Decisions About Medical Treatment in the Last Phase of Life

Withholding and withdrawing medication and other interventions

Eric C.T. Geijteman

Colofon

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Withholding and withdrawing medication and other interventions

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Niet-starten en stoppen van medicijnen en andere interventies

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General introduction

1 End-of-life care and forgoing medical interventions

Improvement of medical care has resulted in an increase in life expectancy in the last decades.(1) Since 1950, life expectancy at birth has increased with almost 10 years to being over 82 years in 2015.(2) In addition to this rise in life expectancy, improvement of medical care has resulted in changes in causes of death. In the 1950s most patients died as a result of acute illness, such as myocardial infarction, stroke, and infectious diseases.(3) Nowadays, chronic diseases, such as cancer and chronic heart failure, are the leading causes of death, accounting for around 60% of all deaths in the Netherlands.(4) This percentage will further rise in the next twenty years.(5)

An important driver of improvement of medical care in the last decades is that our knowledge regarding the pathophysiology of diseases has increased. As a result, new medical interventions have been introduced and optimized, such as cardiopulmonary resuscitation to treat a patient with a cardiac arrest, antiretroviral medications to suppress human immunodeficiency virus (HIV), and chemotherapy and targeted therapy to treat cancer.

Although the benefits of (improved) medical care are widely acknowledged, there are also negative effects to be aware of. Negative effects that may concern almost every medical intervention, especially at the end of life, are physical side effects and complications, sometimes even resulting in (earlier) death. Medical interventions may also cause psychological, social or existential problems, such as false hope and the denial of approaching end of life in patients and their relatives.(6)

Especially in patients who will ultimately die from their chronic disease, there may at some stage during the illness trajectory be a turning point at which the disadvantages of a medical intervention start to outweigh its potential benefits. It is important that caregivers regularly consider whether medical interventions should be continued, adapted or discontinued in such patients. This applies particularly to medical interventions that in all probability can be withheld or withdrawn without negatively affecting the underlying disease. However, for other medical interventions it is also important that caregivers consider whether they should be adapted or discontinued to prevent potential harms outweighing potential benefits. When a medical intervention causes more harm than good, its use is referred to as 'overuse'.(7) Overuse may result in physical, psychosocial, and financial harms,(8) and is therefore seen as poor-quality care.(9)

This thesis concerns the practice of withholding and withdrawing medical interventions in the last phase of life. It focuses on medical interventions in general, and on cardiopulmonary resuscitation and medication discontinuation in particular. In the studies that are described in this thesis, the last phase of life is defined as having a life expectancy of three months or less. In addition, specific attention is paid to the dying phase. This is a phase in which dying is imminent and generally concerns the last days and hours before the patient's actual death.

Do-not-resuscitate (DNR) decisions

Cardiopulmonary resuscitation (CPR) is an emergency procedure to maintain circulatory flow and oxygenation in a patient who is in cardiac arrest. The procedure consists of the use of closed-chest compressions and artificial ventilation. In the early years after its introduction, in the 1960s, the procedure was seen as simple and very successful.(10, 11) However, it soon became clear that not every patient will benefit from CPR. In fact, the majority of the patients who receive CPR die. Until 2000, survival after in-hospital CPR remained below 20 per cent.(12-14) On average, out-of-hospital CPR has even lower survival rates,(15-17) although survival rates in the Netherlands have increased to almost 20 percent since the introduction of widely available automated external defibrillators (AEDs) in the last decade.(18) As the costs resulting from CPR are very high,(19) it has been suggested that CPR is a particularly cost-ineffective medical intervention, with costs being more than 220.000 per gained quality-adjusted life year.(20, 21) These costs include medication costs, costs of staying in the hospital, and labour costs, among others. Moreover, CPR may involve a death that is traumatic for both the patient and his relatives.(10) In the 1970s, so-called do-not-resuscitate (DNR) orders were introduced.(10) Such orders involve the decision not to apply cardiopulmonary resuscitation in a patient experiences a cardiac arrest. From their introduction until now, DNR orders have evoked huge controversy as they might result in withholding patients a potentially life-saving treatment at the end of life.(10, 22) There are three ways in which the DNR decisions can be taken:

1. A competent patient asks not to be resuscitated;
2. The attending physician together with the patient decides that the burden of CPR outweighs its potential benefit;
3. The attending physician unilaterally decides that resuscitation is medically useless.

A DNR decision should in principle always be disclosed to patients and their relatives.(23) Ideally, patients are involved in a DNR decision in order to respect patients' autonomy.(24) It has been shown that between 1990 and 2001 a growing percentage of DNR decisions in the Netherlands was made together with the patient.(25) However, in 2001 still more than half of all DNR decisions were made without involving the patient.(25)

Medication discontinuation

Many recently introduced medications have been shown to be very successful in enhancing patients' quality of life and in prolonging life. As a consequence, patients use more and more medications.(26, 27) Especially older patients who may have different comorbidities often use many medications.(27, 28)

As with other medical interventions, each medication has its harmful profile. An important potential harm relates to so-called adverse drug reactions.(29) The more medications a patient uses, the greater the chance of adverse reactions,(30) including the chance of drug-drug interactions.(31) Another potential harm is pill burden: the effort patients need to take their medications.(32) Especially fragile patients may have problems with taking medications, such as lodging of the medication in the mouth or throat.(33)

When potential adverse effects outweigh the expected benefits of medications, these medications are called 'potentially inappropriate medications' (PIMs).(5) Medications can also be regarded as PIMs when they are overprescribed (i.e. excessive dosages or duration, or when their effect is only achievable beyond the life expectancy of the patient) or misprescribed (i.e. prescribing medication for which there is no proper indication).(34) The process of medication discontinuation is called 'deprescription'.(11)

Especially older patients and patients with a limited life expectancy are prone to use one or more PIMs, as medications may not be as effective as they were in earlier stages, treatment objectives may change during life time, and organ functions may deteriorate. Exposure to PIMs for this group is associated with an increased risk of adverse drug reactions.(35) A meta-analysis showed a 1.6-fold increased mortality when using one or more PIMs compared to no use of PIMS.(36) The use of PIMs in older patients ranges from 35% up to 77%.(37-41) In order to decrease the use of PIMs among patients in a nursing home, in the early 1990s Beers et al defined a list of medications that generally should be avoided in a nursing home.(5) The Beers criteria were based on a combination of evidence from scientific literature and a modified Delphi method with an expert panel. These criteria were expanded and revised several times between 1997 and 2015 to finally include all settings of geriatric care.(42-45) In the meantime, other lists of PIMs for older patients have been developed, among which the Screening Tool of Older person's Potentially inappropriate Prescriptions (STOPP).(26) Both the Beers criteria and the STOPP have been proven to not only reduce the use of PIMs,(27, 40) but more importantly, to improve patients' quality of life.(46)

Less is known about the use of PIMs in (younger) patients with a limited life expectancy due to a chronic life-threatening disease. However, it is also important that medication use of these patients is reconsidered, perhaps even more than in older patients, especially because the time-until-benefit of many medications may exceed a patient's life expectancy.(47) In 2006, a framework for appropriate medication prescribing for patients with a limited life expectancy was published in order to support the discontinuation of inappropriate medications.(48) This framework was built on four components, namely the 'remaining life expectancy of the patient', 'time until benefit of the medication', 'goals of care' (in which the patient expresses his/her priorities

in life), and 'treatment targets' (e.g. life prolongation or prevention of morbidity). In the years that followed, different retrospective chart review studies have highlighted that patients with a limited life expectancy are often prescribed medications that are potentially inappropriate until the very end of life. As also many medications need to be started for symptom relief, these patients use many medications in the last months and days of life.(5, 28, 49-53) Little is known about patients' and physicians' opinions regarding medication management at the end of patients' lives. Moreover, reasons for the continuation of PIMs in this last phase of life are unclear and the perspectives of patients, their relatives and caregivers are not yet known.

Care in the dying phase

Most patients who die from a chronic illness, such as cancer or chronic heart failure, die after a period of imminent dying which normally takes several days to hours.(54) It is not always possible to recognize this dying phase, due to the lack of objective parameters. When the dying phase is recognized and acknowledged, interventions can and should be focused at providing patients with all the comfort they need and wish. All other interventions, such as those with the aim of curing disease or extending life, should be forgone, as the dying phase is a period of irreversible deterioration, where no interventions can affect the outcome.(55) Continuing or starting interventions to prolong life during the dying phase can therefore be seen as medical overuse.(7) This also accounts for diagnostic interventions, such as measurement of blood pressure and blood sampling for laboratory tests.(7)

International studies have shown that aggressive care, such as intensive care unit admission and invasive and burdensome diagnostic or therapeutic procedures, is used in more than half of all dying patients.(56-58) An increasing trend over time has been found towards more aggressive medical interventions when death is approaching.(59, 60) As these medical interventions are not only applied to patients in whom the inevitability of dying at short notice is recognized, but also to patients in order to *prevent* them from dying, it may be difficult to judge retrospectively whether or not continuing or starting medical treatment in patients in the last days of life was 'right' or 'wrong'.

It is stated that end-of-life care in the Netherlands is less aggressive compared to other western countries; e.g. relatively few patients with advanced diseases ultimately die on an intensive care unit in the Netherlands.(61) However, it is unknown how many and which diagnostic and therapeutic interventions are applied by physicians in Dutch hospitals in dying patients. It is also unexplored whether awareness of impending death of the attending physician is associated with the application of these interventions.

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This thesis

This thesis aims to investigate the practice of forgoing medical treatment at the end of life and to formulate recommendations to further improve end-of-life care.

The main research questions are:
DNR decisions
1. What is the frequency of individual DNR decisions and patient involvement in such decisions over the past two decades?

Dying phase
2. How many and which medical treatments are applied by physicians for patients in the last days of life?

Medication discontinuation
3. What are the opinions and experiences of physicians regarding medication discontinuation during the last days to months of life?
4. What factors influence the continuation of (potentially) inappropriate medical treatment during the last days to months of life?
5. What are possible solutions to decrease (potentially) inappropriate medical treatment during the last days to months of life?

To answer these research questions, data were used from nationwide studies on end-of-life decision making practices, the MEDILAST project, and the PalTeC-H project. To reflect further on the different topics that are investigated, this thesis also contains some descriptions of personal experiences.

Nationwide study on end-of-life decision making practices

To answer research question 1, we analyzed data from repetitive nationwide studies on end-of-life decision making practices ('Sterfgevallenonderzoek').(62) The purpose of these studies is to make reliable estimates of the frequency of medical practices pertaining to the end of life, and to assess trends in these frequencies. The study was performed firstly in 1990, and repeated every five years, most recently in 2015. In each of these years, stratified samples of death certificates were drawn from the central death registry of Statistics Netherlands. For all sampled cases for which the cause of death did not preclude an end-of-life decision, attending physicians were mailed a questionnaire that focused on the characteristics of the end-of-life decision making that may have preceded the death of the patient involved. In 1990, 2001 and 2010 the questionnaire contained a question about DNR decisions.

PalTeC-H project

The PalTeC-H project was performed between June 2009 and July 2012, and included cases of patients who died in one of 18 non-intensive care wards of Erasmus MC, a 1300-bed university hospital in Rotterdam, the Netherlands. Aims of the study were 1) to explore and understand the impact of the quality of care on the quality of life during the last three days of life and the quality of dying, and 2) to investigate the contribution of a quality improvement intervention which consisted of the implementation of a network of palliative care nurse champions.(63) Within the PalTeC-H project, attending physicians were asked to fill out a questionnaire within one week after a patient had died. Data from this questionnaire were used together with findings on diagnostic and therapeutic interventions as documented in the medical records to answer research question 2.

MEDILAST project

To answer research questions 2 to 5, we used data from the MEDILAST project. The MEDILAST (MEDIcation management in the LAST phase of life) project was carried out from February 2013 to December 2015 by the VU University Medical Center, Radboud University Medical Center, and Erasmus University Medical Center. The aim of the project was to understand current medication use in the last phase of life and to formulate recommendations to improve medication management at the end of life. A mixed-method approach was used, consisting of 1) a retrospective chart review study including a convenience sample of 179 patient records from hospices, hospitals, and home settings, 2) qualitative interviews with 17 patients, 12 relatives, 20 clinical specialists, 12 general practitioners, and 15 nurses, 3) a questionnaire study among 321 clinical specialists and general practitioners, and 4) a two-round Delphi study with involvement of 42 international experts in the field of medication management and palliative care.

Outline of this thesis

This thesis is divided into three parts. In **Part I**, current practices are described. In **chapter 2**, the frequency of DNR decisions in cases of non-sudden death and patients' and relatives' involvement in these decisions are reported. **Chapter 3** describes medication use in the last seven days of life of patients in the hospital, hospice and home setting. In **chapter 4**, a case of a patient with metastatic pancreatic cancer, and a history of diabetes mellitus type II is described. **Chapter 5** presents the number and

type of diagnostic and therapeutic interventions in hospitalized patients with cancer in their last three days of life. In addition, it explores whether or not physician awareness of impending death affects the use of these interventions.

Part II explores the perspectives of patients, their relatives and physicians regarding (potentially) inappropriate medications, in **chapters 6** and **7**, respectively.

In **Part III**, possible solutions for improvement of medical care at the end of life are described. **Chapter 8** presents recommendations for improvement of medication care in the final months of life based on an international Delphi study. In **chapter 9**, a research design for deprescribing trials is proposed. **Chapter 10** describes the final days of my father's life and proposes possible solutions to prevent patients from dying an undignified death. Finally, in **chapter 11**, the main findings and conclusions of the studies are summarized and discussed.

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NaCl

Part I

Current practice


CPR

Do-not-resuscitate decisions in the Netherlands over the past 20 years

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Abstract

Objective: To assess trends in the frequency of do-not-resuscitate (DNR) decisions in the Netherlands over the past two decades.

Design: A retrospective survey in three stratified samples of people whose death were reported to Statistics Netherlands in 1990, 2001, and 2010. Attending physicians received a questionnaire about the medical decision making that had preceded death.

Results: The frequency of individual DNR decisions among non-sudden deaths rose sharply from 46% in 1990 to 81% in 2010. The involvement of patients in individual DNR decisions rose from 23% (1990) to 45% (2001), and 55% (2010). In most cases in which the DNR decision was made without patient involvement, the patient was incompetent (56% in 1990, 71% in 2001, and 72% in 2010). The main cause of incompetence was unconsciousness (69% in 1990, 40% in 2001, and 43% in 2010).

Conclusions: Non-sudden deaths are increasingly preceded by DNR decisions, which are increasingly discussed with patients. However, patients are not involved in almost half of the DNR decisions, usually because they are unconscious. This implies that DNR decisions are often made late in the illness trajectory. Work needs to be done to establish real patient centered care in case of DNR decisions.

Introduction

There is an increased awareness that cardiopulmonary resuscitation (CPR) is not always in the patient's best interests.(1) As a result, decisions have to be made about who should and should not receive CPR in case of cardiac arrest. Ideally, the physician and patient together decide in advance when CPR is considered either appropriate or inappropriate. This decision should take into account the patient's care goals and clinical judgment of the patient's prognosis.(2)

However, it has been shown that advance do-not-resuscitate (DNR) decisions are discussed insufficiently,(3) particularly in the out-of-hospital setting. (4) DNR decisions are often made very late in the course of a terminal illness.(5, 6) In addition, many of these decisions are made without direct patient involvement, either due to the severity of underlying illness or impaired decision-making capacity.(3, 5)

In the Netherlands, a DNR decision is based on the patient's wish and the medical utility of resuscitation. Physicians may ultimately over-ride the choice of the patient or his relatives when they consider CPR inappropriate, e.g. in imminently dying patients. A decision not to offer CPR should be disclosed to patients and relatives. In addition to these individual DNR decisions, there are so-called institutional DNR decisions, which concern all patients who are permanently staying within an institution. Such decisions are based on the assumption that resuscitation is futile for the patients concerned. Until recently, such institution-wide DNR policy was the rule rather than the exception in many nursing homes in the Netherlands, as was also true for several nursing homes in the United States.(7) However, as stated in recent American and Dutch directives,(8, 9) these institutional DNR decisions should be abandoned, because individualized care should be the norm.

It has been shown that between 1990 and 2001 a growing percentage of DNR decisions in the Netherlands was made with the patient or relatives.(10) In order to assess trends in the frequency of individual DNR decisions and patient involvement over the past two decades, we performed a follow-up study by means of nationwide surveys on end-of-life decision making practices.

Methods

Setting

We used data from subsequent nationwide Dutch studies on end-of-life decision making practices, that were performed in 1990, 2001, and 2010. (11) In each of these years stratified samples of death certificates were drawn from the central death registry of Statistics Netherlands, to which all causes of death are reported. Every case was

assigned to one of five strata: in stratum one, the cause of death precluded any end-of-life decision (e.g. sudden death from a car accident); stratum 2 contains sudden deaths in the presence of pre-existent disease; stratum 3, non-sudden deaths due to chronic disease; stratum 4, deaths due to cancer and other deaths that were (probably) preceded by longer-term terminal disease; and stratum 5, where the death certificate suggested that a physician had assisted in dying. The final sample contained 8,3% of the cases in strata 1 and 2, 12.5% of those in stratum 3, 25% of stratum 4, and 50% of stratum 5.

Patients

For all sampled cases for which the cause of death did not preclude end-of-life decision making (all but stratum 1), the attending physician was asked to fill out a written questionnaire. The response percentages were 76% (1990), 74% (2001), and 74% (2010); the numbers of cases studied were 5,197, 5,617, and 6,263, respectively. The questionnaire focused on end-of-life decision making that might have preceded the death of the patient involved. If the attending physician reported a death to have occurred suddenly and unexpectedly, the case was classified as a sudden death. All other cases were classified as non-sudden deaths. We excluded cases in which the deceased patient was younger than one year.

Study design

In 1990, 2001, and 2010 the questionnaire contained a similar question about a DNR decision: "Did you or another physician clearly agree in advance that in the event of a cardiac and/or respiratory arrest no attempt would be made to resuscitate the patient (a so-called do-not-resuscitate decision)?" Answer options distinguished individual DNR decisions, which are made for individual patients, and institutional DNR decisions. Individual DNR decisions can be agreed upon with the patient, the patient's relatives, and/or with other health care professionals.

Details about the competency of the patient were only asked in cases where death had actually been preceded by an end-of-life decision that concurred with DNR decisions, i.e. a decision to refrain from potentially life-prolonging interventions or to provide medication with a possible or certain life-shortening effect, e.g. high doses of opioids. The competency of the patient to be involved in this end-of-life decision was asked.

The study designs were nearly similar in the three study years. The only exception is that the question about a DNR decision in 2001 was only asked in case an end-of-life-decision had preceded death.

The data were weighted to adjust for the sampling procedure and for differences in response rates by age, gender, and cause and place of death of patients. Multivariate logistic regression analysis was done to identify potential differences in the characteristics of patients for whom DNR decisions were made.

According to Dutch policy, the study did not require review by a Research Ethics Committee, because the data were collected anonymously.

Results

Frequencies

In Table 2.1, the frequencies of DNR decisions are presented. The frequency of individual DNR decisions among non-sudden deaths rose from 1990 to 2010, from 46% in 1990 to 81% in 2010. The frequency of institutional DNR decisions decreased, from 9% of all non-sudden deaths in 1990 to 3% in 2010.

Table 2.1 Do-not-resuscitate decisions in non-sudden deaths, in 1990, 2001 and 2010[a]

	1990		2001		2010	
	All non-sudden deaths N=3983 %	Non-sudden deaths preceded by an end-of-life decision N=2343 %	All non-sudden deaths[b]	Non-sudden deaths preceded by an end-of-life decision N=2763 %	All non-sudden deaths N=4933 %	Non-sudden deaths preceded by an end-of-life decision N=3581 %
Individual DNR decision	46	55		60	81	85
Institutional DNR decision	9	11		8	3	3
No DNR decision	42	31		17	14	10
Missing	3	3		15	2	2

[a] *All percentages were weighted*

[b] *In 2001, the question about do-not-resuscitation decisions was only asked for non-sudden deaths that were preceded by an end-of-life decision*

Characteristics

In Table 2.2, the likelihood is shown of individual DNR decisions in non-sudden deaths in 2010 by patient characteristics. Individual DNR decisions were more often made if patients were 65-79 years (82%) or 80 years or older (85%) when they died, as compared to patients who were 1-64 years old (77%). Cancer (78%) or cardiovascular disease (80%) as the cause of death involved a somewhat lower probability of individual DNR decisions than other causes of death (88%). The highest frequency of individual DNR decisions concerned patients for whom the attending physician at the time of death was a clinical specialist (91%) or a nursing home physician (92%). If the attending physician was a general practitioner the frequency was lower (71%). The characteristics of patients for whom a DNR decision was made in 1990 and 2001 were comparable to those in 2010 (not in table).

