use of the study population, enabling us to explore associations of medication use and covariates with survival, which are highlighted in Kaplan Meier analyses.

A few limitations apply to this study. Firstly, PIM use is not registered in Flem-

ish NHs. Consequently, the STOPPFrail criteria were applied to all medications on the resident's medication chart, and only PIMs for which clinical information is not necessary to determine whether their use is inappropriate or not, could be identified. Thus, the high prevalence of PIM use in this study is an underestimation. Furthermore, this limitation can at least partly explain the null result regarding the associations of polypharmacy and PIM use with mortality. Secondly, unmeasured confounders such as comorbidities and omission of potentially beneficial medications may have caused bias. Research has demonstrated the negative effects of both confounders on survival in older adults (Rizzuto et al., 2017; Wauters et al., 2016). Thirdly, the absence of clinical information limited our findings regarding physical health to activities of daily living measured with the KATZ-ADL, which is mandatory in Flanders. Furthermore, we determined dementia symptoms based on screening of cognitive impairment and resident ability to respond to the questionnaire and not on diagnosis. However, research has demonstrated that cognitive impairment is relevant to predict long-term mortality (Lee, Chau, Hui, Chan, & Woo, 2009). Finally, only medication data at NH admission were used. Polypharmacy and PIM use during follow-up may have changed due to changes in health status or disease burden, but these changes were not taken into account.

## Interpretations of the findings

We found that less than 50% of newly admitted residents survived longer than three years after NH admission. This was concordant with the findings of a large-scale study of three-year mortality of newly admitted NH residents in Iceland (Hjaltadottir, Hallberg, Ekwall, & Nyberg, 2011). However, survival rates may vary among studies in countries with a different healthcare system and different criteria for NH admission. In Flanders extensive home care facilities are available. Thus, NHs provide care for older adults with multimorbidity and serious functional disabilities – ADL and/or cognitive impairment – and increasing care needs that cannot be met in any other way. This is reflected in this study by the most important reasons for admission – physical and cognitive decline, and increasing care needs – and the high prevalence of dementia symptoms and high care dependency at admission. Concordant with earlier research, these findings support the assertion that, generally, older adults or older and frailer at NH admission, and their health has deteriorated to an extent that long-term survival becomes exceptional (Hjaltadottir et al., 2011; Lee et al., 2009; Schlesinger et al., 2016; Sund Levander, Milberg, Rodhe, Tingstrom, & Grodzinsky, 2016).

We found a high prevalence of polypharmacy and PIM use at admission according to STOPPFrail. Comparison with other studies on PIM use in NHs is difficult be-

cause the prevalence of PIMs depends on the method and the tool used. Moreover, the STOPPFrail criteria were published only recently and we found no other studies in NHs using these criteria to measure PIM use.

Surprisingly, and notwithstanding polypharmacy and PIM use are generally considered to be a big problem in frail older adults because of the associated negative health outcomes (Fried et al., 2014; Muhlack et al., 2017), we found no association of polypharmacy and PIM use with long-term survival or mortality. Other studies in NH residents, and in community dwelling and hospitalized older adults on these associations are inconsistent (Franchi et al., 2016; Schlesinger et al., 2016; Wauters et al., 2016). Muhlack et al. found that the intake of PIMs was associated with increased mortality, but only if prevalent users were excluded from the analyses and a new-user study design was applied (Muhlack et al., 2017). In the current study, participants were taking PIMs at NH admission, and in most cases they had probably been taking them for some time before their admission. The treating physician in Flemish NHs is usually the resident's former family physician, which supports the assumption that the same medications were used before and after admission and changes to the medication chart had not been made yet at the time of data collection. Thus, residents using PIMs at admission can be considered as prevalent users who probably tolerate their medication, and benefit from it, which increased the risk of healthy-user / sick-stopper bias and may partly explain the null results (Muhlack et al., 2017). Additionally, the before mentioned limitations of our study regarding the underestimation of PIM use due to the limited applicability of the STOPPFrail criteria and unmeasured confounders are possible explanations for the null results. In this context, Wauters et al found an increased risk of mortality for every additional underused medication that was clearly indicated and likely to benefit the patient in community dwelling older adults, while associations with misuse were less clear (Wauters et al., 2016). Finally, other outcomes might be more relevant for polypharmacy and PIM use than mortality (e.g. quality of life, adverse drug reactions, falls) (Fried et al., 2014; Schlesinger et al., 2016).

### Implications for practice

Our findings on the relatively short survival after NH admission highlight the importance of a palliative approach in NHs. Hence, NH staff should be trained in providing palliative care for these residents, and focus on supporting and preserving quality of life, in accordance with the resident's wishes and preferences. In this context, initiation of advance care planning (ACP) shortly after NH admission is crucial. Furthermore, ACP should be embedded into routine care, involving the resident and his family, and targeting different aspects of care and treatment, e.g. discontinuation

or deprescribing of PIMs. The absence of an association of polypharmacy and PIM use with mortality raises the question if polypharmacy and PIM use have a crucial role in NH residents' mortality, a population with such a high multimorbidity. Probably mortality is not the best outcome measure in this context. Further research should focus on associations with more subtle outcomes such as quality of life and side-effects, taking into account comorbidities and underuse of beneficial medications. Nevertheless, prescribers should always weigh the benefits and risks at the individual level when prescribing medications.

## Conclusion

One year after NH admission, 79% of the residents were still alive. Only 36% survived for four years. At admission, polypharmacy and PIM use were relatively high. Survival did not differ between residents with or without polypharmacy, nor between those who used PIMs and those who did not. Neither polypharmacy nor PIM use at admission were associated with mortality.

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## Chapter 5

### Initiation of advance care planning in newly admitted nursing home residents in Flanders, Belgium: *a prospective cohort study*

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## Abstract

**Aim:** to describe (1) the timing of initiation of advance care planning (ACP) after nursing home (NH) admission, (2) the association of dementia and physical health with ACP initiation, (3) if and how analgesic use and use of lipid modifying agents is related to ACP, in a cohort of newly admitted residents.

**Methods:** Prospective, observational cohort study of NH residents. Data were collected three months, 15 months (year1) and 27 months (year2) after admission, using a structured questionnaire and validated measuring tools.

**Results:** ACP was never initiated during the two-year stay for 38% of the residents, for 22% ACP was initiated at admission, for 21% during year1, and for 19% during year2 (n = 323). ACP initiation was strongly associated with dementia, but not with physical health. Residents without dementia were more likely to have ACP initiation at admission or not at all, while for residents with dementia ACP initiation was postponed. Between admission and year2, analgesic use increased (34%-42%) and use of lipid modifying agents decreased (28%-21%). Analgesic use increased more in residents with ACP initiation during year1 and year2. The use of lipid modifying agents was not associated with ACP.

**Conclusion:** The timing of ACP initiation differed significantly for residents with and without dementia, which highlights the importance of an early onset of ACP before residents lose their decision-making capacity. ACP conversations may create opportunities to discuss adequate pain and other symptom treatment and deprescribing at the end of life.

## Introduction

**A**s age increases, people are confronted with multimorbidity and increasing physical, cognitive and social decline (1), and its consequences, such as frailty, decreasing quality of life, increasing hospitalization rates and related costs, and an increasing need for long-term care (2, 3). On the one hand, recent progress in medicine enables more and more life-prolonging treatment. On the other hand, the main care goal in nursing homes (NHs) is to support and improve their residents' quality of life. To prevent unnecessary treatments and hospitalizations, and support and preserve quality of life, it is crucial to know people's preferences regarding current and future treatment and care goals (4).

Advance care planning (ACP) is defined as 'the ability to enable individuals to define goals and preferences for future medical treatment and care, to discuss these goals and preferences with family and healthcare providers, and to record and review these preferences if appropriate' (5). ACP has been associated with a decrease in hospitalizations and use of resources, lower levels of unwanted life-sustaining treatments, increasing patient and family satisfaction with care, an increasing number of residents dying in their NH instead of in hospital, and increasing compliance with patients' end-of-life care wishes (6-9).

In this study, 'ACP' is used as an umbrella term and includes all forms of forms of ACP, regulated by law or not. Currently, two forms of ACP occur together in Flemish NHs. Firstly, patient driven ACP, which may, but need not to be documented (e.g. in an Advance Directive (AD)), and can include nomination of a proxy decision maker. Both possibilities are provided by the law. Several structured forms in accordance with current legislation are offered by a number of organizations, such as health insurance organizations. Secondly, physician driven ACP by means of written general practitioner (GP) orders, which are medical decisions documented in the medical file in accordance with the institution's protocol. These orders should be discussed with other healthcare professionals, family members or with the resident (10-12). These orders include do-not-resuscitate and do-not-intubate orders, alleviation of pain and other symptoms, etc. (12).

Earlier studies found a varying prevalence of ACP in NHs: between 45% and 77% for physician driven and between 8% and 14% for patient driven ACP (10-14). Documented care plans were rarely ADs, but mostly written GP orders (10, 13, 15).

The prominent prevalence of GP orders, and particularly the order regarding alleviation of pain and other symptoms, raises the question if having any type of ACP is related to medication use. Generally, medication use should be in accordance with the changing care goals of NH residents (16). Supporting and preserving quality of

life should include treating symptoms that are currently undertreated (e.g. pain) and deprescribing of medications which lack short-term benefit. We hypothesize that analgesic use, as an example of adequate treatment according to the definition of palliative care (16), will increase in residents for whom ACP is initiated. Earlier studies have demonstrated an increased use of analgesics in people with pain symptoms caused by advanced disease (17). On the contrary, use of lipid modifying agents, as an evidence based example of preventive medication appropriate for deprescribing in patients with a limited life-expectancy, will decrease in these residents (18). Research has demonstrated that discontinuation of these medications reduces the number of adverse drug events (19). In this context, it is important to include decision-making regarding medication use in ACP discussions.

The aim of this longitudinal study is to determine when ACP is initiated during the NH stay in a cohort of newly admitted residents, and whether ACP initiation is related to dementia symptoms and physical health. This information is crucial to determine the need for a systematic approach of ACP. Adding data on possible relationships with medication use, i.e. analgesic use and lipid modifying agents, will feed future discussions on the content and potential outcomes of ACP.

## Methods

This study uses baseline data at NH admission and follow-up data of year1 and year2 after admission of the Ageing@NH cohort study, examining newly admitted residents' general health. Two other articles reporting on data of this study were published earlier (1, 20).

### Study design and study population

A convenience sample of 67 NHs with at least 60 beds in Flanders, the Dutch speaking part of Belgium, were included in the study. In the participating NHs, all newly admitted residents between September 2013 and December 2013 were invited to participate in the study, if aged  $\geq 65$ , Dutch-speaking and permanently admitted to the NH. All residents were consecutively recruited during the period of four months for the baseline assessment at NH admission. The same residents were invited to participate after one and two years for follow-up assessment, provided that they were still alive and still resided in a participating NH. All residents (or their proxy decision maker in case of dementia) had to provide informed consent before baseline and both follow-up assessments.

## Procedure

Residents were interviewed one to three months after admission, and one and two years later, using a structured questionnaire and validated measuring tools for activities of daily living (Katz-ADL) (21) and cognitive status (MMSE) (22). (Supplementary file S.I.) These data were completed with administrative data, data from the nursing chart, and a copy of the resident's medication chart. In case of dementia, the proxy decision maker (at admission) or the responsible nurse (year1&2) was interviewed.

## Measures

We considered that ACP was initiated if data on ACP initiation were documented in the nursing chart, or mentioned by the responsible nurse where this information was missing. In this study, we refer to all types of documented care plans and all related communication about future medical treatment and care as 'ACP', because our aim was to measure ACP initiation. The available data did not allow to determine if these documented care plans – particularly GP orders – were discussed with the resident himself or not. We determined whether ACP was initiated at 3 months, 15 months and 27 months after admission, for the construction of a new dichotomous variable 'ACP initiation' for every measuring point. We categorized ACP initiation at the different time points into four groups of ACP trajectories throughout the two-year stay or stay until death: no ACP (never), ACP from admission on (initiated within the first 3 months after NH admission), ACP initiation during year1 (> 3 months and ≤ 15 months after admission), and ACP initiation during year2 (> 15 months and ≤ 27 months after admission). Only residents for whom data on ACP initiation at three time points were available were included in further analyses. The categories ACP initiation during year1 and ACP initiation during year2 were collated to one category delayed ACP initiation for further analyses.

Physical health was defined using Katz-ADL, survival time in months and total number of medications. Residents with an MMSE score lower than 16 out of 30, and a KATZ score for disorientation greater than or equal to 6 out of 8 – showing a daily disorientation in time and place – and who were unable to respond adequately to the questionnaire, were considered to have dementia symptoms. (S.I.).

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, the current version of each year of data entering). Focus was on anatomical main groups (first

ATC level) and therapeutic subgroups (second ATC level). Due to difficulties in the collection of the medication charts at year1, data on medication of year1 were not suitable for further analyses. Therefore, we compared medication use at two time points: at admission and year2.

## Data analysis

We used SPSS 23.0 (IBM Statistics Inc., Chicago, IL) for all statistical analyses. We described residents' characteristics using descriptive statistics, and explored factors influencing ACP initiation at NH admission with independent samples t-tests, cross-tabs and chi2. We used ACP initiation at NH admission as outcome variable in logistic regression analyses.

We explored differences between the prevalence of ACP initiation at admission, year1 and year2, and the prevalence of analgesics and lipid modifying agents at admission and year2, with Cochran's Q and McNemar tests. We examined associations between ACP initiation and dementia with crosstabs and chi2, associations with physical health with One Way ANOVA.

We explored associations of ACP initiation with the evolution of the prevalence of analgesics and lipid modifying agents between admission and year2 with Cochran-Mantel-Haenszel and McNemar tests. A statistical significance level of  $p < 0.05$  was set.

## Ethical considerations

The ethics committee (EC) of Antwerp University Hospital and Antwerp University approved the study protocol (EC-number 13/43/420).

The board of directors and the supervising GP of the NH signed a study agreement. Residents, or their proxy decision maker in case of dementia, signed an informed consent.

## Results

### Research population

For 741 residents in 67 NHs informed consent was obtained at NH admission. Mean Katz ADL was 14.69 (range 6-24), and 34% suffered from dementia (Table 5.1). After two years, 342 of the participating residents were still alive, resided in a participating NH, and confirmed informed consent. In this group, mean Katz ADL was 16.12, and 46% suffered from dementia (data not shown).

**Table 5.1.** Socio-demographic characteristics of the baseline population.

Characteristics of the baseline population	All n = 741
Age in years mean (range)	83.94 (65-105)
Gender % (n):	
female	65.7 (486)
male	34.3 (254)
Most important reason for admission <sup>†</sup> % (n):	
physical decline	64.4 (415)
increased care needs	57.4 (372)
cognitive decline	36.2 (234)
increased caregiver burden	16.0 (102)
(risk of) social isolation	10.6 (68)
explicit wish of the resident	10.6 (68)
partner deceased	3.8 (24)
increasing need for palliative care	1.3 (8)
Living situation before admission % (n):	n = 641
alone	61.6 (394)
with partner and children	31.2 (231)
other	7.2 (16)
Highest education % (n):	n = 637
no education	4.9 (32)
primary school	18.9 (119)
low secondary	44.3 (283)
high secondary	22.7 (143)
higher - university	9.2 (60)
Stay before admission % (n):	
hospital	43.7 (318)
at home	21.9 (159)
other	34.5 (250)
Katz ADL mean (SD) (6-24)	14.69 (4.507)
Dementia symptoms <sup>‡</sup> % (n)	34.0 (251)

<sup>†</sup> according to the resident or his proxy decision maker in case of dementia, more than one answer possible.

<sup>‡</sup> based on MMSE-score (cut-off < 16), ability to respond to the questionnaire, and the

## Advance Care Planning (ACP)

*ACP initiation at NH admission:* At NH admission, ACP was initiated for 22% of the participants (n = 741) (Table 5.2). A higher MMSE score increased the odds of having ACP initiation at NH admission with 3.5% per point on the MMSE. No associations were found with physical health.

*ACP initiation at three time points:* Longitudinal data on ACP initiation at three time points were available for 323 of the 342 residents who were still alive in year2 (Table 5.3). ACP was never initiated during the two-year stay for 38% of the residents, for 22% ACP was initiated at NH admission, for 21% during year1, and for 19% during year2.

ACP initiation was associated with dementia symptoms, and the direction of this relationships depended on the measurement time: at NH admission, ACP was initiated for 23% of residents without dementia symptoms and 16% of residents with

**Table 5.2.** ACP initiated at NH admission and its associated characteristics.

ACP initiated at NH admission	No ACP n = 573	ACP n = 168	P-value*	Univariate OR (95%CI)	Multivariate OR (95%CI)
MMSE (mean)	18.03	19.82	0.017	1.034 (1.008-1.060)	1.035 (1.007-1.064)
Reason for admission: physical decline (%)	60.8	75.5	0.001	1.986 (1.315-2.999)	1.776 (1.149-2.744)
Age (mean)	83.79	84.48	0.239	1.016 (0.989-1.043)	
Gender: female	67.1	60.7	0.123	0.757 (0.530-1.080)	
Living alone before admission (%)	51.3	59.5	0.061	1.396 (0.985-1.978)	
Dementia symptoms (%)	35.5	30.1	0.198	0.783 (0.539-1.137)	
Education: ≥ high college (%)	29.3	32.9	0.413	1.182 (0.792- 1.765)	
KATZ-ADL (mean)	15.67	15.45	0.593	0.990 (0.953- 1.028)	
Survival time in months (mean)	19.52	18.58	0.265	0.989 (0.971- 1.008)	
Total number of medications (mean)	8.92	9.11	0.565	1.013 (0.969- 1.059)	

Nagelkerke  $r^2$ : 0.046 \*Independent samples t-test for means,  $\chi^2$  for percentages  
Multivariate controlled for age and female gender.



dementia symptoms, while during year1 and year2, ACP was initiated for respectively 34% and 53% of residents without dementia symptoms, in relation to 38% and 64% of residents with dementia symptoms ( $p = 0.003$ ) (Figure 5.1). No associations were found with physical health (data not shown).

*Associations of ACP initiation with medication use:* At NH admission, 34% of the residents used analgesics and 28% used lipid modifying agents. Between admission and year2, the use of analgesics increased significantly (34%-42%,  $p = 0.001$ ) and the use of lipid modifying agents decreased significantly (28%-21%,  $p = 0.009$ ) (Table 5.3). A significant increase in the use of analgesics between admission and year two was found in residents with delayed ACP initiation ( $p = 0.002$ ) (Figure 5.2). This relationship remained after controlling for dementia with Cochran Mantel-Haenszel tests. ACP initiation was not related to the decreasing use of lipid modifying agents (data not shown).

**Table 5.3.** ACP initiation, analgesics and lipid modifying agents at NH admission and its evolution to year1 and year2.

n = 323	At admission	Year1	Year2	P-value*
Patient driven ACP: resident expressed a wish or preference for future care <sup>†</sup> % (n)	20.3 (68)	36.4 (114)	56.0 (186)	<0.001
Physician driven ACP: written physician's order (GP orders) <sup>‡</sup> % (n)	10.6 (33)	33.7 (105)	53.0 (176)	<0.001
<b>ACP (patient driven or physician driven) % (n)</b>	<b>22.3 (72)</b>	<b>36.2 (114)</b>	<b>56.1 (192)</b>	<b>&lt;0.001</b>
<b>Initiation of ACP % (n):</b>				
ACP initiation at NH admission	22.3 (72)	22.3 (72)	22.3 (72)	
ACP initiation during year1 <sup>§</sup>	/	21.4 (69)	21.4 (69)	
ACP initiation during year2 <sup>§</sup>	/	/	18.6 (60)	
ACP not initiated	77.7 (251)	56.3 (182)	37.8 (122)	
<b>Analgesics (N02<sup>¶</sup>) % (n)</b>	<b>34.2 (117)</b>	<b>NA</b>	<b>41.8 (143)</b>	<b>0.001</b>
<b>Lipid modifying agents (C10<sup>¶</sup>) % (n)</b>	<b>27.8 (95)</b>	<b>NA</b>	<b>21.1 (72)</b>	<b>0.009</b>

\*McNemar for paired comparison of proportions in two groups, Cochran's Q in three groups.

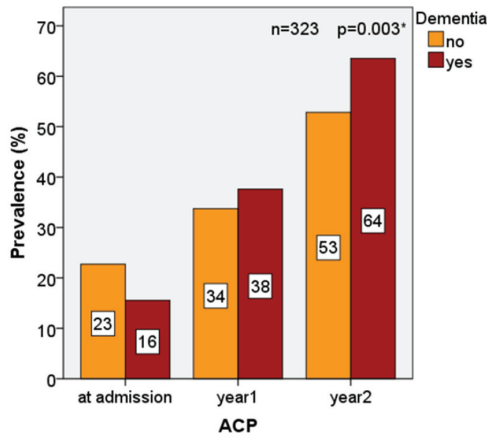
NA = Not available.

<sup>†</sup>Based on the following question which was to be answered by the responsible nurse: "Did the resident express an explicit wish or preference for future care?"

<sup>‡</sup>Based on the following question which was to be answered by the responsible nurse: "Did the GP write down orders for future treatment in the medical file?"

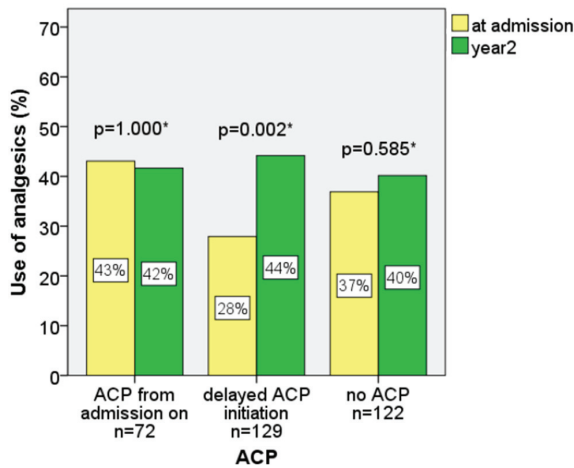
<sup>§</sup>collated to one category 'delayed ACP initiation' for further analyses .

<sup>¶</sup>ATC codes: N02 analgesics, C10 lipid modifying agents.



**Figure 5.1.** Timing of ACP initiation in residents with and without dementia symptoms.

ACP was initiated at admission for 23% of residents without dementia symptoms compared to 16% in those with dementia symptoms. In year 1 and 2 the proportion of residents with dementia symptoms for whom ACP was initiated was resp. 38% and 64%, compared to resp. 34% and 53% in those without dementia symptoms. These findings indicate that the proportion of residents with dementia symptoms for whom ACP was initiated at admission was lower than for those without dementia. In year 1 and 2 the proportion of residents with dementia symptoms exceeded the proportion of residents without dementia symptoms and increased more.



**Figure 5.2.** Evolution of the use of analgesics between admission and year2 in the 3 groups of ACP initiation.

Analgesic use increased significantly in the group of residents for whom ACP initiation was delayed to year 1 or year 2.

## Discussion

### Main findings

*ACP initiation:* ACP was initiated at NH admission for 22% of the residents, and postponed for 40% (i.e. for 21% postponed to year1, for 19% to year2). Moreover, for 38% ACP was never initiated during the two-year stay. The timing of ACP initiation differed significantly for residents with and without dementia symptoms. Residents without dementia symptoms were more likely to have ACP initiated at NH admission or not at all, while residents with dementia symptoms were more likely to have ACP initiation later on during their stay in the NH.

*Medication use:* This study confirms our a priori hypothesis that analgesic use increases in residents for whom ACP has been initiated, but only for residents with delayed ACP initiation. The hypothesis regarding the association between ACP initiation and a decreasing use of lipid modifying agents was not confirmed.

### Strengths and limitations

To the best of our knowledge, this is the first study providing baseline and follow-up data on ACP initiation and its associations with physical health, dementia symptoms and medication use in an observational study with strong design. Moreover, the timing of ACP initiation – or the ‘onset’ – has not been measured before.

A few limitations apply to this study. Firstly, only 323 residents were available for the analyses of admission and follow-up data, mainly due to death, which is common in this frail population. Secondly, this study describes a trend and an indication of the timing of ACP initiation in NHs. This is not a study of the prevalence of normative ACP, but an empiric approach of the practices in the field of ACP, and also the absence of ACP. Neither content, nor quality of ACP were studied. The concept and outcomes of ACP substantially vary between countries, which complicate comparison with international studies. Finally, data on the use of analgesics describe the prevalence and not the initiation of those medications. Furthermore, pain assessment is crucial to determine if the increasing use of analgesics indicates better pain treatment. Therefore, further research is necessary to clarify these aspects.

### Interpretation of the findings

*ACP initiation:* Concordant with earlier studies of ACP engagement in older adults, we found a low prevalence of ACP initiation at every measuring point (7, 23, 24). Furthermore, Bollig et al. found that the majority of residents without dementia had not been engaged in ACP at all (25). In the current study, these residents were more

likely to have ACP initiation at NH admission or not at all. Various explanations for not initiating ACP in NH residents are possible: residents were unwilling to discuss their preferences or rejected ACP, existing pre-admission arrangements for end-of-life care (e.g. ADs) may need no further discussion, residents trust their relatives and NH staff to make important decisions for them, in their best interest, residents were unaware of the possibility to discuss their preferences for future care, or ACP was not embedded in routine care (24-27). Research has demonstrated that lack of knowledge of ACP is an important barrier to engage in or successfully implement ACP. Informing residents and their family about ACP and the ACP policy within the NH is crucial for residents to be able to share their preferences for future care adequately (24). Probably, the minority for whom ACP was initiated at NH admission, were more aware of the possibilities of ACP. Consistent with the findings of Harrison et al., physical health was not associated with ACP initiation in this study (23). Thus, physical decline or illness cannot explain ACP initiation at admission. This supports the previous assumption of an increased awareness. However, physical decline as self-reported reason for admission was associated with ACP initiation at admission. This finding suggests a possible importance of subjective recognition of physical decline to ACP initiation.

For most residents with dementia, ACP was initiated later than three months after admission. Earlier studies confirm that residents are less likely to participate in ACP if they have cognitive impairment (23). This 'delayed' initiation can be explained by difficulties in determining the optimal timing of ACP due to prognostic uncertainty, or unwillingness to participate in ACP because the resident is in denial of his diagnosis or he does not feel the urge to discuss his preferences for future care (28). When this resident loses his decision-making capacity, end-of-life decisions will have to be made by a family member or proxy decision maker. In this context, it is vital that preferences are known and residents are engaged in ACP before their health deteriorates and/or the first signs of dementia appear (12).

*Medication use:* Concordant with earlier studies, we found a significant increase in the use of analgesics, which are considered to be always appropriate at the end-of-life (29, 30). This increasing use of analgesics was associated with ACP initiation, which might indicate an increased attention for pain treatment. This finding has not yet been described in literature, and thus creates opportunities for further research. In accordance with Morin et al., we found a decrease in the use of lipid modifying agents, which might indicate a practice of deprescribing (29). However, this decrease was not associated with ACP initiation.

## Implication for practice / research

This study highlights the necessity of an early onset of ACP in NH residents, and particularly in those with dementia. The low prevalence of ACP initiation at every measuring point implicates that ACP is not embedded into routine care yet. The recently developed consensus definition of ACP and recommendations for its application (5) may be an important impulse to register ACP in the nursing chart and to clarify which aspects of ACP were discussed with the resident himself, his family, and/or the healthcare team.

Our findings regarding medication use may create an opportunity to discuss adequate treatment of pain and other symptoms and deprescribing of 'futile' medications at the end of life. Further research is necessary to confirm the association between ACP and an increasing use of analgesics and to explore the influence of other mediating factors, such as pain. ACP conversations may create opportunities to discuss adequate pain and other symptom treatment and deprescribing at the end of life.

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## Chapter 6

### Balancing medication use in nursing home residents with life-limiting disease

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Balancing medication use in nursing home residents with life-limiting disease.

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## Abstract

**Purpose:** Balancing medications that are needed and beneficial, and avoiding medications that may be harmful is important to prevent drug related problems, and improve quality of life. The aim of this study is to describe medication use, the prevalence of deprescribing of medications suitable for deprescribing, and the prevalence of new initiation of potentially inappropriate medications (PIMs) in nursing home (NH) residents with life-limiting disease in Flanders.

**Methods:** NH residents aged  $\geq 65$ , suffering from end stage organ failure, advanced cancer and/or dementia ( $n = 296$ ) were included in this cross-sectional study with retrospective analyses of medication use at the time of data collection (t2) and three to six months before (t1). The appraisal of appropriateness of medications was done using a list of medications documented as suitable for deprescribing, and STOPPFrail criteria.

**Results:** Residents' (mean age 86 years, 74% female) mean number of chronic medications increased from 7.4 (t1) to 7.9 (t2). In 31% of those using medications suitable for deprescribing, at least one medication was actually deprescribed. In 30% at least one PIM from the group of selected PIMs was newly initiated. In the subgroup ( $n = 76$ ) for whom deprescribing was observed, deprescribing was associated with less new initiations of PIMs ( $r = -0.234$ ,  $p = 0.042$ ).

**Conclusion:** Medication use remained high at the end of life for NH residents with life-limiting disease, and deprescribing was limited. However, in the subgroup of 76 residents for whom deprescribing was observed, less new PIMs were initiated.

## Introduction

**B**alancing medication use at the end of life for nursing home (NH) residents with life-limiting disease means carefully weighing the benefit-risk ratio of every added medication and every medication that was prescribed earlier in the disease trajectory of a life-limiting disease. Physicians should always keep in mind the added drug burden when initiating a new medication or increasing the dosage of a previously prescribed drug in this situation.

Balancing medication use in older adults with multimorbid conditions, such as NH residents, is challenging, particularly when life-expectancy has decreased. Research has demonstrated that people with a life-limiting disease use a mean number of 7 to 11 different medications (1-3). The prevalence of polypharmacy – or the concomitant use of 5 or more chronic medications with systemic effect (4) – in this population varies between 25% and 84%, and the prevalence of excessive polypharmacy ( $\geq 10$ ) between 28% and 69% (1-3). In this frail population with life-limiting disease, polypharmacy and inappropriate medication use have been associated with negative health-related outcomes, such as hospitalizations, falls, drug-related problems, and decreased quality of life (5, 6).

At the end of life, medications to treat life-limiting diseases are generally combined with medications for symptom relief, medications for treatment of co-morbidities, and medications for long-term prevention (3). When death approaches, medications for symptom relief increase (7, 8). Consequently, when previously prescribed medications are continued, drug burden and the risk of drug-related problems, such as adverse drug reactions (ADRs), and drug-drug interactions increase (9, 10). Hence, it is crucial to carefully balance medication use in people with a life-limiting disease, such as frail older adults residing in NHs.

Moreover, according to the definition of palliative care, care goals in those with life-limiting disease should change from quantity to quality of life (11). This should be reflected in medication use near the end of life. In this context, adequate medication use means treating symptoms which are currently undertreated, as well as preventing possible harm caused by - potentially inappropriate – medications. However, research has demonstrated that the diagnosis of a life-limiting disease has little effect on prescribing patterns, particularly for medications for long-term prevention, which use at the end of life is questionable because they lack short-term benefit (3, 12-16).

At the end of life, it is crucial to balance medications that are needed and beneficial for the patient, and avoid initiation and/or continuation of medications that may be harmful or have no short-term benefit. Carefully balancing medications may

improve quality of life, and decrease, or at least not add to, the patient's drug burden and drug related problems.

Deprescribing can be defined as 'the systematic process of withdrawal of an inappropriate medication, supervised by a healthcare professional, with the goal of identifying and discontinuing drugs in instances in which existing or potential harms outweigh existing or potential benefits within the context of an individual patient's care goals, current level of functioning, life-expectancy, values, and preferences' (17). Discontinuation is used as an umbrella term for stopping or tapering medications, e.g. by deprescribing.

Generally, medications are considered inappropriate to continue, and thus suitable for deprescribing when they lack short term benefit, cause additional harm (e.g. ADRs), or when a safer alternative exists (18-20). Recently, international clinical practice deprescribing guidelines were developed to guide clinicians in deprescribing proton pump inhibitors (PPIs), antihyperglycemics, antipsychotics, benzodiazepine receptor agonists, cholinesterase inhibitors and memantine, statins, osteoporosis medications, antihypertensives, vitamins and minerals (21, 22).

At the same time, numerous tools were developed to identify potentially inappropriate medications (PIMs) in older adults with a normal life-expectancy (e.g. Beers (23), STOPP/START (24)). Recently, Lavan et al. (2017) developed a list of criteria to identify PIMs in frail older adults with a limited life-expectancy (STOPPFrail) and to guide clinicians in deprescribing these PIMs at the end of life in all healthcare settings (25). In addition, STOPPFrail can also help clinicians to decide which medications to avoid, and thus not initiate.

The aim of this study is to describe medication use at two time points within a period of three to six months, the prevalence of actual deprescribing of medications suitable for deprescribing, and the prevalence of new initiation of PIMs according to STOPPFrail. This information is important to get more insight in the current situation and to guide future initiatives to optimize and balance medication use in NH residents with a life-limiting disease. Unbalanced medication use may foster polypharmacy, PIM use, and associated health related outcomes, such as falls, hospitalizations and increased risk of mortality. Moreover, the economic cost of polypharmacy and potentially inappropriate prescribing is high and could be reduced by deprescribing (26).

## Methods

### Study design and study population

For this cross-sectional study with retrospective analyses of medication use, NHs were eligible for inclusion if they had at least 100 beds and a mixed population of older adults with and without dementia. Forty-four NHs in Flanders, the Dutch speaking part of Belgium, were provided with study information by telephone and they received the study protocol by email. One week later they received another phone call to confirm consent with participation. Ten NHs agreed to participate (convenience sample) and a first appointment with the researcher was scheduled.

Residents were eligible for inclusion if aged  $\geq 65$ , Dutch speaking, able to answer questions adequately according to the responsible nurse, and suffering from one of the following life-limiting diseases: end stage organ failure, advanced cancer or dementia. Residents with an estimated life expectancy of  $<$  one month were excluded for ethical reasons. Residents diagnosed with dementia who were capable to adequately answer questions (Mini Mental State Examination (MMSE)  $\geq 18$ ) were interviewed themselves. Residents diagnosed with dementia for whom this was not the case were included if their informal caregiver was aged  $\geq 16$  and visited them at least twice a month, and this informal caregiver was questioned instead of the resident himself. Residents who were incapable to answer questions adequately due to dementia, deafness, aphasia or other reasons and for whom no informal caregiver was available were excluded. The selection of eligible residents was done by the NH management or the responsible head nurse. Eligible residents and/or their informal caregivers were provided with study information by the researchers and were asked to sign an informed consent form.

### Procedure

Residents or their informal caregiver were interviewed using a structured questionnaire and the following validated measuring tools: KATZ-ADL (27), Mini Mental State Examination (MMSE) (28), and Minimum Data Set Mortality Risk Index (MDS-MMRI) (29). The Katz index in activities for daily living is mandatory in Belgian NHs and facilitates the detection of functional state with scores ranging from 6 to 24. High scores are associated with high ADL dependency (27). The MMSE is a standard screening tool for cognitive assessment in the clinical setting with scores ranging from 0 to 30 and allows comparison of performance across time and among older adults. Low scores are associated with cognitive impairment (28). The MDS-MMRI estimates mortality risk within the next six months, with scores ranging from 0 to 75.

High scores are associated with a high mortality risk (29).

Medication use was based on a copy of the resident's full medication chart, and was evaluated two times: (t2) at the time of data collection and (t1) retrospectively three to six months before. Sufficient time between t1 and t2 was needed to provide time to adjust prescription. All data were collected from January to March 2018.

## 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). Polypharmacy was defined as the use of five or more prescribed chronic medications with systemic effects, and excessive polypharmacy as the use of ten or more. Discontinuation was defined as stopping or withdrawal of a specific ATC code between t1 and t2.

Medications considered to be potentially suitable for deprescribing were selected based on scientific evidence from clinical practice guidelines and a randomized clinical trial (21, 22, 30-34) and discussed with two experts in clinical pharmacology (TC and RVS). These medications potentially suitable for deprescribing were cross-referenced and linked to the medications at t1 and t2 (Box 1 in online supplementary file). Deprescribing was defined as stopping or lowering the dose of the selected medications between t1 and t2. A new dichotomous variable was constructed with value one if at least one of the medications considered to be suitable for deprescribing was actually deprescribed, and value zero if this was not the case.

Initiation of new medication at the end of life was defined as initiation between t1 and t2 of a specific medication that was not used at t1. Appraisal of the appropriateness of the initiated medications was determined with explicit criteria of PIM using the STOPPFrail criteria (25). The STOPPFrail criteria were cross-referenced and linked to the medications at t1 and t2. Because the clinical information necessary to interpret their (in)appropriateness was not available in this study due to inaccessibility of the medical file, we excluded, based on expert opinions (TC and RVS), the following PIMs: anti-platelets, leukotriene antagonists, muscarinic antagonists, diabetic oral agents, ACE inhibitors, angiotensin receptor blockers, and prophylactic antibiotics. These excluded PIMs may be appropriate in certain clinical situations. The remaining 15 PIMs can be found in table 3. A new dichotomous variable was constructed with value one if at least one PIM was initiated at t2, and value zero if this was not the case.

## Data analyses

All statistical analyses was done using SPSS 24.0 (IBM Statistics Inc., Chicago, IL). Resident characteristics, medication use, deprescribing and initiation were explored with descriptive statistics. Differences between medication use at t1 and t2 were examined with paired samples t-tests and McNemar. Associations of the dichotomous outcomes 'at least one deprescribed' and 'at least one PIM initiated' with socio-demographic and other characteristics were examined using independent samples t-tests and chi2. Correlation between the number of deprescribed medications and the number of new initiated PIMs was explored with Pearson correlations. A significance level of  $p < 0.05$  was set.

## Ethical considerations

The study protocol was approved by the ethics committee (EC) of the Antwerp University Hospital Belgium (EC-number B300201734128). The board of directors and the supervising GP of the NH signed a study agreement. Residents or their informal caregiver signed an informed consent.

## Results

### Study population

Overall, 482 NH residents were eligible for inclusion, of which 181 refused to participate and 5 had incomplete medication data. Consequently, 296 residents – mean age 86 years, 74% female – participated in this study, 135 were questioned themselves and for 161 the questionnaire was filled in by their informal caregiver. Mean KATZ-ADL was 17 and mean MDS-MMRI score was 32, indicating an average six-month mortality risk of 36%. The most prominent life-limiting disease was dementia (73%), followed by heart failure (31%), COPD and renal failure (both 11%), and advanced cancer (7%)(Table 6.1).

**Table 6.1.** Characteristics of the study population.

	Residents (n = 296)
<b>Age</b> mean (SD) (range)	86.2 (6.7) (65-100)
<b>Gender (%)</b> :	
female	74.0
male	26.0
<b>Marital status (%)</b> :	
widowed	66.9
married	22.9
other	10.2
<b>Highest education (%)</b> :	
no education	16.2
primary school	8.6
low secondary	35.7
high secondary	22.1
higher – university	14.6
other	2.8
<b>Informal caregiver available (%)</b>	85.5
<b>Informal caregiver questioned (%)</b>	54.4
<b>MDS-MMRI mean (SD)</b>	32.1 (10.7)
<b>6-month mortality risk (%)</b> :	
< 50%	78.8
≥ 50%	21.2
<b>KATZ-ADL mean (SD)</b>	17.1 (5.3)
<b>Life-limiting disease<sup>a</sup> (%)</b> :	
advanced cancer (%)	6.8
heart failure (%)	31.2
COPD (%)	11.1
renal failure (%)	10.8
dementia (%)	72.6

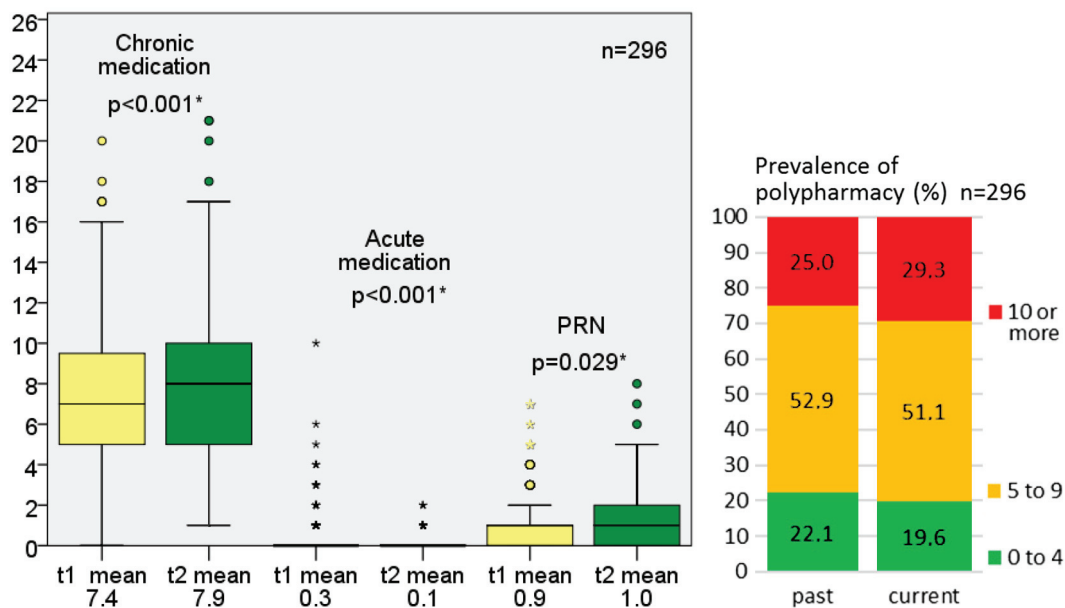
<sup>a</sup>more than one answer possible

### Medication use at the time of data collection (t2) and three to six months before (t1)

The mean number of chronic medications increased from 7.4 (t1) to 7.9 (t2) ( $p < 0.001$ ). At t1, 53% had polypharmacy (5-9) and 25% excessive polypharmacy ( $\geq 10$ ), compared to respectively (resp.) 51% and 29% at t2 ( $p = 0.208$ ) (Figure 6.1).

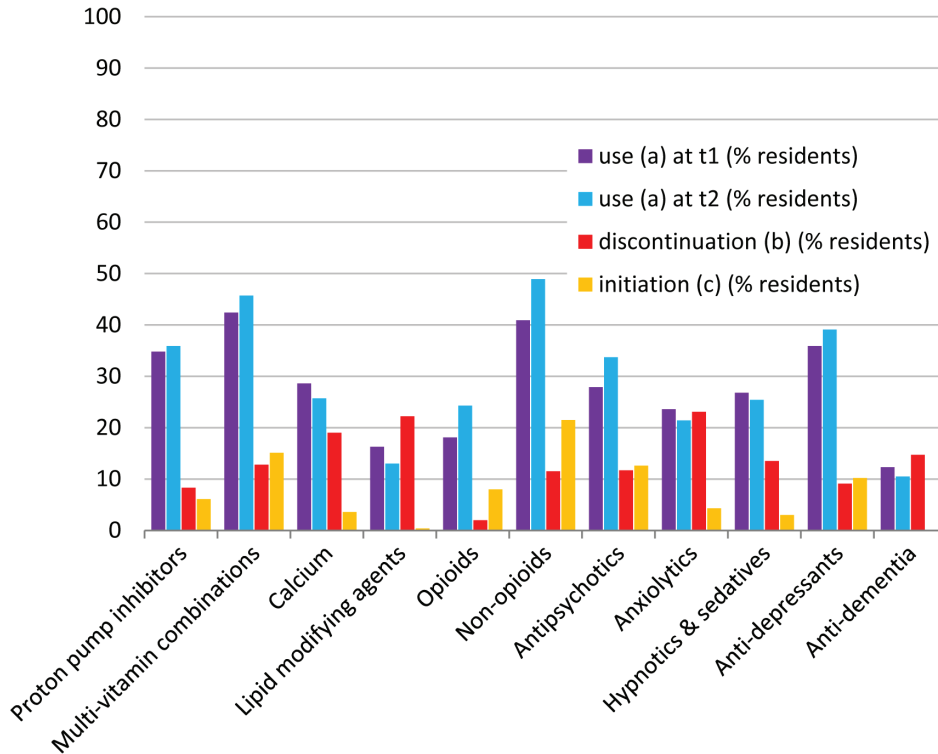
Medication use was high at both time points for the following ATC main anatomic groups: alimentary tract and metabolism (A), blood and blood forming agents (B), cardiovascular system (C), and nervous system (N). In all these groups, the percentage of residents with new initiation exceeded the percentage with discontinuation.





**Figure 6.1.** Evolution of the number of chronic, acute and pro re nata (PRN) medications between t1 (3-6 months before data collection) and t2 (at the time of data collection) and prevalence of polypharmacy.  
 \*Paired Samples t-test.

The most prominent therapeutic subgroups in this population were proton pump inhibitors (PPIs), multivitamin combinations, calcium, lipid modifying agents, opioids, non-opioids, antipsychotics, anxiolytics, sedatives, antidepressants and anti-dementia agents. Between t1 and t2, the prevalence of lipid modifying agents decreased significantly (16% to 13%,  $p = 0.012$ ). The prevalence of analgesics (opioids and non-opioids) and antipsychotics increased significantly (resp. 47% to 58%,  $p < 0.001$  and 28% to 34%,  $p = 0.009$ ). The prevalence of discontinuation was relatively high for anxiolytics and sedatives (resp. 23% and 13.5%), lipid modifying agents (22%), calcium (19%), and anti-dementia agents (15%). For non-opioids, multivitamin combinations, and antipsychotics, the prevalence of new initiation was relatively high (resp. 21.5%, 15%, and 13%). Lipid modifying agents and anti-dementia agents were not newly initiated.



**Figure 6.2.** Prevalence (% users) at t1 and t2, discontinuation (stopping), and initiation for the therapeutic groups that are most commonly used (n = 296).

<sup>a</sup>Use: % residents who were using this medication on denominator all residents (n = 296).

<sup>b</sup>Discontinuation: % residents for whom this medication was discontinued (= stopped) between t1 and t2 on denominator all residents who were using this medication at t1.

<sup>c</sup>Initiation: % residents for whom this medication was initiated at t2 on denominator all residents who were not using this medication at t1.

## Deprescribing of medications potentially suitable for deprescribing

Overall, 236 residents used at least one of the medications potentially suitable for deprescribing. For 76 of them (31%) at least one of the medications potentially suitable for deprescribing was actually deprescribed. The prevalence of deprescribing was relatively high for lipid modifying agents (29%), benzodiazepine receptor agonists (28%), minerals (including calcium) (21%), and antipsychotics (17%) (Table 6.2).

No associations were found with socio-demographic or other characteristics (data not shown).

**Table 6.2.** Percentage of residents for whom medications considered potentially suitable for deprescribing at t1 were actually deprescribed (stopped or tapered) at t2.

Medications potentially suitable for deprescribing	Residents using these medications at t1 (%) (n = 296)	Residents for whom these medications were deprescribed % (n/N <sup>a</sup> )
Proton pump inhibitors	34.8	15.6 (15/96)
Antihyperglycemics	14.5	12.5 (5/40)
Antipsychotics	27.9	16.9 (13/77)
Benzodiazepine receptor agonists	23.6	27.7 (18/65)
Cholinesterase inhibitors	10.9	13.3 (4/30)
Memantine	0.4	0.0 (0/1)
Statins (lipid lowering agents)	16.3	28.9 (13/45)
Antihypertensives	1.4	0.0 (0/4)
Osteoporosis medications	4.7	23.1 (3/13)
Vitamins	42.4	14.5 (17/117)
Minerals	32.2	21.3 (19/89)
<b>Deprescribing score mean (range)</b>		0.44 (0-4)
<b>At least one deprescribed (%)</b>		31.1 (76/236)

<sup>a</sup>n/N: number of residents for whom this medication was deprescribed (= stopped or tapered) between t1 and t2 on denominator Number of residents who used this medication at t1.

## New initiation of PIMs according to STOPPFrail

At least one PIM of the group of selected PIMs according to STOPPFrail was initiated for 83 residents (30%). Thus, 70% did not start using any new PIMs. The highest prevalence of initiation was found for multivitamin combinations (15%) and neuroleptic antipsychotics (13%)(Table 6.3).

Initiation of at least one PIM of the group of selected PIMs was associated with a higher number of chronic medications at baseline (10 versus 7 for residents for whom no PIMs were initiated,  $p < 0.001$ ), and with renal failure (for 16/30 or 53% of residents with renal failure at least one PIM was initiated compared to 27% in residents without renal failure,  $p = 0.003$ ) (data not shown).

## Correlation between deprescribing of medications suitable for deprescribing and new initiation of PIMs according to STOPPFrail

Changes in medication use, i.e. deprescribing of medications potentially suitable for deprescribing and/or new initiation of PIMs were observed in 133 residents. Deprescribing was observed in 76 residents. In this subgroup of 76 residents, an in-

crease in the number of medications potentially suitable for deprescribing that were actually deprescribed was associated with a decrease in the number of PIMs that were newly initiated ( $r = -0.234$ ,  $p = 0.042$ ) (data not shown).

**Table 6.3.** Prevalence of new initiation at t2 of PIMs from the group of selected PIMs of STOPPFrail.

PIM initiation	n = 296
Number of PIMs initiated mean (range)	0.4 (0-5)
<b>Prevalence of PIM initiation (%):</b>	
no PIMs	69.9
1 PIM	24.6
2 PIMs	4.3
≥ 3 PIMs	1.1
<b>STOPPFrail criteria</b>	
	<b>% (n/N<sup>a</sup>)</b>
multi-vitamin combination supplements	15.1 (24/159)
neuroleptic antipsychotics	12.6 (25/199)
PPIs	6.1 (11/180)
theophylline	3.7 (9/243)
calcium supplements	3.6 (7/197)
gastro-intestinal antispasmodics	2.8 (7/246)
long-term oral steroids	2.2 (6/268)
long-term oral NSAIDs	1.5 (4/272)
5-alpha reductase inhibitors	1.2 (3/252)
H2 receptor antagonists	1.1 (3/267)
sex hormones (including SERMS)	0.7 (2/273)
osteoporosis drugs	0.4 (1/263)
lipid modifying agents	0.4 (1/231)
memantine	0.0 (0/275)
anti-hypertensives (incl. alpha blockers)	0.0 (0/272)

<sup>a</sup>n/N: number of residents for whom this medication was initiated between t1 and t2 on denominator Number of residents who were not using this medication at t1.

## Discussion

### Main findings

During the three to six month period between first (t1) and second (t2) evaluation, mean number of chronic medications increased significantly, and the prevalence of polypharmacy and excessive polypharmacy remained high for NH residents with life-limiting disease. For one third, at least one medication potentially suitable for deprescribing was actually deprescribed. On the other hand, for one third, at least one PIM was newly initiated at the end of life. In the subgroup of 76 residents for whom deprescribing was observed, residents for whom more medications were

deprescribed, had less new PIMs initiated. Most changes in medication use were observed in the group of lipid modifying agents, multivitamin combinations, calcium and other minerals, PPIs, and medications indicated to treat diseases of the nervous system.

## Strengths and limitations

The medication data used for this study were extracted from the individual's nurse administration medication chart, which is highly reliable in the NH setting in Flanders, Belgium. Consequently, data on medication use were a representation of what residents actually use, and allowed to examine changes in medication use for a sample of 296 NH residents with life-limiting disease. For the appraisal of the appropriateness of medications, international clinical practice deprescribing guidelines and validated criteria, the STOPPFrail criteria, were used.

This study has certain limitations. First, due to the absence of clinical information, we excluded PIMs for which this information is needed to interpret their (in) appropriateness. This may have led to an underestimation of PIM use in this study. However, by excluding these PIMs, we may have assessed too few disease-specific PIMs, which may have led to an overestimation of PIM use. Moreover, due to the inaccessibility of medical files, we could not determine the indications for medications considered potentially suitable for deprescribing. Thus, we can only draw cautious conclusions regarding deprescribing in this study sample. Second, we selected NH residents with a specific life-limiting disease: advanced cancer, organ failure or dementia, which is only a small selection of life-limiting diseases. Consequently, we may have missed some residents with life-limiting disease due to other diseases. Earlier research has demonstrated that severe dementia represents the main reason for identifying patients as being in need of palliative care (35). Given the high prevalence of residents with dementia in our sample, we assume that this limitation is not important.

## Interpretation of the findings

Consistent with earlier research in older adults with life-limiting disease (6, 8, 36), we found a significant increase in the number of chronic medications and a prevalence of polypharmacy that remained relatively high at the end of life. However, concordant with other studies in NH residents (8) and advanced cancer patients receiving palliative care (7, 37), we found that small efforts were made to engage in deprescribing of medications suitable for deprescribing. For approximately one third of the residents who used medications potentially suitable for deprescribing, at least

one of these medications was actually deprescribed. On the other hand, for the other two thirds, medications were prescribed as before or even increased. Clearly, there is no culture of deprescribing in Flemish NHs. Apparently, a lot of – physician and patient-related – barriers to deprescribing exist. Currently, the evidence on safety and efficacy of deprescribing is limited (38). This is probably one of the most important barriers for physicians to engage in deprescribing and may explain the rather small efforts to engage in deprescribing (39, 40). Interventions to support physicians in initiating deprescribing in clinical practice should take their barriers into account, because if not, these interventions are predisposed to fail.

For one third of the study population at least one PIM was newly initiated at the end of life. The relatively high prevalence of new initiation of PIMs can be explained by an unawareness of existing criteria and tools for appraisal of the appropriateness of prescribing. In Belgium, no tool exists that automatically links PIMs to the patient's medication chart and generates a systematic warning whenever a PIM is prescribed. This supports the assumption of unawareness of the prescriber.

Changes in medication use were observed in 133 residents, deprescribing in 76 residents. The finding that for those 76 people for whom medications suitable for deprescribing were actually deprescribed had less new PIMs initiated at the end of life can be interpreted as an increased attention for appropriate prescribing of medications in the context of a life-limiting disease. In these people medication use can be considered to be carefully balanced. However, this small subgroup only represented 26% of our study sample, which is most likely due to the timing of prognostication: if the negative prognosis was known before t1, deprescribing may have been initiated before t1, and no additional changes in prescribing may have been made between t1 and t2. On the other hand, prescribers may have been unaware of the impending death and have not initiated deprescribing yet. Most changes were observed in the group of lipid modifying agents, multivitamin combinations, calcium and other minerals, PPIs, and medications to treat diseases of the nervous system. For some residents, these medications were newly initiated, and for other residents these medications were discontinued. There is no rational explanation for most of these changes. Lipid modifying agents are one of the few therapeutic groups of medication that are generally considered to be futile at the end of life because these medications have no short-term benefit and no additional value for symptom relief. Clinical trial evidence has shown that these medications can be safely and effectively deprescribed (30). The appropriateness of the other therapeutic groups candidate for deprescribing is still debated, although these medications are included in the recently published international clinical practice deprescribing guidelines (21, 22), aiming to increase physicians' awareness and self-efficacy of deprescribing. Given

our findings on deprescribing, this raises questions regarding the dissemination of these guidelines to clinical practice.

## Implications for practice, policy and further research

Our results indicate that more attention needs to be given to balancing the benefit-risk ratio of medications and to deprescribing medications in NH residents with life-limiting disease. An urgent need occurs for deprescribing interventions in Flemish NHs. Overcoming the barriers to deprescribing is crucial for successful implementation of these deprescribing interventions. The treating GP is generally well aware of the resident's medication, particularly after years of treatment. Therefore, he/she is best fit to estimate the risk-benefit balance of medications in accordance with the changing care goals, and to coordinate a multidisciplinary medication review. Given the formerly developed relationship of trust with the resident and his family, the resident will have more confidence in medication review performed by this physician and this may increase the resident's willingness to have his medications deprescribed (41). Furthermore, discussing care goals and treatment targets with the resident and his family is crucial to succeed in deprescribing medications. This should be included in conversations regarding wishes and preferences at the end of life.

Basic medical curricula and continuing medical education should focus on the harm of polypharmacy and PIM use, and its possible negative health-related outcomes, such as increased hospitalizations and costs, in frail older adults with life-limiting disease. Moreover, the importance of carefully balancing the benefit/risk ratio for every added medication at the time of prescribing and all other chronic medications that the resident is already using should be highlighted.