Table 2.2 Likelihood of individual do-not-resuscitate decisions in non-sudden deaths by patient characteristics, in 2010[a]

	N	Individual do-not-resuscitate decision %	Odds ratio	95% confidence interval
Age (years)				
1-64	1158	77	1	
65-79	1630	82	1.22	1.01 - 1.48
≥80	2047	85	1.37	1.09 - 1.73
Gender				
Male	2432	82	1	
Female	2403	84	1.10	0.94 - 1.30
Cause of death				
Cancer	2875	78	1	
Cardiovascular disease	525	80	1.02	0.84 - 1.25
Other or unknown	1435	88	1.57	1.25 - 1.98
Type of physician				
General practitioner	2587	71	1	
Clinical specialist	1135	91	1.33	1.00 - 1.75
Nursing home physician	1113	92	5.06	4.03 - 6.37

[a] *All percentages were weighted*

Patient's involvement

The proportion of DNR decisions that were made with patient involvement increased between 1990 and 2010 (Table 2.3). However, in 2010 almost half of the individual DNR decisions, 45%, were still made without involving the patient. In most of these cases the decision was made with relatives. In 56% of the cases in 1990 where the

Table 2.3 Patient involvement in individual do-not-resuscitate decisions, in 1990, 2001 and 2010[a]

	1990 N=1563 %	2001 N=1579 %	2010 N=3871 %
Individual do-not-resuscitate decision was made …			
with patient	23	45	55
not with patient, but with relatives	40	51	43
not with patient or relatives, but with health care professionals	37	4	1

[a] *All percentages were weighted*

DNR decision was made without patient involvement, the patient was incompetent to make end-of-life decisions; this percentage was 71% in 2001, and 72% in 2010 (not in table). The main causes of incompetency were that the patient was in a state of reduced consciousness or unconscious (in 1990, 69%, in 2001, 40%, and in 2010, 43%) or that the patient had dementia (in 1990, 30%, in 2001, 37%, and in 2010, 38%) (not in table).

Discussion

We studied the development of DNR decision making in the Netherlands over the past 20 years. The percentage of individual DNR decisions that were discussed with patients or relatives has risen sharply between 1990 and 2010.

Despite the increasing percentage of individual DNR decisions and the decreasing percentage of institutional decisions in our study, there seems to be room for improvement. Almost half of all individual DNR decisions were made without involvement of the patient. In a minority of these cases the patient was probably competent, and thus could have been involved. In most of the cases the patient was incompetent. Non-involvement of incompetent patients may often imply that DNR decisions are made rather late in the illness trajectory.(5)

Earlier end-of-life decisions, including DNR orders, could give patients a better chance to be involved in making decisions about their care.(6) The high percentage of non-involved patients indicates that only some improvement has been made concerning patient-centered care in the last three decades.

Non-involvement of patients in DNR decision making may decrease by advance care planning (ACP);(12) the process in which patients are invited to anticipate and discuss future (end-of-life) treatment options. Indeed, a recent study found that with an intervention designed to facilitate end-of-life decision making for patients with

metastatic cancer DNR decisions were made earlier.(13) Especially general practitioners might be able to engage with their patients in these discussions earlier in the illness trajectory, because they often have a long-standing and committed relationship with their patients. Interestingly, in our study general practitioners reported relatively few individual DNR decisions in comparison with other types of physicians.

In the Netherlands, recently two guidelines were introduced that should stimulate physicians to talk timely with patients about their preferences for and expectations about care at the end of life,(14) and specifically about resuscitation.(9) These measures should contribute to an increase of involvement of competent patients in important decisions about medical care at their end of life.

Conclusions

The frequency of individual DNR decisions substantially increased in the last two decades. However, almost half of these decisions are still made without patient themselves. Work needs to be done to establish real patient-centered care with regard to DNR decisions.

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Medication use in the last days of life in hospital, hospice and home settings in the Netherlands

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Abstract

Objective: To describe medication use in the last week of life for patients dying in hospital, hospice and home settings in the Netherlands.

Design: Retrospective chart review study of medical records of patients who had died in hospice, hospital or at home in three different regions in the Netherlands that cover more than half of the country.

Results: 179 records were analyzed. Medications most frequently used in the last week of life were analgesics (n=168, 94.1%) and psycholeptics (n=150, 84.7%), in particular by hospice patients. The mean number of medications used per patient was nine during day 7 before death and six on the day of dying. On the day of death 48 (26.8%) patients used a preventive medication. This percentage was highest for patients dying in the hospital or at home.

Conclusions: Patients who die an expected death receive many medications in the last week of life, part of which are preventive medications. Medication management in patients' final days of life can be improved, especially in the hospital and home setting.

Introduction

Medications are important in supporting patients for curing, treating, and preventing disease, and in alleviating patients' symptoms. However, all medications have drawbacks, such as the occurrence of side effects, the potential burden of their administration, and their costs. Reconsidering medications is needed when they have more conceivable adverse than beneficial effects, especially during the terminal phase of a patient's life.(1, 2) When death becomes imminent, medications may become inappropriate due to 1) the lag time of their effect; 2) their increased risk of side effects as organ functions changes and 3) changed treatment objectives.(3) These medications are the so-called potentially inappropriate medications (PIMs).(4) In contrast, pharmacological treatment of symptoms is important in the last phase of life, because symptoms such as pain and dyspnoea are common and may jeopardise the patient's comfort and quality of dying.(5)

Research that explores end-of-life medication prescribing patterns has particularly focused on the use of unnecessary, futile medications, such as lipid-lowering and anti-osteoporosis agents.(6-10) They demonstrated that many of these medications are continued until the very end of life. Recently, an observational analysis of medication records from patients with a life expectancy of less than one year revealed that these patients use on average more than 10 medications, with a significant amount of PIMs.(11)Le Blanc et al. have reviewed the literature on studies of medications used at the end of life of patients with cancer and a limited life expectancy. (4) The six included studies showed that as patients approach death, the number of medications they take usually increases, due to an increase of medications aimed at the alleviation of symptoms combined with the continuation of medications for comorbid diseases. All studies focused on medications taken by patients who received care in hospices or from specialized palliative care services. Recently, another multicenter study in hospices underlined the finding of increased symptom-specific medications and continuation of medications for comorbid diseases at the end of life.(12) Hospice care is seen as an example for best practice care at the end of life.(13) The ultimate goal of hospice care is to enable patients to be comfortable. Consequently, medications to treat symptoms will ideally have much more weight than medications with the aim to treat or prevent diseases.

There is scarce information on the use of medications by patients in their last days of life in hospital and in home care settings. The only three studies that assessed medication use in a general hospital setting during the final days showed that many patients receive PIMs, and even medications that are clinically definitely futile in the last days of life.(5, 14, 15) To our knowledge, there have been no studies done in home care settings. It is unknown whether the number and type of medications in patients with a limited life expectancy depend on the place where end-of-life care is provided.

The aim of this study was to describe the medication prescriptions for patients dying in hospice, hospital and home care settings in the Netherlands.

Methods

Study design

This study consisted of a retrospective chart review within the MEDILAST (MEDIcation management in the LAST phase of life) project. MEDILAST is a multi-center mixed-methods research project with the aim of understanding current medication use in the last phase of life. The project is carried out by VU University Medical Center, Erasmus University Medical Center and Radboud University Medical Center in the Netherlands.

Chart review

We selected a convenience sample of medical records of patients who had died in hospice, hospital or at home by asking physicians to select their two to three most recent cases of patients who had died expectedly from a chronic condition. We aimed at including 3x60 medical records in the regions of Amsterdam, Rotterdam and Nijmegen, respectively, and in each region 3x20 medical records from the hospice, hospital and home setting, respectively. For the hospital setting, we included records from patients who had died at geriatrics, neurology, oncology, cardiology or pulmonology departments in a peripheral or academic hospital. In each region, the hospice setting included one high care hospice, where a physician with training in palliative care is at all times available for consultation. Finally, family physician practices were approached by telephone. Following acceptance to participate in the study, three physician-researchers (J.J.A., E.C.T.G., M.K.D.) visited the individual practices and clinical departments to collect the data.

A structured electronic form (MS Access 2013) was used to retrieve the information from the medical records. Demographics included place of death, age at the time of death and diagnoses. Information about medication use in the last week of life was registered which included medication generic names, start and stop dates, administration routes and doses. The physician's notes were manually screened for information about the decision-making on medication use. We reviewed the guidelines for data collection from medical records as developed by Jansen et al.(16)

The Medical Ethics Review Committee from the VU University Medical Center approved the study protocol. Thereafter, approval from the board of directors or relevant authority was obtained prior to data collection in all other participating centers.

Statistical analysis

Medications were coded using the World Health Organization Center for Drug Statistics Methodology's Anatomical Therapeutic Chemical classification (ATC) at the level of therapeutic subgroup (2nd), pharmacological subgroup (3rd) and chemical substance (5th).(17) Descriptive statistics were used to describe the frequency of medication prescription per setting. If it was not clear whether or not a medication was prescribed for preventive reasons, e.g. antihypertensives that may be used to prevent the complications of high blood pressure but also to relieve symptoms of dyspnea, we did not classify this as a preventive medication. Statistical analyses were conducted using IBM SPSS Statistics 21 (IBM Corporation, 2012). Two-sided p-values < 0.05 were considered statistically significant.

Results

A total of 180 medical records were reviewed in this study. One patient died within 24 hours of admission to a hospice and was not included in the analysis. Table 3.1 shows the characteristics of patients per setting. Hospital patients (n=59, 32.8%) comprised the wards of geriatrics (n=8, 13.5%), oncology (n=16, 27.1%), neurology (n=12, 20.3%), cardiology (n=12, 20.3%) and pulmonology (n=11, 18.6%); participating centers included 3 academic and 7 peripheral hospitals. In addition, 3 high care hospices (n=61, 33.9%), and 32 primary care practices which contributed with two to three medical records each (n=59, 32.8%) were included. Patients' age at the time of death ranged from 40 to 103 years. Most patients had a malignancy (n=109) with larger proportions in the home care and hospice settings as compared to the hospital

Table 3.1 Patient characteristics per setting

Characteristics	Home care n=61	Hospice n=59	Hospital n=59	Total n=179	p-value
Age, mean (SD)	76.05 (14.13)	72.56 (12.57)	74.42 (11.57)	74.24 (12.82)	0.328[a]
Male gender, No. (%)	27 (44)	27 (46)	31 (53)	85 (48)	0.755[b]
Region, No. (%)					0.998[b]
Amsterdam	21 (34)	20 (34)	20 (34)	61 (34)	
Rotterdam	20 (33)	20 (34)	20 (34)	60 (34)	
Nijmegen	20 (33)	19 (32)	19 (33)	58 (32)	
Primary diagnosis cancer, N (%)	39 (64)	50 (85)	20 (34)	109 (61)	<0.001[b]

SD: standard deviation

[a] *One-way ANOVA*

[b] *Chi-squared*

setting. Most cancer diagnoses involved malignancies of the bronchus/lung (n=29) or gastrointestinal tract (n=15). Non-cancer diagnoses included heart failure (n=25), cerebrovascular accident (n=12), chronic obstructive pulmonary disease (n=9), ischemic heart disease (n=3), and other conditions (n=21).

Patients used 304 different chemical substances corresponding to 113 pharmacological subgroups and 61 therapeutic subgroups. During the last week of life, analgesics (e.g. morphine, fentanyl, paracetamol) were used by 168 (94.1%) patients, psycholeptics (e.g. midazolam, haloperidol, temazepam) by 150 (84.7%) patients, medications for acid related disorders (e.g. pantoprazole, omeprazole, esomeprazole) by 110 (62.1%) patients, medications for constipation (e.g. macrogol, lactulose, sodium ducosate) by 100 (56.4%) patients, and antithrombotic agents (e.g. nadroparin, acetylsalicylic acid, acenocoumarol) by 87 (49.1%) patients.

The five medications that were most frequently started in the last week of life were opioids (n=66, 80.5%), hypnotics and sedatives (n=63, 52.5%), antipsychotics (n=47, 26.3%), anxiolytics (n=28, 15.6%) and diuretics (n=22, 12.3%). The median (IQR) number of days before death at which these new prescriptions were started was 2 (1-5) days for opioids, 2 (1-4.25) days for hypnotics and sedatives, 3 (2-5) days for antipsychotics, 4.5 (2.5-6) days for anxiolytics, and 4 (2-7) days for diuretics.

The five medications that were most frequently stopped in the last week of life were medications for peptic ulcer and gastro-esophageal reflux disease (n=64, 35.8%), antithrombotic agents (n=50, 27.9%), non-opioid analgesics (n=48, 26.8%), medications for constipation (n=46, 25.7%), and diuretics (n=38, 21.2%). The median (IQR) number of days before death at which these prescriptions were stopped was 2 (1-4) for medications for peptic ulcer and gastro-esophageal reflux disease, 2 (1-4) for antithrombotic agents, 1 (1-3.75) for non-opioid analgesics, 3 (1-4) for medications for constipation, and 2 (1-6) for diuretics.

The preventive medications most frequently used were antithrombotic agents that were used by 87 (48.6%) patients, vitamins by 36 (20.1%) patients, cholesterol-lowering medications by 16 (8.9%) patients, calcium by 10 (5.5%) patients, and iron supplements by 5 (2.7%) patients. Although there was a tendency to stop preventive medications in the last week of life, 48 (26.8%) patients still used preventive medication on the last day of life.

Table 3.2 shows the differences in medication use between settings in the last week of life for the 15 most frequently used pharmacological subgroups. There were statistically significant differences between settings for hypnotic, sedatives and anxiolytics, non-opioid analgesics and antipyretics, medications for constipation, antithrombotic agents, diuretics, antihypertensive agents, antibiotics, and belladonna derivatives. These differences were mostly related to the fact that the hospice setting differed from both other settings. Medications used for symptom control (for instance hypnotics and sedatives; non-opioid pain medication) tended to be used in more patients in the hospice

Table 3.2 Most frequently used medication in the last week of life

Medication pharmacological subgroup	Home care n=61 (%)	Hospice n=59 (%)	Hospital n=59 (%)	Total n=179 (%)	Chi squared p-value
Opioids	53 (86.9)	58 (98.3)	52 (88.1)	163 (91.1)	0.065
Hypnotics, sedatives or anxiolytics	46 (75.4)	55 (93.2)	38 (64.4)	139 (77.7)	0.002
Drugs for peptic ulcer and GORD[a]	33 (54.1)	38 (64.4)	38 (64.4)	109 (60.9)	0.322
Non-opioid analgesics and antipyretics	26 (42.6)	42 (71.1)	29 (40.7)	97 (54.2)	0.006
Drugs for constipation	24 (39.3)	43 (78.9)	33 (55.9)	100 (55.9)	0.001
Antithrombotic agents	28 (45.9)	16 (27.1)	43 (72.9)	87 (48.6)	<0.001
Antipsychotics	28 (45.9)	33 (55.9)	24 (40.7)	85 (47.5)	0.303
Diuretics[b]	25 (41)	14 (23.7)	35 (59.3)	74 (41.3)	<0.001
Corticosteroids for systemic use	16 (26.2)	28 (47.5)	22 (37.3)	66 (36.9)	0.054
Antihypertensive agents[c]	25 (41)	13 (22.0)	34 (57.6)	72 (40.2)	<0.001
Propulsives	15 (24.6)	23 (39)	16 (27.1)	54 (30.2)	0.205
Drugs for obstructive airway disease[d]	15 (24.6)	20 (33.9)	22 (37.3)	57 (31.8)	0.251
Antibiotics[e]	8 (13.1)	3 (5.1)	23 (39)	34 (19)	<0.001
Antiepileptics	8 (13.1)	11 (18.6)	11 (18.6)	30 (16.8)	0.612
Belladona and derivatives	3 (4.9)	13 (22.0)	5 (8.5)	21 (11.7)	0.010

[a] *Gastro-oesophageal reflux disease*
[b] *High-ceiling diuretics + potassium-sparing agents*
[c] *Betablockers, angiotensin converting enzyme inhibitors, vasodilators*
[d] *Inhaled adrenergics, other drugs for obstructive airway disease*
[e] *Beta-lactam antibacterials, quinolones*

setting, whereas predominantly preventive medications (for instance antithrombotics, statins) tended to be used more in both the hospital and home care setting.

The median number of medications used per patient in the last week of life was nine from day 7 through day 2 before death, eight on day 1 before death and six on the date of death. In the home setting the median number of medications per patient was seven during the entire week. Overall, a larger variation in the median number of medications used per patient per day was observed in the hospital setting (seven on day 7 and 6 before death, five on day 5 before death, seven on day 4 before death, five on day 3 before death, six on day two before death, and three 1 day before death and on the day of death) whilst no variation was seen in the home setting. The tendency in both hospice and hospital settings is a reduction in the median number of medications per patient.

When comparing settings with regard to medications that were frequently started in the last week of life it was found that diuretics were started more often in the hospital (18 patients, 38.3%) than in the home (3 patients, 7.5%) and hospice (1 patients, 2.1%) setting (p<0.001). Although not reaching statistical significance, opioids were started more often in the hospice (12 patients, 92.3%) and hospital (37 patients, 86%) than in the home (17 patients, 65.4%) setting (p=0.056).

When comparing settings with regard to medications frequently stopped in the last week of life it was found that antithrombotic agents were stopped more frequently in the hospital (29 patients, 49.2%) than in the home (13 patients, 21.3%) and the hospice setting (8 patients, 13.6%) (p < 0.001); this was also the case for diuretics which were stopped more often in the hospital setting (20 patients, 33.9%) when compared to the home (9 patients, 14.8%) and the hospice setting (9 patients, 15.3%).

The medications most frequently continued until death in the home and hospice setting were opioids (48 and 54), hypnotics and sedatives (35 and 46), and antipsychotics (25 and 24). In the hospital setting these were opioids (49), hypnotics and sedatives (25) and antithrombotic agents (14), respectively.

The comparison between settings of medications classified as preventive is shown in Table 3.3. The use of thromboprophylaxis, vitamins and cholesterol-lowering medications was consistently lower in the hospice setting, but no differences were found in the use of calcium or iron supplements.

Table 3.3 Use of preventive medication in the last week of life

Preventive medication	Home care n=61(%)	Hospice n=59(%)	Hospital n=59(%)	Total n=179	Chi squared p-value
Thromboprophylaxis	28 (46)	16 (27)	43 (73)	87 (49)	< 0.001
Anticoagulant medication	15 (25)	10 (17)	37 (63)	62 (35)	
Antiplatelet medication	18 (30)	9 (15)	20 (34)	47 (26)	
Vitamins and trace elements	19 (31)	1 (1.6)	16 (27)	36 (20)	< 0.001
Vitamin D	8 (13)	1 (1.6)	7 (12)	16 (8.9)	
Folic acid	4 (6.5)	0	2 (3.3)	6 (3.3)	
Vitamin B12	3 (4.9)	0	0	3 (1.6)	
Vitamin B6	0	0	1 (1.6)	1 (0.5)	
Vitamin B1	0	0	3 (5.1)	3 (1.6)	
Vitamin B complex	1 (1.6)	0	3 (5.1)	4 (2.2)	
Cholesterol-lowering drugs	2 (3.2)	1 (1.6)	13 (22)	16 (8.9)	< 0.001
Calcium supplement	4 (6.5)	0	6 (10)	10 (5.5)	0.051
Iron supplement	4 (6.5)	0	1 (1.6)	5 (2.7)	0.076

Discussion

This study showed that the number of medications patients used decreased in the final week of life regardless of whether patients die at home, in a hospice, or a hospital. As could be expected, the number of medications aimed at the alleviation of symptoms, such as opioids and sedatives, increased in the final week. The percentage of patients using such symptom alleviators was the largest in hospices, followed by the percentage in the home setting and in hospital. In all three settings, some patients used preventive medications until the very last days of life, but this most often occurred in patients dying at home and in hospital: more than a third of these patients used one or more preventive medications on the day before their death.

The importance of adapting the use of medications to a patient's life expectancy is increasingly acknowledged.(4) In a Delphi study, palliative care clinicians from nine countries came to the consensus that, ideally, medications aimed at the alleviation of symptoms (opioids, benzodiazepines, antipsychotics and antimuscarinics) should always and everywhere be available for dying patients.(18) In our study, we found that virtually all the patients in the hospice setting used morphine and sedatives and in more than half of them antipsychotics were used. In the home situation and in particular in the hospital, less patients received these medications. Antimuscarinics were not prescribed except for a few patients in the hospice. The added value of these medications to prevent death rattle is doubtful as two placebo controlled randomized studies found no favorable effect of antimuscarinics.(19, 20)

Another important reason for adapting medications for patients with a limited life expectancy is their futility: some medications have a lag time that exceeds the patient's expected life span and therefore might only do harm.(21) This applies primarily to preventive medications. For example, it has been proven that stopping statins in patients with an estimated life expectancy of less than one year is safe and may improve quality of life.(22) Our findings reveal that preventive medications are least often used by patients in the hospice, except for thromboprophylaxis. In the home setting and in hospital, on the other hand, more than 50% of the patients used one or more preventive medications in the week prior to death, including preventive medication other than thromboprophylaxis. For example, nearly a quarter of hospital patients used a statin one week before death. This finding also underlines that in the hospice medication management seems more appropriate and in line with intended care for patients in the last phase of life.(13)

In total, almost 50% of the patients were administered thromboprophylaxis in the week prior to their death, which was often continued until death. In the most recent NICE guideline, it is advised to review decisions about thromboprophylaxis for patients at the end of life on a daily basis, taking into account the views of patients and their relatives and the multidisciplinary team.(23) It seems that many physicians

struggle with the question as to whether thromboprophylaxis should be prescribed to patients who only have a limited life expectancy, mainly due to the lack of studies demonstrating positive and negative effects.(24)

Our study showed that some types of medication were started or continued in the last week of life for some patients, whereas they were stopped in others. Some of these medications have in the literature been classified as PIMs.(4, 5) Our findings underline the difficulty to categorize medications in the end of life as inappropriate. For example, diuretics can be considered to be PIMs when they are solely used as antihypertensive. However, they may relieve a patient's symptoms in case of dyspnea and not at all be inappropriate. It may therefore be better to follow a patient-centered approach rather than an explicit list of – potentially – inappropriate medications.(25) An exception should be long term preventive medications, such as statins, which are medically futile anyway.(9)

Our study had some limitations. First, the reasons for medication prescription were seldom described in the records. Therefore, we cannot draw conclusions about the intention of their administration. Secondly, we cannot rule out the possibility that medications have been discontinued in practice, without it being registered in the records. However, especially in hospice and hospital settings, it is common practice to administer only medications that are listed in the medical record in order to prevent any misunderstandings. Thirdly, differences between settings could be accounted for the illness and stage of disease of patients as well as for the background of the treating physician, however, the distinction between the two could not be established with our data.

Despite these limitations, our study demonstrates that the medication management in patients' final phase of life can be improved, especially in home care and hospital setting.

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Sense and nonsense of treatment of comorbid diseases in terminally ill patients: a teachable moment

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Story From the Front Lines

A 69-year-old woman was diagnosed with metastatic pancreatic cancer. She had a history of diabetes type II, diagnosed 7 years earlier. Initially, her diabetes was controlled by strict adherence to a healthy lifestyle. For example, she had stopped eating ice cream, which she was very fond of. Two years prior to the cancer diagnosis metformin was started and HbA_{1C} levels of 6.8% were achieved.

She was treated with palliative chemotherapy and during each cycle she received dexamethasone to reduce associated nausea. During the first two cycles, blood glucose levels rose as high as 288 mg/dl, for which she received short-acting insulin.

At home, without dexamethasone, blood glucose levels occasionally were slightly above the upper limit of target values. During the third treatment cycle, the patient's husband told the ward physician that his wife treated the slightly high blood glucose levels by not eating until levels came down to normal. The physician – who had an interest in palliative care – told the patient and her husband that higher glucose levels were not a problem as long as they caused no symptoms. Because of her limited life expectancy, development of long-term organ damage was unlikely.

This information was very disconcerting to the patient, who subsequently asked the nurse whether the physicians had thrown in the towel and whether she was going to die soon. She had always been told that it was of utmost importance that glucose levels not exceed target values. The physician repeated that higher glucose levels were unlikely to do her any harm, especially in the absence of symptoms of hyperglycemia. He emphasized that her caregivers were not going to abandon her. In contrast, they were in fact applying tailored therapy. The patient appreciated this explanation and despite her nausea she was keen to eat her beloved ice cream, ignoring its effect on blood glucose levels.

Teachable Moment

Pharmacotherapy is the *appropriate* use of drug therapy aimed at preventing and treating a disease or to relieve symptoms. In the final phase of life, the goals of treatment change, and drugs used to prevent or treat chronic diseases need to be reconsidered. (1) In diabetic patients without complications, no benefit of tight glucose control can be expected for at least a decade.(2) In addition to limiting burden and side effects, discontinuing drugs in patients with limited life expectancy may actually improve quality of life and survival. In a recent randomized trial, discontinuation of statins in patients with a less than one year life expectancy led to improved quality of life and a trend toward longer life span in comparison with continuation of these drugs.(3)

Continuing medications at the end of life also has important impacts on healthcare costs. Discontinuing statins alone in patients with a life expectancy of less than one year could save the US healthcare system $603 million annually.(3)

General considerations when prescribing medication for patients at the end of life include the patient's life expectancy, time until potential benefit of treatment, goals of care, and treatment targets.(4) Guidelines for treatment of diabetes in terminally ill patients recommend reducing or eliminating frequent blood glucose measurement, significantly increasing tolerated glucose levels, and minimizing or discontinuing medications.(5)

As in our patient, decreasing or discontinuing medications at the end of life may run counter to previous management and lead patients to worry that they are being abandoned.(1) Physicians need, therefore, to consider both the physical and psychosocial effects of withdrawing treatment. In our case, the physician initially failed to address the patient's fears, but after full explanation of the altered aims of treatment, she was very satisfied with her care.

Pharmacotherapy in terminally ill patients is not a simple task, since physicians must adapt drug treatments to new objectives.(1) This case illustrates that such adapted management may improve quality of life and potentially reduce unnecessary and costly pharmacotherapy.

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Interventions in the last days of hospitalized patients with cancer: importance of awareness of impending death

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Abstract

Objective: We examined the number and type of diagnostic and therapeutic medical interventions in hospitalized patients with cancer in their last days of life. In addition, we investigated if physician awareness of impending death affected the use of these interventions.

Design: Attending physicians of patients who died in a university hospital between January 2010 and June 2012 were asked whether they had been aware of the patient's impending death. The use of diagnostic and therapeutic interventions and medications was assessed by studying patients' charts. We included 131 patients.

Results: In the last 72 and 24 hours of life, 59% and 24% of the patients received one or more diagnostic interventions, respectively. Therapeutic interventions were provided to 47% and 31%. In the last 24 hours of life, patients received on average 5.8 types of medication.
Awareness of a patient's impending death was associated with a significant lower use of diagnostic interventions (48% vs 69% in the last 72 hours; 11% vs 37% in the last 24 hours) and several medications that potentially prolong life (e.g. antibiotics and cardiovascular medication).

Conclusions: Many patients with cancer who die in hospital receive diagnostic and therapeutic interventions in the last days of life of which their advantages are questionable. To improve end-of-life care, medical care should be adapted.

Introduction

Hospital care is typically focused on cure and prolongation of life. As a result, dying patients may receive interventions that are not aimed at promoting their comfort.(1) This has important negative consequences for both patients and their relatives and is therefore in conflict with what has been found to constitute 'a good death'.(2) For patients it means that they may suffer from pain and other symptoms and that they may not have time to prepare for the end of life.(3) Further, continued efforts to prolong life, e.g. by admitting irreversibly dying patients to the Intensive Care Unit (ICU) or providing them with cardiopulmonary resuscitation (CPR), are associated with complicated grief of bereaved relatives.(3) In addition to negatively affecting patients' quality of dying and bereaved relatives' grieving, futile interventions involve unnecessary costs. Health care costs have been shown to increase sharply when life approaches its final weeks.(4, 5) Data on medical interventions in the last days of life are scarce, but they indicate that expensive interventions are sometimes administered to patients for whom dying is inevitably imminent.(6-8) Unnecessary, burdensome and costly interventions should whenever possible be avoided in dying patients.(1, 9)

In almost all patients with advanced incurable cancer, death is preceded by a more or less clear period of imminent dying.(10) When it is recognized and acknowledged that the dying phase has started, interventions can and should be focused at providing patients with all the comfort they need and wish.(1) In two retrospective studies, one of them including only patients dying in hospitals, it was shown that patients in whom impending death was recognized received significantly fewer undesirable interventions compared to patients in whom the dying phase was not recognized.(7, 8) However, another study demonstrated that patients for whom a comfort plan was used because death was expected at short notice, still received life prolonging treatment.(11)

The purpose of this study was to investigate 1) how many and which diagnostic and therapeutic interventions are applied by physicians in hospital in the last 72 hours of life of inpatients with cancer, and 2) whether awareness of impending death of the attending physician is associated with the application of these interventions.

Methods

This study is part of a study to explore and understand palliative and terminal care in the hospital (PalTec-H).(12) We studied medical care for inpatients with cancer who died between January 2010 and June 2012 during their stay in Erasmus MC, a 1300-bed university hospital in Rotterdam, the Netherlands. All inpatient wards of the hospital participated, with the exception of the department of psychiatry and the

intensive care departments. Attending physicians were asked to fill out a questionnaire within one week after a patient had died. We studied the patients' medical charts. Patients who died within 72 hours of their hospital admission were excluded.

The questionnaire included a question about the physicians' awareness of a patient's impending death. Physicians were asked: 'had it prior to death been clear that the patient would die within hours or days?' They could answer 'yes', 'more or less', or 'no'. When physicians answered 'yes' they were asked: 'when did this become clear?' This question could be answered with 'more than three days before death'; 'at day 3 (72-48 hours) before death'; 'at day 2 (48-24 hours) before death'; '24-12 hours before death'; '12-6 hours before death'. We defined a physician as having been aware of a patients' impending death when he answered that it had been clear that the patient would die within hours or days more than 24 hours before the patient actually died. The questionnaire also included a question on whether the patient was treated with a curative or palliative intent.

Two physician researchers (EG, MvdG) and one medical student (SvN) reviewed the medical chart of each patient about whom physicians filled out a questionnaire. All diagnostic and therapeutic medical interventions in the last three days were registered, as well as medication use during this period. We assessed whether or not an intervention or medication was used in either of two periods: the last 72 hours and the last 24 hours of life. All medications were coded using the World Health Organization Center for Drugs Statistics Methodology's Anatomical Therapeutic Chemical Classification (ATC).(13)

The PalTec-H-study was approved by the medical ethical research committee of the Erasmus MC. According to Dutch policy, informed consent of patients was not required as the data were obtained after patient's death and all data were processed anonymously.

Statistical analysis

The statistical significance of bivariate associations between physicians' awareness of a patient's impending death and the use of diagnostic and therapeutic interventions was analyzed with chi-square tests. An alpha of 0.05 was used as the cutoff for significance. We used Statistical Package for Social Sciences (SPSS), version 24.0, for all calculations.

Results

Physicians completed the questionnaire for 150 patients with cancer who died during the study period. Data of 19 patients could not be analyzed, either because of missing information on the physician's awareness of the patient's impending death or because

of an incomplete medical chart. Data about 131 patients could be used for the analysis. The characteristics of these 131 patients are summarized in Table 5.1. In 63 patients (48%), physicians had been aware of the patient's impending death. The mean age of patients for whom the physician had or had not been aware of their impending death was 62 years (standard deviation (sd) 12,8 years) and 63 years (sd 11,2 years), respectively. The mean duration of the final hospital stay was 13 days for both groups (sd 11,0 and 10,3, respectively). The most common cancer types were lung cancer (n=21), cancer of the urological tract (n=17), and hematological cancer (n=15). 92% of all patients were treated with a palliative intent during their stay in the hospital (Table 5.1).

Table 5.1 Patient characteristics

	Total N=131 N (%)	Physician had been aware of impending death N=63 N (%)	Physician had not been aware of impending death N=68 N (%)	P-value[a]
Age (years)				.352
<50	19 (15)	12 (19)	7 (10)	
50-64	52 (40)	21 (33)	31 (46)	
65-79	55 (42)	27 (43)	28 (41)	
≥80	5 (4)	3 (5)	2 (3)	
Duration of final hospital stay (days)				
3-7	40 (31)	17 (27)	23 (34)	.358
8-14	54 (41)	30 (48)	24 (35)	
>14	37 (28)	16 (25)	21 (31)	
Female gender	51 (39)	25 (40)	26 (38)	.865
Cancer type				.131
Lung	21 (16)	7 (11)	14 (21)	
Gastrointestinal	18 (14)	11 (17)	7 (10)	
Urological	17 (13)	6 (9)	11 (16)	
Hematological	15 (11)	5 (8)	10 (15)	
Head and neck	13 (10)	7 (11)	6 (9)	
Breast	11 (8)	9 (14)	2 (3)	
Melanoma	6 (5)	2 (3)	4 (6)	
Other	27 (21)	15 (24)	12 (18)	
Unknown	3 (2)	1 (2)	2 (3)	
Treatment intention				
Curative	4 (3)	2 (3)	2 (3)	.568
Palliative	120 (92)	59 (94)	61 (90)	
Unknown	7 (5)	2 (3)	5 (7)	

[a] *Chi-square test*

Diagnostic interventions

In the last 72 and 24 hours of life, 59% and 24% of the patients, respectively, received one or more diagnostic interventions, mostly blood sampling and radiologic procedures (Table 5.2). Among patients for whom the physician had been aware of their impending death, 48% received one or more diagnostic interventions in the last 72 hours compared to 69% of the patients in the other group (p=0.013) (Table 5.2). In the last 24 hours of life, these percentages were 11% and 37% (p=0.001), respectively.

Table 5.2 Diagnostic interventions in the last days of life

	Total n=131 n (%)	Physician had been aware of impending death n=63 n (%)	Physician had not been aware of impending death n=68 n (%)	p-value[a]
Diagnostic interventions in the last 72 hours				
Blood sampling[b]	67 (51)	24 (38)	43 (63)	.004
Cultures other than blood culture	31 (24)	5 (8)	26 (38)	.000
Urinalysis	13 (10)	3 (4)	10 (16)	.028
Radiology	45 (34)	14 (22)	31 (46)	.005
Electrocardiography	13 (10)	3 (5)	10 (15)	.057
Fine needle aspiration and/or biopsy	6 (5)	1 (2)	5 (7)	.115
Other[c]	2 (3)	0 (0.0)	2 (2)	.170
Any diagnostic intervention	77 (59)	30 (48)	47 (69)	.013
Diagnostic intervention in the final 24 hours				
Blood sampling[b]	27 (21)	6 (10)	21 (31)	.003
Cultures other than blood cultures	6 (5)	0 (0.0)	6 (9)	.016
Radiology	10 (8)	1 (2)	9 (13)	.012
Electrocardiography	3 (2)	0 (0.0)	3 (4)	.092
Fine needle aspiration and/or biopsy	3 (2)	0 (0.0)	3 (4)	.092
Other[d]	2 (3)	0.0	2 (2)	.170
Any diagnostic intervention	32 (24)	7 (11)	25 (37)	.001

[a] *Chi-square test*
[b] *Including vena punctures (lab or culture), arterial blood gas sampling, glucose measurement*
[c] *Concerned: in one patient a gastrointestinal endoscopy and echocardiography, and in one patient a bone marrow puncture and electroencephalogram*
[d] *Concerned: in one patient a bone marrow puncture and electroencephalogram, and in one patient urinalysis*

Therapeutic interventions

In the last 72 hours and 24 hours of life, 47% and 31% of the patients received one or more therapeutic interventions, respectively. The interventions that were most often applied were intravenous fluids and enteral tube feeding. In almost all patients who received enteral tube feeding, this feeding was continued until the patient passed away. Two patients for whom the physician had not been aware of impending death were shortly admitted to the ICU in the last 24 hours of life. One of these patients was treated

Table 5.3 Non-pharmacological therapeutic interventions in the last days of life

	Total n=131 n (%)	Attending physician had been aware of impending death n=63 n (%)	Attending physician had not been aware of impending death n=68 n (%)	p-value[a]
Interventions in the last 72 hours[b]				
Blood transfusion	17 (13)	5 (8)	12 (18)	.098
Intravenous fluids (>500ml/24 hours)	43 (33)	16 (25)	27 (40)	.081
ICU-admission	4 (3)	0 (0.0)	4 (6)	.051
Intervention radiology	8 (6)	4 (6)	4 (6)	.911
Resuscitation	2 (2)	0 (0.0)	2 (3)	.170
Enteral tube feeding	18 (14)	12 (19)	6 (9)	.089
Other therapeutic interventions[c]	4 (3)	1 (2)	3 (4)	.348
Any therapeutic intervention	62 (47)	27 (43)	35 (51)	.324
Interventions in the final 24 hours[a]				
Blood transfusion	7 (5)	1 (2)	6 (9)	.066
Intravenous fluids (>500ml/24 hours)	24 (18)	5 (8)	19 (28)	.003
ICU-admission	2 (2)	0 (0.0)	2 (3)	.170
Resuscitation	2 (2)	0 (0.0)	2 (3)	.170
Enteral tube feeding	16 (12)	10 (16)	6 (9)	.218
Other therapeutics[d]	1 (1)	1 (2)	0 (0.0)	.297
Any therapeutic intervention	40 (31)	15 (24)	26 (38)	.075

[a] *Chi-square test*
[b] *Two times or more*
[c] *Concerned: in one patient in which the physician was aware of impending death intervention radiology; in two patients radiotherapy, and in one patient operation*
[d] *Concerned: intervention radiology*

Table 5.4 Use of medication in the last 72 hours of life

	Total n=131 n (%)	Physician had been aware of impending death n=63 n (%)	Physician had not been aware of impending death n=68 n (%)	p-value[a]
Opioids[b]	100 (76)	50 (79)	50 (74)	.43
Benzodiazepines	69 (53)	37 (59)	32 (47)	.18
Antipsychotics	58 (44)	31 (49)	27 (40)	.27
Medications for constipation treatment	54 (41)	22 (35)	32 (47)	.16
Other analgesics[c]	45 (34)	19 (30)	26 (38)	.33
Cardiovascular medications	42 (32)	13 (21)	29 (43)	.007
Antithrombotics	41 (31)	18 (29)	23 (34)	.52
Antimicrobials[d]	37 (28)	13 (21)	24 (35)	.06
Medications for acid related disorders	36 (27)	15 (24)	21 (31)	.36
Antiemetics[e]	35 (27)	21 (33)	14 (21)	.10
Medications for obstructive airway diseases	23 (25)	6 (10)	17 (25)	.02
Corticosteroids	21 (16)	10 (16)	11 (16)	.96
Minerals-electrolytes[f]	18 (14)	9 (14)	9 (13)	.86
Anesthetics	15 (11)	8 (13)	7 (10)	.67
Glucose lowering medications	10 (8)	3 (5)	7 (10)	.23
Antiepileptics	8 (6)	3 (5)	5 (7)	.54
Antidepressants[g]	4 (3)	2 (3)	2 (3)	.94
Vitamins	3 (2)	2 (3)	1 (2)	.51
Antihemorragics	3 (2)	2 (3)	1 (2)	.51
Antimuscarinics[h]	2 (2)	2 (3)	0 (0.0)	.14
Lipid modifying agents	2 (2)	2 (3)	0 (0.0)	.14
Others[i]	23 (18)	8 (13)	15 (22)	.16
Mean number of different medications (range)	7.2 (0-20)	6.7 (1-18)	7.6 (0-20)	.12

[a] *Chi-square test*
[b] *Including strong-acting opioids, not tramadol*
[c] *Including paracetamol, tramadol, and antirheumatics*
[d] *Including antibiotics, antifungals, antivirals*
[e] *Including aprepitant, domperidon, and metoclopramide*
[f] *Including treatment of mineral supplement, magnesium, potassium, treatment of hyperkalemia, combinations Including amitryptillin*
[g] *Including amitryptillin*
[h] *Belladonna*
[i] *Other medications that were prescribed to less than four patients (including opioid dependence, loperamide, melatonin, baclofen, pamidronate, ferrous, folic acid, levetiracetam, levothyroxin, chlorhexidin, somatostatin, clemastin, methylnaltrexone, multienzymes, nicotin, oxybutynin, phytomenadione, methylphenidate, clemastine*

Table 5.5 Use of medication in the last 24 hours of life

	Total n=131 n (%)	Physician had been aware of impending death n=63 n (%)	Physician had not been aware of impending death n=68 n (%)	p-value[a]
Opioids[b]	99 (76)	49 (78)	50 (74)	.57
Benzodiazepins	69 (53)	37 (59)	32 (47)	.18
Antipsychotics	52 (40)	26 (41)	26 (38)	.83
Medication for constipation treatment	49 (37)	21 (33)	28 (41)	.35
Other analgesics[c]	42 (32)	18 (29)	24 (35)	.41
Cardiovascular medications	37 (28)	11 (17)	26 (38)	.008
Antithrombotics	36 (27)	15 (24)	21 (31)	.36
Medications for acid related disorders	33 (25)	13 (21)	20 (29)	.25
Antimicrobials[d]	32 (24)	8 (13)	24 (35)	.00
Antiemetics[e]	30 (23)	17 (27)	13 (19)	.28
Medication for obstructive airway diseases	20 (23)	5 (8)	15 (22)	.02
Corticosteroids	18 (14)	8 (13)	10 (15)	.74
Anesthetics	13 (10)	7 (11)	6 (9)	.66
Minerals-electrolytes[f]	11 (8)	5 (8)	6 (9)	.85
Glucose lowering medications	8 (6)	2 (3)	6 (9)	.18
Antiepileptics	7 (5)	3 (5)	4 (6)	.78
Antidepressants[g]	4 (3)	2 (3)	2 (3)	.94
Vitamins	3 (2)	3 (5)	0 (0.0)	.07
Antihemorragics[h]	3 (2)	2 (3)	1 (2)	.51
Antimuscarinics	2 (15)	2 (3)	0 (0.0)	.14
Lipid modifying agents	1 (1)	1 (2)	0 (0.0)	.30
Others[i]	19 (15)	8 (13)	11 (16)	.57
Mean number of different medications taken (range)	5.8 (0-17)	5.2 (0-15)	6.4 (0-17)	.038

[a] *Chi-square test*
[b] *Including strong-acting opioids, not tramadol*
[c] *Including tramadol, and antirheumatics*
[d] *Including antibiotics, antifungals, antivirals*
[e] *Including aprepitant, domperidon, and metoclopramide*
[f] *Including treatment of mineral supplement, magnesium, potassium, treatment of hyperkalemia, combination*
[g] *Including amitryptillin*
[h] *Belladonna*
[i] *Other medications that were prescribed to less than four patients in the last day of life (Including opioid dependence, loperamide, melatonin, baclofen, pamidronate, ferrous, folic acid, levothyroxin, chlorhexidin, somatostatin, clemastin, methylnaltrexone, multienzymes, nicotin, oxybutynin)*

with a palliative intent, for the other patient treatment intention is not known. Two other patients, both treated with a curative intent, were resuscitated in the last 24 hours of life. Chemotherapy was not provided to any of the patients in the last 72 hours of life.