Further research should focus on reinforcing the evidence on safe and effective deprescribing of medications, on barriers and enablers to deprescribing, and on implementation of safe and effective deprescribing interventions in clinical practice.

## Conclusion

Medication use remained high at the end of life for NH residents with life-limiting disease, and deprescribing was limited. However, in the subgroup of 76 residents for whom deprescribing was observed, less new PIMs were initiated. In these 76 people medication use can be considered to be carefully balanced.

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## Chapter 7

### Discontinuation of medications at the end of life. A population study in Belgium, based on linked administrative databases

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## Abstract

**Aim:** To examine Potentially Inappropriate Medication (PIM) use in relation to time before death, to explore if PIMs are discontinued at the end of life, and the factors associated with this discontinuation.

**Methods:** We conducted a retrospective register-based mortality cohort study of all deceased in 2012 in Belgium, aged at least 75 years at time of death ( $n = 74368$ ), using linked administrative databases. We used STOPPFrail to identify PIMs received during the period of twelve to six months before death (P1) and the last four months (P2) of life.

**Results:** Median age was 86 (IQR:81-90) at time of death, 57% female, 38% was living in a nursing home, and 16% was admitted to hospital two years to four months before death. Overall, PIM use was high, and increased towards death for all PIMs. At least one PIM was discontinued during P2 for one in five (20%) of the population, and 49% had no discontinuation. Being hospitalized in the period before the last four months of life, living in a nursing home, female gender, and a higher number of medications used during P1 were associated with discontinuation of PIMs (respective aOR (95%CI): 2.89 (2.73-3.06), 1.29 (1.23-1.36), 1.26 (1.20-1.32), 1.17 (1.16-1.17)).

**Conclusion:** Initial PIM use was high and increased towards death. Only in one in five PIM users discontinuation was observed. More guidance for discontinuation of PIMs is needed: practical, evidence-based deprescribing guidelines and implementation plans, training for prescribers and a better consensus on what inappropriate medication is.

## Introduction

**M**anaging medication use in people suffering from advanced stages of a life-limiting disease is very challenging. In accordance with the definition of palliative care, care goals at the end of life should shift from quantity to quality of life (1). This should be reflected in medication prescription and use near the end of life. Adequate medication use in this situation means treating symptoms which are currently undertreated, as well as preventing possible harm caused by Potentially Inappropriate Medications (PIMs).

PIM use has been studied in older adults with a normal life-expectancy. Implicit (e.g. MAI (2)) and explicit criteria (e.g. Beers (3), STOPP/START (4)) have been developed and validated, aiming to identify PIM use in this population, and to assist physicians with deprescribing of these PIMs. However, some medications considered to be inappropriate in the general older population may be used appropriately – e.g. for symptom relief – in a palliative care setting. Thus, these criteria require adaptation in order to be applicable in palliative care (5).

In advanced stages of a life-limiting disease, medication for symptom relief is often combined with medication to treat life-limiting diseases, co-morbidities and medication for long-term prevention (6). However, many of these medications can be considered as potentially inappropriate at the end of life (7, 8). Moreover, some of these PIMs are often involved in drug-drug interactions with medications for symptom relief (9-11).

Recently, explicit criteria to identify PIM use in frail older adults with limited life-expectancy (STOPPFrail) were developed and validated (12). Due to age-related changes in pharmacokinetics and pharmacodynamics, and a high prevalence of polypharmacy and inappropriate prescribing, frail older adults are extra susceptible to ADRs and related negative health outcomes such as hospitalizations (12-14). Discontinuation of PIMs in frail older adults with a limited life-expectancy may improve medication use at the end of life, reduce ADRs and negative health outcomes, and support and improve quality of life. It is crucial to get an insight in the current prescribing and use of PIMs in this population to determine the need for guidance in this area, e.g. for development of clinical practice deprescribing guidelines and interventions to reduce PIM use.

For this study, discontinuation is considered as an umbrella term for tapering or stopping PIMs in the specific context of limited life-expectancy, e.g. by deprescribing those PIMs. Discontinuation of anti-hypertensives, benzodiazepines, neuroleptics, and statins has been associated with physical and cognitive benefits, and no significant harm in patients with a life-limiting disease (15, 16). However, research

has demonstrated that the diagnosis of a life-limiting disease has little effect on the use and continuation of these PIMs (6, 17-21).

This retrospective register-based mortality cohort study aims to (1) get an insight in PIM use according to STOPPFrail in relation to time before death in a large population of deceased in 2012 in Belgium, (2) to explore to what extent PIMs are discontinued at the end of life, and (3) to examine the factors associated with discontinuation of PIMs.

## Methods

### Study design and population

We conducted a retrospective register-based mortality cohort study of people aged 75 years or older at time of death, who died in Belgium in 2012 and were registered by one of the seven healthcare insurers, which is mandatory for all legal residents.

### Data source

Death certificate data, census data and fiscal data were obtained from Statistics Belgium, and were deterministically linked at the individual level to the InterMutualistic Agency's (IMA) national registry of healthcare claims data of the seven healthcare insurers in Belgium, and to the Belgian Cancer Registry. The resulting database covers approximately 99% of the full population who died in 2012. All databases were linked in a secure and ethically responsible manner to guarantee anonymity of the deceased. More information on the different databases, the linking procedure, and the data protection approvals was published elsewhere (22).

### Assessment of outcomes

All medication data in this study were dispensing data from all hospital and community pharmacies, for all medications that were prescribed by any physician and reimbursed by the seven healthcare insurers in Belgium. Healthcare insurance is legally mandatory in Belgium, so data are complete for all legal residents, and registered in the IMA database. However, data on dispensing over-the-counter medications are not included in the database. Medications were classified based on the World Health Organization's ATC classification (23) that divides drugs into different groups in accordance with the organ or system on which they act and their chemical, pharmacological and therapeutic properties. ATC codes at all levels – from one

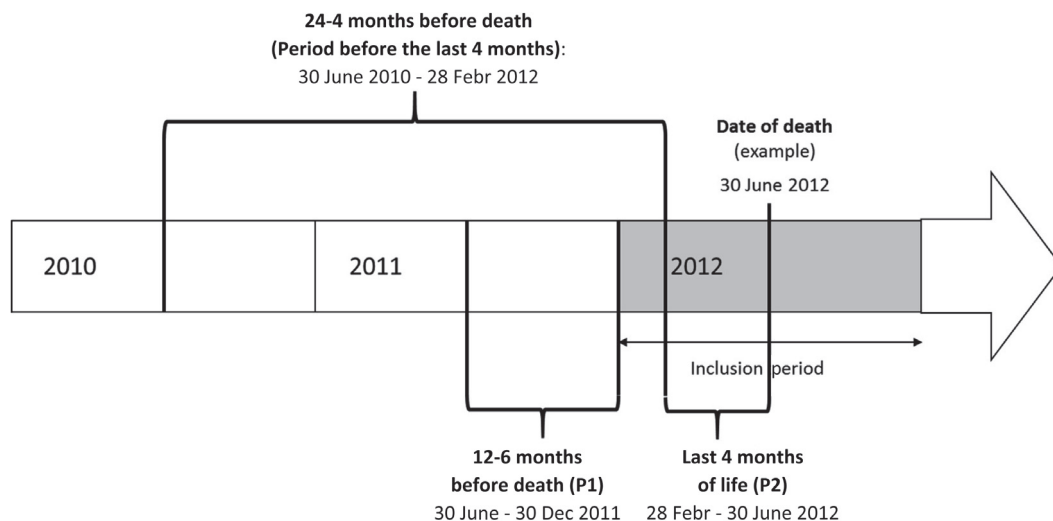
(anatomical main group) to five (chemical substance) – of every medication were traceable in the database.

We selected PIMs available on the Belgian market and listed on the STOPPFrail list of explicit criteria for PIM use in frail older adults with limited life-expectancy, for which no specific patient-level clinical information was needed to determine inappropriateness (12). Based on experts' opinions (RVS and TC) and the available evidence, we categorized these PIMs into three groups: medications for long-term prevention, medications for which chronic use is inappropriate, and (outdated) medications for which a safer alternative exists. Box 7.1 provides a more detailed description of the selected PIMs and our categorization.

**Box 7.1. Potentially Inappropriate Medications according to STOPPFrail selected for this study.**

<b>STOPPFrail criteria</b> (Lavan et al., 2017)	<b>STOPPFrail criteria</b> (Lavan et al., 2017)
<b>PIMs for long-term prevention</b>	<b>Medications not selected because clinical information is needed to determine their appropriateness</b>
lipid modifying agents	anti-platelets
calcium supplements	leukotriene antagonists
osteoporosis drugs	muscarinic antagonists
SERMS for osteoporosis	diabetic oral agents
<b>PIMs for which chronic use is inappropriate</b>	ACE inhibitors for diabetes
memantine	angiotensin receptor blockers
sex hormones	prophylactic antibiotics
neuroleptic antipsychotics	<b>Medications not available because they are not reimbursed in Belgium</b>
proton pump inhibitors (PPIs)	multi-vitamin combination supplements
H2-receptor antagonists	nutritional supplements
gastrointestinal antispasmodics	
long-term oral steroids	
<b>(Outdated) PIMs for which a safer alternative exists</b>	
theophylline	
long-term oral NSAIDs	
5-alpha reductase inhibitors	
alpha-blockers	

We defined discontinuation as no dispensing during the last four months of life (P2) of selected PIMs that were dispensed at least two times during the period of twelve to six months before death (P1). We defined initiation as no dispensing of PIMs during P1, and at least one dispensing during P2. Although our aim was to examine to what extent PIMs were discontinued at the end of life, we added data on new initiation of PIMs to counterbalance our results on discontinuation and situate these results in a proper context. P1 is identified in the database as day 365 to day 180 before death, and P2 as day 120 before death to day of death (Figure 7.1). All data on the prevalence of PIMs were based on dispensed prescription data of



**Figure 7.1.** Timeline.

reimbursed medications from hospital and community pharmacies registered in the IMA database.

## Measurement of individual characteristics

Study participants' age at time of death and gender were derived from the IMA database. Other socio-demographic characteristics at time of death, such as household type, highest attained educational level, net taxable income and urbanisation, were obtained through record-linkage at the individual level with the socio-demographic dataset and socio-economic survey from Statistics Belgium. The household category 'collective household' includes mainly nursing homes. To identify those with a cancer diagnosis, the Belgian Cancer Registry was linked to the other databases.

Characteristics on healthcare use during the period of two years to four months before death, such as hospitalization, visits by family physician, specialist palliative care and legal palliative care status were derived from the IMA database. In this article, we refer to this period as the period before the last four months of life. Individuals received 'specialist palliative care' when they were admitted to a palliative care unit in hospital or consulted a specialist multidisciplinary palliative home care team. Individuals acquired 'legal palliative care status' after being diagnosed by a physician as suffering from advanced irreversible disease, with poor prognosis, and expected death in a relatively short term (24).



## Data handling

For every selected PIM, the corresponding ATC-code was selected from the IMA database. In Belgium, each prescription of medications is valid for three months. Therefore, the prevalence of a specific PIM during P1 is counted as the percentage of people for whom this specific PIM was dispensed at least twice during this period. If this specific PIM was dispensed only once during P1 or not at all, it was not counted. For the prevalence during P2, the specific PIM had to be dispensed only once to be counted (25). Thus, we can distinguish four groups in our population for every selected PIM: (1) a group for whom a specific PIM is dispensed at least twice during P1 and not dispensed during P2 (= discontinuation), (2) a group for whom a specific PIM is dispensed at least twice during P1 and at least once during P2 (= continuation), (3) a group for whom a specific PIM is not dispensed during P1 and dispensed once during P2 (= initiation), and (4) a group for whom a specific PIM is not dispensed during P1 nor during P2 (those who never used this PIM). A dichotomous variable was constructed to distinguish people for whom at least one of the selected PIMs was discontinued from those without discontinuation. This variable was used as outcome for the logistic regression analyses. All other individuals – not belonging to any of these two subgroups – were excluded from further analyses.

To count the number of chronic medications during P1, every fifth level ATC code that was dispensed at least twice was counted. For the number of medications dispensed during P2, every dispensed fifth level ATC code was counted. PIMs were included in the number of medications and were not counted separately.

## Statistical analyses

All statistical analyses were performed using Statistical Analysis Software (SAS®) 9.4 and SAS® Enterprise Guide 7.1 (SAS® Institute Inc., North Carolina, USA).

We used descriptive methods to describe the characteristics of the study population, use, discontinuation and initiation of PIMs. In a sensitivity analysis, people who died from sudden and possibly unexpected causes of death were excluded, but this rendered no meaningful differences in population characteristics and outcomes, so the general 75+ population was retained for analysis. A logistic regression model was used to examine the factors which were independently associated with discontinuation of PIMs. The variables considered for the multivariable logistic regression were those considered to be clinically important, i.e. those for which 5 percentage point difference was found between the different categories of those variables in the univariate analyses. For continuous variables, a mean difference of at least three was considered clinically important. We adjusted the model for the remaining covariates.

**Table 7.1.** Characteristics of the study population and subgroups.

	<b>All deceased ≥75 years n = 74 368</b>	<b>At least one PIM discontinued n = 14 395</b>	<b>No discontinua- tion of PIMs n = 36 696</b>	<b>Others (not included in the two subgroups) n = 23 277</b>
<b>Age</b> in years at time of death median (IQR)	86.0 (81-90)	85.0 (81-89)	85.0 (81-89)	87.0 (82-91)
<b>Gender† (%)</b> :				
male	43.3	40.7	46.8	39.3
female	56.7	59.3	53.2	60.7
<b>Household type† (%)</b> :				
single person	25.1	23.6	28.2	21.1
couple with no children living at home	27.1	27.3	31.1	20.4
couple with children living at home	3.9	3.8	4.4	3.3
single parent family	4.0	3.6	4.5	3.3
nursing home*	37.9	39.9	29.7	50.2
unknown	1.9	1.8	2.2	1.8
<b>Highest attained educational level (%)</b> :				
no education	8.5	9.1	8.5	8.2
primary education	37.5	38.2	37.6	36.9
lower secondary education	21.0	21.5	21.2	20.4
upper secondary education	11.3	11.3	11.6	10.8
higher education	7.2	6.9	7.6	6.8
unknown	14.5	13.1	13.5	16.9
<b>Net taxable income (%)</b> :				
< €10.000	23.4	23.9	23.7	22.8
€10.000-€15.000	27.1	27.2	26.6	27.9
€15.001-€20.000	26.8	27.2	27.1	25.9
> €20.000	22.7	21.7	22.6	23.4
<b>Urbanisation category (%)</b> :				
low	12.3	12.5	12.2	12.2
middle	25.7	25.8	26.4	24.5
high	27.6	27.7	27.8	27.1
very high	31.3	31.9	31.3	30.9
unknown	3.1	2.1	2.2	5.3
<b>Cancer diagnosis (%)</b>	23.3	27.2	27.8	13.7
<b>Hospitalization</b> between 720 and 121 days before death†:				
(%)	16.0	25.5	8.8	21.5
n days median (IQR)	5.0 (3-7)	6.0 (4-9)	4.0 (3-7)	4.0 (3-7)
<b>Visits by family physician</b> between 720 and 121 days before death median (IQR):	16.0 (7-26)	19.0 (10-30)	17.0 (8-26)	14.0 (4-23)
<b>Specialist palliative care:</b>				
onset: median (IQR) days before death	22.0 (6-85)	36.0 (8-128)	18.0 (5-58)	28.0 (5-189)
never onset (%):	85.4	81.3	83.2	91.5
very early onset (720-121) (%)	0.5	1.0	0.3	8.5
later onset (120-0) (%)	14.1	17.7	16.5	8.1
<b>Legal palliative care status:</b>				
onset: median (IQR) days before death	38.0 (11-122)	56.0 (16-158)	31.0 (10-86)	42.0 (8-187)
never onset (%):	89.4	85.5	88.2	93.8
very early onset (720- 121)	2.1	3.5	1.7	1.7
later onset (120-0)	8.5	11.0	10.1	4.5

## Ethics

Data were anonymized. In accordance with Belgian law, approvals for access to the various databases and the database integrating all databases were obtained from two separate national sectoral committees for privacy protection: the Sectoral Committee of Social Security and Health, Section Health and the Statistical Supervisor Committee. Both are subcommittees of the Belgian Commission for the Protection of Privacy. In addition, the ethics committee of Ghent University Hospital provided approval (B670201422382).

## Results

### Characteristics of the study population

Overall, 74 368 deceased individuals - median age 86 (IQR: 81-90) at time of death, 57% female - were included in this study. As shown in Table 7.1, 38% was living in a nursing home, and 23% was diagnosed with cancer. During the period before the last four months of life, 16% was admitted to hospital, with a median stay of five days (IQR: 3-7).

### Potentially Inappropriate Medication (PIM) use during P1 and P2

In the total population ( $n = 74\,368$ ), mean number of dispensed chronic medications was 6 (SD 4.86) during the period of twelve to six months before death (P1). Most prominent PIMs for long term prevention during P1 were lipid modifying agents (21.5%). In the group of PIMs for which chronic use is inappropriate, proton pump inhibitors (PPIs) (28%) and neuroleptic antipsychotics (14%) were most common, and in the group of outdated PIMs, long-term oral non-steroidal anti-inflammatory drugs (NSAIDs) were most prominent (7%).

#### *Footnotes to Table 7.1.*

\*collective household including mostly nursing homes, long-term care institutions for disabled persons, jail.

†variables with at least 5 percentage point difference or mean difference of at least 3 between the group with at least one PIM discontinued and no discontinuation of PIMs.

At least one PIM discontinued: at least one of the selected PIMs was discontinued between the period of 12-6 months before death (P1) and the last 4 months of life (P2).

Specialist palliative care was defined as being admitted to a palliative care unit in hospital or receiving palliative care at home from a specialist multidisciplinary palliative home care team. Legal palliative care status in Belgium is acquired after being diagnosed by a physician as suffering from advanced irreversible disease, with poor prognosis, and expected death in a relatively short term (Maetens et al., 2017).

The number of dispensed medications increased to 19 (SD 11.79) during the last four months of life (P2). The prevalence of all PIMs increased, more specifically to 25% for lipid modifying agents, 52% for PPIs, 31% for neuroleptic antipsychotics, and 16% for NSAIDs (Table 7.2).

**Table 7.2.** Prevalence, discontinuation and initiation of dispensed potentially inappropriate medications (PIMs) (%) according to STOPPFrail (n = 74 368).

Medications	P1 n = 74 368	P2 n = 74 368	Discontinuation % (n/N)	Initiation % (n/N)
<b>n medications</b> mean (SD)	6.38 (4.86)	18.86 (11.79)	NA	NA
<b>PIMs for long-term prevention</b>				
lipid-modifying agents	21.5	25.1	21.1 (3383/16016)	4.6 (2421/52582)
calcium supplements	4.8	11.3	40.8 (1443/3539)	7.6 (5145/67858)
osteoporosis drugs	6.3	8.3	28.5 (1337/4687)	2.9 (1969/67620)
SERMS for osteoporosis	0.2	0.1	34.4 (42/122)	0.01 (6/74208)
<b>PIMs for which chronic use is inappropriate</b>				
memantine	1.1	1.0	31.6 (269/851)	0.2 (156/73411)
sex hormones	0.9	1.0	29.2 (192/656)	0.4 (284/73632)
neuroleptic antipsychotics	14.4	31.4	16.7 (1790/10742)	20.6 (12311/59646)
proton pump inhibitors (PPIs)	28.2	51.8	8.9 (1869/20993)	31.8 (15081/47416)
H2-receptor antagonists	6.3	13.9	28.6 (1346/4709)	9.2 (6194/67122)
gastrointestinal antispasmodics	4.1	26.6	41.2 (1256/3049)	24.3 (16185/66632)
long-term oral steroids	9.9	29.3	22.2 (1642/7390)	21.9 (13458/61471)
<b>(Outdated) PIMs for which a safer alternative exists</b>				
theophylline	2.1	2.8	18.0 (276/1536)	0.8 (602/72298)
long-term oral NSAIDs	6.8	15.8	47.0 (2386/5079)	11.6 (7202/62102)
5-alpha reductase inhibitors	1.6	4.5	36.0 (437/1214)	3.1 (2226/72251)
alpha-blockers	0.2	0.8	30.8 (36/117)	0.6 (460/74103)

P1 = 12-6 months before death (denominator: total population  $\geq 75$ ); P2 = the last 4 months of life (denominator: total population  $\geq 75$ ); D = Discontinuation of PIMs (P1 = 1 & P2 = 0) = within the group taking PIMs at 12-6 months before death, prevalence of discontinuation of these PIMs the last 4 months of life (denominator: total population  $\geq 75$  for whom P1 = 1), I = Initiation of PIMs (P1 = 0 & P2 = 1) = within the group taking no PIMs at 12-6 months before death, prevalence of initiation of these PIMs the last 4 months of life (denominator: total population  $\geq 75$  for whom P1 = 0).

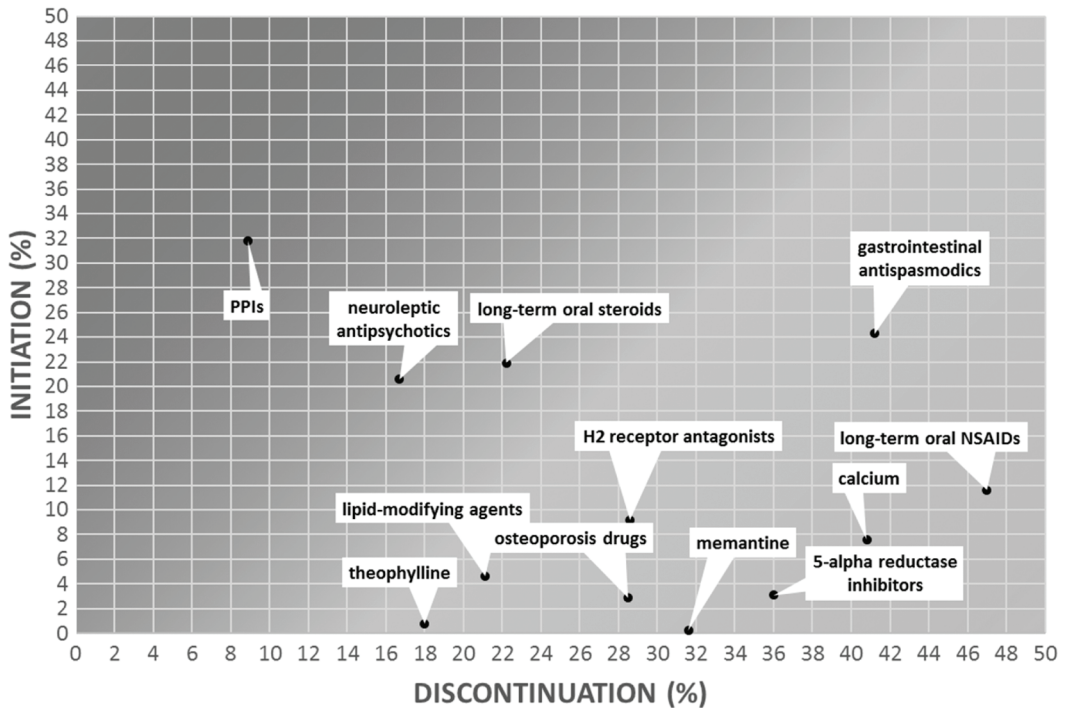
## Discontinuation of PIMs

Between P1 and P2, at least one selected PIM was discontinued for one in five (20%) (n = 14 395) of the population. No discontinuation of PIMs was observed for 49% (n = 36 696). People for whom at least one PIM was discontinued had a median age of 85 years (IQR: 81-86), 59% were female, 40% were living in a NH, and 26% were hospitalized in the period before the last four months of life, with a median stay of six days (IQR: 4-9). For those without discontinuation of PIMs, median age was 85 (IQR: 82-91), 53% were female, 30% were living in a NH, and 9% were hospitalized in the period before the last four months of life (Table 7.1). The mean number of chronic

medications used during P1 was 9.6 (SD 5.71) for those with at least one selected PIM discontinued compared to 5.7 (SD 4.23) for those with no discontinuation of PIMs (data not shown).

### Discontinuation of PIMs versus initiation of new PIMs

Among the users of the selected PIMs during P1, the percentage of discontinuation varied between 8.9% for PPIs and 47% for long-term NSAIDs. The prevalence of newly initiated PIMs during P2 varied between < 1% for Selective Estrogen Receptor Modulators (SERMs), memantine, sex hormones, alpha-blockers, and theophylline; and 32% for PPIs. The prevalence of discontinuation exceeded the prevalence of initiation for theophylline, lipid modifying agents, osteoporosis drugs, H2-receptor antagonists, sex hormones, alpha-blockers, memantine, SERMs, 5-alpha reductase inhibitors, calcium, gastrointestinal antispasmodics, and long-term NSAIDs. For PPIs and neuroleptic antipsychotics the prevalence of initiation exceeded the prevalence of discontinuation. For long-term oral steroids, the prevalence of discontinuation and initiation were equal (Table 7.2 & Figure 7.2).



**Figure 7.2.** Prevalence (%) of discontinuation versus initiation of the selected PIMs during the last four months of life.

## Factors associated with discontinuation of PIMs

For the variables 'being hospitalized within the period before the last four months of life', 'living in a nursing home', and 'female gender', a 5 percentage point difference was found between the categories at least one PIM discontinued and no discontinuation of PIMs in the univariate analyses. For the mean number of chronic medications during P1 a mean difference greater than 3 between the two subgroups was found. These variables were considered to be clinically important and their association with discontinuation of at least one PIM was examined in the multivariate logistic. We controlled for age, educational level, net taxable income, urbanisation, cancer diagnosis, visits by family physician, specialist palliative care and legal palliative care status. The odds of discontinuation of PIMs increased significantly in association with the variables 'being hospitalized within the period before the last four months of life', 'living in a nursing home', 'female gender', and a higher number of chronic medications used during P1 (respective aOR (95%CI): 2.89 (2.73-3.06), 1.29 (1.23-1.36), 1.26 (1.20-1.32), 1.17 (1.16-1.17)) (Table 7.3).

**Table 7.3.** Factors† associated with discontinuation of Potentially Inappropriate Medications (PIMs).

At least one PIM discontinued	OR (95%CI)	p-value
<b>Hospitalization (720-121) vs no hospitalization</b>	2.89 (2.73-3.06)	<0.001
<b>Living in a nursing home vs in private home</b>	1.29 (1.23-1.36)	<0.001
<b>Gender: female vs male</b>	1.26 (1.20-1.32)	<0.001
<b>Number of chronic medications at T1</b>	1.17 (1.16-1.17)	<0.001
<b>Legal palliative care status vs no legal status</b>	1.09 (1.04-1.14)	<0.001
<b>Cancer diagnosis vs no cancer diagnosis</b>	0.94 (0.90-0.99)	0.018

†Variables with a  $\geq 5$  percentage point difference or mean difference  $\geq 3$  between the category with at least one PIM discontinued and no discontinuation of PIMs in univariate analyses were considered to be clinically important (grey background). At least one PIM discontinued: at least one of the selected PIMs was discontinued between the period of 12-6 months before death (P1) and the last 4 months of life (P2). Model was adjusted for age, education level, net taxable income, urbanisation, cancer diagnosis, visits by family physician, specialist palliative care, legal palliative care status.

## Discussion

### Key findings

Overall, PIM use according to STOPPFrail was high during the last year of life and increased towards death. Apparently, physicians continue to prescribe medications that are potentially inappropriate until the very end of life. Probably, prognostic uncertainty plays an important role here, as well as a lack of consensus on which medications are inappropriate at the end of life. The prevalence of PIMs during both time periods differs for each PIM, figures can be found in table 2. In the group of PIMs for long term prevention, the prevalence of lipid modifying agents was high. For these medications discontinuation exceeded new initiation in the last four months of life. In the group of medications for which chronic use is inappropriate, the prevalence of PPIs and neuroleptic antipsychotics was high. Furthermore, in both therapeutic groups new initiation exceeded discontinuation in the last four months of life. The prevalence, discontinuation and new initiation of outdated medications was more limited.