Awareness of impending death was not significantly associated with receiving therapeutic interventions in the last 72 and 24 hours of life (Table 5.3).

Medication

On average, patients used 7.2 types of medication (sd 4.38) in the last 72 hours of life (Table 5.4) and 5.8 (sd 4.24) in the last 24 hours of life (Table 5.5). Patients for whom the physician had been aware of their impending death used fewer medications in the last 24 hours of life than patients for whom the physician had not been aware of their impending death, but this difference was not statistically significant (mean 5.2 vs 6.4, p=0.38).

The percentage of patients who used cardiovascular medications and medications for obstructive airway diseases in the last 72 hours and 24 hours of life was significantly lower when the imminence of death had been acknowledged (Table 5.4 and 5.5). In the last 24 hours of life, antibiotics were less often prescribed to patients in whom the physician had been aware of impending death. There were no significant differences in the use of other medications.

Discussion

Our study shows that many patients with cancer who died in hospital received diagnostic and therapeutic interventions in the last days of life. Our study also indicates the importance of physicians' awareness of impending death, as it may reduce the use of – often burdensome and futile – interventions.

There are roughly four different scenarios for the last days of life of a patient who dies from a chronic disease, where physicians either do (scenario 1 and 2) or do not (scenario 3 and 4) acknowledge a patient's impending death, and either do (scenario 2 and 4) or do not (scenario 1 and 3) provide life-prolonging interventions. In our study physicians had been aware of impending death more than 24 hours before they actually died in about half of the patients. This is in line with another hospital study in which awareness of dying was present in 51% of the patients more than 24 hours before they died.(14) However, this study also included patients who died unexpectedly without having serious life-threatening conditions. Our findings may be indicative of the difficulty of diagnosing dying. In current practice, clinical experience and team decision making seem to be key elements in accurately diagnosing dying. (10) When diagnosing dying, caregivers cannot rely on vital sign changes, such as

a decreased systolic blood pressure or increased heart rate, as many patients with chronic diseases have normal vital signs until very shortly before death; in addition, these signs are also common in patients who are not dying.(15, 16) Other clinical signs, such as death rattle and cyanosed extremities, are rather specific for imminently dying patients, but tend to occur very late in the dying process.(10)

Ideally, when the attending physician is aware of the imminence of a patient's death, burdensome interventions with the aim of prolonging life are avoided (scenario 1).(1, 17) Although some patients in whom the attending physician had been aware of the imminence of death received one or more diagnostic or therapeutic interventions with the potential of prolonging life (scenario 2), our study shows that acknowledgment of the imminence of death is associated with less diagnostic interventions. This finding is in line with earlier research in which diagnostic interventions were also found to be applied significantly less often in patients for whom the dying phase was recognized.(8) We did not find an association between awareness of patient's impending death and therapeutic interventions. Veerbeek et al's findings in a study on end-of-life care in hospitals and other settings were similar.(8) It should be noted that in Veerbeek's study, interventions such as daily washing and routine turning, were also included as therapeutic interventions. In our study, we focused on medical interventions.

In many cases where patients received therapeutic interventions despite the fact that their imminent dying was acknowledged, the intervention involved enteral tube feeding. The use of enteral tube feeding in the dying phase is highly questionable as it may cause harm as a result of complications, such as aspiration and sepsis.(18) However, its withdrawal may lead to distress for the patient and their family members.(19, 20) This may be an important reason why in almost all patients in our study who received enteral tube feeding this intervention was continued until the last 24 hours before death, regardless of whether impending death was recognized.

Our study suggests that extensive interventions, such as resuscitation and mechanical ventilation, are rare in the last three days of life of hospitalized patients. This is contrary to the landmark-trial Support, in which about half of the patients who died in hospital received mechanical ventilation within three days of death.(21) This difference may be explained by the fact that, in contrast to the SUPPORT trial, we did not include patients who died in the ICU. In the Netherlands, very few patients with advanced cancer are admitted to an ICU.(22) Further, after the 1990s, when the SUPPORT-trial was conducted, awareness of the limited value of extensive procedures at the end of life may have increased.(23) Finally, interventions to prolong life at the end of life may be used more often in the United States as compared to the Netherlands.(22)

Although extensive interventions were used in only a small percentage, many patients received other interventions in their last days of life, also if their imminent death was acknowledged (scenario 2). There seems to be room for improvement as

even less extensive interventions could have great impact on dying patients and their relatives.(24) A plausible reason for the use of these interventions until shortly before death may be that caregivers just persist in their daily routine of work.(7, 8)

Our study highlights that patients use many medications in the last 72 and 24 hours of life, either with the potential of prolonging life or of symptom control. Awareness of a patient's impending death slightly decreased the number of medications. However, both patients in whom the attending physician had or had not been aware of the imminence of death used so-called preventive medications, such as statins, which can be considered inappropriate in the last phase of life as they have no short-term benefit.(25) In two recent retrospective studies it was also shown that many inappropriate medications are continued until shortly before death.(26, 27) In order to decrease the number of (potentially) inappropriate medications at the end of life, evaluation of the medication list should be performed routinely for patients with a limited life expectancy.(28) In addition, guidelines should be developed as there is a lack of guidance on which medications can be discontinued safely in the last phase of life.(23, 29) Further, many patients experience severe suffering due to symptoms such as pain during their dying phase.(30) It is important to prescribe medications to alleviate these symptoms. We did not find significant differences in prescriptions of medication to relieve symptoms such as opioids; our study design precludes inferences on whether this indicates that symptom control was adequate regardless of the acknowledgment of the imminence of death.

Some limitations of this study need to be considered. First, this was a retrospective study which has inherent limitations such as recall bias among physicians when answering the question on whether or not they were aware of the patient's impending death. Second, this study was performed in one hospital which limits its generalizability. Third, we cannot rule out the possibility that interventions were discontinued without this being registered in the charts. However, in hospital settings, it is common practice that all interventions that are listed in the medical chart are actually applied and that all interventions that are applied are registered, in order to prevent any misunderstandings.

To obtain more insight into medical care in the last days of life, prospective studies are needed in which patients are followed until death and where recall bias can be avoided. In addition, further studies, such as ethnographic studies, are needed to find explanations for continuing or starting medical interventions that are undesirable for dying patients.

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Part II

Perspectives

Understanding the continuation of potentially inappropriate medications at the end of life: perspectives from individuals and their relatives and physicians

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Abstract

Objective: To identify barriers and considerations which contribute to continued use of potentially inappropriate medications (PIMs) in the final phase of life.

Design: Semi structured face-to-face interviews with 17 patients with an estimated life expectancy of less than three months, 12 of their relatives, 20 of their attending clinical specialists and 12 of their family physicians. All interviews were transcribed verbatim. Two researchers independently coded the first interviews, after which the codes were discussed until consensus was reached. Then, an adapted coding scheme was used for further use. Finally, the ultimate coding scheme was grouped into tentative categories and key themes.

Results: Patients, their relatives and physicians felt that PIMs should ideally be discontinued at the end of life. Patients and their relatives are willing to discontinue medications. Still, patients reported that stopping might give them the feeling that their physician has given up on them. Physicians mentioned several reasons for not considering withdrawal of PIMs: limited awareness, low priority and uncertainty about the consequences. Other reasons were concerns that by discussing discontinuation of PIMs patients can be confronted with their impending death and might think they are not receiving optimal medical care.
When physicians communicate with patients about discontinuing medications, they tend to focus on the inappropriateness of continuing PIMs instead of on the advantages of stopping them.

Conclusions: Physicians have pragmatic reasons not to discuss discontinuation of PIMs at the end of life, but also mention concerns about the reaction of patients and relatives. However, patients report to be open to discuss discontinuation of PIMs. Careful communication about the benefits of discontinuing PIMs seems of the essence.

Introduction

Patients with a limited life expectancy often use a range of medications.(1) Some of these might have been prescribed at an earlier stage to treat or prevent (chronic) illnesses. They might also have been prescribed to reduce the burden of symptoms. Symptom alleviation is primarily administered during the last months of life, when the burden is at its height.(2)

The administration of medication with a focus on the prevention and treatment of illnesses should be reconsidered in the final stages of life, i.e. when a patient's life expectancy is only months or weeks.(1, 3, 4) There are ample medical reasons to do so. Firstly, medications are not as effective anymore, given the limited life expectancy. This mainly applies to preventive medication – such as statins – that have benefits which take months to years to accrue. Secondly, treatment objectives may change at the end of life. An example is the treatment of diabetes mellitus. In general, it is recommended to keep a patient's glycated hemoglobin (A1C) value below 7% in order to avoid long-term complications.(5) If a patient has a limited life expectancy, however, it may be better to raise this upper level to prevent short-term complications, such as hypoglycaemia.(6) A third reason for the reconsideration of prescribed medication is that organ functions may undergo changes when death is nearing. Blood pressure may drop, for instance, so that anti-hypertensive medication may no longer be necessary.(7)

In practice, however, reconsidering a patient's medication use in the last phase of life seems to be rare.(8-10) Patients often take multiple medications that may not have beneficial effects in view of their limited life expectancy and changing organ function: so-called potentially inappropriate medications (PIMs).(3, 11-13) PIMs can have different side-effects – some of them harmful – and may pose patients with the burden of taking them.(3, 13) In addition, the use of PIMs involves costs.(13)

Factors contributing to continuing PIMs are largely unknown. We performed an interview study to identify barriers and considerations which contribute to continued use of PIMs in the final phase of life, from the perspectives of patients, relatives and physicians. This insight may contribute to the development of guidelines to improve medication prescription for patients who are in the final phase of life.

Methods

Design and setting

This study is part of a larger research project (MEDILAST: MEDIcation management in the LAST phase of life), that has the aim of understanding current practices of medication prescription in the last phase of life.

In this qualitative study, we interviewed patients who were estimated to have a life expectancy of less than three months. In addition, if possible, a relative of each patient, the attending clinical specialist(s), and the patient's family physician were interviewed.

Recruitment and sampling

We recruited patients by asking physicians whether they cared for a patient who fulfilled inclusion criteria described below and, if so, to inform them about the interview study and ask them if they could be approached by the investigators. The inclusion criteria were that the patient: 1) had a life expectancy of less than three months; 2) knew their life expectancy was limited; 3) was compos mentis and was able to participate in an interview.

The physicians who were asked to suggest patients were employed in a general or academic hospital, a hospice or in a home care setting. Only one patient per physician was included.

Patients who were willing to participate in the study received written information about the interview from the investigators. In case a patient consented to participate, they were contacted by the interviewer.

After the patient signed an informed consent form the interview took place. Afterwards, the patient was asked for permission to approach a relative, their family physician and their attending clinical specialist(s) to participate in an interview. If the patient agreed, the same process of recruiting took place for these potential participants.

Purposive sampling was used to ensure diversity in patients' age, diagnosis, social background and religious beliefs. To further maximize variation, we included comparable numbers of patients from the three different care settings.

The study was approved by the Medical Ethics Committee of the Radboud University Medical Centre. In addition, approval from the Board of Directors or relevant authority was obtained in all the settings where the patients were recruited.

Interviews

Data for this study were collected from October 2013 to February 2015 through face to face, semi-structured interviews. The interviews were conducted by E.G., M.D., B.H., J.A. and R.P. and lasted 30-60 minutes. We interviewed the patients and their relatives in their home, a hospital or in a hospice. The interviews with health care professionals took place in their office.

We used a topic list that was developed by the project team, guided by a review of the literature on this topic and interviews with experts. The topic list was refined on the basis of new insights during the interviews.

Data analysis

All the interviews were audio-recorded and transcribed verbatim. The transcripts were subjected to qualitative analysis by using the constant comparative method. This method is part of the grounded theory approach in which concepts emerge as theory is formed. The analysis was facilitated by using qualitative research software (ATLAS.ti version 7.5.6). Two researchers (E.G. and M.T.) independently read through the first few interviews in each respondent group and attached open codes to all issues that seemed relevant to provide insight into our research topic.

Thereafter, the codes were discussed until consensus was reached. Then, an adapted coding scheme was developed for further use, after which E.G. and M.T. coded the remaining interviews. New codes could be added. We decided that saturation had been reached after 59 interviews. The final codes of the two researchers were compared and discussed again to reach consensus, and then were grouped into tentative categories. These categories were discussed and summarized in key themes with the whole project group.

Results

Characteristics

Interviews were held with 17 patients, 12 relatives, 20 clinical specialists and 12 GPs. Most patients had cancer (n=12). Their average age was 71 years (range 47-91), and the average age of their relatives was 53 years (range 20-75). Three patients were still alive six months after the interview. The other 15 patients deceased on average 55 days after interviewing them (range 5-117 days). Ten of the 20 clinical specialists were specialized in internal medicine, 5 of whom focusing on oncology or hematology. The average age of the GPs involved was 40 years (range 29-66), and for specialists it was 42 years (range 30-64).

Thoughts about discontinuation

The patients and their relatives as well as the medical professionals indicated that PIMs should ideally be discontinued when the final phase of life is reached. However, patients and relatives stated that they had never thought about the appropriateness of the medications that were prescribed. They fully relied on the knowledge of their attending physician.

Experiences with discontinuation

It was the experience of the physicians that if PIMs were discontinued, this mostly followed so-called reference moments that usually occurred just before the patient's death. Such reference moments were: the start of the dying phase, patients' inability to swallow medication and the occurrence of side effects of the medication. Patients' and their relatives' concerns about the amount of medication could also be a reason to discontinue medication.

Consideration of discontinuation

Physicians stated that they are not very aware of opportunities to discontinue medications at an earlier stage of the disease.

Clinical specialist (CS16): I don't think it [discontinuation] is always looked into. No, and this is speaking for myself, you understand, I do think it should be. Now that I've been asked to collaborate in the study, well you start thinking about it.

Further, in cases where the use of medications is considered, no actions follow due to time constraints and lack of priority. In addition, uncertainty about the consequences of discontinuation also makes it difficult for physicians to stop PIMs. Some physicians said they were afraid that the discontinuation of certain medications could lead to serious medical problems. They indicated that when more evidence of the potential consequences of discontinuation would be available, this would be supportive in their decision-making.

Negative consequences

Although physicians believed that patients should preferably use as few medications as possible in the last phase of life, they also thought that discontinuation can be harmful. Physicians are concerned that raising the topic of discontinuation can confront patients with their approaching death and make them feel that they may receive less care than needed, or that the attending physician is throwing in the towel.

Family physician (FP15): If you stop something, it also makes people feel like, 'Well apparently it's no use anymore to treat me in the long term because…,' and this confronts people with death, with finiteness, I think.

This particularly applied to cases where physicians were unsure as to whether patients were aware that their life expectancy was limited. The physicians stated that this uncertainty stopped them from discussing the discontinuation of medications, as they felt the patient might not be receptive to the idea.

Patients and relatives, however, said that they do not want to be given false hope and preferred health care professionals to tell them the truth.

Interviewer: If so [when discontinuing medication], would it feel as if the end was approaching rapidly?
Patient (P2): Yes, perhaps a teeny bit, but I would not like him to give me false hope and just continue swallowing them either, no, I would not like that either. No, this would actually be a very honest way of openly discussing whatever is or isn't of any use anymore.

At the same time, their statements confirmed physicians' beliefs that the suggestion to stop PIM's might give them the idea that their end was near and that they were given up upon, especially if they were still undergoing life-extending treatment. The feeling of 'being abandoned' was explicitly mentioned by patients and relatives.

Patient (P3): Then you're beyond treatment; then they can't really do anything else for you; and only then does this way [discontinuation of medication] come up.
Interviewer: Is this a good moment to get rid of several medications?
Patient: Yes, the previous times it wasn't an issue, and now it is.
Interviewer: Imagine that the doctors had discussed such matters with you at an earlier stage, how would you have felt about it then?
Patient: Yes, I find that difficult. No, I believe I would then have felt something like: 'Guys, do you want to get rid of me or something' [chuckles].

Communication about discontinuation

Physicians said that in their communication with patients they primarily focus on the medical uselessness of PIMs in relation to the patient's limited life expectancy.

Clinical Specialist (CS11): Yes, it sometimes happens that they're still taking statins and certain medications that may make you wonder, 'Is it any use continuing with those?' But, on the other hand, as a doctor it's sometimes confrontational to say, 'Right, you'll never get well again.' You often also have to say, 'We've run out of treatment options.' Bad news, I must say,… I personally find it sometimes difficult to say, 'Oh, well, you don't need this statin anymore either.'

For patients and their relatives, the use of terms such as medical uselessness can lead to misunderstanding and even anger.

Patients and their relatives indicated that they would better understand suggestions to discontinue medication if other reasons are provided, such as stable blood count and other stable body parameters (e.g. blood pressure) which make

the use of medication redundant. Some physicians indicated that when discussing discontinuation of PIMs they focus on the positive effects of discontinuation. In their experience, this approach results in patients being virtually always prepared to stop taking one or more medications. Moreover, patients believed that starting with a temporary discontinuation would make the final discontinuation less of an issue.

Discussion

The patients and relatives as well as the physicians believed that, ideally, PIMs should be discontinued in the final stage of life. The interviews with physicians made it clear that there are various reasons why, in practice, medication is usually continued until very late in the terminal phase. Insufficient awareness and lack of priority and fear of negative medical consequences seem to be important factors. Further, physicians fear that breaching the topic of the discontinuation of PIMs may do the patient mental harm. When physicians breach the subject to the patient, they primarily discuss the medical uselessness of the continuation of PIMs, whereas patients and their relatives expressed that they would certainly be prepared to stop taking them if the positive reasons would be emphasized.