For one fifth of the population at least one PIM was discontinued in the last four months of life, while no discontinuation of PIMs was observed for nearly half of the population. People who were admitted to hospital during the period before the last four months of life, nursing home residents, and women had more chance of discontinuation of PIMs. People for whom at least one PIM was discontinued during the last four months of life used more chronic medications during the period of twelve to six months before death.

### Strengths and limitations

We used a population-level linked database with detailed demographic, socio-economic and healthcare use information on all decedents in 2012 in Belgium. This allows following back the dispensing of reimbursed prescribed medications up to one year before death. Although only services covered by insurers are included, in Belgium, where healthcare insurance is mandatory, data are relatively complete for healthcare services in the hospital, nursing home and at home (22). Consequently, we were able to examine PIM use and discontinuation of PIMs in the full population of those deceased at age 75 years and older. The number of 74 368 decedents at age 75 years and older is in accordance with the Belgian population statistics (26). To the best of our knowledge, this is the first study that includes the balance between discontinuation of PIMs and initiation of new PIMs, which adds some refinement to the current picture of discontinuation of medications at the end of life.

The use of – in hospital and community – pharmacy dispensing data to determine PIM use has certain limitations: first, as the data are based on reimbursed dispensed medication we have to rely on the assumption that patients who received these medications also take them. In accordance with studies on compliance using administrative databases (25, 27, 28), we defined discontinuation as “at least two” dispensing during P1, and no dispensing during P2, to counterbalance this limitation. Second, administrative data are generally coarse grained: in Belgium, prescribed medications are dispensed for three months, and neither data on prescribed daily dose nor number of days of supply were available for this study. Consequently, we cannot examine concomitant use of medications, which complicates assessing their appropriateness. Third, some of the selected PIMs are difficult to observe in the IMA database because of their availability over-the-counter (e.g. NSAIDs, calcium). Prevalence of discontinuation might be overestimated for these PIMs if patients only get their first prescription filled at the pharmacy and afterwards buy these medications over-the-counter. However, these PIMs are more expensive when bought over-the-counter. Hence, the influence of this limitation on our results is likely to be minimal. Fourth, due to inaccessibility of clinical patients data, only PIMs for which no clinical information is needed to determine whether their use is inappropriate or not – 14 out of the 26 on the STOPPFrail list – were included in the analyses. Thus, the high prevalence of PIMs overall in this study is likely an underestimation. However, research has demonstrated that criteria for which clinical information is not required can be reliably used to identify PIMs with a structured screening tool such as STOPP (29), which applicability is comparable to STOPPFrail. The absence of clinical patient information complicates interpretation of our findings and does not allow for e.g. estimation of the treatment risk-benefit ratio of a specific medication for a specific patient. Moreover, given we had no access to clinical patient-level information, we were not able to adjust our multivariate model for comorbidities. Thus, residual confounding is possible. Finally, the relatively low prevalence of discontinuation must be interpreted with caution, since healthy-user/sick-stopper bias and prognostic uncertainty are common in a population aged 75 and older (30).

With these strengths and limitations in mind, we can identify dispensing of PIMs during well-defined time periods, and draw cautious, coarse grained conclusions regarding their discontinuation. Research has demonstrated that the main determinant of PIM use is the number of prescribed medications (14, 31, 32), which is probably confounded by the number and type of co-morbidities (32). Adding clinical patient data and data on concomitant use of medications and treatment duration would create extensive opportunities for further research.



## Interpretation in the context of literature

Overall, when death approached, prescribers continued treatment as before: PIM use was high at both time points, and increased towards death. Few changes in prescribing patterns were observed in relation to time before death: discontinuation and new – probably symptom driven and therefore not necessarily negative - initiation of PIMs was very limited. In a palliative care context, initiation of some of these PIMs may be indicated and likely to benefit the patient at the end of life, e.g. initiation of haloperidol to treat delirium when death is imminent or chemotherapy induced nausea and vomiting. Other studies on discontinuation of PIMs in relation to time before death are scarce and report similar findings on use and discontinuation of lipid modifying agents (33-35), proton pump inhibitors (PPIs) (35, 36), and neuroleptic antipsychotics (37). PPIs and neuroleptic antipsychotics are considered as problematic PIMs and candidates for deprescribing. Recently, clinical practice deprescribing guidelines, including an algorithm to guide deprescribing, were developed for both groups (38, 39). The high prevalence of initiation of both groups in our study raises questions about the dissemination and implementation of these guidelines in clinical practice. Lipid modifying agents are one of the few therapeutic groups of medication that are generally considered to be futile at the end of life because these medications have no short-term benefit and no additional value for symptom relief. Clinical trial evidence has shown that these medications can be safely and effectively discontinued (16).

For only one fifth of the population 75 and older at least one PIM was discontinued close to death, and for nearly half of the population no discontinuation was observed. This is consistent with Barcelo et al. who found that a large number of elderly patients with limited life-expectancy continue to receive inappropriate medications (33). Clearly, there is no culture of discontinuation of PIMs at the end of life in Belgium. Apparently, many barriers to discontinuation or deprescribing exist. Overcoming these barriers is crucial to enable embedding of deprescribing in routine prescribing patterns. In order to be successfully implemented, all interventions to support physicians to engage in deprescribing should take these barriers into account.

Concordant with Chang et al., this study demonstrated that hospitalization is associated with discontinuation of PIMs (40). In Belgium, older adults are preferably hospitalized on a geriatric ward and treated by a multidisciplinary team including a geriatrician and healthcare professionals specialized in care for geriatric patients. Moreover, if hospitalized on another ward, the treating physician is encouraged to consult a geriatric support team – including a geriatrician – for patients with a positive geriatric risk profile, indicating increased frailty (41). Research has demonstrated

that geriatricians prescribe fewer PIMs compared to other clinicians (32). Possibly, geriatricians are more aware of existing criteria and tools to identify PIMs and to support deprescribing and clinical practice deprescribing guidelines due to the need to change care goals and treatment targets in severely ill or frail older patients with limited life-expectancy. Moreover, multidisciplinary collaboration, which is more prominent in hospital or in a nursing home compared to at home, in itself may lead to an increased attention for – multidisciplinary - medication review and discontinuation of PIMs, and partially explain the association we found between discontinuation of PIMs and hospitalization, and living in a nursing home.

Living in a nursing home was associated with decreased PIM use. This is consistent with Morin et al., who found a 15% reduction in the likelihood of receiving inadequate medications during the last month of life in institutionalized older adults with dementia (14). In Belgium, extensive home care facilities are available. Thus, NHs provide care for older adults with multimorbidity, severe functional impairment and increasing care needs that cannot be met in any other way. Ivanova et al. found that medication use in general in residents with dementia – who represented 46% of the population they studied at follow-up – decreased between NH admission and follow-up after two years in Flanders, the Dutch speaking part of Belgium (42). The high prevalence of dementia within the NH population may partly explain the association between living in a NH and discontinuation of PIMs. Another possible explanation is that the limited life-expectancy after NH admission (43) may lead to different – more cautious – patterns of prescribing and discontinuation of PIMs.

Chronic medication use was higher in the group for whom at least one PIM was continued. Since the number of prescribed medications was found to be the main driver of PIM use in earlier studies (31, 32, 44), these people were likely to use more PIMs.

## Implications for clinical practice and further research

More guidance on deprescribing in the context of limited life-expectancy is needed in order to prevent unnecessary harm caused by PIMs at the end of life, taking into account prognostic uncertainty. Physicians urgently need practical evidence-based guidelines and implementation plans, lists of candidate medications for deprescribing, training in how to initiate deprescribing and a better consensus on what inappropriate medication is. Furthermore, adaptation of existing international deprescribing guidelines to the context of limited life-expectancy in combination with a more realistic estimation of prognosis or prediction of death is crucial to optimize medication use in this situation.

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## Chapter 8

### Changes in medication use in a cohort of patients with advanced cancer: *the international multicenter prospective European Palliative Care Cancer Symptom (EPCCS) study*

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## Abstract

**Background:** Information on medication use in the last months of life is limited.

**Aim:** To describe which medications are prescribed and deprescribed in advanced cancer patients receiving palliative care in relation to time before death and to explore associations with demographic variables.

**Design:** Prospective study, using case report forms for monthly data collection. Medication included cancer treatment and 19 therapeutic groups, grouped into four categories for: (1) cancer therapy, (2) specific cancer-related symptom relief, (3) other symptom relief and (4) long-term prevention. Data were analysed retrospectively using death as the index date. We compared medication use at 5, 4, 3, 2 and 1 month(s) before death by constructing five cross-sectional subsamples with medication use during that month. Paired analyses were done on a subsample of patients with at least two assessments before death.

**Setting/participants:** We studied the medication use of 720 patients (mean age 67, 56% male) in 30 cancer centres representing 12 countries.

**Results:** From 5 to 1 month(s) before death, cancer therapy decreased (55%–24%), most medications for symptom relief increased, for example, opioids (62%–81%) and sedatives (35%–46%), but medication for long-term prevention decreased (38%–27%). The prevalence of chemotherapy was 15.5% in the last month of life, with 9% of new courses started in the last 2 months. With higher age, chemotherapy and opioid use decreased.

**Conclusion:** Medications for symptom relief increased in almost all medication groups. Deprescribing was found in heart medication/anti-hypertensives and cancer therapy, although use of the latter remained relatively high.



## Introduction

**P**olypharmacy, or ‘the use of several medications concurrently for the treatment of one or more coexisting diseases’ (1) remains common in patients with a limited life-expectancy, such as those with advanced cancer receiving palliative care (2–4). In accordance with the definition of palliative care, care goals and treatment targets, including the use of medication, for people in this situation should change from quantity to quality of life (5). Optimal symptom management is crucial to support quality of life (6). Cancer therapy (e.g. chemotherapy) is often combined with multiple drugs for relief of frequent cancer symptoms, for example, opioids, anti-emetics, corticosteroids, paracetamol and laxatives (7), as well as different medications for chronic diseases and long-term prevention, for example, anti-hypertensives and statins (4). However, 22%–95% of advanced cancer patients take at least one unnecessary medication, for example, medication for which the time until benefit is estimated to be longer than the remaining life-expectancy (e.g. statins), or (some) medication for treatment of non-life-threatening comorbidities (2, 8–12). Besides time until benefit and remaining life-expectancy, other decision-making factors to avoid inappropriate medication use in palliative care must be considered, for example, goals of care (in accordance with the patient’s preferences), treatment targets, numbers needed to treat, numbers needed to harm and adverse drug reactions (13). Polypharmacy increases the risk of adverse drug events, such as drug–drug and drug–disease interactions. Reducing the number of medications may reduce the number of adverse drug events and the associated healthcare-related costs and improve quality of life (1–4). Therefore, it is crucial to examine which medications are prescribed in advanced cancer patients receiving palliative care and which are suitable for deprescribing when death approaches.

Deprescribing is the process of withdrawal of inappropriate medication, supervised by a healthcare professional with the goal of managing polypharmacy and improving outcomes (14). So far, research has been confined primarily to geriatric patients. Only a few studies have focused on these issues in palliative cancer care (3, 9, 15–20). Large-scale longitudinal cross-national studies on medication use in palliative cancer care, which focus on changes in medication use related to time before death, are scarce. Therefore, the aim of this study is to describe which medication is prescribed and deprescribed in advanced cancer patients receiving palliative care in different countries, in relation to time before death, and to examine associations with demographic variables. Our a priori hypothesis is that medication for symptom relief will increase as death approaches, while cancer therapy and medication for

long-term prevention will be decribed.

## Methods

### Study design and setting

We used data from the European Palliative Care Cancer Symptom (EPCCS) study, an international multicentre cohort study in which palliative care services in 24 hospitals, 4 hospices, 1 nursing home and 1 palliative care home-care service participated, representing the following countries: Australia, Belgium, Canada, Denmark, Georgia, Germany, Italy, Norway, Portugal, Spain, Switzerland, and the United Kingdom. Details of the study and the participating centres are described elsewhere (21).

### Study participants

All patients aged over 18 and diagnosed with advanced cancer (local, loco-regional or metastatic disease) were eligible for inclusion, if receiving palliative care, able to provide written informed consent, able to complete the data collection tool without help and available for at least two assessments after inclusion. Patients were excluded if they were receiving cancer therapy with a curative intent, or if they were unable to comply due to psychotic disorders, obvious cognitive impairment, language problems or inability to attend follow-up for medical, social or geographical reasons. Patients were identified upon first referral for non-curative cancer treatment to the centre, department, clinic or hospice, depending on the local organization. All eligible patients were asked to participate and were then followed every 4 weeks (3–5) for at least 3 months or until death.

All patients were recruited at the same time (not consecutively) with a minimum of 50 per centre and this cohort was followed as described above.

### Data collection

Data collection case report forms (CRFs) were based on an early version of the European Association for Palliative Care (EAPC) basic data set, developed in two steps: a systematic literature review and a Delphi consensus process conducted in 2011, and published recently (22). CRFs were supplemented with a few additional diagnostic and treatment-related variables and medication related data (21).

All data were collected longitudinally between April 2011 and October 2013. The same data were collected at each site at each approximately monthly encounter for up to at least 3 months before death or study withdrawal, whichever came first.

Socio-demographic variables and screening items on symptoms were filled in by the patients themselves. Patient self-reported symptoms are not considered in this article. Related methods and results are described elsewhere (21, 23).

Medical and treatment-related variables were filled in by the healthcare provider, as well as a four-item version of the mini-mental state examination for screening of cognitive impairment (24, 25), and the Karnofsky Performance Status Scale (KPS), an assessment tool for functional impairment, ranging from 0 to 100, with lower scores indicating worse functional status and a worse likelihood of survival than higher scores (26). Data on medication were based on dichotomous questions (use: yes/no) for cancer treatment (radiation therapy (RT) and anti-tumour medication) and 19 other therapeutic groups (for which the term 'medication groups' is used in this article). Data collection on medication was simplified regarding the number of medication groups and the method of questioning to make it comprehensible for all healthcare professionals responsible for filling in the questionnaire. Box 8.1 provides more details on the 19 medication groups.

## Data handling

For this study, we grouped medication into four main categories, based on the opinion of experts (R.V.S. and T.C.): cancer therapy, medication specific for cancer-related symptom relief, medication for other symptom relief and medication for long-term prevention. For the analysis, the different treatments for cancer were combined into 'all' cancer therapy, antidepressants for depression and for conditions other than depression into 'antidepressants', coanalgesics and non-opioids into 'non-opioid analgesics', and prokinetics and anti-emetics into 'prokinetics/antiemetics'. Details of these four categories of medication are described in Box 8.1.

Our analyses included both longitudinal and cross-sectional data. First, we created cross-sectional subsamples for every month before death for every patient with a verified date of death and with at least one CRF during the last 5 months before death. Every subsample covered medication use each month before death for every patient who had an assessment during that month. Medication use at 5, 4, 3, 2 and 1 month(s) before death refers to the periods of 5–4, 4–3, 3–2, 2–1 and 1–0 month(s) before death. The rationale behind the cross-sectional analysis was that an exact monthly registration of data was not possible across all sites, because patient visits varied in regularity. This resulted in a large number of missing values, which is common in prospective studies in palliative care. Second, the repeated measures encompassed all patients with at least one CRF within month 5–3 (= period 1) and at least one CRF during the last 2 months (= period 2) before death (= 'the cohort'). Age was divided into the following four age groups:  $\leq 54$ , 55–64, 65–74 and  $\geq 75$ .

**Box 8.1.** Grouping of cancer therapy and the 19 medication groups on the CRF into 4 categories for this study.

<b>4 categories</b>	<b>Medication on case report form (CRF)</b>
<b>Cancer therapy</b>	chemotherapy <sup>(1)</sup> radiotherapy <sup>(1)</sup> hormonal therapy <sup>(1)</sup> other, anti-cancer treatment <sup>(1)</sup> none
<b>Medication specifically for cancer-related symptom relief</b>	non-opioid analgesics <sup>(2)</sup> co-analgesics <sup>(2)</sup> opioids corticosteroids laxatives prokinetics <sup>(3)</sup> anti-emetics <sup>(3)</sup> psychostimulants oral nutritional supplements with high protein level
<b>Medication for other symptom relief</b>	antidepressants for depression <sup>(4)</sup> antidepressants for conditions other than depression <sup>(4)</sup> neuroleptics sedatives/anxiolytics stomach acid-suppressing drugs antibiotics diuretics antithrombotic agents other medication
<b>Medication for long-term prevention</b>	heart medication/anti-hypertensives
<b>Medication groups (excl. cancer therapy)</b>	n = 19 <sup>(5)</sup>

(1) Combined for analyses to cancer therapy 'all'.

(2) Combined for analyses to 'non-opioid analgesics'.

(3) Combined for analyses to 'prokinetics/antiemetics'.

(4) Combined for analyses to 'antidepressants'.

(5) Combining the above mentioned medication groups resulted in 16 (instead of the 19 on the CRF) medication groups (excl. cancer therapy) for analyses.

## Data analysis

IBM Statistical Package for the Social Sciences (SPSS 23.0, IBM Corporation USA) was used for all data analyses. Data were analysed retrospectively using death as the index date, including only patients with a verified date of death and with at least one CRF during the last 5 months before death. Medication was expressed as a percentage of overall users and as a mean (standard deviation, SD) number of medication groups by summing up the flagged medication groups at every time point. Patient characteristics were expressed as means (SD) for continuous variables and percen-

tages for discontinuous variables. Differences in patient characteristics and medication use between time points were explored with chi-square for proportions and independent samples t-tests and one-way analysis of variance (ANOVA) for comparing means. To explore the changes in medication use in the last 5 months before death, we used ANOVA for trend in the continuous outcome and crosstabs with linear by linear associations and the Cochran Armitage test for trend in the dichotomous outcomes. Patient characteristics at study entry were compared between the cohort and participants excluded from the cohort, using chi-square for proportions and independent samples t-tests for means. For repeated measures in the cohort, paired analyses were performed, using paired samples t-tests for the continuous variable and crosstabs and McNemar tests for dichotomous variables. Associations of 'mean number of medication groups', use of chemotherapy and opioids in period 1 and period 2 with demographic variables (age, gender, living situation and education) were explored in univariate analyses using paired samples t-tests for the continuous outcome, and crosstabs, McNemar and Mantel Haenszel tests for both discontinuous outcomes. A significance level of  $p < 0.05$  was set.

### Ethical considerations

This study was performed according to the Declaration of Helsinki and was registered in the ClinicalTrials.gov database (No. NCT01362816). Ethical approval was obtained at each site. All participants gave written informed consent prior to study start at each site.

## Results

### Characteristics of the study population

Overall, data were collected on 1689 patients in 30 centres from 12 countries in the EPCCS study. In the present analyses, 720 (43%) were included, because they had had at least one assessment during the last 5 months before death. At study entry, these 720 participants had a mean age of 67, and 56% were male. Their most common diagnoses were cancer of digestive organs (37%), respiratory organs (21%) and breast (8%), and 62% suffered from one or more comorbidities. Cancer therapy was provided for 41%, particularly chemotherapy (31%). No differences in demographic characteristics were found in the five cross-sectional subsamples which were constructed to compare medication use at 5 (n = 249), 4 (n = 293), 3 (n = 361), 2 (n = 417) and 1 (n = 400) month(s) before death (data not shown).

The cohort with at least two assessments during the last 5 months of life (one

**Table 8.1.** Characteristics of the study population at study entry.

Characteristics	All* n = 720	Cohort° n = 209
<b>Age</b> in years (yrs) mean (SD)	67.09 (12.505)	67.04 (11.371)
<b>Gender (%)</b> :		
female	44.0	44.5
male	56.0	55.5
<b>Living situation (%)</b> :		
alone	22.5	23.2
with spouse/partner	47.9	44.9
with spouse and children	17.0	20.3
other	12.6	11.6
<b>Education (%)</b> :		
< 9 yrs of schooling	35.1	36.1
10-12 yrs of schooling	39.7	41.0
college/university	25.2	22.9
<b>Primary cancer diagnosis (%)</b> :		
digestive organs	37.4	38.9
respiratory organs	21.1	22.1
breast cancer	8.1	9.1
male genital organs	5.2	3.4
gynaecological	5.9	3.8
urinary	5.3	4.8
other <sup>§</sup>	16.8	17.9
<b>Comorbidity (%)</b> :	61.5	68.9
<b>Type of comorbidity (%)</b> :		
heart disease	26.6	30.8
COPD	9.5	10.6
arthritis	7.4	9.6
renal disease	4.2	6.3
liver disease	3.9	2.9
other	40.0	46.9
<b>Karnofsky<sup>+</sup></b> mean (SD)	<b>60.06</b> (15.930)	<b>64.02</b> (13.087)
<b>Cancer therapy (%)</b> : yes		
all	<b>40.6</b>	<b>51.7</b>
chemotherapy	<b>30.5</b>	<b>43.3</b>
hormonal treatment	5.3	3.4
radiotherapy	6.3	7.7
other treatment	3.5	4.3

\*at least 1 assessment during the last 5 months before death (n = 720).

°subpopulation with at least 2 assessments of which at least 1 in period 1 (5 to 3 months before death) and at least 1 in period 2 (2 months before death until death) (n = 209, paired measures).

§head, leukaemia or lymphoma, malignant connective/soft-tissue tumours, skin cancer/malignant melanoma, CNS tumours, secondary/ill-defined malignant tumours, malignant endocrine tumours, malignant bone tumours and other, each less than 3%.

+Karnofsky = Karnofsky Performance Status Scale, assessment tool for functional impairment, range 0-100, lower scores indicate a worse functional status and a worse likelihood of survival.

in period 1 and one in period 2) consisted of 209 participants (29% of all 720 patients). The characteristics of the cohort were not significantly different from those of the total population ( $n = 720$ ) and from those of the participants excluded from the cohort ( $720 - 209 = 511$ , data not shown), except for cancer therapy, comorbidities and KPS. More members of the cohort received cancer therapy, specifically chemotherapy, and suffered from one or more comorbidities compared with the total population and those excluded from the cohort. On average, KPS scores in the cohort were higher than in the total population and in participants excluded from the cohort (Table 8.1).

## Medication use

*Medication use in the cross-sectional observations.* A significant increase in the number of medication groups was observed as death approached, from six groups at 5 months to seven at 1 month before death. Furthermore, a significant decrease was found in the use of cancer therapy, an increase in most medications for specific cancer-related and other symptom relief, and a decrease in medications for long-term prevention.

Cancer therapy (RT excluded) in general decreased significantly from 55% at 5 months to 24% at 1 month before death. Regarding medication specifically for cancer-related symptom relief, opioids were used in 81%, non-opioids in 56%, corticosteroids in 71% and laxatives in 66% of participants during the last month before death, relative to 62%, 60%, 44% and 57% at 5 months before death. Most medications for other symptom relief increased. Heart medication/anti-hypertensives decreased from 38% at 5 months to 27% at 1 month before death (Table 5.2).

*Medication use in the cohort.* Similar trends were found in the paired analyses of the cohort, but with fewer differences that were significant. Cancer therapy in general decreased from 55% in period 1 (= 5 to 3 months before death) to 45% in period 2 (= 2 months before death until death) (Table 5.3).

However, 9% of new courses of chemotherapy were started during period 2 (data not shown). A significant increase was found in the prevalence of opioids (73%–79%), corticosteroids (55%–68%), psychostimulants (1%–5%) and stomach acid-suppressing drugs (65%–71%) between period 1 and period 2. Heart medication/anti-hypertensives decreased significantly from 41% in period 1 to 35% in period 2.

*Association of demographic characteristics with medication use in the cohort.* All demographic characteristics, that is, age, gender, living situation and education, were included in the analyses (data not shown). Only associations with age were found. Generally, chemotherapy and opioid use decreased with higher age (Figure 8.1).

**Table 8.2.** Use of cancer therapy and medication at 5, 4, 3, 2, 1 month<sup>§</sup> time to death.

Medication (%)	Time to death in months					p for trend*	Direction trend
	5 n = 249	4 n = 293	3 n = 361	2 n = 417	1 n = 400		
<b>n of medication groups</b> (max. 16) (excl. cancer therapy) mean (range)	5.67 (0-12)	5.90 (0-11)	6.04 (0-13)	6.43 (0-13)	6.77 (0-13)	<b>&lt;0.001</b>	↑
<b>Cancer therapy (%)</b> :							
all	55.0	57.7	49.3	39.6	24.0	<b>&lt;0.001</b>	↓
chemotherapy	43.8	47.4	36.2	29.7	15.5	<b>&lt;0.001</b>	↓
hormonal treatment	7.4	7.3	5.3	3.4	4.6	<b>&lt;0.001</b>	↓
radiotherapy	4.5	4.2	6.4	6.4	4.3	0.358	
other treatment	4.5	4.2	4.7	4.4	2.8	<b>0.004</b>	↓
<b>Medication specifically for cancer-related symptom relief (%)</b> :							
non-opioid analgesics	59.5	67.8	65.1	63.8	56.4	<b>0.019</b>	↓
opioids	61.8	68.7	71.6	71.4	80.5	<b>&lt;0.001</b>	↑
corticosteroids	43.9	51.6	50.3	60.7	70.6	<b>&lt;0.001</b>	↑
laxatives	56.5	54.8	57.6	61.4	65.5	<b>&lt;0.001</b>	↑
prokinetics/anti-emetics	42.6	42.0	44.9	47.2	44.0	0.378	
psychostimulants	2.5	2.8	3.1	4.2	2.8	0.091	
oral nutritional supplements high protein level	12.6	15.6	15.6	16.3	13.8	<b>0.033</b>	↑
<b>Medication for other symptom relief (%)</b> :							
antidepressants	26.3	25.5	20.3	20.5	21.9	0.213	
neuroleptics	9.6	11.5	11.1	14.8	19.6	<b>&lt;0.001</b>	↑
sedatives/anxiolytics	35.1	34.8	33.1	41.3	46.0	<b>&lt;0.001</b>	↑
stomach acid-suppressing drugs	57.3	61.9	62.3	68.4	67.9	<b>0.002</b>	↑
antibiotics	9.7	9.3	10.2	14.8	18.6	<b>&lt;0.001</b>	↑
diuretics	18.9	18.3	20.8	28.0	28.0	<b>&lt;0.001</b>	↑
antithrombotic agents	27.1	25.9	28.2	36.8	38.3	<b>&lt;0.001</b>	↑
other medication	65.1	62.6	63.7	59.7	63.3	0.223	
<b>Medication for long-term prevention (%)</b> :							
heart medication/anti-hypertensives	37.9	36.6	34.7	32.7	26.9	<b>0.013</b>	↓

<sup>§</sup>5 (4, 3, 2, 1) = medication use in the period of 5-4 (4-3, 3-2, 2-1, 1-0) months before death \*Cochran Armitage for trend in percentages, ANOVA for trend in means.



Changes in medication use in patients with advanced cancer

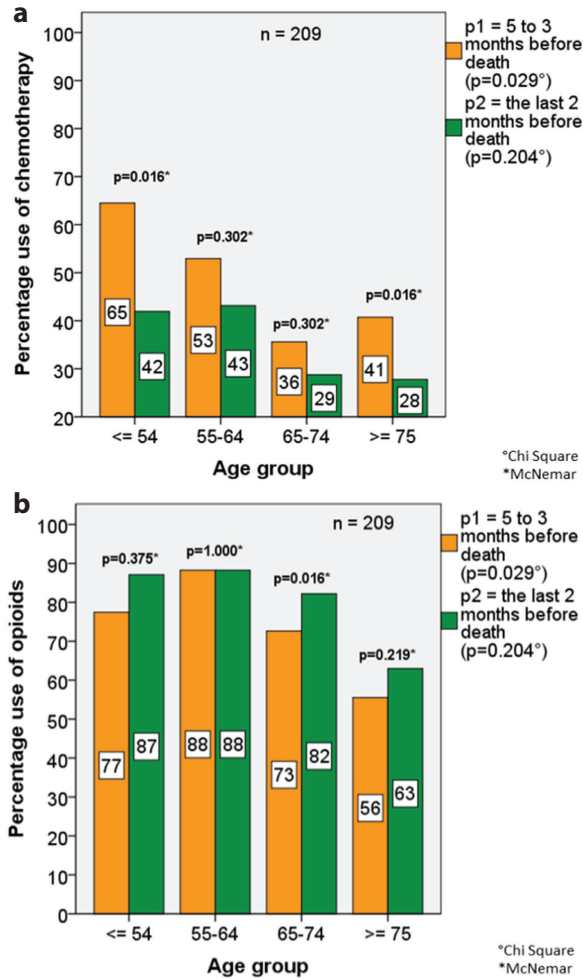
**Table 8.3.** Use of cancer therapy and medication (%) at period1 and period2\$ of the cohort° (n = 209).

Medication (%)	Time to death in months		p for paired samples*	Direction trend
	Period 1 (5-3)	Period 2 (2-0)		
<b>n of medication groups</b> (max. 16) (excl. cancer therapy) mean (range)	6.64 (1-14)	7.11 (1-13)	<b>0.002</b>	↑
<b>Cancer therapy (%)</b> :				
all	55.1	44.5	<b>&lt;0.001</b>	↓
chemotherapy	45.5	34.0	<b>&lt;0.001</b>	↓
hormonal treatment	4.3	2.9	0.250	
radiotherapy	9.6	7.2	0.424	
other treatment	5.7	4.8	0.774	
<b>Medication specifically for cancer-related symptom relief (%)</b> :				
non-opioids	72.2	66.5	0.096	
opioids	72.7	79.4	<b>0.003</b>	↑
corticosteroids	55.1	67.9	<b>0.001</b>	↑
laxatives	63.2	67.9	0.143	
prokinetics/anti-emetics	52.2	55.0	0.504	
psychostimulants	1.4	5.3	<b>0.021</b>	↑
oral nutritional supplements high protein level	17.2	22.0	0.076	
<b>Medication for other symptom relief (%)</b> :				
antidepressants	18.2	23.7	0.052	
neuroleptics	15.8	18.2	0.442	
sedatives/anxiolytics	41.6	43.5	0.665	
stomach acid-suppressing drugs	64.6	71.3	<b>0.034</b>	↑
antibiotics	16.7	17.2	1.000	
diuretics	22.5	27.8	0.052	
antithrombotic agents	36.4	41.6	0.080	
other medication	73.2	68.9	0.222	
<b>Medication for long-term prevention (%)</b> :				
heart medication/anti-hypertensives	41.1	35.4	<b>0.029</b>	↓

\$period 1 = 5 to 3 months before death, period 2 is 2 months before death until death.

°participants with at least 2 assessments during the last 5 months before death, of which at least 1 assessment in period 1 and at least 1 assessment in period 2.

\*McNemar for percentages, paired samples t-test for means.



**Figure 8.1.** Association between age and chemotherapy (a), and opioid use (b) in the cohort in period1 (p1) and period2 (p2) (n = 209).

°participants with at least 2 assessments during the last 5 months before death, of which at least 1 assessment in period 1 and at least 1 assessment in period 2.

\$period 1 = 5 to 3 months before death, period 2 is 2 months before death until death.

## Discussion and conclusion

### Main findings

To the best of our knowledge, this was the first international multicentre cohort study on medication use in advanced cancer patients already receiving palliative care. Both longitudinal and cross-sectional data on medication use were analysed. The number of medication groups increased significantly from six at 5 months before death to seven at 1 month before. From 5 to 1 month(s) before death, cancer therapy (RT excluded) in general decreased (from 55% to 24%), most medications for cancer-related and other symptom relief increased (e.g. opioids from 62% to 81% and sedatives from 35% to 46%) and medication for long-term prevention (heart medication/anti-hypertensives) decreased (from 38% to 27%).

The results of this study confirm our a priori hypothesis, but show important differences in the extent of usage in the different medication groups. Although our population consisted of advanced cancer patients receiving palliative care, and patients being treated with chemotherapy with possible curative intent were excluded, our findings show a relatively high use of chemotherapy even close to death. Most participating centres were hospitals and provided cancer therapy as part of their palliative care programme, which might partly explain these findings (21). Both categories of medication for symptom relief (specific cancer-related and other) increased towards death, which is in accordance with the definition of palliative care, emphasizing the importance of symptom treatment to support and improve quality of life (5), as is recommended as good practice (6).

The decrease in prevalence of cancer therapy and medication for long-term prevention when death approaches may indicate the existence of a practice of de-prescribing.

### Strengths and limitations

This is probably one of the largest prospective studies in a specifically defined palliative care population (n = 720) conducted in a variety of palliative care settings across Europe and beyond. Moreover, data collection was standardized, using validated measures (e.g. KPS) to improve generalizability of results. Nevertheless, our study has some limitations which need to be acknowledged. First, data collection of medication in 19 not mutually exclusive medication groups was rather coarse grained, which may have led to some misclassification by healthcare professionals. However, this classification was straightforward and comprehensible for all healthcare professionals responsible for filling in the questionnaire. Data on prescribed

daily dosage were not available, which may mask more subtle ways of deprescribing. Second, although based on expert opinion, our grouping of medications into four main categories was also coarse grained. Some medications could not be unequivocally assigned to one category, and differences between some therapeutic groups were unclear, even to experts, who nevertheless agreed on the final categorization. However, many medication groups were not listed, especially in the section of medication for long-term prevention.

Therefore, our results regarding the overall number of medication groups and specifically the category for long-term prevention are probably an underestimation of the actual number. Third, our five cross-sectional subsamples consist of repeated measures for some but not all included patients. Therefore, we used statistical techniques for unpaired analyses for the cross-sectional population. The point of 5 months before death was chosen as the earliest because of the sample size, which was still 249 at 5 months before death, declining to 185 at 6 months before death. Moreover, in these subsamples, the number of participants increased from 249 (at month 5) to 417 (at month 2) and decreased to 400 during the last month before death. This is probably due to loss to follow-up caused by deterioration of the patient's condition at the time of that month's assessment. In addition, the inclusion criteria for our analyses reduced the number of participants from 720 to 209. For paired analyses, only 209 were available, which is a relatively small sample. On one hand, this small sample size and the difference in characteristics between the cohort and the total population may cause some bias, while on the other hand, the cross-sectional findings in the larger sample confirm those of the cohort, indicating that the bias was probably of minor effect. Finally, the prevalence of medication use and practices regarding prescribing and deprescribing may vary by site and country, but the available data did not allow to make any statements about these aspects.

## Interpretation of results in the context of the literature

We found a relatively high use of cancer therapy, and specifically of chemotherapy, which was prescribed to 15.5% of participants as late as 1 month before death (coming from 44% at 5 months). Other studies show varying percentages of chemotherapy use in advanced cancer patients during the last month of life, ranging from 10% to 29% (27–31). Chemotherapy is usually provided to advanced cancer patients aiming to relieve symptom burden and/or prolong life. However, earlier research shows that this treatment does not enhance survival nor improve quality of life near death, and it is associated with more aggressive life-prolonging care, a high risk of adverse events and higher end-of-life care costs (32–34). The American Society of Clinical Oncology (ASCO) recommends avoidance of the use of chemotherapy

near the end of life, particularly for patients with a poor performance status who have not responded to earlier lines of treatment and who are not eligible to participate in clinical trials (32, 35). Palliative chemotherapy might be useful, but the real intent of this therapy remained unclear from the available data. Intensive treatment with chemotherapy at this stage should remain subject of discussion. The focus at the end of life should be on shared decision making and patient–physician communication in order to extend targeted medical cancer treatment with personalized palliative considerations regarding the appropriate level of treatment intensity (31, 36). Integration of palliative care into oncology might stimulate a shift in focus towards symptom palliation and psychological and spiritual/existential support for patients for whom further chemotherapy is almost certain to have no benefit at all (32).

We found an increasing use of medication for symptom relief, which has been confirmed in other studies in advanced cancer patients (4, 37–40). During the last month before death, we found a high use of opioids (81%) and corticosteroids (71%), while fewer non-opioids were given, which is in line with earlier research (39, 41). Concordant with previous studies, we found a steady reduction in heart medication/anti-hypertensives as death approached (4, 37).

## Implications for research and clinical practice

The primary aim of pharmacotherapy in palliative care should be symptom relief and preservation of quality of life, taking into account patient preferences. In this study, nearly all medications for symptom relief increased when death approached, as recommended in clinical practice guidelines for high-quality palliative care (6).

Our results regarding the prevalence of cancer therapy and heart medication in relation to time before death indicate a practice of deprescribing in palliative cancer care. Still, the proportion of these medications during the last months of life remained high. These results emphasize the complexity of pharmacotherapy and determining the appropriateness of medication at the end of life. Clear evidence-based practical guidelines regarding deprescribing in advanced disease are needed. This may support physicians and patients in making decisions about discontinuation of anti-cancer and other medications that may have discernible effects at this stage of life (e.g. by systematic symptom-driven medication review). Future research should focus on the development of deprescribing guidelines, interventions for medication review and implementation strategies.

Regarding palliative chemotherapy, it is crucial to identify those patients who are likely to benefit from it close to death, for example, using validated prognostic scores and/or assessing a patient's symptom burden and quality of life prior to and during treatment (31, 42, 43).

## Conclusion

The prevalence of medication use for specific cancer-related and other symptom relief increased in almost all medication groups among advanced cancer patients in the last months before death. Deprescribing was found in heart medication/anti-hypertensives and cancer therapy, although the use of the latter remained relatively high.

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## Chapter 9

# Barriers and enablers to deprescribing in people with a life-limiting disease: *A systematic review*

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## Abstract

**Background:** Knowing the barriers/enablers to deprescribing in people with a life-limiting disease is crucial for the development of successful deprescribing interventions. These barriers/enablers have been studied, but the available evidence has not been summarized in a systematic review.

**Aim:** To identify the barriers/enablers to deprescribing of medications in people with a life-limiting disease.

**Design:** Systematic review, registered in PROSPERO (CRD42017073693).

**Data sources:** A systematic search of MEDLINE, Embase, Web of Science and CENTRAL was conducted and extended with a handsearch. Peer-reviewed, primary studies reporting on barriers/enablers to deprescribing in the context of explicit life-limiting disease were included in this review.

**Results:** A total of 1026 references were checked. Five studies met the criteria and were included in this review. Three types of barriers/enablers were found: organizational, professional and patient (family)-related barriers/enablers. The most prominent enablers were organizational support (e.g. for standardized medication review), involvement of multidisciplinary teams in medication review and the perception of the importance of coming to a joint decision regarding deprescribing, which highlighted the need for interdisciplinary collaboration and involving the patient and his family in the decision-making process. The most important barriers were shortages in staff and the perceived difficulty or resistance of the nursing home resident's family – or the resident himself.

**Conclusion and implications of key findings:** The scarcity of findings in the literature highlights the importance of filling this gap. Further research should focus on deepening the knowledge on these barriers/enablers in order to develop sustainable multifaceted deprescribing interventions in palliative care.

## Introduction

People with a life-limiting disease are often confronted with a high symptom and drug burden. Research has demonstrated that these people use a mean number of medications between 7 and 11, with a prevalence of polypharmacy (5–9 chronic medications) of 25%–84% and an excessive polypharmacy of 28%–69% ( $\geq 10$ ) (1–3). In these people, medications for symptom relief are often combined with medications to treat their life-limiting disease and comorbidities, and with medications for long-term prevention (3). The latter category is usually considered to be inappropriate at the end of life, because of a lack of short-time benefit. Moreover, drug–drug interactions with medications for symptom relief (e.g. with anti-emetics, neuroleptics) are common (4–6). Earlier studies have found a relatively high prevalence of medications for long-term prevention: for example, 8%–22% for lipid-modifying agents (7, 8), 23% for anticoagulants (2, 7), 10%–56% for anti-platelets (1, 2, 7), 58% for anti-hypertensives (1), and 20%–36% for anti-dementia in people with advanced dementia (8, 9).

Discontinuation of inappropriate medications or deprescribing would reduce the drug burden, decrease the number of drug–drug interactions and might improve quality of life in people with a life-limiting disease (3, 10–12). The term ‘deprescribing’ is used to describe the process required for safe and effective cessation of medication (13). Deprescribing is the process of withdrawal of an inappropriate medication, supervised by a healthcare professional with the goal of managing polypharmacy and improving outcomes (14). Following from this definition, end-of-life non-treatment decisions, such as not initiating a curative treatment when death is imminent (e.g. chemotherapy, antibiotics), are not considered as deprescribing. Deprescribing can be defined as ‘the systematic process of identifying and discontinuing drugs in instances in which existing or potential harms outweigh existing or potential benefits within the context of an individual patient’s care goals, current level of functioning, life-expectancy, values, and preferences’ (15). Earlier studies have demonstrated physical and cognitive benefits, and no significant harm, to be related to deprescribing of anti-hypertensives, benzodiazepines, neuroleptics and statins in patients with a life-limiting disease (16–18).

Five relevant systematic reviews about the topic of deprescribing were published earlier (19–23), three of which focused on barriers/enablers of deprescribing in people with a normal life-expectancy (19, 22, 23). One systematic review focused on the use of preventive medications in patients with reduced life expectancy (21), and one on the discontinuation of preventive medications in older adults with a life-limiting disease (20). However, the barriers/enablers to deprescribing in people with a life-

limiting disease were not described in these reviews.

Multiple competing barriers and enablers can influence a patient and physician's decision to stop or reduce a medication, such as beliefs, knowledge and attitudes of the prescriber and the patient (19, 23). Barriers and enablers to deprescribing in people with a life-limiting disease have been studied before, but the available evidence has not been summarized in a systematic review yet. Knowing

these barriers and enablers is crucial to guide the development and implementation of sustainable deprescribing interventions. Therefore, the purpose of this systematic review is to identify factors that facilitate and/or hinder deprescribing of medications in people with a life-limiting disease.

## Methods

This systematic review was performed conforming to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) standardized guidelines to ensure quality and clarity (24). The protocol of this systematic review was developed according to the Cochrane Guidelines for review protocols and the PRISMA statement for protocols (25,26). This protocol was registered in PROSPERO (registration no. CRD42017073693) and can be accessed at [www.crd.york.ac.uk/PROSPERO](http://www.crd.york.ac.uk/PROSPERO).

### Eligibility criteria

No limits were placed on the type of methods used in the studies (quantitative, qualitative or mixed), or on time/date, or on language for full texts.

#### *Inclusion criteria*

- Peer-reviewed, primary studies reporting original data, with a clearly formulated research question, and an abstract in English;
- Population – people with any of the following life-limiting diseases: advanced cancer, heart failure, COPD, renal failure, dementia and/or receiving palliative care;
- Scope of the study – deprescribing of medications in the context of explicit life-limiting disease;
- Topic – barriers and/or enablers to deprescribing.

#### *Exclusion criteria*

- Case reports, case series, letters to the editor and opinion papers.

## Search methods

First, four electronic databases were systematically searched for relevant studies: MEDLINE (via the PubMed interface), Embase, Web of Science and CENTRAL (Cochrane Central Register of Controlled Trials) from the date of inception until 12th September 2017. A combination of controlled vocabulary and free text words was used to search in titles and abstracts. The final keywords used were (deprescri\* or (withholding treatment and drug prescription) or ( (discontinuati\* or withdrawal or cessation or tapering or stop\*) and (medication or drug treatment))) AND (challeng\* or enabler\* or facilitat\* or barrier\* or belief\* or perception\* or attitude\* or perspective\* or preference\* or insight\* or view\* or health knowledge) AND (frail elderly or palliative care or dementia or chronic obstructive pulmonary disease or advanced cancer or heart failure or renal failure or life-limiting disease or life-threatening disease or limited life-expectancy). The full electronic search strategy for MEDLINE can be found in Appendix 1. Second, the cited and citing references of the included studies were checked via Web of Science. Third, the first author of every included study and 10 known experts in the field of deprescribing were contacted for additional peer-reviewed studies. Finally, the most recent issues (September 2016–September 2017) of *Drugs & Aging* and *Journal of the American Geriatrics Society (JAGS)* were hand searched for more articles.

## Data collection and analysis

*Selection of studies.* In a first phase, the selection was based on title and abstract and, in a second phase, on full text. In both phases, selection was performed by two independent reviewers (K.P. and R.V.S.), using the Covidence (27) tool. Disagreement about the relevance of studies was resolved by discussion, and where necessary a third reviewer (M.E.) was consulted for arbitration. Endnote X8 citation management software was used for deduplication of references. Multiple reports of the same study were collated.

*Data extraction and management.* Characteristics of the included studies were extracted using a self-developed data extraction form. One reviewer (K.P.) extracted data on country, type of research, method, research question (aim), setting, participants and scope of the study. These data were checked by the second reviewer (R.V.S.). Two reviewers (K.P. and R.V.S.) independently extracted data on barriers/enablers. Discrepancies between reviewers were discussed and, where consensus could not be reached, a third reviewer (M.E.) was consulted for arbitration.

Data on the topic of this review were classified as barriers and/or enablers to deprescribing of medications in the context of explicit life-limiting disease. Barriers

and enablers were reported as mentioned in the article. Where information was missing or clarification was needed, authors of primary studies were contacted, using email addresses in the study's publication.

*Quality assessment.* The quality assessment was conducted by two reviewers (K.P. and R.V.S.) independently. Disagreement was resolved by discussion, and if necessary a third reviewer (M.E.) was consulted for arbitration. The quality of studies was appraised using the Critical Appraisal Skills Programme (CASP) (28). Since no CASP tool was available for cross-sectional studies, the Critical Appraisal Checklist for Cross-Sectional Study and The Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Analytical Cross-Sectional Studies were used (29, 30). The assessment tools used in this systematic review are different from the protocol. Instead, we chose quality assessment tools that were best fit and comprehensive for the studies we had selected. Total quality assessment scores for all studies were presented as scores on a scale from 0 to 10. The individual studies were categorized as high-quality studies (scores from 9 to 10), medium-quality studies (scores from 6 to 8) and low-quality studies (scores equal to 5 or less).

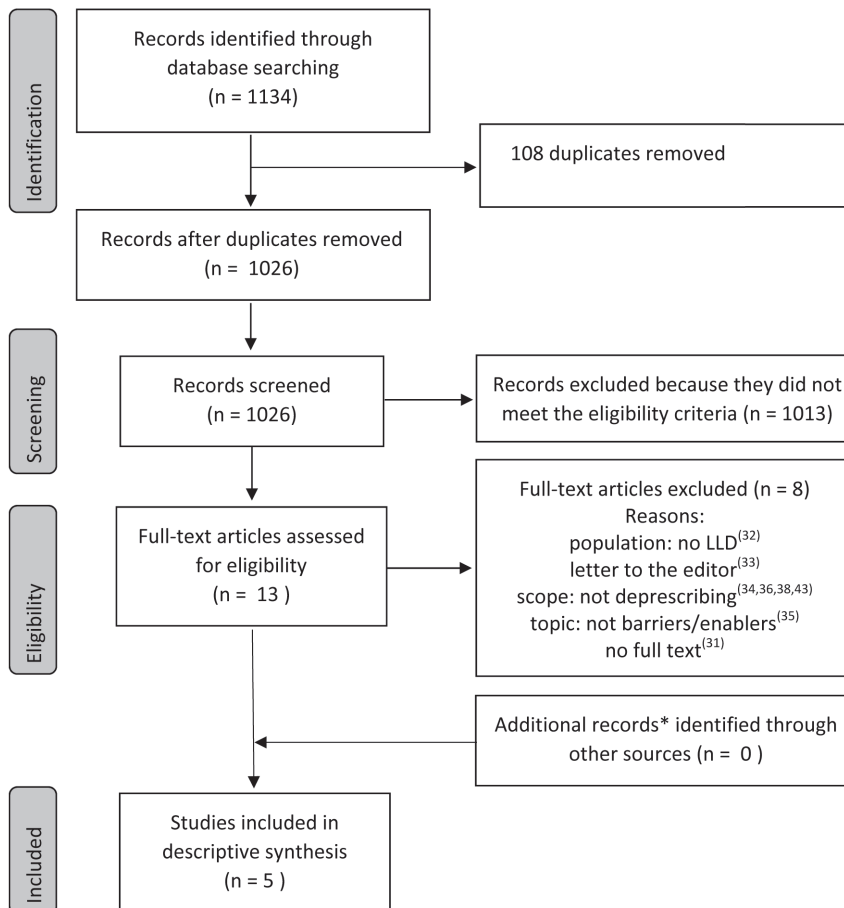
*Data analyses.* Because of the nature of the topic of this systematic review, the results were reported in a pragmatic and descriptive way with textual data from the studies included.

## Results

### Study selection

The electronic searches resulted in 1134 potentially eligible records retrieved from the four databases. After removing 108 duplicates, 1026 records were assessed for eligibility based on title and abstract. Full texts of the 13 articles that appeared to potentially meet the inclusion criteria were sought (31–43). Full-text screening of those 13 records resulted in the exclusion of 8 articles because they did not meet the inclusion criteria (31–36, 38, 43). The remaining five articles were included in this review (37, 39–42). Checking the cited and citing references of the included studies in Web of Science did not lead to any additional studies, nor did the hand search in Drugs & Aging and JAGS. The first authors of the included studies and 10 known experts in the field of deprescribing were contacted by email. This resulted in one additional manuscript, which reported on the same study as Sawan et al. (39, 44) and, thus, both manuscripts were collated. Figure 9.1 provides more details on the study selection results.





**Figure 9.1.** Flow diagram with the study selection results.

\*one additional manuscript was found (44) reporting on the same study as one of the already included manuscripts (39). Both manuscripts were collated.

## Characteristics and quality assessment of relevant studies

Only five studies were found, of which two were qualitative studies (39, 42, 44), two were quantitative cross-sectional studies using a survey design (37, 40) and one was a secondary analysis of baseline data from a pragmatic clinical trial (41). Quality scores ranged from 6 to 8 on a scale of 10 for the quantitative studies. Both qualitative studies scored a 9 out of 10. Based on these scores, all quantitative studies were appraised as medium-quality studies and both qualitative studies as high-quality studies (Table 9.1).

**Table 9.1.** Characteristics and quality assessment of relevant studies.

Study (year)	Country	Type of research	Research question / aim	Method	N	Setting	Participants	Scope of the study	Quality assessment*
A. Parsons et al. (2014) (37)	Northern Ireland (NI) & Republic of Ireland (RoI)	Quantitative (cross-sectional survey)	To evaluate the extent to which patient-related factors and physicians' country of practice influence decision-making regarding medication use (continuing or discontinuing) in patients with end-stage dementia	Factorial survey design comprising four vignettes	662	Primary care (general practice) and hospitals (geriatric medicine)	General practitioners (GPs) and hospital physicians in NI and RoI	Withholding or continuation / discontinuation of key medications in patients with end-stage dementia	8
B. Shega et al (2009) (40)	USA	Quantitative (cross-sectional survey)	To describe hospice medical directors practice patterns and experiences in the use and discontinuation of cholinesterase inhibitors and NMDA receptor antagonists in hospice patients that meet the Medicare hospice criteria for dementia	Mail survey with multiple choice questions and hypothetical vignettes	152	A random sample of 500 hospice sites in the USA	Hospice medical directors	Discontinuation of cholinesterase inhibitors and NMDA receptor antagonists in hospice patients that meet the Medicare criteria for dementia	7
C. Sawan et al. (2016 & 2017) (39, 44)	Australia	Qualitative	To explore how visible artefacts in nursing homes influenced the prescribing and use (initiation, administration, monitoring, continuation, and cessation) of psychotropic medicines and how these artefacts were operationalized across nursing homes, from the perspective of on site and visiting staff	Semi-structured interviews	40	8 high care, low care, and high care specific dementia nursing homes	On-site and visiting staff (managers, registered nurses, nursing assistants, GPs, pharmacists, specialist medical practitioner)	Use of psychotropic medicines for management of BPSD (Behavioural and Psychological Symptoms of Dementia) in nursing homes	9

D. Tjia	USA	Quantitative (cross-sectional, but using baseline data from a multicentre, pragmatic clinical trial)	To quantify the perceived benefits and concerns of statin discontinuation among patients with life-limiting disease (LLD)	Questionnaire (nine self-developed questions regarding patients' perceptions about discontinuing statins)	297	10 academic medical centers and 5 community-based hospice / palliative care organizations	Cognitively intact patients with LLD, 62% cancer patients, 14% COPD, 8% cardiovascular disease, 4% renal disease, 12% other	Discontinuation of statins	6
E. Todd	UK	Qualitative (phenomenology)	To explore the lived experience of patients, carers and healthcare professionals in the context of medication use in life-limiting illness (LLI)	In-depth interviews	36	Day care centre at a specialist palliative care unit	12 patients with a life-expectancy <18 months (7 cancer patients, 2 COPD, 1 heart failure, 2 other disease); 12 healthcare professionals (3 palliative medicine consultants, 3 advanced nurse practitioners, 6GPs), 12 carers (all family members of the patient)	Medication use in LLI and deprescribing of statins	9

\*CASP for qualitative studies (28), Critical Appraisal Checklist for Cross-Sectional Study for Surveys (30), JBI Critical Appraisal Checklist for Analytical Cross-Sectional Studies (29). Total quality assessment scores for all studies presented as scores on a scale from 0 to 10.

## Barriers and enablers to deprescribing

Different types of barriers and enablers were found and categorized as organizational, professional and patient/family-related barriers and enablers. Two studies reported on organizational and professional barriers/enablers (39, 40, 44), one study on professional and patient/family-related barriers/enablers (42), one study only reported on organizational barriers/enablers (37) and one study only described patient/family-related barriers/enablers (41). Table 9.2 provides a detailed overview of the barriers/enablers identified in the literature.