The finding that physicians are hardly aware of the importance of discontinuing PIMs and attach little priority to the matter, corresponds to a prior study that looked into the factors that play a role in the continuation of potentially superfluous medications among the general population.(11) In current practice, therefore, the discontinuation of PIMs is mostly reactive, in response to problems, rather than proactive. According to experts, physicians should more often consider to discontinue PIMs.(12) In order to safeguard optimal pharmacotherapeutical care for patients with a limited life expectancy, the prescribed medications should be evaluated at an earlier stage, as soon as it becomes clear that the patient has an advanced disease that cannot be cured.(12, 14) Reconsidering medication policy can be regarded as an element of advance care planning.(15)

Another important reason to continue medications is fear for the medical consequences of discontinuation. This fear has to do with the limited availability of scientific evidence of the consequence of discontinuation, among other things.(3, 12) This applies specifically to the consequences for patients with a limited life expectancy.(3) To date, only one randomized study has been conducted into the consequences of stopping medications in patients with an estimated life expectancy of less than one year, which revealed that patients could safely stop using statins.(13) However, this study had its methodological limitations, such as contamination among patients in the control group.(16)

Physicians indicated that a main obstacle for breaching the topic of the discontinuation of PIMs is their idea that this might upset patients. A similar result was found in a focus group study on the discontinuation of PIMs for vulnerable elderly patients with multimorbidity among GPs.(17)

Our interviews with patients and relatives, however, revealed that they were actually willing to stop taking medication. A questionnaire study among patients with multiple chronic morbidities also found that virtually all patients (>90%) are in principle willing to discontinue medication.(18) However, when it comes to practice, they seem less willing.(19) It should be noted here, however, that the studies that found a low percentage of patients willing to stop medication looked into the discontinuation of medication that may result in dependency, such as benzodiazepines.(19) A 'deprescribing' study among vulnerable elderly patients in which the entire list of medications was reviewed, also revealed a high percentage of patients who were prepared to stop.(20) For virtually all of these patients, one or more potentially superfluous medications could indeed be successfully discontinued.

Our finding that patients and relatives preferred the health care professionals to tell them the truth underlines the outcomes of another interview study, which found that prognostic disclosure is of great importance to patients with a limited life expectancy and their family members.(21)

An important finding from our interview study is that communication with patients about deprescription could be improved. In practice, this communication seems to have a negative connotation due to the emphasis that is put on the uselessness of continuing certain medications given the limited life expectancy.(22) This can make the discontinuation of PIMs an extremely precarious subject, both for patients and relatives and for physicians.(14) Emphasizing the positive aspects of quitting – e.g. to reduce the risk of adverse effects and the burden of taking pills – may increase patients' willingness to stop medications.(23)

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Medication discontinuation at the end of life: a questionnaire study on physicians' experiences and opinions

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Abstract

Objective: To explore physicians' opinions and experiences regarding medication management during the last phase of life, and to identify factors influencing the continuation of potentially inappropriate medications.

Design: A questionnaire study among 500 general practitioners and 500 clinical specialists working in three regions in the Netherlands that represent more than half of the Dutch population.

Results: Questionnaires were returned by 321 physicians (response rate: 37%). The majority of them (73%) agreed with the statement that patients who are in the last phase of life use too many medications. When presented with a vignette of a patient with end-stage COPD with different limited life expectancies, preventive medications would be stopped right early before death (e.g. 90% of the physicians would discontinue a cholesterol inhibitor when life expectancy was about three months). Medications to relieve symptoms, e.g. paracetamol, would not be stopped or stopped right before death. For medications to treat (chronic) illnesses, e.g. metformin, there was a huge inter-physician variability.
All statements about possible reasons why medications are continued in the last phase of life, e.g. patients feeling abandoned and lack of time, were agreed upon by a small minority of respondents.

Conclusions: Although physicians agree that patients use too many medication at the end of life, they quite regularly seem to give patients medications for chronic diseases for which the benefit at the end of life may be debatable. More scientific evidence on whether or not these types of medication might be discontinued in the last phase of life is needed.

Introduction

Many patients who are in the last phase of life use multiple medications that are continued until shortly before they ultimately die.(1-5) On the one hand, this seems inevitable, because patients' symptom load generally increases when their death approaches.(6, 7) Furthermore, patients who are in the last phase of their life often have multiple comorbidities for which different medications are needed.(8) On the other hand, the benefit of a considerable number of medications at the end of life is debatable. This is especially the case for preventive medications, which are often used for positive effects that occur beyond the life-expectancy of the patient. Moreover, in the last stage of life potential disadvantages may outweigh the benefits of several types of medication, such as blood glucose lowering medications.(9) In practice, however, such potentially inappropriate medications (PIMs) are often continued until death.(4, 10)

There is increasing awareness that medications at the end of life should be reconsidered.(11, 12) The scarce literature on medication management in the final phase of life suggests that when a patient has a life expectancy of only months to weeks, physicians should especially reconsider medications that are not aimed at symptom relief.(12, 13) However, the clinical effects of the discontinuation of many PIMs are not well known.(11, 14) A recently published meta-analysis showed a 1.6-fold increased mortality in patients older than 60 years who were using one or more PIMs as compared to patients who did not use such medications.(15) So far only one randomized study on discontinuing medications in patients with a limited life expectancy has been published.(16) This study evaluated the safety of discontinuing statins for patients with an estimated life expectancy between one month and one year. The results made clear that statins can be safely stopped and discontinuation may even be associated with improved quality of life. However, generalizability of the results was limited.(17)

Little is known about physicians' opinions regarding medication management at the end of patients' lives. A recent interview study reported that physicians prefer to wait with the discontinuation of medications in patients with a limited life expectancy until patients themselves accept their illness and limited life expectancy and then attach less importance to taking certain medications.(18) In a previous interview study we identified several reasons why physicians may fail to stop PIMs, including lack of priority and fear of negative medical consequences.(19) Until now, there is a lack of quantitative data about the opinions of physicians regarding medication management in the last phase of life.

The purpose of this study was to determine physicians' opinions on and experiences with medication management during the final phase of life, and to identify factors influencing the continuation of PIMs at the end of a patient's life.

Methods

Study design

We conducted a questionnaire study among general practitioners and clinical specialists working in the regions of Amsterdam, Rotterdam, and Nijmegen, respectively. This study was part of the MEDILAST (MEDIcation management in the LAST phase of life) project with the aim of understanding current medication use in the last phase of life. This project was carried out by the VU University Medical Center, Radboud University Medical Center, and Erasmus University Medical Center.

Study participants and recruitment

We randomly selected physicians from a database (Cegedim) of addresses of physicians. Eligibility criteria were:

1. physicians working in the region of Amsterdam, Nijmegen, or Rotterdam (adherence areas of the above-mentioned three medical centers). These regions are in the western and eastern part of the Netherlands and represent more than half of the Dutch population;
2. physicians working as general practitioners or as clinical specialists in geriatrics, cardiology, pulmonology, medical oncology, or neurology.

The selection contained 500 general practitioners and 100 physicians from each clinical specialty. The invitation letters and paper questionnaires were sent in May 2014. A web-based reminder was sent by e-mail to non-respondents till 28 weeks after the original invitation. Recruitment was completed in February 2015.

Questionnaire

We developed a questionnaire based on insights from a literature search on this topic. The questionnaire was pilot-tested by four physicians filling it out; two general practitioners and two clinical specialists. Their comments were discussed within our research team and addressed in the final version of the questionnaire.

The questionnaire consisted of three sections. Section one included questions on the respondents' age, gender, medical specialty, and working experience. Section two included a vignette about a patient with multimorbidity (Box). In the first part of the vignette the patient's life expectancy was unspecified; subsequently it was added that the patient's life expectancy was three months and one week, respectively. For each situation, respondents were asked whether or not they would discontinue medication, and, if yes, which types of medication. Respondents were invited to comment on their answer. In order to identify whether the patient's attitude towards life-prolonging

treatment options had an impact on the respondents' opinions on medication management, we presented the vignette in two versions. In version A, the female patient had a fulfilled life and was aware of and accepted upcoming death. In version B, the patient enjoyed her life being with her family, In addition, she expected to become a great-grandmother within three months (Box). Section three of the questionnaire comprised several statements about medication management for patients with a life expectancy of three months or less. Respondents were asked whether they agreed with each statement on a 5-point Likert scale: strongly disagree, disagree, neutral, agree, and strongly agree.

We coded the questionnaires in order to guarantee anonymity. The study was approved by the Medical Ethics Review Committee from the VU University Medical Center.

Box: vignette

Mrs Bruin is an 88-year-old woman with COPD Gold stage III-IV. A week ago she came back from hospital where she had been treated for an exacerbation of her COPD, the third admission within two months. In addition to COPD, her medical history includes a cerebrovascular accident (two years earlier), hypertension, diabetes mellitus type 2 and severe arthralgia. During the most recent hospital admission she was also diagnosed with deep venous thrombosis in her left lower leg. Besides shortness of breath, she has no other complaints. Her blood pressure is 135/70 mmHg and her blood glucose level is 6.2 mmol/L (112mg/dl).
Her medication list includes salmeterol/fluticasone 50ug/500ug BID one inhalation; prednisolone QD 5 mg; enalapril QD 20mg; hydrochlorothiazide QD 12,5mg; metformin TID 500mg; paracetamol TID 1000mg; simvastatin QD 40mg; carbasalate calcium QD 100mg; omeprazole QD 40 mg; acenocoumarol.

Version A: Mrs Bruin has decided she does not want to be admitted to the hospital anymore. She is aware of her limited life expectancy and is comfortable with her situation.
Version B: Mrs Bruin knows that her condition is deteriorating. Nevertheless, she enjoys life as much as she can, together with her children and grandchildren. She is eagerly looking forward to the birth of her first great grandchild, which is expected in about three months.

Statistical analysis

Frequencies, proportions and means with standard deviations were calculated where appropriate. To examine differences between subgroups we used chi-square tests and McNemar tests. *P*-values of less than 0.05 were considered to indicate statistical significance. We recoded responses to the statements into disagree, neutral and agree. We used the Statistical Package for Social Sciences (SPSS), version 24.0, for all analyses.

Results

Respondent characteristics

In total, 122 of the selected physicians had retired from working, did not work as a physician, or could not be reached because the right contact address was lacking. The final sample therefore included 878 physicians. 321 physicians completed the questionnaire, resulting in a response rate of 37%. Of these physicians, 174 (54%) were general practitioners and 147 (46%) were clinical specialists (Table 7.1). The majority

Table 7.1 Background characteristics of respondents

	General practitioners		Clinical specialists		Total	
	N	%	N	%	N	%
All	**174**	**100**	**147**	**100**	**321**	**100**
Age (yrs)						
<40	124	71	50	34	174	54
40-49	27	16	36	25	63	20
≥50	23	13	60	41	83	26
Gender						
Male	50	29	89	61	139	43
Female	124	71	58	39	182	57
Specialty						
Medical oncologist			33	22		
Geriatrician			35	24		
Cardiologist			25	17		
Pulmonologist			25	17		
Neurologist			29	20		
Working experience (yrs) experience[a]						
0-9	137	80	66	45	203	64
10-19	13	7.6	43	29	56	18
20-29	12	7.0	28	19	40	13
≥30	9	5.3	9	6,2	18	5,7

[a] *Missing values range from 1 to 10 physicians*

of the general practitioners were female (71%). The mean age (SD) of the general practitioners was 38.5 (8.8) years and their mean working experience (SD) was 7.2 (8.9) years. The mean age (SD) of the clinical specialists was 46.4 (9.2), with a mean working experience (SD) of 12.5 (9.6) years.

Vignette

Table 7.2 shows the preferences of respondents with regard to the discontinuation of medications for the patient presented in the vignette (both versions). For patients with a limited but unspecified life expectancy a majority of respondents preferred stopping the cholesterol inhibiting drug (simvastatin) (71%) and the anti-clotting drug (carbasalate calcium) (62%). More clinical specialists than general practitioners preferred stopping carbasalate calcium (68% and 57%, respectively,

Table 7.2 Physicians' opinions on medication management for a vignette of a patient with a limited life expectancy

	Patient's life expectancy is unspecified N (%)	Patient's life expectancy is three months N (%)	P-value[a,b] N=321	Patient's life expectancy is one week N (%)	P-value[d] N=321[c]
Physician would prefer to stop:					
Acenocoumarol	43 (13)	85 (26)	.000	253 (79)	.000
Salmeterol/fluticason	3 (0.9)	3 (0.9)		39 (12)	.000
Prednisolone	16 (5.0)	26 (8.1)	.006	100 (31)	.000
Enalapril	85 (26)	158 (49)	.000	285 (89)	.000
Hydrochlorothiazide	123 (38)	191 (60)	.000	278 (87)	.000
Metformin	57 (18)	104 (32)	.000	224 (70)	.000
Omeprazole	31 (10)	68 (21)	.000	163 (51)	.000
Simvastatin	227 (71)	289 (90)	.000	293 (91)	.344
Carbasalate calcium	199 (62)	239 (74)	.000	280 (87)	.000
Paracetamol	14 (4.4)	21 (6.5)	.016	59 (18)	.000
None of the above	34 (11)	15 (4.7)	.005	2 (0.6)	.000

[a] *McNemar*
[b] *Comparison between uncertain life expectancy with life expectancy of three months*
[c] *1 missing value*
[d] *Comparison between life expectancy of three months versus one week*

Table 7.3 Physicians' opinions on medication management for a vignette of a patient with a limited life expectancy: importance of patient's attitude towards death

	Version A N=150 N (%)	Version B N=171 N (%)	P-Value[a]	Total N=321[b] N (%)
Patient's life expectancy is unspecified				
Preference physician to stop:				
Acenocoumarol	30 (20)	13 (7.6)	.001	43 (13)
Salmeterol + fluticason	0 (0.0)	3 (1.8)	.103	3 (0.9)
Prednisolone	10 (6.7)	6 (3.5)	.195	16 (5.0)
Enalapril and/or hydrochlorothiazide	85 (57)	69 (40)	.004	154 (48)
Enalapril	53 (17)	32 (10)	.001	85 (26)
Hydrochlorothiazide	68 (45)	55 (32)	.015	123 (38)
Metformin	33 (22)	24 (14)	.062	57 (18)
Omeprazole	18 (12)	13 (7.6)	.183	31 (9.7)
Simvastatin	123 (82)	104 (61)	.000	227 (71)
Carbasalate calcium	96 (64)	103 (60)	.488	199 (62)
Paracetamol	4 (2.7)	10 (5.8)	.164	14 (4.4)
None of the above mentioned	15 (4.7)	19 (5.9)	.747	34 (11)
Patient's life expectancy is three months				
Preference physician to stop:				
Acenocoumarol	50 (33)	35 (20)	.009	85 (26)
Salmeterol + fluticason	0 (0.0)	3 (1.8)	.103	3 (0.9)
Prednisolone	13 (8.7)	13 (7.6)	.727	26 (8.1)
Enalapril and/or hydrochlorothiazide	115 (77)	109 (64)	.012	224 (70)
Enalapril	83 (55)	75 (44)	.040	158 (49)
Hydrochlorothiazide	101 (67)	90 (53)	.007	191 (60)
Metformin	55 (37)	49 (29)	.126	104 (32)
Omeprazole	41 (27)	27 (16)	.012	68 (21)
Simvastatin	140 (93)	149 (87)	.064	289 (90)
Carbasalate calcium	123 (82)	116 (68)	.004	239 (74)
Paracetamol	8 (5.3)	13 (7.6)	.412	21 (6.5)
None of the above mentioned	3 (0.9)	12 (3.7)	.034	15 (4.7)

Table 7.3 Continued

	Version A N=150 N (%)	Version B N=171 N (%)	P-Value[a]	Total N=321[b] N (%)
Patient's life expectancy is one week				
Preference physician to stop:				
Acenocoumarol	120 (80)	133 (78)	.627	253 (79)
Salmeterol + fluticason	21 (14)	18 (11)	.342	39 (12)
Prednisolone	52 (35)	48 (28)	.203	100 (31)
Enalapril and/or hydrochlorothiazide	142 (95)	154 (90)	.124	296 (92)
Enalapril	134 (89)	151 (88)	.771	285 (89)
Hydrochlorothiazide	136 (91)	142 (83)	.045	278 (87)
Metformin	110 (73)	114 (67)	.194	224 (70)
Omeprazole	89 (59)	74 (43)	.004	163 (51)
Simvastatin	140 (93)	153 (89)	.221	293 (91)
Carbasalate calcium	136 (91)	144 (84)	.084	280 (87)
Paracetamol	30 (20)	29 (17)	.483	59 (18)
None of the above mentioned	0 (0.0)	2 (0.6)	.184	2 (0.6)

[a] *chi-square test*
[b] *1 missing value*

p=0.041). Cardiologists and neurologists were less eager to stop the cholesterol inhibiting drug than other clinical specialists (52-62% and 71-82%, respectively, *p*=0.016). Most frequently mentioned reasons to stop cholesterol inhibiting drugs were medical futility because of the patient's limited life expectancy and potential side effects of the medication. Carbasalate calcium would be stopped most often due to concomitant treatment with acenocoumarol.

When the life expectancy of the patient was stated to be about three months, 90% of the respondents preferred stopping the cholesterol inhibitor and 74% preferred stopping the anti-clotting drug. In addition, antihypertensive treatment (enalapril and/or hydrochlorothiazide) would be stopped by 70% of the respondents, 26% would stop anticoagulant therapy (acenocoumarol). Cardiologists and neurologists preferred stopping enalapril and hydrochlorothiazide less often than other clinical specialists (40-55%, and 71-73%, respectively, *p*=0.004). Most frequently mentioned reasons to discontinue enalapril and hydrochlorothiazide or

acenocoumarol were medical futility because of the patient's limited life expectancy and potential side-effects of the medications. Another reason to discontinue enalapril and hydrochorothiazide was that the patient's blood pressure was already low enough.

When the patient's life expectancy was stated to be limited to one week, the physicians preferred stopping the majority of medications. For all types of medication significantly more physicians stated that they preferred to stop in case of a life expectancy of one week in comparison with a life expectancy of three months, except for the cholesterol inhibitor that was already discontinued by the large majority when the patient had a life expectancy of three months. The most frequently mentioned reason to stop medications in case of a life expectancy of one week of life was that they would not contribute to improved quality of life.

In the version in which the patient with an unspecified life expectancy or a life expectancy of three months stated that she had a fulfilled life and had accepted her impending death (version A), physicians significantly more often stated that they would stop medication than in the version in which the patient enjoyed her life and expected to become a great-grandmother (version B) (Table 7.3). The patient's attitude towards death did not have an impact on physicians' preferences about medication management in case the patient had a life expectancy of only one week.

Statements about medication management in the last phase of life

The majority of the respondents (73%) agreed with the statement that patients who are in the last phase of life use too many medications (Table 7.4). In addition, most of the respondents (79%) agreed that patients' views about possible discontinuation of drugs that are no longer medically necessary are very important to them. Opinions about the importance of nurses' views about medication management were divided. Clinical specialists more often than general practitioners stated that nurses' views are very important to them (44% vs 25%, p=0.002).

Table 7.4 Physicians' views on medication management at the end of life

	N(%)[a,b] 321(100)		
	Disagree (%)	Neutral (%)	Agree (%)
Patients with a limited life expectancy use too many medications	37 (12)	49 (15)	235 (73)
Evaluating a patient's use of medications together with the patient provides me with a good opportunity to discuss his/her impending death	86 (27)	110 (35)	121 (38)
Patients' views about the discontinuation of medications that are not medically necessary are very important to me	19 (6.0)	47 (15)	251 (79)
Relatives' views about the discontinuation of medications that are not medically necessary are very important to me	67 (21)	100 (32)	150 (47)
Nurses' views about the discontinuation of medications that are not medically necessary are very important to me	101 (32)	108 (34)	107 (34)

[a] *Missing values range from 0 to 5 physicians (0.0% to 1.6 %)*
[b] *All statements concern patients with a life expectancy of < three months*

Experiences with medication management in the last phase of life

In Table 7.5, respondents' experiences with medication management in patients with a limited life expectancy are presented. Virtually all respondents stated that they regularly check if symptom treatment is still adequate for patients in the last phase of life (96%); about 80% stated that they regularly check which drugs may be discontinued. Further, the large majority of respondents (91%) stated that patients with a limited life expectancy often accept their proposal to stop certain medications.

All statements about possible reasons why medications are continued in the last phase of life were agreed upon by a small minority of respondents. Statements that were agreed upon most often were: the unknown consequences of medication discontinuation (16%) and the expectation that patients may feel abandoned (13%). General practitioners more often than clinical specialists agreed that medications are continued as a result of a lack of insight in the potential consequences of discontinuation (21% and 10%, respectively, p= 0.006).

Of the respondents, 21% stated that they are often not able to evaluate the use of medications of patients with a limited life expectancy due to lack of time. Significantly more general practitioners than clinical specialists agreed with this statement (26%, and 16%, respectively, p= 0.005).

Table 7.5 Experiences of physicians with medication management at the end of life

	N(%)[a,b] 321(100)		
	Disagree N(%)	Neutral N(%)	Agree N(%)
What is your general policy for patients with a limited life expectancy:			
I check regularly which medications may be discontinued because of a patient's limited life expectancy	14 (4.4)	50 (16)	255 (80)
I check regularly if symptom treatment is still adequate	4 (1.3)	10 (3.1)	305 (96)
I regularly discontinue a medication in patients with a limited life expectancy if:			
That medication has no therapeutic benefit	6 (1.9)	21 (6.6)	292 (92)
Side effects may be expected more frequently	26 (8.2)	59 (18)	234 (73)
The patient is not capable to take his/her medication	6 (1.9)	23 (7.2)	290 (91)
Costs of that medication are not proportional to the expected benefits	268 (84)	0 (0.0)	51 (16)
I consider discontinuation of a certain medication in patients with a limited life expectancy if:			
Limited life expectancy is sufficiently certain	18 (5.6)	48 (15)	253 (79)
Treatment goals have changed (i.e. from curative to palliative)	12 (3.8)	37 (12)	270 (85)
Side effects occur	7 (2.2)	10 (3.1)	302 (95)
The patient feels burdened by the number of medications he/she has to take	7 (2.2)	36 (11)	276 (87)
If I propose to stop certain medications to a patient with a limited life expectancy, it regularly happens that			
The patient accepts this proposal	3 (0.9)	25 (7.9)	290 (91)
The patient asks for explanation before he/she will accept this proposal	29 (9.1)	91 (29)	198 (62)
The patient does not accept this proposal	244 (83)	39 (13)	10 (3.4)
I continue medications more regularly than I discontinue them because:			
It is not known what the consequences of discontinuation are	177 (56)	90 (28)	50 (16)
It is difficult for me to talk with patients about their impending death	276 (87)	31 (9.8)	10 (3.2)
Discontinuation may give the patient the feeling that he/she is abandoned	209 (66)	66 (21)	42 (13)
Discussing medication withdrawal may result in patient's emotional reactions	255 (80)	39 (12)	23 (7.3)

[a] *Missing values range from 2 to 28 physicians (0.6% to 8.7%)*
[b] *All statements below devote to patients with a limited life expectancy (i.e. < three months)*

Discussion

The results of our study suggest that physicians believe that patients use too many medications at the end of life. In a vignette, if the patient's end of life was imminent, many physicians preferred stopping medications, particularly preventive medications. However, preferences varied widely and some physicians indicated that they would continue some medications for which potential disadvantages, in view of the limited life expectancy, may outweigh the benefits.

Discontinuing medications in a vignette

We found that in a vignette physicians preferred stopping several medications if the patient's life expectancy was limited, which is in line with recommendations for medication management in the final phase of life.(11, 12) The vignette made clear that there are roughly three groups of medications that would be stopped at different times before death. First, preventive medications, e.g. statins, that would be stopped relatively early. Second, medications patients frequently use for a long time to treat (chronic) illnesses, e.g. metformin and enalapril. We found a huge inter-physician variability in preferences regarding if and when such medications should be stopped. Third, medications that are prescribed to alleviate symptoms. Physicians preferred not stopping these medications or to stop them right before death. Especially for the second group of medication, more scientific evidence on whether or not they might be discontinued is needed. Until now, physicians seeking guidance regarding medication use in patients with a limited life expectancy have to rely on a handful of so-called implicit criteria that state if and when medications should be reconsidered, based on, for example, their potential benefit compared with the risk of current or future harm.(12, 13) In addition to such implicit guidelines, an expert opinion-based guideline is available that provides explicit guidance on how to proceed when patients with diabetes mellitus are in the final phase of life.(20) This guideline states that if a patient's life expectancy is only weeks to months, metformin can be discontinued, as it barely reduces glucose levels and is especially aimed at preventing long-term complications. It is possible that awareness of this guideline among physicians is poor.

There is also a lack of clear guidance regarding medications that should be continued, or tapered, during the final phase of life.(21) In the vignette, 31% of physicians indicated that they would stop prednisolone during the last week of life. However, (abrupt) discontinuation of prednisolone may cause adrenal insufficiency, or even an adrenal crisis,(22) which can influence the last days of life in a negative manner.

Reasons for continuing medications

The finding that physicians indicated that they prefer stopping medications, such as statin therapy, if the patient had a limited life expectancy is in contrast with the reality of patients continuing medications up till death.(1-5) Only a small minority of physicians recognized some potential drivers of continuing potentially futile or harmful medications in the last phase of life. It thus remains unclear why such continuation is common practice. Possibly, continuation of PIMs is not considered or recognized as a problem in clinical practice. This lack of awareness also emerged from our interview study.(19)

There were, however, several statements in our questionnaire that were agreed upon by small groups of physicians and may reflect important reasons why physicians continue medications in clinical practice. First, the unknown consequences of withdrawing medication, as highlighted above. General practitioners especially agreed with this explanation while they may be best positioned to discontinue medications as they often have a long and trusted relationship with patients.(23) Second, physician's expectation that patients may feel abandoned if medications are discontinued. As a consequence, there is a risk that physicians do not discuss medication discontinuation with their patients at the end of their life.(19, 24, 25) Most patients with a limited life expectancy are in fact willing to discontinue PIMs.(18, 19) Further, the large majority of respondents (91%) of our questionnaire study stated that patients with a limited life expectancy often accept their proposal to stop certain medications. Third, lack of time to evaluate the use of medications. Of course, discussing medication management in the last phase of life is time-consuming and just one of many other issues in end-of-life care. In our opinion, medication management in the last phase of life should be incorporated into advance care planning, which informs and empowers patients to have a say about their current and future treatment, and positively impacts the quality of end-of-life care.(26, 27)

Limitations

Our study has some limitations. First, the response was low, similar to other physician surveys,(28) and therefore there is a possibility of nonresponse bias. A second limitation concerns the possibility of social desirability bias, i.e. that respondents have answered questions based on their views of what is socially most acceptable. Third, the vignette may contain too little clinical information to guide the respondents in their decision making preferences. For example, laboratory test results (such as blood glucose levels) were not available.

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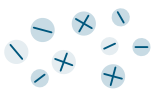
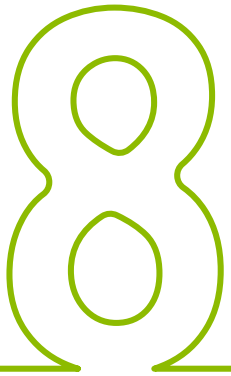
Part III

Solutions



Better drug use in advanced disease: an international Delphi study



Submitted

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Abstract

Objective: To identify possible solutions for difficulties concerning medication management and formulate recommendations to improve medication management at the end of life.

Design: A two-round Delphi study with experts in the field of medication management and end-of-life care (based on ranking in the citation index in Web of Science and relevant publications) were invited to participate. We developed a questionnaire with 58 possible solutions for problems regarding medication management at the end of life that were identified in previously performed studies.

Results: A total of 42 experts from 13 countries participated. Response rate in the first round was 93%, mean agreement between experts for all solutions was 87% (range 62-100%); additional suggestions were given by 51%. The response rate in the second round was 74%. Awareness, education and timely communication about medication management came forward as top priorities for guidelines. In addition, solutions considered crucial by many of the experts were development of a list of inappropriate medications at the end of life and incorporation of recommendations for end-of-life medication management in disease-specific guidelines.

Conclusions: In this international Delphi study, experts reached a high level of consensus on recommendations to improve medication management in end-of-life care. These findings may contribute to the development of clinical practice guidelines for medication management in end-of-life care.

Introduction

Patients with a limited life expectancy use many medications, including potentially inappropriate medication.(1-3) Use of multiple medications might lead to adverse effects.(4) The impact and burden of using potentially inappropriate medications in end-of-life care is not clear. In geriatrics, however, negative consequences of inappropriate medication use and polypharmacy have been demonstrated: this practice e.g. results in an increased rate of hospitalizations, an increased risk of falls and cognitive impairment.(5) Physicians, nurses, patients and their relatives agree that inappropriate medications should be discontinued at the end of life.(6) However, in clinical practice a medication review and timely discontinuation of potentially inappropriate medications is not self-evident.(7)

Several barriers impede adequate medication management by health care professionals. Physicians show a limited awareness of the issue and report a variety of reasons for not considering withdrawal of potentially inappropriate medications, which include low priority, uncertainty about the consequences, and avoiding confronting patients with their impending death.(8) Preliminary recommendations have been formulated for (dis)continuing medication groups at the end of life, such as antihyperglycemic agents, antimicrobials, cholinesterase inhibitors and bisphosphonates.(9, 10) However, no comprehensive guidelines are available for medication management in end-of-life care.

A recent interview study illustrates the framework of medication management at the end of life and decisions concerning (dis)continuation of specific medications. Also the perspectives on medication management and priorities in end-of-life care of patients, their relatives, nurses and physicians, their roles in decision-making, organizational aspects and communication should be taken into account.(6) The aim of our study was to identify possible solutions for impediments and formulate recommendations for adequate medication management at the end of life. Therefore, we decided to consult international experts on recommendations regarding all relevant aspects of medication management in end-of-life care, and perform a Delphi study.

Methods

This study was conducted within the MEDILAST (MEDIcation management in the LAST phase of life) project. MEDILAST is a multi-center mixed-methods research project with the objective of understanding current medication use in the last three months of life and the associated process of decision-making, and formulating recommendations to optimize medication management in end-of-life care. The project is carried out in a collaboration of VU University Medical Center, Erasmus University Medical Center and Radboud University Medical Center in the Netherlands.

Experts

A two-round Delphi survey was conducted among experts in the field of medication management and end-of-life care. Considering the scope of this Delphi procedure, we sought for experts with a clear track record in palliative care, and experts with a relevant background in medication management in care for the elderly. We aimed to include experts with different professional backgrounds in order to account for the multidisciplinary nature of palliative care. The selection of experts was based on ranking in the citation index in Web of Science (Search: Palliative Care / Terminal Care / Hospice Care AND Medication / Drug Utilization / Inappropriate Prescribing/ Drug Prescriptions / Polypharmacy) and relevant publications regarding medication management. In addition, experts from the Dutch multidisciplinary guideline on polypharmacy in elderly (11), Palliative care practice guidelines (12) and Palliative care expertise centers (13) in the Netherlands were invited to participate. We aimed for an expert panel of about 40 experts. We used purposive sampling to ensure diversity of background and nationality. Experts who did not respond received a reminder e-mail four weeks after sending the original invitation. In total 76 experts were invited, until at least forty participants had given their written consent.

Questionnaire and study design

From literature and previous studies in our MEDILAST-project (medical record review, in-depth interviews and a questionnaire study), barriers for adequate medication management at the end of life were identified.(6, 8, 14) Based on these findings we formulated possible solutions addressing these barriers. The solutions were reviewed internally by our project group (that consists of a general practitioner (MD), internal medicine resident and clinical pharmacologist (EG), medical oncologist (LZ), anesthesiologist (BH), medical doctor-philosopher (Wim J.M. Dekkers) and two researchers in palliative care (AH, RP)) and pilot tested among colleagues, forming a list of statements or recommendations. These were divided in the seven domains that were identified in our interview study (6): awareness and organization (5 solutions), education (8), research and development (8), tools (2), roles (18), decision-making (7) and communication (10). Participants were provided with definitions of central concepts in this study (see Box).

The Delphi study was performed in 2015. The first round questionnaire included 58 solutions. The experts were asked if they agreed or disagreed with the solutions, or they could tick 'no answer'. Participants were asked to suggest modifications or additional solutions. Besides, experts were requested to answer eleven questions concerning their background.

The second round questionnaire was also reviewed within the project group. This questionnaire consisted of two parts. First, the list of solutions that resulted from

round 1 was presented, including the items additionally suggested or adapted by the experts. The participants were then requested to give a top ten ranking score of the solutions they considered most relevant to formulate guidelines for medication management in end-of-life care (most relevant as number 1; 2 for next most relevant, and so on). Second, the solutions discarded in the first round were presented. Experts could indicate if they agreed with rejection of these solutions, or whether they considered them crucial for guidelines about medication management at the end of life.

The questionnaires were sent by electronic mail. Experts were asked to respond within four weeks for the first round and within six weeks for the second round. A reminder was sent in the case of non-response within the given time range.

Data processing

The data were processed using MS Excel 2010 (Microsoft Corporation, Redmond). We defined the first round cutoff value for inclusion in the second round questionnaire as agreement of 75%. Based on the top ten ranking score given in the second round a priority score was calculated (10 points for the first, nine for the second, etc.) for each solution to provide a ranked rating of the most important solutions as suggested by the experts.

Results

Figure 1 shows a flowchart of the Delphi process. In total 76 experts were invited. Two invitations were returned by the recipient's mail server as undeliverable, eight experts were not available or on leave, two considered themselves not an expert in the field, two had no time, two refused because of a possible conflict of interest and 18 did not respond. Forty-two experts agreed to collaborate in our Delphi study.

Round 1

The response rate was 93% (39 out of 42). The respondents had a mean age of 53 years (range 35-59 years), and a mean working experience of 19 years (range 4-41 years). In addition, they originated from the Netherlands (n=19), Argentina (n=1), Australia (n=2), Brazil (n=1), Czech Republic (n=1), Germany (n=2), Israel (n=1), Italy (n=1), Northern Ireland (n=1), Norway (n=1), Slovenia (n=1), Sweden (n=2), and the USA (n=5). Of one expert the nationality was unknown. Different specialties were represented: family medicine, nursing care, geriatrics, elderly care, cardiology, oncology, pulmonology, anesthesiology, neurology, psychiatry, pharmacy, pharmacology and

palliative medicine. Moreover, ethicists, researchers and medical advisors participated. The mean level of agreement for 58 statements was 87.7% (median 89.7%, range 62-100%, SD 9.2, IQR 10.3). "No answer" was selected by a mean of 5.9% (range 0-20.5%). Suggestions were given by 51.3% of the experts, ranging from new statements, general comments or experiences, to adjustment of solutions or the vocabulary.

Because the degree of agreement was much higher than expected, we adjusted the cut-off value for selection of statements for the second round to the mean agreement found in this first round. Thirty-one solutions exceeded this new cut-off point (87.7%). For seven of these statements the wording was slightly adapted based on suggestions of the participants. Based on the comments in the first round a definition of *palliative care specialist* was added in the second questionnaire (see Box). Twenty-seven solutions were deleted in the second questionnaire and twelve additional solutions were presented.

Box: Definitions of concepts used in the questionnaires

Medication management: patient-centered care to optimize safe, effective and appropriate use of prescription and over-the-counter drugs

Medication review: an assessment of the pharmacotherapy based on a structural and critical evaluation of the medical, pharmaceutical and clinical information

End of life: the last 3 months of life

Patient and/or family: indicating the family especially when the patient is not mentally competent.

Palliative care specialist: physician or nurse specialist/practitioner with a formal training in palliative care medicine or equivalent expertise due to clinical experience. (Added in Round 2)

Round 2

The response rate in the second round was 74% (29 experts). One participant was on leave, one withdrew consent and eight experts did not respond. Only two out of 43 solutions were not included in the ranking by any of the experts. The scores calculated for the different solutions ranged from 5 to 133 (mean 36.8, median 28). The solutions with a score above the average are presented in Table 8.1. The experts graded solutions concerning roles, awareness, education and communication as most important.

Table 8.1 Top 15 solutions based on their ranking score (and their category)

	Solution	Score
1	Physicians should discuss the wishes, treatment goals and priorities regarding medication management at the end of life with the patient in a timely manner. (Roles)	133
2	A medication review should be an integral part of the care for patients at the end of life. (Awareness)	130
3	Physicians should discuss the end of life with the patient in a timely manner. (Roles)	90
4	Medication management at the end of life should be individualized, based on the patient's clinical situation. (Awareness - Newly added in round 1)	89
5	Health care professionals should be trained in communicating with patients and/or their family about decision-making on medication management at the end of life. (Education)	74
6	Education in medication management at the end of life should be incorporated in all medical training (nursing school, medical students, residencies and fellowships). (Education - Newly added in round 1)	71
7	It should be discussed with the patient and/or family that the goal of medication management at the end of life is improving/maintaining the quality of life. (Communication)	70
8	Education in medication management at the end of life should be organized for health care professionals. (Education)	61
9	Health care professionals should be trained in the pharmacological treatment of symptoms at the end of life. (Education)	60
10	Palliative care specialists should be available for consultation regarding medication management for patients at the end of life. (Awareness)	56
11	A list of drugs with a high risk of inappropriateness at the end of life should be developed. (Research)	54
12	In communicating about medication management at the end of life nurses and physicians should take into account the norms and values of the patient and/or family. (Communication)	52
13	It should be discussed with the patient and/or family how the medication can be adjusted at the end of life and what can be expected of these changes. (Communication)	37
14	Patient or proxy based assessment tools (e.g. ESAS, EORTC, symptom diary, PPS, PPI) should be used to aid symptom assessment and treatment at the end of life. (Tools)	36
14	At the end of life each drug should be revised for its potential congruence with the clinical aims of the specific situation in a specific patient. (Research - Newly added in round 1)	36

Experts indicated that the physicians should primarily discuss the end of life and wishes, treatment goals and priorities regarding medication management at the end of life with the patient. Awareness is considered crucial: medication management should be an integral part of end-of-life care and be performed duly. Participants

agree that this should be an individualized process, based on the patient's clinical situation. Moreover, they agreed that palliative care specialists should be available for consultation.

Specific domains that should be addressed in the education of health care professionals were mentioned. Physicians should be trained in communication with patients and their family about medication management at the end of life. Further, education in pharmacological treatment of symptoms at the end of life was considered necessary. Accordingly, education in medication management at the end of life should be part of health care professionals training, in residencies, fellowships, medical schools and in nursing schools. Besides, such education should also become available for health care professionals. The main concern regarding communication was that it should include conversations about the goals of end-of-life care in relation to quality of life.

Twenty-seven out of 29 experts selected one or more of the 27 solutions which were initially rejected in the first round. Solutions considered crucial for guidelines about medication management by more than one third of the experts are presented in Table 8.2. Participants most frequently prioritized solutions regarding research

Table 8.2 First round solutions selected by more than one third of experts not to be rejected

	Solution	Score
1	In current treatment guidelines (e.g. for hypertension, heart failure, diabetes etc.) recommendations for medication management at the end of life should be incorporated. (Research)	20
2	A list of drugs that could be tapered off or discontinued at the end of life under certain conditions should be developed (e.g. anticoagulant, antihypertensive, blood glucose lowering, antibiotic, antipsychotic, antidepressant or anticonvulsive drugs). (Research)	17
3	Physicians lacking experience with medication management at the end of life should consult a palliative care specialist. (Awareness)	16
4	Marking of the end of life should be part of education for health care professionals. (Education)	12
	The primary treating physician should formulate an end-of-life care plan with the patient and/or family. (Roles)	12
	The general practitioner is the primary treating physician when the patient resides at home. (Roles)	12
5	The primary treating physician is responsible for recording the medication management at the end of life. (Roles)	10
	Nurses should contribute to medication management at the end of life by providing information, explanation and advice to the patient and/or family. (Roles)	10

and development, awareness, education and roles. Specific suggestions for research and development included incorporation of recommendations for medication management at the end of life in disease-specific clinical practice guidelines and development of a list of medications that could be tapered or discontinued at the end of life. Regarding awareness, the experts stressed that physicians lacking experience with medication management at the end of life should consult a palliative care specialist. Explicit identification of the last phase of life was added as a focus for education for health care professionals. They stated that the primary treating physician is responsible for recording the medication management and for formulating an end-of-life care plan with the patient. For patients residing at home the general practitioner is considered to be the primary treating physician. Nurses should have a supportive role by providing information, explanation and advice to the patient and relatives.