**Table 9.2.** Barriers and enablers to deprescribing identified in the literature.

	Barriers	Enablers
<b>Organizational</b>	<p><b>Contextual factors:</b></p> <ul style="list-style-type: none"> <li>→ <u>shortages in staff levels</u> at night time hindered deprescribing of psychotropic medications<sup>C</sup></li> <li>→ involvement of nursing assistants in care decisions involving psychotropic medications <u>not supported by management</u> hindered nursing assistants to participate while such participation contributed to cessation<sup>C</sup></li> </ul>	<p><b>Contextual factors:</b></p> <ul style="list-style-type: none"> <li>→ when discontinuation of cholinesterase inhibitors and NMDA receptor antagonists is a <u>part of the hospice care plan</u> for patients with advanced dementia, those medications are more likely to be discontinued<sup>B</sup></li> <li>→ <u>formally organized drugs and therapeutic committee meetings</u> (e.g. MAC meetings in Australia, audits, case conferences) raised awareness of GPs to review the continued use of psychotropic medications<sup>C</sup></li> <li>→ <u>pharmacist led medication review</u> can be used as a lever to implement changes such as cessation of psychotropic medications<sup>C</sup></li> <li>→ <u>formal case conference meetings with families</u> at NH admission to discuss the resident's medication history often resulted in cessation<sup>C</sup></li> <li>→ <u>positive attitude of NH management</u> towards non-pharmacological treatment of behavioural and sleep disturbances resulted in NH staff highlighting the need to review continuation of psychotropic medications to the GP when the welfare of the resident became a concern<sup>C</sup></li> <li>→ <u>support of management</u> for interdisciplinary participation in medication review contributed to cessation of psychotropic medications<sup>C</sup></li> </ul>
	<p><b>Care setting:</b> /</p>	<p><b>Care setting:</b></p> <ul style="list-style-type: none"> <li>→ Place of residence: when the patient was <u>resident in hospital (compared with resident at home or in a nursing home (NH))</u> it was more likely that simvastatin and quetiapine would be discontinued in patients with dementia at the end of life<sup>A</sup></li> </ul>

	Barriers	Enablers
	<p><b>National healthcare system:</b></p> <p>→ <u>Physician's country of residence</u>: if the physician practiced in Republic of Ireland (RoI) (compared with Northern Ireland (NI)) it was less likely that quetiapine was discontinued in patients with dementia at the end of life<sup>A</sup></p>	<p><b>National healthcare system:</b></p> <p>→ <u>Physician's country of residence</u>: If the physician practiced in hospital in RoI (compared with NI) it was more likely that donepezil hydrochloride and memantine hydrochloride were discontinued in patients with dementia at the end of life<sup>A</sup></p>
Professional	<p><b>Perceived patient related characteristics:</b></p> <p>→ <u>perceived difficulty or resistance of family</u> regarding deprescribing can be a barrier for physicians to discontinue cholinesterase inhibitors and NMDA receptor antagonists<sup>B</sup></p> <p>→ <u>resistance from the resident's family or the resident</u> himself was challenging for the NH staff and GPs when attempting to withdraw psychotropic medications<sup>C</sup></p>	<p><b>Perceived patient related characteristics:</b></p> <p>→ NH staff found it important to <u>explain the pros and cons</u> of use of psychotropic medications to the resident and his family to facilitate withdrawal<sup>C</sup></p>
	<p><b>Perceived medication related characteristics:</b></p> <p>→ <u>physicians</u> were significantly less likely to recommend discontinuing cholinesterase inhibitors and NMDA receptor antagonists if they <u>believe that these therapies have positive effects</u><sup>B</sup></p> <p>→ physicians were significantly less likely to recommend discontinuing cholinesterase inhibitors and NMDA receptor antagonists if <u>they believe that discontinuation has negative effects</u><sup>B</sup></p> <p>→ once treatment with psychotropic medications was initiated, most <u>GPs felt that cessation was unwelcomed by NH staff as it would result in escalation of behavioural and sleep disturbances and increase their workload</u><sup>C</sup></p>	<p><b>Perceived medication related characteristics:</b></p> <p>→ the acknowledgement that medications were burdensome interventions facilitated a willingness to rationalize them in this context<sup>E</sup></p>
	<p><b>Perceived knowledge:</b></p> <p>→ <u>nursing assistants' uncertainty about their ability to participate in medication review</u> because of their level of medical knowledge was perceived as a barrier to provide any input in medication review (such participation contributed to cessation of psychotropic medications)<sup>C</sup></p>	<p><b>Perceived knowledge:</b></p> <p>/</p>
	<p><b>Interdisciplinary communication:</b></p> <p>→ <u>healthcare professionals found communicating with each other frustrating</u> given the complexity of care for patients with life-limiting illness and this was acknowledged as a barrier to change. This challenge was particularly evident for the interfaces between primary, secondary and tertiary care<sup>E</sup></p> <p>→ <u>traditional and hierarchical norms in physicians</u> hinder nurses to present their suggestions for review and cessation of psychotropic medications<sup>C</sup></p> <p>→ <u>absence of GPs in formal drug and committee meetings hindered communication of concerns regarding prescribing</u> of psychotropic medications<sup>C</sup></p>	<p><b>Interdisciplinary communication:</b></p> <p>→ <u>coming to a joint decision between healthcare professional, patient and carer</u> was perceived as important by all participants when considering deprescribing medications<sup>E</sup></p> <p>→ <u>collegial attitude of GPs towards NH staff and their feedback and suggestions</u> facilitated the review and cessation of psychotropic medications<sup>C</sup></p>

	Barriers	Enablers
Patient/family related	<p><b>Perceived medication related characteristics:</b></p> <p>→potential risks and concerns related to discontinuation<sup>D</sup>:</p> <ul style="list-style-type: none"> <li>that they will experience another problem in addition to those they already have</li> <li>that they have been previously told they should never discontinue their statins</li> <li>that stopping would mean that all previous effort was wasted</li> <li>that stopping means that their doctor has given up on treating them</li> <li>that stopping means that their doctor thinks they are about to die</li> </ul>	<p><b>Perceived medication related characteristics:</b></p> <p>→potential benefits about discontinuation<sup>D</sup>:</p> <ul style="list-style-type: none"> <li>that if they stop their statins, they will spend less money on medications</li> <li>that if they stop their statins, they will have a better quality of life</li> <li>that if they stop their statins, they will have fewer symptoms</li> <li>that if they stop their statins, they may be able to stop other medications that they take</li> </ul> <p>→patients with cardiovascular disease as their primary diagnosis were significantly <u>more likely to respond that they may be able to stop other medications if they stop their statins</u><sup>D</sup></p> <p>→patients with cardiovascular disease as their primary diagnosis were significantly more likely than the two other diagnosis groups to agree that stopping statins may result in fewer symptoms or better quality of life<sup>D</sup></p> <p>→In many cases, patients were <u>overwhelmed by the volume of medications</u>, which was further exacerbated when patients had difficulty in swallowing medication → facilitated the willingness for change<sup>E</sup></p>
	<p><b>Communication with healthcare professionals:</b></p> <p>→In some cases, when medication was initiated, <u>patients were told that they would be taking this medication for 'the rest of their life'</u>: this was literally interpreted by patients that they would be taking the medication until the day they died. This experience created a mismatch of expectations between healthcare professional and patient and carer regarding treatment and appeared to be a significant barrier to deprescribing approaches<sup>E</sup></p>	<p><b>Communication with healthcare professionals:</b></p> <p>→ (family) carers would embrace deprescribing approaches, <u>providing the risks and benefits were properly explained</u> and it was done for the benefit of the patient<sup>E</sup></p> <p>→<u>coming to a joint decision between healthcare professional, patient and carer</u> was perceived as important by all participants when considering deprescribing medications<sup>E</sup></p>

A: Parsons et al. (2014) (37); B: Shega et al. (2009) (40); C: Sawan et al. (2016 & 2017) (39, 44); D: Tjia et al. (2017) (41); E: Todd et al. (2016) (42).

Studies A, B and D are quantitative studies, studies C and E are qualitative studies.

## Organizational barriers and enablers

*Contextual factors.* Shortages in staff levels and lack of organizational support were described as barriers in one study, for example, inadequate staffing and training when handling behavioural disturbances caused reliance on psychotropic medications and hindered deprescribing (39, 44). The same study found that formally organized events, supported by the nursing home (NH) management, were enablers (39, 44). This was the case for drugs and therapeutic committee meetings when they were utilized by managers to highlight the overuse of psychotropic medications or for case conferencing of individual residents, and for pharmacist-led medication management reviews. Moreover, one study found that discontinuation of medication as part of the hospice care plan can be an enabler to deprescribing: 80% of hospice medical directors would recommend deprescribing of cholinesterase inhibitor and N-methyl-D-aspartic acid receptor antagonists in these circumstances (40).

*Care setting.* One study found that the patient's residence was an enabler: simvastatin and quetiapine were more likely to be discontinued in hospitalized patients with dementia (37).

*National healthcare system.* One study found that the national healthcare system can be a barrier as well as an enabler (37).

## Professional barriers and enablers

*Perceived patient-related characteristics.* Two studies described the perceived difficulty or resistance of the NH resident's family – or the resident himself – as a barrier (39, 40, 44). One study described communication with the resident and his family as an enabler: explaining the pros and cons of psychotropic medications facilitated deprescribing (39, 44)

*Perceived medication-related characteristics.* Physicians' perceived benefits of medications and negative effects of deprescribing were described as barriers in one study (40). Another study described negative reactions of NH staff towards the prescriber as a barrier: physicians felt that cessation of psychotropic medications was unwelcomed by NH staff because they feared escalation of behavioural and sleep disturbances, resulting in an increase in their workload (39, 44). One study found that the acknowledgement that medications were burdensome interventions was an enabler (42).

*Perceived knowledge.* One study found that nursing assistants' uncertainty about their level of medical knowledge was a barrier to provide any input in medication review, while this input was found to facilitate deprescribing of psychotropic medi-

cations (39, 44).

*Interdisciplinary communication.* Two studies found that interdisciplinary communication can be a barrier as well as an enabler, for example, the complexity of care can hinder discussing changes in medication, a collegial attitude of physicians towards the involvement of NH staff in medication review facilitates deprescribing of psychotropic medications (39, 42, 44).

## Patient/family-related barriers and enablers

*Perceived medication-related characteristics.* One study found that the patient's perception of potential risks and concerns can be a barrier towards deprescribing. On the contrary, the patient's perception of potential benefits was found to facilitate deprescribing (41). Another study described the volume of medications and difficulties with swallowing as enablers (42).

*Communication with healthcare professionals.* One study found that a mismatch of expectations between healthcare professional and patient and carer regarding treatment was a barrier (42). The same study described shared decision-making as an enabler (42).

## Discussion

### Main findings

To the best of our knowledge, this is the first study providing a systematic overview of the existing literature about barriers and enablers to deprescribing in people with a life-limiting disease. Only five studies, describing three different types of barriers/enablers were found: organizational, professional and patient/family-related barriers/enablers. The most prominent factors were organizational support (e.g. for standardized interdisciplinary medication review), interdisciplinary communication and collaboration, and communication with the patient and his family.

### Interpretation in the context of literature

Research on the barriers/enablers to deprescribing of medications in people with a life-limiting disease is scarce, which is highlighted by this limited collection of findings from the literature. Deprescribing of potentially inappropriate medications (PIMs) is more intensely studied in the broader context of older adults with a normal life-expectancy, with regard to type of intervention as well as to its barriers/enablers (23, 45). These findings are not entirely transferable to a population with a limited



life-expectancy and to palliative care, since the medical focus on long-term profit changes entirely into a focus on the different aspects of comfort of the individual. In this context, all medications for primary and secondary prevention are eligible for deprescribing, while restrictions regarding addiction (e.g. to opioids) are irrelevant when short-term benefit and comfort have absolute priority. Nevertheless, we found some similarities. As in studies in older adults, we found that pharmacist-led medication reviews may improve prescribing appropriateness (46, 47). Furthermore, involvement of multidisciplinary teams (e.g. audit and feedback at multidisciplinary meetings) and regulatory policies (e.g. mandatory pharmacy services in NHs), which were acknowledged as enablers for deprescribing in this review, positively affected inappropriate prescribing in other studies (19, 46, 48, 49). One important barrier regarding multidisciplinary meetings that was not described in any of the selected studies for this review is the limited time available for GPs and other healthcare professionals to discuss goals of care and to closely monitor patients after treatment discontinuation. Deprescribing is time consuming, and additional time is required to implement a strategic approach to deprescribing (48–50). The average primary care physician consultation length varies internationally from 48 s to 22.5 min, which is likely to negatively affect patient care (51). Finding additional time to participate in multidisciplinary meetings aiming to review and deprescribe unnecessary medications is a critical impediment for physicians' willingness to attend these meetings (48).

Concordant with the findings of Dilles et al. (52), we found that the input of nurses in medication review, that is, by reporting their observations of symptom and drug burden, may facilitate medication changes. Consistent with Turner et al. (53), both interdisciplinary communication and communication with the patient and/or his family (e.g. in case of resistance towards deprescribing) were considered to be challenging for healthcare professionals. Earlier research has demonstrated that NH residents and their families have minimal experience in discussing and questioning prescribing decisions with the physician (48). Residents and their families appear to have strong expectations about medications keeping them alive or prolonging their life, which can result in fear of deprescribing (48). Physicians fear to upset patients and their families if their recommendations to deprescribe are misinterpreted as a sign that they are giving up on the patient, or as withdrawal of care (49, 50). Moreover, they fear that patients experience a deterioration in their health or a potentially preventable outcome shortly following deprescribing (49, 50). Discussing medication-related issues and involving the patient (and his family) in prescribing and deprescribing decisions might counterbalance these potential misbeliefs and misinterpretations. In this study, the perceived value of interdisciplinary collabora-

tion and involving the patient and his family in the decision-making process was highlighted by the perception of the importance of coming to a joint decision regarding deprescribing interventions. This was found to be essential for successful implementation of interventions aiming to reduce inappropriate medication use in earlier research (46).

Our results are similar in many respects to those from previous studies on barriers/enablers of deprescribing in people with a normal life expectancy (19, 22, 23), but we did not find any specific barriers/enablers to deprescribing in the context of explicit life-limiting disease or palliative care.

This finding supports our assumption that the same barriers/enablers to deprescribing play a role in palliative care as in general care. However, these barriers/enablers might be more compelling and urgent in palliative care, due to the patient's limited life-expectancy. In this context, we would like to point out some relevant issues. First, the probability of drug–drug interactions with medications for symptom relief should facilitate deprescribing of futile medications which lack short-term benefit in palliative care, but this was not described as an enabler in any of the studies included in this systematic review (12). It remains an open question whether this is an indication of prognostic uncertainty or an unreasonable tenacity to continue treatment that has no benefit, regarding the use of preventive medications in patients with a life-limiting disease. Second, advance care planning embedded in routine and standard care in the facility should provide opportunities to discuss patient preferences regarding care goals and treatment targets, and facilitate deprescribing of preventive medications. Shega et al. (40) found that discontinuation of medications at the time of hospice enrolment facilitated deprescribing for patients with advanced dementia, but also reported that three-quarters of families have difficulty stopping these therapies. Moreover, this enabler was described in none of the other studies. Finally, this raises the important question of whether conversations about deprescribing are more difficult in a palliative care context compared to general care. One of the most important reasons for continuing futile treatment is lack of communication between the medical team and the patient and/or his family. It is therefore strongly recommended that options regarding futile treatment and palliative care are discussed with the patient and his family (54). Although the prescriber is responsible for making decisions about deprescribing of futile medications, consent from the patient or his legal representative is still necessary. In this context, the healthcare team needs to take up their responsibility to start a discussion.

## Strengths and limitations

We conducted this systematic review according to the methodology of the

Cochrane Handbook of Systematic Reviews of Interventions (25). The Covidence (27) tool was used for the selection of studies to ensure a systematic approach. A few limitations apply to this study. First, all barriers and enablers were described in only one study, except for the perception of difficulty or resistance of the resident's family which was described as a barrier in two studies (39, 40, 44) and interdisciplinary communication which was described as a barrier as well as an enabler in two studies (39, 42, 44).

Hence, a grading of the barriers/enablers was not possible. Second, the different methods used in the studies complicated summarizing – quantitative and qualitative – findings and did not allow to pool data across the studies for meta-analysis. Thus, the results were reported in a pragmatic and descriptive way.

## Implications for practice and research

A whole system approach supported by the organization, involving the patient and his family in the decision-making process regarding deprescribing, and an interdisciplinary approach towards medication use are necessary for successful implementation of any deprescribing intervention.

The same elements are crucial in an end-of-life context. Moreover, it is crucial that prescribers are aware of polypharmacy-related harm at the end of life, such as drug–drug interactions with medications for symptom relief. Hence, education and training of healthcare professionals should provide more insight in the negative consequences of polypharmacy. Furthermore, care goals and treatment targets, such as deprescribing of medications, should be discussed with the patient and his family. Timely initiation of these conversations is necessary to make sure that patients' wishes and preferences are known before the patient loses his cognitive capacity to make his own decisions. Healthcare professionals should focus on communication strategies to facilitate shared decision-making regarding medication use and deprescribing.

## Conclusion

Three different types of barriers and enablers to deprescribing of medications in people with a life-limiting disease were found: organizational, professional and patient/family-related barriers/enablers. The most prominent factors were organizational support, interdisciplinary communication and collaboration, and communication with the patient and his family. The scarcity of findings in the literature regarding barriers/enablers to deprescribing of medications in people with a life-limiting

disease highlights the importance of filling this gap. Further research should focus on deepening the knowledge on these barriers/enablers in order to develop sustainable multifaceted deprescribing interventions in palliative care.

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## Chapter 10

General discussion  
and conclusions

## Introduction

The overall aim of this research was to develop the prerequisites for an intervention to support the initiation of deprescribing in clinical practice for people with advanced disease and limited life-expectancy. In this dissertation, we described the current situation regarding medication use in general, and polypharmacy and PIM use in particular, in NH residents with a normal life-expectancy and in NH residents with life-limiting diseases, in patients with advanced cancer receiving palliative care and in the Belgian population aged 75 years and older at time of death. We explored relationships between these aspects and socio-demographics, survival, hospitalization, mortality, and initiation of advance care planning, to gather information regarding the context of deprescribing in Flanders, Belgium and 11 other countries in Europe and beyond. Subsequently, we examined whether PIMs are actually discontinued and medications suitable for deprescribing are actually deprescribed in Flanders, Belgium and internationally and if yes, we determined the prevalence of discontinuation of PIMs and deprescribing. Finally, we explored barriers and enablers to deprescribing in people with a life-limiting disease. This dissertation addressed six research questions in chapter 4 to 9.

1. What is the prevalence of polypharmacy and potentially inappropriate medication use according to the STOPPFrail criteria in an inception cohort of newly admitted nursing home residents in Flanders and is there a relationship with the length of survival?
2. Is there a relationship between deprescribing and initiation of advance care planning in a cohort of newly admitted nursing home residents in Flanders?
3. Is there deprescribing at the end of life in nursing home residents with life-limiting diseases in Flanders and what is the prevalence of deprescribing?
4. Is there discontinuation of potentially inappropriate medications according to the STOPPFrail criteria in the year before the end of life in the full population of deceased aged 75 or older at time of death, in 2012, in Belgium, and what is the prevalence of discontinuation of potentially inappropriate medications?
5. Is there deprescribing in patients with advanced cancer receiving palliative care in 12 countries in Europe and beyond, and what is the prevalence of deprescribing?
6. What are the factors that facilitate and/or hinder (enablers/barriers) deprescribing in people with a life-limiting disease?

In this part of the dissertation, the main findings of the included studies are discussed. First, the main findings will be summarized, followed by a discussion of the methodological strengths and limitations of the included studies. Next, a general discussion will explore the results in depth and will relate the findings to previous research. Finally, implications for practice, policy and research will be discussed.

**Box:** *Overview of the studies in this dissertation*

Name study	Chapter	Research question	Article title
Ageing@NH	4	1	Associations of potentially inappropriate medication with four-year survival in an inception cohort of NH residents
Ageing@NH	5	2	Initiation of ACP in newly admitted NH residents in Flanders, Belgium: a prospective cohort study
Cross-sectional NH study	6	3	Balancing medication use in NH residents with life-limiting disease
Population database study	7	4	Discontinuation of medications at the end of life. A population study in Belgium, based on linked administrative databases
EPCCS cancer study	8	5	Changes in medication use in a cohort of patients with advanced cancer: the international multicentre prospective European Palliative Care Cancer Symptom (EPCCS) study
Systematic review	9	6	Barriers and enablers to deprescribing in people with a life-limiting disease: A systematic review

## Summary of the main findings

The main findings for each research question are summarized below.

### Prevalence of polypharmacy and PIM use and relationship with the length of survival of an inception cohort of NH residents (Ageing@NH study)

In Chapter 4, we described the prevalence of polypharmacy and PIM use at NH admission and the relationship with length of survival and mortality. At NH admission, participants used a mean of 9 medications, 47% had polypharmacy (5-9 chronic medications), and 40% excessive polypharmacy ( $\geq 10$  chronic medications). Mean number of PIMs at admission was two (range 0-6), 11% did not use any PIMs, and respectively 28%, 29%, and 32% used one, two and three or more PIMs at admission according to the STOPPFrail criteria.

One year after NH admission, 79% of the residents were still alive. Only 36% survived for four years. Survival analyses with Kaplan Meier showed no difference in survival between no polypharmacy, polypharmacy and excessive polypharmacy at

admission, nor between PIM use and no PIM use at admission. Due to the limitations of this study – the evolution of PIM use and polypharmacy was not taken into account – we cannot make any statements or draw conclusions about a possible association with mortality.

### Relationship between deprescribing and initiation of ACP in a cohort of newly admitted NH residents (Ageing@NH study)

In chapter 5, we hypothesized that analgesic use, as an example of adequate treatment according to the definition of palliative care (1), would increase in residents for whom ACP was initiated between admission and follow-up after two years (year2). Earlier studies have demonstrated an increased use of analgesics in people with pain symptoms caused by advanced disease (2). On the contrary, we hypothesized that use of lipid modifying agents, as an evidence based example of preventive medication suitable for deprescribing in patients with a limited life-expectancy, would decrease between admission and year2 in these residents (3).

At NH admission, 34% of the residents used analgesics and 28% used lipid modifying agents. Between admission and year2, the use of analgesics increased significantly (34%-42%,  $p=0.001$ ) and the use of lipid modifying agents decreased significantly (28%-21%,  $p=0.009$ ). ACP was never initiated during the two-year stay for 38% of the residents, for 22% ACP was initiated at NH admission, for 40% ACP initiation was delayed. A significant increase in the use of analgesics between admission and year two was found in residents with delayed ACP initiation ( $p=0.002$ ). ACP initiation was not related to the decreasing use – or deprescribing - of lipid modifying agents.

Our results confirm our a priori hypothesis that analgesic use increased in residents for whom ACP has been initiated, but only for residents for whom ACP was initiated more than three months after NH admission. However, the hypothesis regarding the association between ACP initiation and a decreasing use of lipid modifying agents was not confirmed.

### Prevalence of deprescribing in NH residents with life-limiting disease (cross-sectional NH study)

In Chapter 6, we evaluated medication use of NH residents with life-limiting disease twice: a first evaluation was based on the medication chart of three to six months before data collection (t1), and a second evaluation based on the medication chart at the time of data collection (t2). Based on scientific evidence and expert opinions, we selected medications suitable for deprescribing and we examined if these medications were actually deprescribed. Furthermore, we examined if and

which PIMs from the selected PIMs on the STOPPFrail list (4) were newly initiated.

During the three to six month period between first (t1) and second (t2) evaluation, mean number of chronic medications increased significantly, and the prevalence of polypharmacy and excessive polypharmacy remained high for NH residents with life-limiting disease. For one third, at least one medication suitable for deprescribing was actually deprescribed. On the other hand, for one third, at least one PIM was newly initiated at the end of life. These changes in medication use were observed in a small subpopulation (n=133). In the subgroup of people for whom medications were deprescribed (n=76), the prevalence of newly initiated PIMs was limited. Most changes in medication use – deprescribing as well as new initiation - were observed in the group of multivitamin combinations, calcium and other minerals, PPIs, and medications indicated to treat diseases of the nervous system. In the group of lipid modifying agents, the focus was mainly on deprescribing, for only one resident this medication was newly initiated.

### Prevalence of deprescribing in the Belgian population deceased at age 75 or older in 2012 (population database study)

Chapter 7 is a retrospective register-based mortality cohort study of people aged 75 years or older at time of death, who died in Belgium in 2012. We explored PIM use according to the STOPPFrail criteria (4) during two periods: twelve to six months before death (P1) and the last four months of life (P2). We defined discontinuation as at least two dispensings of the selected PIMs during P1, and no dispensing during P2. We distinguished three groups of PIMs, based on expert opinions: PIMs for long term prevention, PIMs for which chronic use is inappropriate, and outdated PIMs for which a safer alternative exists.

In the total population (n=74 368), mean number of dispensed chronic medications was 6 during P1. Most prominent PIMs for long term prevention during P1 were lipid modifying agents (21.5%). In the group of PIMs for which chronic use is inappropriate, proton pump inhibitors (PPIs) (28%) and neuroleptic antipsychotics (14%) were most common, and in the group of outdated PIMs, long-term oral non-steroidal anti-inflammatory drugs (NSAIDs) were most prominent (7%).

The number of chronic medications increased during P2. The prevalence of all PIMs increased, more specifically to 25% for lipid modifying agents, 52% for PPIs, 31% for neuroleptic antipsychotics, and 16% for NSAIDs.

Between P1 and P2, at least one selected PIM was discontinued for 20% (n=14 395) of the population. No discontinuation of PIMs was observed for 49% (n=36 696). Being hospitalized within the period before the last four months of life and living in a NH was associated with discontinuation of PIMs (respective OR

(95%CI): 2.89 (2.73-3.06), 1.29 (1.23-1.36)). A higher number of medications used during P1 was associated with a higher number of discontinued PIMs (1.17 (1.16-1.17)).

### Deprescribing in patients with advanced cancer receiving palliative care (EPCCS cancer study)

In Chapter 8, we examined medication use and deprescribing in a cohort of patients with advanced cancer receiving palliative care. Medication data from the European Palliative Care Cancer Symptom (EPCCS) study were analysed. We hypothesized (a priori) that medication for symptom relief would increase as death approached, while cancer therapy and medication for long-term prevention would decrease. Our results confirm our a priori hypothesis, but show important differences in the extent of usage in the different medication groups. The number of medication groups increased significantly from six at five months before death to seven at one month before. From five to one month(s) before death, cancer therapy (RT excluded) in general and chemotherapy in particular decreased (resp. from 55% to 24%, and from 44% to 15.5%), most medications for cancer-related and other symptom relief increased (e.g. opioids from 62% to 81% and sedatives from 35% to 46%), and medication for long-term prevention (heart medication / anti-hypertensives) decreased (from 38% to 27%). Deprescribing (of medications suitable for deprescribing) in patients with advanced cancer receiving palliative care was limited to a small, but significant decrease in the prevalence of heart medication / anti-hypertensives.

### Barriers and enablers to deprescribing of medications in people with a life-limiting disease (systematic review)

In Chapter 9, we explored enablers and barriers to deprescribing of medications in people with a life-limiting disease and we summarized the available evidence in a systematic review.

For this systematic review, 1026 references were checked. Five studies met the eligibility criteria and were included in this review. Three types of barriers/enablers were found: organizational, professional and patient (family) related barriers/enablers. The most prominent enablers were organizational support (e.g. for standardized medication review), involvement of multidisciplinary teams in medication review, and the perception of the importance of coming to a joint decision regarding deprescribing, which highlighted the need for interdisciplinary collaboration and involving the patient and his family in the decision making process. The most important barriers were shortages in staff, and the perceived difficulty or resistance of the NH resident's family - or the resident himself.

## Methodological strengths and limitations

In this dissertation, data were used from four different datasets. For the studies in chapters 4 and 5, data from the ageing@NH study, a prospective cohort study examining the general health of newly admitted NH residents in Flanders were used. In the study in chapter 6, we used data from a cross-sectional NH study examining symptom burden and medication use in NH residents with life-limiting disease. For the population database study in chapter 7, data from a retrospective register-based mortality cohort were analysed. For the study in chapter 8, data from the international multicentre prospective EPCCS cancer study were used. In chapter 9, a systematic review about the barriers and enablers to deprescribing was conducted in accordance with the methodology of the Cochrane Handbook of Systematic Reviews of Interventions (5). Each of these studies had its specific strengths and limitations, as well as having strengths and limitations in common.

In this section, we will discuss the general strengths and limitations of the studies in this dissertation. The study-specific strengths and limitations can be found in chapter 4 to 9, under the heading 'strengths and limitations' in every chapter.

### Strengths

This thesis has contributed to the national and international body of knowledge regarding discontinuation of PIMs and deprescribing of medications at the end of life by determining the current prevalence of (potentially inappropriate) medication use, discontinuation of PIMs and deprescribing, and exploring barriers and enablers to deprescribing in people with life-limiting disease. Using four different datasets to examine medication use, discontinuation of PIMs or actual deprescribing of medications suitable for deprescribing, and the associated factors, allowed us to get an insight in these areas in different populations: from a small population of NH residents with life-limiting disease, to a large inception cohort of NH residents, the full Belgian population aged 75 or older at time of death in 2012, and a large international cohort of patients with advanced cancer receiving palliative care.

Given the use of structured questionnaires and validated measuring tools, such as KATZ-ADL (6), MMSE (7), MMRI (8), Karnofsky Performance Scale (9), data collection was standardized, which will improve the generalizability of our results. In the Ageing@NH and EPCCS cancer study, the study population was followed during a pre-specified period of time or until death, allowing for inclusion of follow-up measurements in our analyses, and for trend analyses of medication use in the EPCCS cancer study.

Validated criteria, the STOPPFrail criteria (4) were used to appraise the appropri-

ateness of medications and to determine which PIMs were suitable for discontinuation. Clinical practice deprescribing guidelines (10, 11) were used to identify medications suitable for deprescribing, which is considered to be a summary of the highest level of available evidence for deprescribing at this moment.

We used robust methods for data-analyses such as Kaplan Meier survival analyses and logistic regression analyses. Our systematic review was done according to the methodology of the Cochrane Handbook of Systematic Reviews of Interventions (5), which is also considered a robust methodology.

## Limitations

Firstly, regarding the appraisal of the appropriateness of medications: in Belgium, no tool exists that automatically links PIMs to the patient's medication chart and generates a systematic warning whenever a PIM is prescribed in daily practice. Tommelein et al. (2016) developed an explicit screening tool to detect relevant inappropriate prescribing: the Ghent Older People's Prescriptions community Pharmacy Prescription tool (GheOP3S) (12). However, the computerized version of this tool is still not available for a broader use outside the research and teaching context. In this thesis, we used the STOPPFrail tool because of its applicability in frail older adults with limited life-expectancy. The STOPPFrail criteria (4) for the appraisal of the appropriateness of medications in frail older adults were applied to all medications on the resident's medication chart in the Ageing@NH and cross-sectional NH study, and to all reimbursed dispensed prescribed medications registered in the InterMutualist Agency's (IMA) register of in our population database study. The use of a list of criteria to identify PIMs on a patient's medication chart with or without clinical patient-level information generates different results. In our NH studies and in the population database study, clinical patient-level information was not available. Thus, only a selection of PIMs for which clinical patient-level information is not necessary to determine their appropriateness, could be identified. Therefore, our findings regarding the high prevalence of PIMs should be interpreted with caution. Given that we were not able to use the full list of explicit criteria, the prevalence of PIMs in our studies may be an underestimation. On the other hand, due to the absence of clinical patient-level information, we may have used too few disease-specific PIMs, which can lead to overestimation of the prevalence of PIMs. This limitation reflects the complex relationship between multimorbidity and judicious and tailored medication use in frail older adults with limited life-expectancy.

Secondly, unmeasured confounders such as comorbidities and omission of potentially beneficial medications may have caused bias. Furthermore, due to the unavailability of clinical patient-level information, we were not able to take indications



and contra-indications of medications into account and to draw any conclusions with regard to clinical impact of potentially inappropriate prescribing.

Thirdly, in chapter 4, we examined if the length of survival was different for NH residents with and without polypharmacy, and residents who used no PIMs and one, two, three or more PIMs at NH admission. Due to the limitations of this study – polypharmacy and PIM use were examined only at admission, and the evolution of polypharmacy and PIM use during the two years of follow-up was not taken into account – we cannot make any statements or draw conclusions about a possible association with mortality.

Fourthly, prognostic uncertainty plays an important role when studying medication use and deprescribing in the last year of life. For the cross-sectional NH study presented in chapter 6, we selected NH residents with a specific life-limiting disease: advanced cancer, organ failure or severe dementia, under the assumption that life-expectancy in these residents would be limited. However, our results indicate that this was not always the case. It is very difficult, if not impossible to accurately predict the time of death (15), particularly in residents with dementia. In our population database study, we included all deceased aged 75 and older, and we analyzed medication use retrospectively. The same limitation occurs in this study: at the time of prescription or discontinuation of medication the prescriber was probably not capable of accurately predicting the time of death.

Finally, the studies presented in this thesis use longitudinal and cross-sectional observational data. Subsequently, we can only conclude potential associations and no causal relations.

## Discussion of the findings

### Medication use at the end of life

Our findings indicate that at the end of life nearly all medications are continued as before or their use increased in relation to time before death. Medication use at the end of life was high and increased towards death in NH residents as well as in patients with advanced cancer receiving palliative care. This concerns both the number of chronic medications and the prevalence of nearly all medication groups. As expected, the prevalence of medications for symptom relief – particularly analgesics, corticosteroids, proton pump inhibitors (PPIs) and sedatives - was high in both groups and increased when death approached. But the prevalence of medications for long-term prevention – particularly lipid modifying agents and anti-hypertensives - was also high and decreased only slightly when death approached. In the

group of psychotropic medications, the prevalence of sedatives and anxiolytics was relatively high in patients with advanced cancer, while the prevalence of neuroleptic antipsychotics was low. As expected, in NH residents, the prevalence of neuroleptic antipsychotics was higher than in patients with advanced cancer. Patients with advanced cancer used more cancer therapy, as expected.

In patients with advanced cancer receiving palliative care, we found a high use of *opioid analgesics* and corticosteroids during the last month before death, while fewer non-opioids were prescribed, which is in line with earlier research (16-18). Both medication groups are used to relieve symptom burden, and their increase at the end of life is in accordance with the definition of palliative care, emphasizing the importance of symptom treatment to support and improve quality of life (1), as is recommended as good practice (19). However, assessment and initiation of treatment of pain and other symptoms was not considered in the studies in this thesis. Consequently, no conclusions can be drawn with regard to clinical impact.

In NH residents, we found a significant increase in the prevalence of *analgesics* at the end of life. This is in line with the recommendations of the American Geriatric Society for treatment of pain in frail older adults (20). However, an increase in pharmacological pain treatment does not necessarily mean adequate pain treatment, nor appropriate treatment. Pain (e.g. due to neuralgia secondary to diabetes, claudication, arthritis) is a common symptom in older adults, particularly in those living in NHs (21). Moreover, pain is frequently undertreated, particularly in residents with cognitive impairment or dementia as they are not capable to verbally communicate pain (22-24). Instead they often express pain as disruptive behaviour (e.g. agitation, aggression) (23). If this pain-related behaviour is misinterpreted as behavioural and psychological symptoms of dementia, this may lead to inappropriate prescribing of sedatives and/or neuroleptic antipsychotics (23). Adequate pain assessment is a first step towards adequate pain treatment. For analgesic use, considerations regarding addiction, evolution of renal function, and guidelines recommending limiting the use of analgesics are considered to be of less importance in an end-of-life context (17).

*Proton Pump Inhibitors* (PPIs) are one of the most commonly used medications in older adults. Long-term treatment with PPIs, however, is only indicated in very specific situations such as Barrett's esophagus. For other indications, discontinuation is recommended after a short period of treatment (25). The practice by some physicians of prolonging treatment after the symptoms cease to exist surely contributes to the high prevalence of these medications (26). Another possible explanation for the increasing use of PPIs is their indication to treat side-effects of non-steroidal anti-inflammatory drugs (NSAIDs) including acetylsalicylic acid, and oral corticoste-

roids. In patients with advanced cancer receiving palliative care, the prevalence of both corticosteroids and PPIs was high and increased towards death. However, the prevalence of NSAIDs and oral corticosteroids in our population database study and cross-sectional NH study was lower, although it increased slightly towards death, but not in the same amount as the increasing prevalence of PPIs. Furthermore, the use of NSAIDs for treatment of chronic pain is not recommended unless these medications are clearly indicated (e.g. for treatment of arthritis), because of the high risk of gastro-intestinal side-effects (20). Morin et al. (2018) used a Delphi technique to achieve consensus on the appropriateness of continuation and initiation of certain medications during the last three months of life for older adults aged 75 years and older. For the group of PPIs, consensus was not reached, which reflects the discussion on their appropriateness in clinical practice (27).

Long-term use of *hypno-sedatives* for treatment of insomnia is inappropriate for NH residents because it can lead to physical and psychological dependence, but may be appropriate at the end of life to relieve anxiety and emotional distress. Moreover, benzodiazepines are the preferred drug to control delirium in the last days of life instead of the off-label use of haloperidol, due to the latter's anticholinergic properties (28). This is reflected in our findings in the EPCCS cancer study: prevalence of sedatives was high and increased towards death, while the prevalence of antipsychotics remained low in patients with advanced cancer. However, comorbidities were not taken into account in this study. On the other hand, in the cross-sectional study of NH residents with limited life-expectancy, only the use of antipsychotics increased towards death.

Our findings on the prevalence of *lipid modifying agents* are consistent with other studies reporting a relatively high use of lipid modifying agents – approximately 20% in populations with limited life-expectancy – and a small decrease in their use towards death (29, 30). Surprisingly, and notwithstanding the existence of high level evidence that these medications – particularly statins – can be safely and effectively deprescribed (3), approximately one out of five people in our studies were prescribed lipid modifying agents until the very last months of life. These medications provide limited short-term benefit and are therefore inappropriate for people with limited life-expectancy. However, they are often continued during the last year of life and usually only deprescribed very close to death (29, 31, 32).

Concordant with Tjia et al., we found a relatively high prevalence of *neuroleptic\_ antipsychotics* in NH residents (36) (Tjia et al., 2011). Previous studies have demonstrated an increasing use of these medications in NHs for treatment of behavioural and psychological symptoms of dementia (BPSD) (37, 38). The difficulty for health-care professionals to manage behavioural disorders in a group of people who are

more or less obliged to live together, can lead to physicians continuing to prescribe these medications because they feel pressurized by the NH staff (39, 40). Moreover, resistance of family or the resident himself was found to be very challenging for physicians attempting to discontinue these medications (39, 40). Fear of escalation of disturbing behaviour and/or of increasing the workload in the NH can probably explain our findings, but we did not know the clinical context.

The use of *anti-cancer therapy*, and particularly *chemotherapy*, for patients with advanced cancer receiving palliative care remained high at the end of life, however with a small decrease immediately before death. This is striking, especially because the population we studied in the EPCCS cancer study consisted of patients with advanced cancer receiving palliative care, and patients being treated with chemotherapy with possible curative intent were excluded. Most participating centres in the EPCCS cancer study were hospitals and provided cancer therapy as part of their palliative care programme, which may partly explain these findings (41). However, this 'palliative' chemotherapy is very controversial and highly debated. Chemotherapy is usually provided to patients with advanced cancer aiming to relieve symptom burden and/or prolong life. However, earlier research has demonstrated that this treatment does not enhance survival nor improve quality of life near death, and it is associated with more aggressive life-prolonging care, a high risk of adverse events, and higher end-of-life care costs (42-44). The American Society of Clinical Oncology (ASCO) recommends avoidance of the use of chemotherapy near the end of life, particularly for patients with a poor performance status who have not responded to earlier lines of treatment and who are not eligible to participate in clinical trials (44, 45). Yeung and Hebert describe end-of-life chemotherapy as a 'prisoner's dilemma' where the patient is inclined to accept or decline and the oncologist is inclined to offer or not offer end-of-life chemotherapy (46). Based on various factors, they conclude that the default scenario is for the oncologist to offer and for the patient to accept end-of-life chemotherapy, despite the fact that this often results in worse clinical and societal outcomes (46). One of these factors is that most patients expect treatment instead of watchful waiting and are willing to pursue chemotherapy for small benefits with major toxicity to preserve (false) hope and reduce anxiety (46). In this case, the oncologist's clinical decision is influenced by the patient's expectation and preference for chemotherapy (46). Moreover, the emotional distress caused by a sense of failure, disappointment and guilt if they do not offer the patient any treatment, makes it difficult for oncologists to refuse chemotherapy at the end of life (46). Nevertheless, intensive treatment with chemotherapy at this stage should remain subject of discussion. The focus at the end of life should be on shared decision making and patient-physician communication in order to extend targeted medical can-

cer treatment with personalized palliative considerations regarding the appropriate level of treatment intensity (47, 48). Integration of palliative care into oncology might stimulate a shift in focus towards symptom palliation and psychological and spiritual/existential support for patients for whom further chemotherapy is almost certain to have no benefit at all (44).

## Prevalence of Potentially Inappropriate Medications (PIMs) at the end of life

PIM use was high at the end of life in our population database study. Given the high number of chronic medications used in all studies, which is generally considered to be the main driver of PIM use (49), this result was as expected. Furthermore, older adults are likely to be prevalent users who have been taking their medications for a long time and probably tolerate it, and have no side-effects, although these medications are considered to be potentially inappropriate due to increased multimorbidity. When older adults have no observable side-effects of their chronic medication, it may be hard to convince them of the importance of discontinuing these medications. This is particularly difficult if the patient and/or his family are convinced that these medications keep them alive or prolong their lives. Adding medications or increasing the dose of previously prescribed medications because symptom burden increases e.g. due to multimorbidity at older age may create opportunities for discussing discontinuation of PIMs with the patient and his family, after thorough medication review. The argument that one medication will be replaced by another may be an argument to initiate the discussion about appropriate medication use with the patient and his family. Explicit lists for the appraisal of the appropriateness of medications (e.g. STOPP (50)) can be used to identify PIMs in older adults with normal life-expectancy and to assist physicians in discontinuing these PIMs. Other medications than the ones listed on these explicit lists are suitable for deprescribing in the explicit context of life-limiting disease, because death is imminent, although there is some overlap. However, it is difficult to determine which medications are suitable for deprescribing at the end of life.

## Deprescribing

Although the two populations we studied – NH residents and patients with advanced cancer receiving palliative care – differ functionally and clinically, and different medications and PIMs are used, we can conclude from our findings that deprescribing was very limited in both populations. It is important to note, that both groups were studied in the context of end-of-life care, which explains the similar re-

sults for deprescribing.

STOPPFrail was developed to identify PIMs in frail older adults with an estimated life-expectancy of less than 12 months (4). However, some medications on the STOPPFrail list are frequently used to relieve symptom burden at the end of life and are therefore might be appropriate in this situation (e.g. neuroleptic antipsychotics such as haloperidol to treat delirium when death is imminent). Hence, some of the STOPPFrail criteria are less applicable at the very end of life, when symptom relief is the main, if not the only, goal of care.

Morin et al. identified drugs and drug classes most often adequate, questionable or inadequate for use in older adults aged 75 years or older with an estimated life-expectancy of less than 3 months, based on a Delphi consensus survey (27). Consensus remained unachieved for some very commonly prescribed drugs such as PPIs, haloperidol, zopicone, and selective serotonin reuptake inhibitors (SSRIs). All of these medications are recommended for treatment of specific symptoms in palliative care (e.g. SSRI are recommended as first-line treatment of depression in palliative care, haloperidol for treatment of nausea and vomiting in palliative care), but are also considered as PIMs in older adults with normal life-expectancy (e.g. zopicone for long-term treatment of insomnia) (27). Up to now, no list of explicit criteria to identify medications that are inappropriate at the end of life, and thus suitable for deprescribing exists.

Generally, deprescribing is a judicious act of the prescriber, that should be discussed in advance with the patient, his family and other healthcare professionals. The preferences and wishes of the patient and/or his family should be known before deprescribing is initiated (51).

Thompson et al. describe the deprescribing process as a continuum on which clinicians first need to create a 'deprescribing mindset' by getting instructions on how to approach deprescribing, then they need to evaluate the entire medication list, and finally they require guidance on how to deprescribe one or more specific medications (52). A first step would then be using a deprescribing framework that considers goals of care, time to benefit, life-expectancy, clinical status and whether treatment is in line with care goals (53, 54). Secondly, medications suitable for deprescribing should be identified and prioritized by evaluating the entire medication list, e.g. by using a selection of criteria applicable at the end of life from STOPPFrail (4) and/or a selection of the consensus criteria (27). Finally, medication-specific tools that provide detailed guidance on tapering, monitoring or weighing benefit and harms for deprescribing of individual medications can be used, e.g. clinical practice deprescribing guidelines (10, 11, 52).

In the studies in this dissertation, we have examined only one specific part of the

deprescribing process: we have identified and prioritized which medications were potentially inappropriate and thus suitable for discontinuation using explicit criteria, the STOPPFrail criteria (4), for the appraisal of the appropriateness of medications, and medications suitable for deprescribing using a selection of the STOPPFrail criteria applicable at the end of life and clinical practice deprescribing guidelines (10, 11). Subsequently, we examined if PIMs were discontinued and if medications considered suitable for deprescribing were actually deprescribed. However, it is difficult to determine if deprescribing was beneficial because underlying diagnoses and indications were not known in the studies in this thesis. This approach provided important information that was missing before, on the current prevalence of actual deprescribing, nationally and internationally, and allowed us to conclude that, currently, there is no practice of deprescribing in Belgium, nor in other countries. However, our findings in the cross-sectional NH and EPCCS cancer study indicate that some efforts are made to carefully balance medications in older adults with life-limiting disease and in patients with advanced cancer, although only in a small subgroup. Nevertheless, in order to get the whole picture, the mindset of the prescriber should be explored in the future and the findings must be linked with clinical data such as diagnosis and indications for prescribing.

Given the limited prevalence of deprescribing and notwithstanding that few barriers to deprescribing specifically for people with a life-limiting disease were identified in our systematic review, we must assume that many barriers to deprescribing exist. These barriers are likely to be the same as for discontinuation of PIMs in older adults with normal life-expectancy, but we expect them to be more urgent and compelling when life-expectancy is limited. Furthermore, we did not study the existence of a 'deprescribing mindset', nor how physicians deprescribe medications in clinical practice and who – patients, families, other healthcare professionals – is involved in the decision-making process. More research is absolutely necessary to explore these aspects, as well as the specific enablers/barriers to deprescribing for people with a life-limiting disease into depth, before we can even start thinking about the development of a deprescribing intervention.

## Implications for practice, public and research

It is a real challenge to give advices for daily practice starting from analyses from databases and meta data. Our type of research is hypothesis forming and has to be a stimulus for clinicians to think about possible further research resulting in improvements in care. Deprescribing has to be considered in a broader process with first medications review followed by an assessment of quality of prescriptions in relation

with the clinical context of the patient and taking into account the patient's preferences.

The primary aim of pharmacotherapy for people with life-limiting disease should be symptom relief and preservation of quality of life, taking into account patient preferences. In the studies in this dissertation, nearly all medications for symptom relief increased when death approached, as recommended in clinical practice guidelines for high-quality palliative care (19). However, the proportion of chemotherapy in patients with advanced cancer receiving palliative care, and the proportion of preventive medications and PIMs suitable for deprescribing/discontinuation in patients with advanced cancer, older adults aged at least 75, and NH residents remained high when death approached. Furthermore, discontinuation of PIMs and deprescribing were very limited in the samples we studied and in the population database study. These results emphasize the complexity of pharmacotherapy and determining the appropriateness of medication at the end of life.

Our findings suggest that deprescribing for people with life-limiting disease is still in its infancy. Currently, it is still unclear which medications can be safely and effectively deprescribed at the end of life, what the effects of deprescribing are on important health-related outcomes such as quality of life, and how to deprescribe medications in clinical practice. Clinical patient-level information was not available for the studies in this thesis. Hence, we cannot weigh our findings in the context of comorbidities, indications and contra-indications. However, the findings in the studies in this dissertation allow for proposing possible implications for practice, policy and research regarding deprescribing of medications for people with life-limiting disease that should be kept in mind when developing interventions to support the initiation of deprescribing in clinical practice.

## Implications for practice

From the findings in our systematic review we learned that a whole system approach supported by the organization, involving the patient and his family in the decision-making process regarding deprescribing, and an interdisciplinary approach towards medication use and deprescribing are necessary for successful implementation of any deprescribing intervention.

### *Place of tools and guidelines in interdisciplinary medication review*

Our findings about limited deprescribing of medications at the end of life suggest the need of clinical tools. A selection of explicit criteria for the appraisal of the appropriateness of medications, such as the STOPPFrail criteria that are applicable when death is imminent (4), can be used to evaluate the entire medication list at the end



of life and to identify medications suitable for deprescribing as part of a judicious process in concordance with the original definition of deprescribing. However, no list of explicit criteria specific for palliative care or for people at the end of life exists.

The actual decision to deprescribe a certain medication or not is the responsibility of the physician, who should take the wishes and preferences of the patient, nurse observations and report of symptoms, clinical status, time to benefit, remaining life-expectancy, and pharmacist recommendations into account. Detailed guidance on how to taper, monitor or weigh benefit and harms for deprescribing of individual medications can be found in clinical practice deprescribing guidelines (10). However, these guidelines are limited in number as well as in their applicability to the context of limited life-expectancy. More guidance on deprescribing in the context of limited life-expectancy is needed in order to prevent unnecessary harm caused by medications at the end of life, taking into account prognostic uncertainty. Adaptation of existing international deprescribing algorithms to the context of limited life-expectancy in combination with a more realistic estimation of prognosis or prediction of death is crucial to optimize medication use in this situation.

#### *Concerns regarding palliative chemotherapy*

Our finding that chemotherapy is often used in patients with very limited life-expectancy is troubling. Chemotherapy is usually provided to patients with advanced cancer aiming to relieve symptom burden and/or prolong life. However, earlier research has demonstrated that this treatment does not enhance survival nor improve quality of life near death, and it is associated with more aggressive life-prolonging care, a high risk of adverse events, and higher end-of-life care costs (42-44). The ASCO recommends avoidance of the use of chemotherapy near the end of life, particularly for patients with a poor performance status who have not responded to earlier lines of treatment and who are not eligible to participate in clinical trials (44, 45). Intensive treatment with chemotherapy at the end of life should remain subject of discussion. It is crucial to identify those patients who are likely to benefit from palliative chemotherapy close to death, for example, using validated prognostic scores and/or assessing a patient's symptom burden and quality of life prior to and during treatment (55, 56), and to discuss the risks and benefits of end-of-life chemotherapy with the patient and his family (46). The focus at the end of life should be on shared decision making and patient-physician communication in order to extend targeted medical cancer treatment with personalized palliative considerations regarding the appropriate level of treatment intensity (47, 48). Integration of palliative care into oncology might stimulate a shift in focus towards symptom palliation and psychological and spiritual/existential support for patients for whom further chemotherapy is almost certain to have no benefit at all (44).

## Implications for health policy

### *Training and education of healthcare professionals*

Our findings on the relatively short survival after NH admission highlight the importance of a palliative approach in NHs. Hence, nurses should be trained in providing palliative care, and focus on supporting and preserving quality of life, in accordance with their patients' wishes and preferences. Moreover, the communication skills of all healthcare professionals need to be improved in education and training to facilitate interprofessional communication e.g. in the context of implementation of interdisciplinary discussion.

## Implications for research

### *Need for evidence for safe and effective deprescribing*

A strong need occurs for adequately powered high-quality deprescribing studies with strong methodological design (e.g. randomized clinical trials (RCTs)) to establish causal relationships of deprescribing medications with important clinical health outcomes such as mortality, hospitalizations, emergency room visits, quality of life and quality of dying. Possibilities for these studies are limited due to ethical restrictions regarding randomisation in people with limited life-expectancy. It seems contradictory to examine the effect of deprescribing on mortality for people with advanced disease and limited life-expectancy. However, the fear of deterioration in health condition or even death shortly after deprescribing a certain medication is a barrier for physicians to deprescribe (57). Hence, looking for alternatives for RCTs is essential in this population.

Future studies should focus on alternative methodologies, including N=1 trials or the use of routinely collected data in administrative databases for approximate RCTs to examine the effect of changes in medication use on more subtle health-related outcomes than mortality (e.g. quality of life). The use of these 'big data' provides new insights in healthcare utilization (e.g. prescribing and dispensing of medications) and allows for determining causal relationships between healthcare utilization and specific health-related outcomes (e.g. mortality, hospitalization), prediction of specific health-related outcomes using algorithms, etc. However, routinely collected data are generally coarse grained, and not collected to meet the objectives of the envisaged study. Consequently, researchers search for proxies of the aspects they aim to examine. On the contrary, in field research, data are collected in accordance with the envisaged study's objectives and the researcher can decide which measuring instruments to use for data collection (58). Therefore, it is crucial that additional

data are collected in field research, using quality measuring instruments for e.g. pain assessment, quality of life, etc. Linking these data from field research to patient-level clinical data and routinely collected data would allow us to take patient-reported outcomes (e.g. pain, quality of life), diagnosis, co-morbidities, laboratory results etc. into account and provide numerous opportunities to study these aspects into depth.

### *Need for evidence-based clinical practice deprescribing guidelines in end of life*

The lack of pharmacological guidance regarding safe deprescribing of medications at the end of life can be considered as a major barrier to initiate deprescribing for physicians. Physicians need lists of medications suitable for deprescribing, based on high-level evidence e.g. for statins this high-level evidence exists. They need tools that provide guidance and measure what they claim to measure. Future tools should include guidelines on how to deprescribe the medications identified as suitable for deprescribing instead of disposing into checklists that can only be used to flag inappropriate medications. The development and validation of these approaches is a priority for future research.

Evidence-based clinical practice deprescribing guidelines were recently developed for proton-pump inhibitors (25), anti-hyperglycemic agents (59), antipsychotics (60), benzodiazepine receptor agonists (61), and cholinesterase inhibitors and memantine (10). These guidelines provide the necessary guidance for physicians on how to taper, monitor and weigh benefits and harms when deprescribing these individual medications. Future research should focus on translating these guidelines to the context of advanced disease and limited life-expectancy, and on the development of new clinical practice deprescribing guidelines for deprescribing other medications, for which guidance is still missing.

### *Need for qualitative studies to explore how to approach and involve patients and their families*

Future research should focus on the patient and his family's point of view and explore their perceptions on how they were involved in deprescribing at the end of life and to what extent they want to be involved, using a qualitative study design. Given the limited findings in our systematic review on barriers and enablers to deprescribing, patient and family-related barriers and enablers to deprescribing should be further explored into depth.

## Conclusion

In this dissertation, we described the current situation regarding medication use, polypharmacy, PIM use and use of medications suitable for deprescribing at the end of life in particular, in NH residents with a normal life-expectancy and NH residents with life-limiting disease, in patients with advanced cancer receiving palliative care and in the Belgian population aged 75 years and older at time of death. We explored relationships between these aspects and socio-demographics, survival, hospitalization, and initiation of ACP, to gather information regarding the context of discontinuation / deprescribing in Flanders, Belgium and 11 other countries in Europe and beyond. Subsequently, we examined whether PIMs were discontinued and medications suitable for deprescribing were actually deprescribed in Flanders, Belgium and internationally and if yes, we determined the prevalence of discontinuation and/or deprescribing. Finally, we explored barriers and enablers to deprescribing in people with a life-limiting disease.

Medication use was high at the end of life and increased when death approached. PIM use in the Ageing@NH and in the population database study remained high. Hardly any changes in prescribing patterns were observed in relation to time before death. Discontinuation of PIMs and deprescribing were limited. Only in small subgroups of the study samples and population, small efforts to discontinue PIMs and deprescribe medications suitable for deprescribing were observed (e.g. in people living in NHs, people who were admitted to hospital when death was not imminent yet). Clearly, there is no practice of deprescribing at the end of life in Belgium. Notwithstanding the limited findings in our systematic review on barriers and enablers to deprescribing in people with life-limiting disease, apparently, many barriers to deprescribing exist. Overcoming these barriers is crucial to enable embedding of deprescribing in routine prescribing patterns. Hence, it is crucial to know these barriers and enablers before starting with the development of an intervention. In order to be successfully implemented, all interventions to support physicians to engage in deprescribing should take these barriers into account. If not, every initiative to enable deprescribing is predisposed to fail. Our findings reflect important prerequisites for the development of a sustainable multifaceted deprescribing intervention. Given the limited collection of findings in literature regarding barriers and enablers to deprescribing, the next step in further research will be to further explore these barriers and enablers into depth, using qualitative methodology.

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## Summary

The population aged 65 years and over, and the share of people aged 85 years and over, is growing in Belgium as well as in other countries of the European Union. Aging has been associated with multimorbidity, geriatric syndromes and physical and cognitive decline. Multimorbidity often leads to polypharmacy, which has been associated with adverse outcomes such as falls, ADE, hospitalizations, admission to a NH and mortality. Moreover, due to pharmacokinetic and pharmacodynamic changes, older adults are extra susceptible for adverse drug events.

In Flanders, Belgium, extensive home care facilities are available. Thus, NHs provide care for older adults with multimorbidity and serious functional disabilities, and increasing care needs that cannot be met in any other way. Generally, older adults are frail at NH admission, and their health has deteriorated to an extent that long-term survival becomes exceptional. Between 52% and 85% of nursing home residents have dementia, which is considered as a life-limiting disease. Other diseases associated with a limited life-expectancy in older adults are cardiovascular disease, chronic obstructive pulmonary disease, end-stage kidney disease and advanced cancer. Given the increased risk of multimorbidity, which can lead to admission to a NH, and the high prevalence of life-limiting diseases, particularly dementia, in NH residents, advance care planning and a palliative approach are relevant for NH residents.

Care goals and treatment targets for people with life-limiting disease should shift from cure to care and from quantity to quality of life. This should be reflected in medication use. Treatment of symptom burden is crucial to preserve and support quality of life. Hence, the focus of medication use in palliative care should be on treatment of symptoms which are currently undertreated and on prevention of additional harm due to medication use. For people with limited life-expectancy, the medical focus on long-term profit changes entirely into a focus on the different aspects of comfort of the individual. In this context, all medications for primary and secondary prevention are questionable, while restrictions regarding addiction (e.g. to opioids) are irrelevant when short-term benefit and comfort have absolute priority.

Lists exist to prevent underuse of medications that are clearly indicated (e.g.

medications for symptom relief) and likely to benefit the patient with limited life-expectancy (e.g. WHO list of essential medicine in palliative care). These lists can be used to guide clinicians in prescribing appropriate medications for patients in this situation. Furthermore, numerous tools have been developed to identify PIMs in older adults with normal and limited life-expectancy (e.g. STOPP, STOPPFrail) and to guide prescribers in not initiating and/or not continuing PIMs in clinical practice. However, the appraisal of appropriateness of the medications involved is based on low-level, weak evidence. Robust evidence for their (in)appropriateness from RCTs, the classic experimental design for estimating treatment effects, is missing, mainly due to ethical and practical concerns about randomization. Consequently, the effects of discontinuation of PIMs and deprescribing of medications at the end of life on health-related outcomes such as quality of life, hospitalizations and mortality are difficult to measure.