Discussion

This Delphi study shows that experts in palliative care and medication management from different professions in thirteen countries agree on the most important issues concerning medication management at the end of life. Key solutions indicated by the experts concern the central role of the physician in medication management, necessity of awareness on medication management at the end of life, the need for education on medication management for health care workers and trainees, and the importance of timely communication with the patient in the process of medication management.

Physicians' awareness of medication management

This Delphi study makes clear that according to experts the physician has a central role in medication management at the end of life. Two highly-ranked solutions indicate that it is up to the physicians to discuss the medication and do this evaluation with patients in a timely manner. The urge for attention on a medication review and discussion with the patient is in line with several studies indicating the high prevalence of potentially inappropriate medications (PIMs) used by patients at the end of life.(2, 15) Physicians do affirm that patients at the end of life use too many medications and that they should not use PIMs (16), but apparently discontinuation of PIMs is still not standard practice. As Anderson et al. discuss in their study, awareness on PIMs refers to the level of insight a prescriber has into the appropriateness of his/her prescribing. They found that poor insight was an observed rather than reported barrier and that prescriber beliefs at a population level did not necessarily translate to prescribing practices for the individual patient.(17) Similar findings came forward in an interview study on views of patients, relatives, nurses and physicians on medication management at the end of

life.(6) Although all involved parties agreed that PIMs should be discontinued and that in this process physicians should take the lead, a medication review was generally not a matter of course. These findings, altogether with the five recommendations of the experts of this Delphi study regarding education, urgently call for education on medication management in end-of-life care.

Timely communication

Multiple factors are described in literature as deprescribing barriers explaining the discrepancy between the ideal situation and practice, like lack of time, established beliefs in the benefits and harms of medication use, unknown consequences of withdrawing medications and avoidance of negative consequences.(6, 18) Even more importantly, physicians need to recognize a limited life expectancy of their patient and initiate end-of-life conversations as a prerequisite for decision-making conversations. (19) Hancock et al. describe that many health care professionals express discomfort at having to broach the topic of a limited prognosis, and may withhold information or not disclose prognosis. These difficulties perceived by healthcare professionals in regard of speaking to patients with limited life expectancy may act as a barrier toward discontinuing medication.(2) Conforming to these barriers in communication, experts in our Delphi study stress the importance of communication with patients and/or their family about decision-making on medication management at the end of life and the need for training of health care professionals specifically in communication concerning this topic.

Implications

Before starting the MEDILAST project, no guidelines for medication management in end-of-life care were available. Many tools and guidelines are available to manage medication for the aged, for example the Beers criteria,(20) (21) STOPP and START criteria (22) and the Medication Appropriateness Index (MAI).(23) Meanwhile, the OncPal deprescribing guideline (24) and Screening Tool of Older Persons Prescriptions in Frail adults with limited life expectancy (STOPPfrail) (25) were published. Lindsay et al. developed the OncPal deprescribing guideline to assist in the de-escalation of specific medications or medication classes (like aspirin, dyslipidemia medications and antihypertensives) in patients with advanced cancer.(24) Lavan and colleagues published the STOPPfrail, a list of 27 criteria determined in a Delphi consensus survey. The criteria relate to medications that are potentially inappropriate in frail older patients with limited life expectancy and may assist physicians in deprescribing medications in these patients.(25) Our Delphi study indicates that translation of these tools into practice as a deprescribing guideline will also need to address the

other steps of the deprescribing process, like communication about treatment goals, planning medication withdrawal (tapering if required), monitoring, and follow-up after cessation.

Experts in our study gave specific suggestions for research and development. Whereas a substantial part of medications in end-of-life care are prescribed for comorbid diseases,(14) there is an urge for reflection on how to manage those medications at the end of life and to address this issue in treatment guidelines. Pharmacological guidelines rarely give any recommendations for discontinuation. Experts in our study suggested research investigating discontinuation or tapering off medications at the end of life under certain conditions, for example in chronic conditions like diabetes and cardiovascular disease. Koekkoek et al. give a good example of how to deal with oral anticonvulsants in the end of life of patients with glioma who develop swallowing difficulties.(26) Although this applies to a very specific patient group, their suggestions could be extrapolated to other populations.

Strengths and limitations

A strength of our study is the systematic and rigorous approach adopted in this Delphi procedure (27) and the inclusion of views of experts from all over the world and coming from primary care, hospital and hospice care. The response was satisfactory, namely 93% in the first Delphi round and 74% for the second round.

There were some limitations. First, since half of the consulted experts were Dutch, solutions may have been biased towards those relevant for the health care system in the Netherlands. However, in both rounds of the Delphi study there appeared to be a high degree of consensus among all experts. Although experts of different professions participated and the average length of working experience (19 years) suggests that our panel represents a broad and experienced group, it is not possible to determine if the panel is representative of the population of palliative care and medication management experts.

Secondly, a pre-Delphi survey or focus group might have contributed to prepare the first survey of our Delphi study to address the study aim. Finally, the consensus for the first round was predefined as 75% agreement, a cut-off common according to acknowledged Delphi guidelines.(28) The high degree of consensus in our study (87.7%) drove us to redefine the cut-off point. The exact limit could be a matter of discussion.

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Selecting the optimal design for drug discontinuation trials in a setting of advanced, life-limiting illness

Letter to the editor to the article 'Safety and benefit of discontinuing statin therapy in the setting of advanced, life-limiting illness: a randomized clinical trial' *JAMA Intern Med. 2015;175:1724-5*

Eric C.T. Geijteman, Henning Tiemeier, Teun van Gelder

To the Editor

We read with great interest the article by Kutner et al.(1) The authors showed that discontinuing statins in patients with a limited life expectancy is safe and may lead to improved quality of life. The accompanied editorial(2) states that the statin trial provides a starting point for deprescribing trials in frail patients with advanced illness.

We argue that the design of the statin trial(1) (a conventional block randomized controlled trial) is not the most suitable design and should not be the norm for future deprescribing trials. First, the high refusal rate of eligible patients limits generalizability of the study's results. Second, the design can impact the validity of the results because of contamination among patients in the control group. Due to the consent procedure, these patients might think their drug is not worth taking anymore. Subsequently, their compliance with drug therapy may be reduced. Third, asking patients with a limited life expectancy whether they are prepared to discontinue a drug can lead to feelings of depression and abandonment.(3) This is particularly true if physicians do not sufficiently take such feelings into account,(3) as may be the case during study enrollment. As a consequence, the trial may harm eligible patients.

In 1979, a design was proposed(4) in which randomization takes place before consent to participate: the postrandomized consent design, or Zelen's design. There are 2 variants of this design: the single consent and double consent methods. In the single consent method, only patients allocated to the experimental group are asked whether they consent to their treatment. Control treatment consists of best standard care. In the double consent method patients allocated to the control group are also asked to consent, and if they decline, they may cross over to the other treatment.(5) Zelen's design typically results in a more representative patient sample.(5) However, due to lack of patient consent, the design has been much discussed and contended. Not asking consent is usually viewed as unethical, but some argue that under certain circumstances, that we feel are met here, Zelen's design has been brought forward as an ethical option.(5) Several studies in past decades undertaken in the United States, the Netherlands, and other Western countries applied this design.(5) We propose the Zelen's design as the alternative in future deprescribing trials to improve patient participation, validity, and generalizability of results.

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Denying the inevitability of death

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Eric C.T. Geijteman

My father was 61 when he died. He was diagnosed in the mid-1990s with heart failure due to hereditary hypertrophic cardiomyopathy. Over the last years, he had to be admitted several times for atrial fibrillation and dyspnea due to fluid retention. Cardioversion and intravenous treatment with diuretics made his condition more bearable, after which he always returned home. But subsequent severe dyspnea and tiredness led to re-admission.

This admission was different from all earlier admissions. This time medication failed to relieve his dyspnea. He felt exhausted and had no appetite. In addition, he had fever caused by pneumonia and antibiotics were prescribed. While the daily worsening of his condition had me and my mother worried, his treating physicians were rather positive as his laboratory results were improving. They told my father that he should have confidence in the outcome. The possibility of further deterioration was not mentioned. So, my father remained hopeful and continued to fight against his physical decline. He panted for breath, struggled to slurp his nourishing foods and to take his pills. Yet my father's condition continued to deteriorate.

It was day 20 of his admission – my father's respiratory rate had gone up to 30 breaths per minute and he was receiving high-flow oxygen therapy – when he underwent various diagnostic tests, including a transabdominal ultrasound and laboratory tests. These diagnostics were done in a vain attempt to identify the cause of his persistent fever and dyspnea.

The night that followed my mother – a nurse in a nursing home – decided on her own to stay with him. During the night his dyspnea worsened and he became restless. After several hours of struggle, my father's condition declined even further. The cardiac monitor detected ventricular fibrillation and alerted the night nurses. When two of them rushed into the room to start resuscitation, my brave mother told them not to. She based this tough decision not only on the severe condition of my father, but also on several discussions she and my father had had on this topic. My father died several minutes later in my mother's arms.

Unfortunately, my father's story is not an isolated case. Too many patients die an undignified death, especially in hospitals.(1) There is no question that a bad dying process has negative consequences on patients themselves. They may suffer from pain and other symptoms and they may not have time to prepare for the end of life.(2) But a bad death also has negative consequences on patients' relatives, who may find it more difficult to cope with their bereavement.(2) It is not without reason that Dame Cicely Saunders, the founding mother of modern hospice care, said that 'how people die remains in the memory of those who live on'. When I think of my father's final days, I picture him suffering from pain and dyspnea. I will never forget the terrible scene of him having to hold his breath during the abdominal ultrasound in order to get a good picture of his intra-abdominal organs, at a time when he was already enormously short of breath.

Although the definition of a good death mainly reflects the personal values of the patient, many of us agree on common factors. For example, a good death involves attending pain and other suffering, and the patient being aware of impending death and able to direct his or her treatment.(2) For me personally, as a resident in internal medicine with an interest in end-of-life care, my father's death made me aware of two important reasons why all too many patients still die an undignified death.

The first is a failure to recognize that a patient is dying or to delay such recognition. In patients who die of chronic diseases such as heart failure, cancer or COPD, death is usually preceded by a period of imminent dying, and it is this period just days before the patient's actual death that physicians might be aware of.(1) Research has shown that the number of undesirable interventions is significantly lower in patients whose impending death is recognized than in patients in whom the dying phase is not recognized.(3) Recognizing dying is, however, a highly challenging task for physicians as there is no single symptom pathognomonic for dying.(2) As a result, the diagnosis of dying is often made at a stage very close to death, when a patient is already comatose. Another possible reason why doctors do not diagnose dying is that death is still seen as a failure, as the culture of medicine is focused on cure and life prolongation.(1) Paradoxically, this may well mean that the imminence of inevitable death results in an increase in medical efforts to prevent death.

About six months after my father died, I spoke to the likeable cardiologist who treated my father during the last four days of his life. He acknowledged that when he saw my father for the first time, he was already aware of his presumably impending death. While that awareness grew as death approached, he did not inform us and did not adapt my father's treatment as he was not 100% sure of the diagnosis because he knew of cases where patients in similar conditions had survived such critical moments. This reasoning corresponds with reports in the literature.(2) Indeed, a devastating condition may return to near-baseline after treatment, especially in patients with heart failure.(1) However, if a physician estimates that a patient is about to die, very often that patient will indeed die. Since the diagnosis of dying has crucial implications, dying must be placed high on the differential diagnosis list if a patient's condition worsens despite optimal therapy.

Which brings me to the second reason why patients die an undignified death: in terms of informing patients and their relatives of the possibility of impending death, communication by physicians is inadequate. Although diagnosing dying is very difficult, it is still essential that in the gray zone, in which a patient may be dying, the possibility of dying is discussed with patients and their relatives. This can be done by applying the 'hope for the best, and prepare for the worst' strategy,(4) that originates from oncology setting. Such strategy leaves also room for patients to exchange their views on appropriate end-of-life care with caregivers. Patients, in general, do not talk about their end-of-life preferences with their physicians until physicians broach this

theme.(5) Studies have shown that communication about imminent death and about end-of-life care goals not only improves quality of life but also reduces non-beneficial medical care.(5, 6) Such communication also increases the chances of upholding the principles of a good death.(6) During his final days, my father told us that while he really wanted to fight his illness and live a longer life, he was no longer capable of doing so because of his severe dyspnea and fatigue. If at the time he had been informed about the probability of dying, I think – however strange that sounds – he would have been relieved. He may then have been able to resign himself to impending death and to find peace. As a result, the last days of his life, aided by sufficient symptom control and avoidance of futile interventions, would likely have been far more satisfactory and have given us enough time to say our goodbyes.

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CPR

Part IV

Summary, general discussion and appendices

Summary and general discussion

This thesis is aimed at providing more insight into the practice of withholding and withdrawing medical interventions in the last phase of life. The first part of the thesis focused on current end-of-life practices. In part two, we explored the perspectives of patients, their relatives and physicians regarding potentially inappropriate medications in the last phase of life. In the third part, possible solutions for improvement of medical care at the end of life are described. In the current chapter, the main findings of the different studies will be summarized and discussed. In addition, recommendations for clinical practice and directions for further research are presented.

Part I Current practice

Do-not-resuscitate decisions

Do-not-resuscitate (DNR) decisions can be made when the likelihood of a successful resuscitation is limited.(1) A DNR decision is an anticipatory decision to withhold a medical treatment. Since the introduction of the DNR code in the 1970s, the frequency of DNR decisions has increased.(2) Ideally, patients are involved in a DNR decision in order to respect patients' autonomy.(2) When a physician decides that resuscitation would be medically useless, patients and their relatives should be informed that this decision has been taken.(3) In **chapter 2**, we assessed trends in the frequency of individual DNR decisions and the extent of patient involvement in such decisions over the past two decades. Based on subsequent nationwide Dutch questionnaire studies on end-of-life decision making practices in 1990, 2001, and 2010,(4) we found that the frequency of individual DNR decisions among non-sudden deaths rose from 46% in 1990 to 81% in 2010. The proportion of DNR decisions that were made with patient involvement increased from 23% (1990) to 45% (2001), to 55% (2010). In most of the cases in which the DNR decision was made without involving the patient this decision was made by the attending physicians in consultation with relatives. In 1990, of all cases in which DNR decisions were made without patient involvement, half of the patients were incompetent to make end-of-life decisions; this increased to 72% in 2010. The main causes of incompetency were that the patient was in a state of reduced consciousness or was unconscious, or that the patient had dementia.

Our findings were in line with other, smaller studies in which patient involvement varied from 25% to 82%.(5) In most of the cases in which a DNR decision was made without involvement of the patient, the patient was incompetent.(5) This indicates that DNR decisions are often made late in the illness trajectory.(6) It is important that physicians talk timely with patients about their preferences for and expectations about care at the end of life. Patients, in general, tend not to talk about their end-of-life preferences until physicians broach this theme.(7) With the increasing frequency of

DNR decisions, it may be expected that the percentage of successful cardiopulmonary resuscitations will increase as only patients with good chances of success will be resuscitated.(2) Unfortunately, exact percentages of successful resuscitations in the Netherlands and their trend in the last decades are lacking. A study in the United States has shown that the percentage of successful in-hospital resuscitations increased between 2000 (13.7%) and 2009 (22.4%),(8) after decades of stagnating success percentages. In this period the technique of cardiopulmonary resuscitation remained the same, but the awareness of making DNR decisions increased. The increased rate of DNR decisions may very well have led to an increase of the percentages of successful resuscitations.

Medication discontinuation

Another type of treatment that should be reconsidered in the last phase of life is the use of medication.(9-13) In this phase, treatment objectives and organ functions may change. Several studies have shown that many potentially inappropriate medications are continued until the very end of life.(9, 14-18) To investigate whether the number and type of (potentially) appropriate and inappropriate medications in patients with a limited life expectancy depend on the place where end-of-life care is provided, we did a retrospective chart review study that is described in **chapter 3**. This study was part of the MEDILAST study. MEDILAST was a multicenter mixed methods research project with the aim of understanding current medication use in the last phase of life. This project was carried out by VU University Medical Center, Erasmus University Medical Center, and Radboud University Medical Center in the Netherlands and lasted from February 2013 until December 2015. In our retrospective chart review study we found that the mean number of medications used per patient was nine at day 7 before death and six on the day of dying. The number of medications aimed at symptom relief increased in the final week, whereas the number of preventive medications and medications to treat chronic diseases slightly decreased. However, in all three settings, some patients used preventive medications, including long-term preventive medications, until the day of dying. Fewer patients dying in the hospice used preventive medications than patients dying in the home setting or in the hospital. Moreover, in the hospice setting patients used more medications for symptom relief.

During the past years, many other retrospective chart review studies were done. All studies have shown high percentages of patients using potentially inappropriate medication in the last months of life.(19-26) Recently, different systematic reviews were published regarding the use of preventive medications in patients with a limited life expectancy.(27-29) These studies confirmed the results of our chart review study.

Fueled by awareness that in the last phase of life medications to prevent or treat chronic diseases need to be reconsidered, I had, as a resident during my round on an inpatient ward, a discussion with a patient who was diagnosed with metastatic

pancreatic cancer. She also had a history of type 2 diabetes mellitus. This patient is described in **chapter 4**. The case shows that the discussion on optimization of medication may induce a broader discussion on the patient's values and wishes in the last phase of life. It also illustrates that physicians need to consider both the physical and psychosocial effects of withdrawing treatment.(30) A reflection on this process is described in part II of the thesis.

Care in the dying phase

If the imminence of death in incurably ill patients is recognized, it is important that care is adapted. In the dying phase, care aimed at modifying the course of the underlying disease – which can be undignified and distressing – is ideally no longer given.(31, 32) In **chapter 5** we describe a study in which we investigated how many and which diagnostic and therapeutic interventions were applied by physicians in patients with cancer in a hospital in the last 72 hours of life. In addition, we studied whether awareness of impending death of the attending physician is associated with the application of interventions. We found that in the last 72 and 24 hours of life, 59% and 24% of the patients, respectively, received one or more diagnostic interventions. The interventions that were most often applied were blood tests and radiological procedures. Furthermore, in the last 72 hours and 24 hours of life, 47% and 31% of the patients received one or more therapeutic interventions, respectively, mostly intravenous hydration and enteral tube feeding. On average, patients used 7.2 types of medication in the last 72 hours of life, and 5.8 in the last 24 hours of life. Patients of whom the physician had been aware of impending death received less diagnostic interventions. In addition, fewer medications were used by patients of whom the physician had been aware of their impending death in the last 24 hours of life. However, in both groups patients were still using preventive medications during the last days of life.

Our study shows that many patients with cancer who die in hospital receive interventions in the last days of life. Some of these interventions are aimed at prolonging life. Most interventions are potentially burdensome. The results were in line with an earlier study on interventions in the last days of life.(33) The number of medications used in the last days of life was comparable with the number we found in our retrospective chart review study that is described in chapter 3. One of the proposed strategies to decrease the number of potentially burdensome interventions in the last days of life is to increase physicians' awareness of impending death.(34-36) Indeed, our study highlights that physicians' awareness of patients' impending death was associated with reduced use of diagnostic interventions and life-prolonging medications. It was striking, however, that even patients of whom the attending physician was aware of their impending death still received interventions that have doubtful benefits in the last days of life.

Part II Perspectives on medication management in the last phase of life

The perspectives of patients, their relatives and physicians regarding the use of potentially inappropriate medications in the last phase of life are largely unknown. In addition, barriers and considerations which contribute to continued use of these medications have not been identified. We therefore performed an interview study that is described in **chapter 6**. We interviewed 17 patients with an estimated life expectancy of less than three months, 12 relatives, 20 clinical specialists, and 12 general practitioners, who cared for these patients. Physicians mentioned several reasons for not considering withdrawal of potentially inappropriate medications: limited awareness, low priority, and uncertainty about the consequences. Patients and their relatives stated that they were willing to discontinue inappropriate medications. In their communication with patients about discontinuation of inappropriate medications, physicians tend to focus on the inappropriateness of continuing medications, instead of on the appropriateness of discontinuing.