In this thesis, we use the term 'discontinuation' in the context of tapering or stopping PIMs in older adults with normal life-expectancy. The term 'deprescribing' is used for tapering or stopping medications that have become futile or potentially inappropriate in the explicit context of a life-limiting disease, because death is imminent. Medications considered as PIMs in older adults with normal life-expectancy may be used appropriately for symptom relief in a palliative care setting and vice versa, although some overlap is possible depending on the tool used. In the studies in this dissertation, we used the STOPPFrail criteria to appraise the appropriateness of medications. These criteria contain medications considered as PIMs for frail older adults with limited life-expectancy that are not always inappropriate when death is imminent (e.g. neuroleptic antipsychotics, proton pump inhibitors), as well as medications that are inappropriate in both situations (e.g. lipid modifying agents, multi-vitamin combinations).

Since 2017, international clinical practice deprescribing guidelines have been developed based on the highest level of evidence available for proton pump inhibitors, anti-hyperglycaemic agents, benzodiazepines and Z-drugs, antipsychotics, and cholinesterase inhibitors and memantine. However, not all recommendations are based on high level evidence.

In summary, the existing evidence regarding deprescribing of medications at the end of life is weak. Research on which medications can be safely and effectively deprescribed and the effects of deprescribing on health-related outcomes such as quality of life, hospitalization and mortality in an end-of-life context is still at the very beginning. Two urgent needs for guidance regarding safe and effective deprescribing of medications at the end of life occur. First, we need pharmacological guidance to determine which medications can be safely and effectively deprescribed in

order to develop a list of medications suitable for deprescribing for people with limited life-expectancy. Second, behavioural guidance is necessary to explore how to deprescribe medications in this situation.

The overall aim of this research is to develop the prerequisites for an intervention to support the initiation of deprescribing in clinical practice for people with advanced disease and limited life-expectancy. The development and implementation of a sustainable multifaceted deprescribing intervention in clinical practice may improve appropriate medication use, decrease drug burden, preserve and support quality of life and prevent negative health-related outcomes in people with advanced disease and limited life-expectancy in clinical practice. The studies in this dissertation provide information to guide the development of such a deprescribing intervention.

The research questions are:

1. What is the prevalence of polypharmacy and potentially inappropriate medication use according to the STOPPFrail criteria in an inception cohort of newly admitted nursing home residents in Flanders and is there a relationship with the length of survival?
2. Is there a relationship between deprescribing and initiation of advance care planning in a cohort of newly admitted nursing home residents in Flanders?
3. Is there deprescribing at the end of life in nursing home residents with life-limiting diseases in Flanders and what is the prevalence of deprescribing?
4. Is there discontinuation of potentially inappropriate medications according to the STOPPFrail criteria in the year before the end of life in the full population of deceased aged 75 or older at time of death, in 2012, in Belgium, and what is the prevalence of discontinuation of potentially inappropriate medications?
5. Is there deprescribing in patients with advanced cancer receiving palliative care in 12 countries in Europe and beyond, and what is the prevalence of deprescribing?
6. What are the factors that facilitate and/or hinder (enablers/barriers) deprescribing in people with a life-limiting disease?

To address the research questions of this dissertation, quantitative analyses and a systematic review were performed. Quantitative analyses were performed to examine the current situation regarding discontinuation of PIMs and deprescribing for people with advanced disease and limited life-expectancy, using four different datasets. For chapters 4 and 5, data from the ageing@NH cohort study examining the general health of newly admitted NH residents in Flanders were used (research question [RQ] 1 and 2). For chapter 6, data from a cross-sectional NH study examin-

ing symptom burden and medication use in NH residents with life-limiting diseases were used (RQ 3). For chapter 7, data were analysed from linked administrative databases containing healthcare data on the full population aged 75 and older at time of death, deceased in 2012 in Belgium (RQ 4). For chapter 8, data from the international multicentre prospective European Palliative Care Cancer Symptom study were used (RQ 5).

In chapter 9, a systematic review about the barriers and enablers to deprescribing was conducted in accordance with the methodology of the Cochrane Handbook of Systematic Reviews of Interventions (RQ 6).

In chapter 4, we found a prevalence of 47% for polypharmacy (5-9 chronic medications), and 40% excessive polypharmacy ( $\geq 10$  chronic medications) at NH admission in NH residents in Flanders. Mean number of PIMs was two (range 0-6), 11% did not use any PIMs, and respectively 28%, 29% and 32% used one, two and three or more PIMs according to STOPPFrail. One year after admission, 79% of the residents were still alive. Only 36% survived for four years. No difference in survival was found between no polypharmacy, polypharmacy and excessive polypharmacy at admission, nor between PIM use and no PIM use at admission. However, due to the limitations of this study – the evolution of PIM use and polypharmacy was not taken into account – we cannot make any statements or draw conclusions about a possible association with mortality. In chapter 5, we found a decreasing use of lipid modifying agents from 28% at admission to 21% in year 2 (deprescribing), but no association was found with initiation of ACP in NH residents with normal life-expectancy in Flanders. In chapter 6, for 30% of our sample at least one medication suitable for deprescribing was actually deprescribed at the end of life in NH residents with life-limiting diseases in Flanders. In chapter 7, for 20% of the total population aged 75 and older who died in 2012 in Belgium, at least one PIM was discontinued at the end of life. In chapter 8, we found that from five to one month before death, the prevalence of anti-cancer therapy – mainly chemotherapy - decreased from 55% to 24% and the prevalence of medication for long-term prevention decreased from 38% to 27% in patients with advanced cancer receiving palliative care. However, the use of chemotherapy remained high in the last month of life (15.5%). In chapter 9, we found three types of barriers/enablers to deprescribing: organizational, professional and patient (family) related barriers/enablers. The most prominent enablers were organisational support (e.g. for standardized medication review), involvement of multidisciplinary teams in medication review, and the perception of the importance of coming to a joint decision regarding deprescribing, which highlighted the need for interdisciplinary collaboration and involving the patient and his family in the decision making process. The most important barriers were shortages in staff, and the perceived dif-

ficuity or resistance of the patient's family - or the patient himself.

Our findings indicate that, generally, nearly all medications are continued as before at the end of life. Medication use at the end of life was high and increased towards death in the general population aged 75 and older at time of death in 2012, NH residents as well as in patients with advanced cancer receiving palliative care. This concerns both the number of chronic medications and the prevalence of nearly all medication groups. Hardly any changes in prescribing patterns were observed in relation to time before death. Discontinuation of PIMs and deprescribing were limited. Only in small subgroups of the study samples and population, small efforts to discontinue PIMs and deprescribe medications suitable for deprescribing were observed. Clearly, there is no practice of deprescribing at the end of life in Belgium, nor internationally. Notwithstanding the limited findings in our systematic review on barriers and enablers to deprescribing in people with life-limiting disease, apparently, many barriers to deprescribing exist. Overcoming these barriers is crucial to enable embedding of deprescribing in routine prescribing patterns. Hence, it is crucial to explore these barriers and enablers further into depth before starting with the development of an intervention. In order to be successfully implemented, all interventions to support physicians to engage in deprescribing should take these barriers into account. If not, every initiative to enable deprescribing is predisposed to fail. Our findings reflect useful prerequisites for the development of a sustainable multifaceted deprescribing intervention. Given the limited collection of findings in literature regarding barriers and enablers to deprescribing, the next step in further research will be to further explore these barriers and enablers into depth, using qualitative methodology.

For clinical practice, we recommend: the use of a selection of existing clinical practice deprescribing guidelines and explicit criteria for the appraisal of the appropriateness of medications, applicable to people with life-limiting disease at the end of life to provide guidance for physicians in deprescribing, and a critical attitude towards palliative chemotherapy e.g. by identifying patients who are likely to benefit from palliative chemotherapy close to death, discussing the risks and benefits of end-of-life chemotherapy with patients and their family before starting treatment. For policy, we recommend to provide education and training for healthcare professionals in interprofessional communication e.g. in the context of implementation of interdisciplinary discussions. For research, we recommend: firstly, to conduct adequately powered high-quality deprescribing studies with strong methodological design to establish causal relationships of deprescribing medications with important clinical health outcomes such as mortality, hospitalizations, emergency room visits, quality of life and quality of dying. Secondly, to focus on the development of

## Summary

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lists of medications suitable for deprescribing, based on high-level evidence. Finally, to focus on the patient and his family's point of view and explore their perceptions on how they were involved in deprescribing at the end of life and to what extent they want to be involved, using a qualitative study design.



## Samenvatting

Het aandeel oudere personen (boven de 65 jaar) en het aandeel personen boven de 85 jaar in België en in andere landen van de Europese Unie neemt toe. Door veroudering neemt de kans op het krijgen van meerdere ziekten of multimorbiditeit, geriatrische syndromen en fysieke en cognitieve achteruitgang toe. Multimorbiditeit leidt vaak tot het gebruik van veel verschillende chronische geneesmiddelen tegelijkertijd ( $\geq 5$ ) of polyfarmacie, dat op zijn beurt nadelige gevolgen kan hebben, zoals valincidenten, nevenwerkingen, hospitalisatie, opname in een woonzorgcentrum (WZC) en overlijden. Bovendien zijn ouderen gevoeliger voor negatieve gevolgen van geneesmiddelen door farmacokinetische en farmacodynamische veranderingen.

In Vlaanderen zijn uitgebreide voorzieningen voor thuiszorg beschikbaar. Daardoor verlenen WZC zorg aan ouderen met multimorbiditeit en ernstige functionele beperkingen, en toenemende zorgnoden die niet op een andere manier opgevangen kunnen worden. Algemeen zijn ouderen kwetsbaar geworden bij opname in een WZC en is hun gezondheid zodanig achteruit gegaan, dat overleving op lange termijn uitzonderlijk wordt. Tussen 52% en 85% van de residenten in WZC hebben dementie. Dementie wordt algemeen beschouwd als een aandoening die leidt tot een verminderde levensverwachting. Andere ziekten die geassocieerd worden met een verminderde levensverwachting bij ouderen zijn cardiovasculaire aandoeningen, chronisch obstructief long lijden, eindstadium nierfalen en vergevorderde kanker. Gezien het verhoogd risico op multimorbiditeit, dat kan leiden tot een opname in een WZC, en de hoge prevalentie van ziekten die geassocieerd worden met een verminderde levensverwachting, zoals dementie, zijn vroegtijdige zorgplanning en een palliatieve benadering relevant bij residenten van WZC.

Bij mensen met een verminderde levensverwachting veranderen de zorg- en behandelingsdoelen van genezing naar verzorging en van kwantiteit naar kwaliteit van leven. Dit moet ook zichtbaar zijn in het gebruik van geneesmiddelen. De behandeling van de symptoomlast is cruciaal om de kwaliteit van leven te behouden en te verbeteren. Daarom moet het geneesmiddelen gebruik in palliatieve zorg gefocust zijn op het behandelen van symptomen die onder behandeld zijn en op het voorkomen van bijkomende schade veroorzaakt door geneesmiddelen. Bij mensen

met een verminderde levensverwachting verandert de medische focus op lange termijn voordeel volledig in een focus op de verschillende aspecten van comfort van het individu. In deze context kunnen alle geneesmiddelen voor primaire of secundaire preventie in vraag gesteld worden, terwijl beperkingen met betrekking tot verslaving (bvb aan opiaten) niet relevant zijn wanneer korte termijn voordeel en comfort absoluut prioritair zijn.

Er bestaan lijsten om ondergebruik te voorkomen van geneesmiddelen die duidelijk geïndiceerd zijn en wellicht voordeel opleveren voor patiënten met beperkte levensverwachting (Bvb WHO lijst van essentiële geneesmiddelen voor palliatieve zorg). Deze lijsten kunnen gebruikt worden door artsen als ondersteuning bij het voorschrijven van geschikte geneesmiddelen in deze situatie. Daarnaast werden verschillende lijsten en tools ontwikkeld voor het identificeren van potentieel ongeschikte geneesmiddelen (PIMs) bij ouderen met een normale en verminderde levensverwachting (Bvb. STOPP, STOPPFrail) en voor het ondersteunen van artsen bij het niet opstarten en/of niet verderzetten van deze PIMs in de klinische praktijk. Maar deze beoordeling van de geschiktheid van geneesmiddelen is gebaseerd op zwakke evidentie. Robuuste evidentie voor hun (on)geschiktheid op basis van gerandomiseerde klinische studies ontbreekt, vooral door ethische en praktische bezorgdheden in verband met de randomisatie. Bijgevolg zijn de effecten van het afbouwen of stoppen van PIMs en van geneesmiddelen aan het einde van het leven op gezondheids-gerelateerde uitkomsten zoals kwaliteit van leven moeilijk te meten.

In deze thesis gebruiken we de term 'discontinuation' (Nederlands: niet meer verderzetten) in de context van het afbouwen of stoppen van PIMs bij ouderen met een normale levensverwachting. De term 'deprescribing' (hier is geen Nederlands woord voor) wordt gebruikt voor het afbouwen of stoppen van geneesmiddelen die futiel of potentieel ongeschikt zijn in de expliciete context van een aandoening die geassocieerd wordt met een verminderde levensverwachting, omdat de dood nadert. Geneesmiddelen die beschouwd worden als potentieel ongeschikt voor ouderen met een normale levensverwachting kunnen wel geschikt zijn voor de behandeling van de symptoomlast in een palliatieve zorgsetting en vice versa, al is enige overlapping mogelijk afhankelijk van de tool die gebruikt wordt. In de studies in deze thesis gebruikten we de STOPPFrail criteria voor de beoordeling van de geschiktheid van geneesmiddelen. Deze criteria omvatten geneesmiddelen die beschouwd worden als potentieel ongeschikt voor kwetsbare ouderen met een verminderde levensverwachting, maar niet altijd ongeschikt zijn wanneer de dood nadert (bvb antipsychotica, protonpomp-inhibitoren). Maar zij omvatten ook geneesmiddelen die ongeschikt zijn in beide situaties (bvb statines, multivitaminen).



Sinds 2017 werden internationale deprescribing richtlijnen voor de klinische praktijk ontwikkeld, gebaseerd op het hoogst beschikbare niveau van evidentie, voor protonpomp-inhibitoren, antidiabetica, benzodiazepines en Z-drugs, en cholinesterase inhibitoren en memantine. Maar, niet alle aanbevelingen zijn gebaseerd op evidentie van hoog niveau.

Samengevat kunnen we stellen dat de bestaande evidentie met betrekking tot deprescribing van geneesmiddelen aan het einde van het leven zwak is. Het onderzoek naar welke geneesmiddelen in aanmerking komen voor deprescribing, en de effecten van deprescribing op gezondheids-gerelateerde uitkomsten zoals kwaliteit van leven, hospitalisaties en mortaliteit in de context van het levenseinde staat nog in zijn kinderschoenen. Twee dringende noden met betrekking tot begeleiding bij deprescribing aan het einde van het leven, dringen zich op. Ten eerste, de nood aan farmacologische begeleiding om te bepalen voor welke geneesmiddelen deprescribing op een veilige en effectieve manier kan gebeuren, zodat een lijst van geschikte geneesmiddelen voor deprescribing aan het levenseinde kan ontwikkeld worden. Ten tweede, is gedragsmatige begeleiding noodzakelijk om te exploreren hoe deprescribing in deze situatie uitgevoerd moet worden.

Het algemene doel van dit onderzoek is het ontwikkelen van de randvoorwaarden voor een interventie die de initiatie van deprescribing voor mensen met een vergevorderde ziekte en een beperkte levensverwachting in de klinische praktijk ondersteunt. De ontwikkeling en implementatie van een duurzame, veelzijdige deprescribing interventie voor de klinische praktijk kan het gebruik van geschikte geneesmiddelen verbeteren, de belasting door geneesmiddelen verminderen, de kwaliteit van leven behouden en bevorderen en negatieve gezondheids-gerelateerde uitkomsten voorkomen bij mensen met een vergevorderde ziekte en een beperkte levensverwachting. De studies in deze thesis voorzien informatie om de ontwikkeling van deze deprescribing interventie te begeleiden.

De onderzoeksvragen zijn:

1. Wat is de prevalentie van polyfarmacie en PIM gebruik volgens de STOPPFrail criteria in een cohort van WZC residenten die allen bij opname in het WZC in de cohort werden opgenomen ('inception cohort') in Vlaanderen, en is er een relatie met de overlevingsduur?
2. Is er een relatie tussen deprescribing en initiatie van vroegtijdige zorgplanning in een cohort van nieuw opgenomen WZC residenten in Vlaanderen?
3. Is er deprescribing aan het einde van het leven bij WZC residenten met een verminderde levensverwachting in Vlaanderen, en wat is de prevalentie van deprescribing?
4. Worden PIMs afgebouwd en gestopt volgens de STOPPFrail criteria in het jaar

voor het levenseinde bij de volledige populatie van 75 jaar en ouder op het moment van overlijden in 2012 in België, en wat is de prevalentie van het afbouwen en stoppen van PIMs?

5. Is er deprescribing bij patiënten met een vergevorderde kanker die palliatief verzorgd worden in 12 landen in en buiten Europa, en wat is de prevalentie van deprescribing?
6. Wat zijn de factoren die deprescribing bij mensen met een aandoening die geassocieerd wordt met een verminderde levensverwachting bevorderen en/of verhinderen?

Om deze onderzoeksvragen te kunnen behandelen werden kwantitatieve analyses en een systematische literatuurstudie uitgevoerd. Deze kwantitatieve analyses werden uitgevoerd om de huidige situatie te onderzoeken met betrekking tot het afbouwen en stoppen van PIMs en deprescribing bij mensen met een vergevorderde ziekte en een verminderde levensverwachting. Hiervoor werden vier verschillende databanken gebruikt. Voor hoofdstuk 4 en 5 werden data gebruikt van de Ageing@NH cohort studie. In deze studie werd de algemene gezondheid van nieuw opgenomen WZC residenten in Vlaanderen onderzocht (onderzoeksvraag (OV) 1 en 2). Voor hoofdstuk 6 werden data gebruikt van een cross-sectionele studie die de symptoomlast en het medicatiegebruik van WZC residenten met een verminderde levensverwachting onderzocht (OV 3). Voor hoofdstuk 7 werden data geanalyseerd uit gelinkte administratieve databanken, over het gebruik van gezondheidszorgen van de volledige populatie van 75 jaar en ouder op het moment van overlijden in 2012 in België (OV 4). In hoofdstuk 8 werden data gebruikt van de internationale multicentrische prospectieve European Palliative Care Cancer Symptom (EPCCS) studie (OV 5). In hoofdstuk 9 werd een systematisch literatuur onderzoek uitgevoerd over barrières en faciliterende factoren tegenover deprescribing bij mensen met een aandoening die geassocieerd wordt met een verminderde levensverwachting, in overeenstemming met de methodologie van het Cochrane Handbook of Systematic Review of Interventions (OV 6).

In hoofdstuk 4 vonden we dat 47% van de recent opgenomen WZC residenten polyfarmacie (5-9 chronische geneesmiddelen) en 40% excessieve polyfarmacie ( $\geq 10$  geneesmiddelen) had bij opname in een WZC in Vlaanderen. Het gemiddeld aantal PIMs dat gebruikt werd bij opname was twee (range 0-6), 11% gebruikte geen PIMs, en respectievelijk 28%, 29% en 32% gebruikte één, twee en drie of meer PIMs. Eén jaar na opname leefde 79% van deze residenten nog. Slechts 36% leefde nog na vier jaar. Er werd geen verschil in overleving gevonden tussen mensen zonder polyfarmacie, met polyfarmacie en met excessieve polyfarmacie, noch tussen mensen die geen PIMs gebruikten en deze die wel PIMs gebruikten. Door de beperkingen van

deze studie, met name het ontbreken van data over de evolutie van polyfarmacie en PIM gebruik, kunnen we echter geen algemene conclusies trekken met betrekking tot een associatie met mortaliteit. In hoofdstuk 5 vonden we een gedaald gebruik van statines van 28% bij opname naar 21% in jaar 2 (deprescribing), maar we vonden geen associatie met de initiatie van vroegtijdige zorgplanning bij WZC residenten met een normale levensverwachting in Vlaanderen. In hoofdstuk 6 vonden we dat voor 30% van onze steekproef deprescribing van minstens één geneesmiddel dat geschikt is voor deprescribing effectief gebeurde bij WZC residenten met een verminderde levensverwachting in Vlaanderen. In hoofdstuk 7 werd voor 20% van de totale populatie van 75 jaar en ouder op het tijdstip van overlijden in 2012 in België minstens één PIM gestopt. In hoofdstuk 8 vonden we dat, in de periode tussen vijf en één maand voor overlijden, het gebruik van anti-kanker behandeling (voornamelijk chemotherapie) daalde van 55% naar 24% en de prevalentie van medicatie voor preventie op lange termijn daalde van 38% naar 27% bij patiënten met een vergevorderde kanker die palliatief verzorgd worden. Nochtans bleef het gebruik van chemotherapie hoog in de laatste maand van het leven (15.5%). In hoofdstuk 9 vonden we drie types van barrières en faciliterende factoren tegenover deprescribing: factoren gerelateerd aan de organisatie, de professional en de patiënt en/of zijn familie. De meest prominente faciliterende factoren waren ondersteuning door de organisatie (bvb. voor herziening van de medicatielijst), betrokkenheid van multidisciplinaire teams bij de herziening van de medicatielijst, en de perceptie van het belang om samen tot een beslissing te komen met betrekking tot deprescribing. Deze laatste factor benadrukt de nood aan interdisciplinaire samenwerking en het betrekken van de patiënt en zijn familie in de besluitvorming. De belangrijkste barrières waren personeelstekort en de houding van verzet van de familie of de patiënt zelf.

Onze bevindingen impliceren dat aan het einde van het leven bijna alle geneesmiddelen verder voorgeschreven worden zoals voordien. Het geneesmiddelen gebruik aan het einde van het leven was hoog en steeg naar de dood toe, en dit zowel bij de populatie van 75 jaar en ouder op het tijdstip van overlijden in 2012, bij WZC bewoners als bij patiënten met een vergevorderde kanker die palliatief verzorgd worden. Dit geldt zowel voor het aantal chronisch gebruikte geneesmiddelen als voor de prevalentie van bijna alle groepen geneesmiddelen. Er werden weinig wijzigingen gevonden in voorschrijf patronen in relatie tot de tijd voor overlijden. Het afbouwen of stoppen van PIMs en deprescribing waren beperkt. Enkel in kleine deelgroepen van onze studie populatie werden kleine inspanningen geobserveerd voor het stoppen van PIMs en deprescribing van geneesmiddelen die hiervoor in aanmerking komen. Het is duidelijk dat deprescribing aan het einde van het leven nauwelijks wordt toegepast in België, noch internationaal. Ondanks de beperkte

bevindingen met betrekking tot barrières en faciliterende factoren tegenover deprescribing voor mensen met een aandoening die geassocieerd wordt met een verminderde levensverwachting in onze systematische literatuurstudie, bestaan er wellicht veel barrières tegenover deprescribing. Opdat deprescribing een onderdeel kan worden van routine voorschrijf gedrag, zullen eerst deze barrières moeten overwonnen worden. Daarom is het cruciaal om deze barrières en eventuele faciliterende factoren te grondig te exploreren vooraleer te starten met de ontwikkeling van een interventie. Om een succesvolle implementatie te verzekeren, zullen alle interventies die ontwikkeld worden om artsen te ondersteunen om te starten met deprescribing rekening moeten houden met deze barrières. Indien dit niet gebeurt, dan is elke interventie voorbeschikt om te mislukken. Onze bevindingen voorzien in belangrijke randvoorwaarden voor de ontwikkeling van een duurzame, veelzijdige deprescribing interventie. Gezien de beperkte bevindingen met betrekking tot barrières en faciliterende factoren tegenover deprescribing, is het verder exploreren van deze barrières en faciliterende factoren tegenover deprescribing, gebruik makend van kwalitatieve onderzoeksmethodes, de volgende stap in verder onderzoek.

Voor de klinische praktijk bevelen we het volgende aan: een selectie van bestaande deprescribing richtlijnen voor de klinische praktijk en expliciete criteria voor het beoordelen van de geschiktheid van geneesmiddelen, die van toepassing zijn voor mensen aan het einde van hun leven, te gebruiken om artsen ondersteunen bij deprescribing. Een kritische houding tegenover palliatieve chemotherapie moet aangenomen worden, bijvoorbeeld door het identificeren van patiënten die wellicht voordeel zullen halen uit palliatieve chemotherapie wanneer de dood nadert, en door het bespreken van de voor- en nadelen van chemotherapie aan het einde van het leven met patiënten en hun familie vooraleer te starten met deze behandeling. Aangaande het beleid voor de toekomst adviseren we om gezondheidszorgverleners op te leiden en te trainen in communicatieve vaardigheden bvb in de context van implementatie van interdisciplinaire discussies. Voor verder onderzoek adviseren we om, ten eerste, deprescribing studies met voldoende power, van hoge kwaliteit en met een sterk methodologisch design uit te voeren om causale verbanden aan te tonen tussen deprescribing van geneesmiddelen en belangrijke klinische gezondheidsuitkomsten, zoals mortaliteit, hospitalisaties, spoedopnames, kwaliteit van leven en van sterven. Ten tweede, om te focussen op de ontwikkeling van lijsten van geneesmiddelen die geschikt zijn voor deprescribing, gebaseerd op evidentie van hoog niveau. Ten slotte, om te focussen op het standpunt van de patiënt en zijn familie en hun percepties te exploreren over hoe zij betrokken werden en wensen betrokken te worden bij deprescribing aan het levenseinde, gebruik makend van kwalitatieve onderzoeksmethoden.



# Curriculum Vitae

## About the author

Kristel Paque (°01/05/1973, Tongeren) obtained a bachelor's degree in nursing from Provinciale Hogeschool Limburg (1996) and a master's degree in nursing and midwifery from Antwerp University (2014). After her studies, she conducted a qualitative, phenomenological study on existential loneliness in nursing home residents at Antwerp University (2014-2016). She conducted 11 in-depth interviews with nursing home residents who struggled with their feelings, which she analyzed using Interpretative Phenomenological Analyses. The scientific article reporting her findings has been published recently. In September 2016, Kristel started her jointPhD on deprescribing at the end of life at the Clinical Pharmacology Research Unit of the Heymans Institute for Pharmacology at Ghent University and the End-of-Life Care Research Group of the Vrije Universiteit Brussel (VUB) and Ghent University.

Between 1996 and 2016, she worked as a nurse at the University Hospital Leuven (1996-1997) and as a teacher, educating and training student nurses at the bachelor and vocational level.

## Publication and presentation list

### A1 articles published

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## Presentations

**Poster presentation** of the above EPCCS study ('Changes in medication use in advanced cancer patients receiving palliative care') at the wintermeeting of the Belgian Society of Geriatrics and Gerontology on 17th February 2017.

**Oral presentation** of the above EPCCS study ('Changes in medication use in advanced cancer patients receiving palliative care') at the 15th World Congress of the European Association of Palliative Care (EAPC) on 18-20 May 2017.

**Oral presentation** Medicatiegebruik in palliatieve zorg, 'Changes in medication use in advanced cancer patients receiving palliative care' (12/06/2017, UZ Gent)

**Poster presentation** 'Advance care planning and associated changes in medication use' EuroDURG Glasgow, UK, 15-17/11/2017

**Poster presentation** 'Advance care planning and associated changes in medication use' Wintermeeting, 24/02/2018, BVGG, Oostende

**Oral presentation** 'Associations of potentially inappropriate medication use with four year survival in an inception cohort of nursing home residents' CARE4 international scientific nursing and midwifery congress, 4-6/02/2019, Leuven.

**Poster presentation** 'Associations of high care dependency and dementia symptoms with four year survival in an inception cohort of nursing home residents' CARE4 international scientific nursing and midwifery congress, 4-6/02/2019, Leuven.







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