In another interview study, it was found that physicians prefer to wait with the discontinuation of medication until patients have accepted their limited life expectancy.(37) Physicians are afraid to give patients the impression that they are being abandoned.(38) Our study, however, suggests that patients and their relatives are open to discuss discontinuation of medications. This is in line with a questionnaire study in individuals with multiple chronic morbidities, that showed that more than 90% of the participants were willing to discontinue medications.(39) In addition, in a study on discontinuation of statins in patients with a life expectancy of less than a year, it was shown that less than 10% of the patients expressed concerns that deprescribing potentially inappropriate medications could suggest that the physician abandons them, or that the physician thought they were going to die.(40) Another study also showed that the large majority of patients with advanced cancer do not object to the discontinuation of unnecessary medications.(41)

In **chapter 7** we describe a questionnaire study to assess physicians' opinions on and experiences with discontinuation of medication during the last phase of life, and identified factors influencing the continuation of potentially inappropriate medications at the end of a patient's life. The questionnaire consisted of a vignette about a patient with multimorbidity, and several statements about medication discontinuation for patients in the last phase of life. This study was conducted among general practitioners and clinical specialists in geriatrics, cardiology, pulmonology, medical oncology, and neurology. The response rate of the questionnaire study was 37% (total n=321). For the vignette, the majority of physicians preferred to stop preventive medications. For medications to treat chronic diseases, respondents' preferences varied widely: some physicians would continue such medications, others would discontinue them. Only a

small minority of respondents recognized potential drivers of continuing potentially inappropriate medications in the last phase of life as derived from medical literature on this topic, e.g. the unknown consequences of withdrawing medication and physicians' expectation that patients may feel abandoned if medications are discontinued.

Our results were in line with retrospective chart review studies, that physicians tend to continue potentially inappropriate medication in the last phase of life. Especially for medications to treat chronic diseases, e.g. diabetes mellitus and hypertension, more scientific evidence about the consequences of continuing or discontinuing is needed. It was striking that only few respondents recognized potential drivers of continuing inappropriate medications in the last phase of life. It might be possible that lack of awareness of considering withdrawal of medications is an important cause of continuing potentially inappropriate medications in clinical practice, which is consistent with the interview study results (chapter 6).

Part III Solutions

To further improve care at the end of life, part III of this thesis describes solutions that may improve care at the end of life. In **chapter 8** recommendations for improvement of medication management in the last phase of life are presented, based on an international Delphi study. A Delphi study is a structured process aimed at achieving consensus among experts on a particular topic.(42) In our two round Delphi study, we used a questionnaire with 58 possible solutions to optimize medication management at the end of life. A total of 42 experts from 13 countries participated. In the first round, agreement between experts for all solutions was very high (mean 87% (range 62-100%)). Key solutions indicated by the experts in the second round concerned the central role of the physician in medication management, the necessity of improving physicians awareness of the importance of adequate medication management at the end of life, the need for education on medication management for health care professionals, and the importance of open and honest communication with the patient and/or family. A suggestion for research included development of a list of medications that could be tapered or discontinued at the end of life.

So far only one randomized controlled study on discontinuing medication in patients with a limited life expectancy has been published.(43) This study evaluated the safety of discontinuing statins for patients without recent cardiovascular events and an estimated life expectancy between one month and one year. The results demonstrated that statins can be safely stopped in this patient population and discontinuation was even associated with improved quality of life. **Chapter 9** contains a letter in which we criticize the method that was used in this study. This method was a so-called conventional block randomized clinical trial (RCT). In such a design, full informed

consent of patients to participate is needed prior to randomization. As a result, participants in the control group and their physicians are aware of the intervention being studied. This may be problematic in deprescription trials, where contamination, i.e. participants in the control arm adopting the intervention, is likely to occur. The main message of our letter is that to prevent suboptimal research outcomes in deprescription trials, researchers should use appropriate study designs. We stated that Zelen's design may be a promising design for future deprescription trials. In Zelen's design, patients' informed consent to participate is sought after randomization. Participants in the control group are not informed about the intervention and, as a result, the risk of contamination is substantially reduced.

Chapter 10 contains a personal account of my father's final days of life. This story provides important reasons why too many patients die an undignified death: failure to recognize that a patient is dying and inadequate communication with the patient and their relatives about the possibility that death may come soon. My father's story also underscores that medical interventions were continuously offered, which created the false hope that he had a long time to live. These interventions were proposed without any discussion of their pros and cons. In the case of my father, it concerned interventions that would normally have few negative effects, such as an abdominal ultrasound. However, due to his very poor condition, they still had a major influence on his well-being. Rather than simply providing medical interventions to patients with a limited life expectancy, physicians should discuss their pros and cons, with patients and their families.

Overall discussion

Part I of this thesis shows that patients with a limited life expectancy are exposed to potentially futile and even harmful medical interventions. This specifically concerns medical interventions that were originally used for other indications in other patient groups. Over the course of time, the use of some medical interventions has expanded without evidence on their added value. An example is cardiopulmonary resuscitation. After its introduction in the 1960s, cardiopulmonary resuscitation was reserved to otherwise healthy individuals who experienced a cardiopulmonary arrest,(44, 45) as a result of, among others, acute myocardial infarction, anesthetic accident, surgery, and untoward effects of drugs.(44) Soon it became common practice to resuscitate every patient with a cardiac arrest, also those with a poor health condition. As a result, the outcomes of resuscitation are unsuccessful in most cases,(46-53) especially in patients with irreversible serious medical conditions.(52, 54)

As for medication that is prescribed for other indications and to other patient groups than those originally investigated in pharmaceutical studies, their value for

patients with a limited life expectancy is often unclear. Given the negative effects that medical interventions might have and the positive consequences of the optimisation of the medical policy (chapter 4) for patients with a limited life expectancy, physicians should reconsider whether or not medical interventions should be used or may be discontinued in these patients. Considerations pertaining to the use or withdrawal of medical interventions should be discussed well in advance. A specific form of such early communication is advance care planning (ACP).(55) ACP is a process of communication between the patient and their health care professionals in which the patient's end-of-life goals and values are discussed.(56) This communication process may help determine the appropriate care in the short term and provides directions for appropriate care in future scenarios. ACP should not be established in a single conversation between health care professionals and patients and their relatives, but in a continuing process of communication.(55, 57) It has been found that ACP improves quality of end-of-life care and of patient-physician communication.(58, 59) The best moment to start a discussion about ACP may be the occurrence of milestones in a patient's disease trajectory, such as (repeated) hospital admission, or progression of disease.(60)

An advance decision about resuscitation is an example of ACP. There has been some outcry in recent years with regard to resuscitation decisions, especially in the hospital setting. In the Netherlands and according to current practice, it is required to individually agree on a policy for potential resuscitation whenever a patient is admitted to hospital. Some experts suggest that it is undesirable to discuss this issue with each and every admitted patient.(61) They regard it as a serious, incommensurate and, therefore, disproportionate breach of privacy, as a patient's resuscitation preferences may not be important for their current treatment.(61, 62) In addition, the resuscitation question may cause significant distress to patients as they might get the idea that they have a poor prognosis or a limited life expectancy.(63) The discussion of resuscitation policy is only relevant and appropriate for patients with a significant risk of respiratory and cardiac failure.(61, 62) This policy would be in line with resuscitation policies in other countries, for example United Kingdom.(3) The proposal to discuss resuscitation decisions solely with people with a risk of respiratory and cardiac failure may have the disadvantage that physicians usually overestimate life expectancy and focus on curing disease and postponing death.(35, 64) It may thus have the consequence that resuscitation decisions, particularly the decision not to resuscitate, will be taken at an even later stage than at present (chapter 2), or not at all.

A plausible reason for the use of potentially inappropriate medical interventions until shortly before death, shown in chapter 5, may be that health care professionals persist in their daily routine of work.(33, 65) In order to avoid this persistence and to optimise symptom management for patients in the dying phase, health care professionals may use the Care Programme for the Dying (CPD), a Dutch instrument for multidisciplinary

care for patients in the dying phase that was originally based on the Liverpool Care Pathway for the dying patient (LCP).(66-68) This care pathway is controversial in the United Kingdom due to its misuse outside palliative care settings.(69) In the Netherlands and other countries, however, derivates of the LCP (such as the CPD) have been proven to have some positive effects on end-of-life care.(70, 71) As a result, the care programme has been implemented in multiple healthcare institutions.(72)

The results in part II of this thesis underline that limited awareness among physicians seems to be an important factor to explain why many patients use one or more potentially inappropriate medications in the last months before their expected death. The results of chapter 6 highlight that physicians insufficiently contemplate the discontinuation of medications at the end of life. Such awareness should obviously be enhanced, not only through (continuous) education of physicians, but also by specifically including discontinuation of medications in guidelines and protocols. This would make physicians ask themselves the standard question as to whether a specific medication should be discontinued in order to optimize care and ideally also discuss this with the patient. Our interview study (chapter 6) revealed that physicians are afraid that such discussions might give patients the idea that the physician has 'given up' on them and has 'thrown in the towel'. To decrease the likelihood of patients worrying about being abandoned it may be important to emphasize the positive aspects of stopping potentially inappropriate medications. We therefore suggest that when a physician considers deprescribing medications, the advantages of discontinuation – e.g. to reduce the risk of adverse effects and the burden of taking pills –, rather than the uselessness of continuation should be at the forefront of communication. This 'positive' communication style might also be applied when discussing forgoing other types of treatment at the end of life, such as cardiopulmonary resuscitation. Positive communication is also promoted in other medical fields.(73) A study among children with acute respiratory tract infections highlighted that providing well-founded positive reasons to refrain from medications may result in increased patient/parent satisfaction with the received care.(74)

Low priority and uncertainty about the consequences were other important causes of not considering withdrawal of potentially inappropriate medications that were found in our interview study. Uncertainty seems the most important factor to explain why physicians greatly vary in their deprescription of medication, as the findings in chapter 7 showed. This especially holds for deprescription of medication for the treatment of chronic diseases, such as anticoagulants and blood glucose lowering medications, for which discontinuation may have a direct negative impact on the patient's underlying disease. Until now, there is hardly any guidance to support the physician in their deprescription policies. Recently, two guidelines were published to manage discontinuation of medication in patients with a limited life expectancy. The

first is the OncPal deprescribing guideline. This guideline was developed and validated to assist in discontinuation of inappropriate medications in patients with advanced cancer.(75) The second is the Screening Tool of Older Persons Prescriptions in Frail adults with a limited life expectancy (STOPPfrail). This tool contains 27 criteria for medications that are potentially inappropriate in frail older patients with a limited life expectancy. The criteria were developed in a Delphi consensus process.(76) The effects and safety of the OncPal deprescribing guideline and the STOPPfrail have not been evaluated yet. In addition to these guidelines, an expert-opinion based guideline is available that provides explicit guidance for patients with diabetes mellitus who are in the final phase of life.(77) This guideline states, among others, that if a patient's life expectancy is only weeks to months, metformin can be discontinued, as it barely reduces glucose levels and is especially aimed at preventing long-term complications. More of this guidance is needed to optimise the use of medication for patients with a limited life expectancy.

The results in Part III of this thesis reveal that there is a great need of research into the consequences of deprescribing medication at the end of life, but that there are some important methodological hurdles to be taken. Research among patients in the final stage of life has its difficulties, since it is a very vulnerable patient population. Studying the consequences of stopping statins in patients with a life expectancy of less than a year has been a landmark, the potential beginning of a 'new wave of research'.(78) However, deprescribing studies require research methods that limit the risk of contamination, i.e. participants in the control arm adopting the intervention. In chapter 9, we suggest to use Zelen's design in future research, in which patients' informed consent is asked after randomisation rather than in advance.(79) Since only the patients in the experimental group are fully informed about the study, Zelen's design has been criticised. The cohort multiple RCT design may be another appropriate design.(80) The basis of a cohort multiple RCT design is an observational cohort of patients in whom outcome measures are regularly assessed. Within this observational cohort, patients eligible for an intervention are randomized. Patients who are randomized to receive the intervention are informed about the intervention, which they can accept or refuse. Patients not randomized to the intervention arm will receive usual care. This process can be repeated for randomized evaluation of other interventions within the cohort. In case of a *cluster* cohort multiple RCT, where the unit of randomization is e.g. a care institution, both patients in the control group and their physicians would not be aware of the trial intervention, which would prevent contamination.

Methodological considerations

The methods used in this thesis have some limitations. First, the limited response rates for the questionnaire studies. The response rate for the questionnaire study that is described in chapter 7 remained low at 37%, despite intensive reminder procedures. When asked for the reasons why physicians did not complete the questionnaire, they mentioned their lack of time or that the topic had a low priority in the midst of many requests to fill in questionnaires. The response rate for the PalTeC-H questionnaire study that is described in chapter 5 was 45%. Currently, a questionnaire study among physicians hardly ever achieves a response rate of 70% or higher.(81) This percentage is often seen as the limit above which it is assumed that the results are generalizable.(82) Any result below this percentage increases the chance of non-response bias. In our questionnaire studies it might be possible that especially physicians with affinity for end-of-life care participated in the studies. In recent years, researchers have searched for strategies to increase response rates. None of the interventions they examined, such as reducing the number of questions,(83) or digitising the questionnaire,(84) had a significant impact. The only intervention that seems to increase the response rate is a financial compensation.(81, 85) Second, in our interview study described in chapter 6, selection bias cannot be ruled out, because we interviewed patients who knew that they were going to die soon and were prepared to participate. Third, the questionnaire studies and interview study might be influenced by so-called social desirability bias, i.e. that respondents have answered questions based on their views of what is socially most acceptable. Fourth, recall bias may have influenced data from the PalTeC-H questionnaire study, described in chapter 5, because physicians were asked to fill in the questionnaire after the patients' death. Because the questionnaires were distributed within one week after the patient's death, this form of bias may be limited.

Recommendations for clinical practice

Awareness

Physicians should acknowledge that every patient with an incurable disease will die at some time during the progression of their disease. Death usually comes earlier than physicians expect.(64, 86) Physicians often seem to persist in the provision of care that is focused on modifying the course of the underlying disease.(33, 65) As a result, end-of-life care too often involves overuse of medical interventions,(33, 87-89) which is a barrier to patient's experience of a good death.(90) As long as death is mostly seen as a medical failure,(31) the care provided to dying patients will remain below par. Physicians must be more aware that interventions aimed at life-prolongation are not in a patient's best interest in all cases. Providing less or no interventions aimed at

prolonging life may be the better option. This requires physicians to openly discuss thoughts and feelings of hope with the patient, but also the pros and cons of therapies – instead of suggesting the next intervention on the list. Patients nowadays sometimes have to convince their treating physician that not choosing for treatment aimed at prolonging life might be a better choice.(94, 95) It is important that physicians move away from 'we did everything we could' to prevent dying, towards striving at 'we avoided doing too much' to fight an inevitable death. Various initiatives to raise physicians' awareness came to fruition in recent years.(91-93) In 2013, the Royal Dutch Medical Association (KNMG) published a report to promote the provision of appropriate end-of-life care in the Netherlands.(91) Such awareness should also be included in medical curricula.

On the other hand, physicians may also be put under pressure by patients and their relatives to start or continue futile medical treatments in the last phase of life. Patients and their relatives sometimes have unrealistic expectations about the effectiveness of medical interventions.(94) For example, many patients have been shown to believe that more than 60% of patients will survive in-hospital resuscitation, which is three times higher than the actual rate.(95) After receiving information about realistic survival rates, some patients wanted to change their code status into a do-not-resuscitate code.(95) Another important reason for demanding futile treatment in the last phase of life is patients' hope for cure and life prolongation.(96) Although it is stated that maintaining hope is important for patients in the last phase of life,(97, 98) this does not mean that physicians should not reveal the truth to their patients as other forms of hope, e.g. hope to be free of pain, may replace unrealistic hopes.(96)

Decision-making and communication

The ultimate treatment decision is the responsibility of the attending physician and should be based on the medical utility of the treatment and the patient's values, goals, and beliefs.(99) Physicians are never obligated to provide interventions which are seen as medically futile.(54, 100) The model of medical decision making in which the physicians unilaterally determine what treatment is given, is called the paternalistic medical model. This model was common in the 1950s. Nowadays, shared decision making is a widely supported model.(101) In this model, the physician and the patient together decide about medical treatment and care. The shared decision making model especially applies to so-called preference sensitive decisions, in which there is no single best choice but, rather, different options with different (side) effects.(102) Temel's landmark study among patients with metastatic non-small cell lung cancer showed that patients who are actively involved in the decision making as to whether or not to start certain treatments, were not as inclined to opt for aggressive treatments as control patients.(103) This result may underline the abovementioned suggestion: if patients are

informed adequately about the pros and cons of different treatment options in light of their life expectancy, they may choose for less aggressive treatment. It was striking that not only this group's quality of life but also their survival outshone those of the control group. A Dutch questionnaire study among patients and relatives showed that when care in the last phase of life is seen as inappropriate this is most commonly associated with overtreatment.(104) However, this study also showed that continuing (potentially) life-prolonging treatment may be seen as appropriate care by both patient and relatives in case treatment led to severe side effects and not to prolongation of life.(104)

Some critics state that health care has gone overboard in putting the patient's role in medical decision making at the centre.(105, 106) They argue that not all patients may be able to adequately make medical choices, as they e.g. might be too ill to do so. It has been found that the majority of patients overestimate the benefits of medical interventions and underestimate the harms.(95, 107) Another reason for criticising the shared decision making model is that it may make patients with a limited life expectancy and their relatives feel that they have to make a choice between life and death, or that they opt for a premature death when they refuse life-prolonging treatment.(108)

In the last decade, the so-called model of libertarian paternalism has been introduced.(109) In this model, the treating physician acts as a choice architect, by encouraging the patient to choose for the option that would be in their best interest as judged by the physician while still allowing the patient the freedom to choose otherwise. In other words, the physician sets a default option, without removing any options.(110) This way of exerting influence on choices is also referred to as 'nudging', since the person choosing is directed towards a (rational) choice.(111) Libertarian paternalism allows freedom of choice, but limits the aforementioned disadvantages of shared decision making.

In both the shared decision making and the libertarian paternalism model, it is important to discuss medical decisions at an early stage, as this considerably increases the chance of patients' input in the decision making process and enables patients to cope with the consequences of potential decisions.

Recommendations for future research

In order to provide patients with good information about the pros and cons of treatments in the last phase of life, it is important to know the consequences of their continuation and discontinuation. The available data about in-hospital cardiopulmonary resuscitations are almost all American. Information about Dutch practices is still lacking. It is therefore promising that a Dutch study into the consequences of in-hospital resuscitation has recently started (the 'Resuscitation

outcomes in the Netherlands' (ROUTiNE) study). This study will look into the one-year survival rate, quality of life and functional status of patients who were resuscitated in hospital.(112) Further, there is hardly any information on the experiences and thoughts of patients and their relatives about discussing resuscitation upon admission to the hospital. The limited literature shows that the question mainly comes across to patients as a choice between life and death.(108, 113-115) More research into patients' and relatives' experiences and thoughts is needed.

An important cause of the continuation of potentially inappropriate medications in the last phase of life is the lack of insight into the potential consequences of their discontinuation. More research on deprescribing medications, aimed at the prevention or treatment of diseases that are irrelevant in the light of patients' limited life expectancy, is needed.(116) Results from such studies should feed into guidelines that support physicians and patients in the optimisation of the use of medication in the final stage of life.

In our study into medical interventions in the last few days before death (chapter 5), we found that the dying phase had been recognised more than 24 hours in advance in approximately 50% of the cases. More research is needed to further unravel the process of dying, to enable physicians to better recognise nearing death and to adjust care accordingly.

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Samenvatting en discussie

Het doel van dit proefschrift was om meer inzicht te krijgen in de praktijk van het niet-starten en het stoppen van medische interventies in de laatste fase van het leven. Het eerste deel van het proefschrift richtte zich op de huidige praktijk van beslissingen rond het levenseinde. Voor deel twee van het proefschrift hebben we de perspectieven van patiënten, hun naasten en artsen onderzocht op het gebruik van potentieel overbodige medicatie in de laatste fase van het leven. In het derde deel zijn mogelijke oplossingen om de medische zorg aan het einde van het leven te verbeteren beschreven. In dit hoofdstuk zullen de belangrijkste bevindingen van de onderzoeken worden samengevat en bediscussieerd. Verder worden adviezen voor de dagelijkse praktijk en suggesties voor toekomstig onderzoek gepresenteerd.

Deel I Huidige praktijk

Niet-reanimeerbeslissingen

Niet-reanimeer(NR)-beslissingen kunnen worden genomen wanneer de kans op een succesvolle reanimatie nihil is. Een NR-beslissing is een zogenaamde anticiperende beslissing om een medische behandeling niet in te zetten. Vanaf de introductie van de NR-code in de jaren 70 is het aantal NR-beslissingen toegenomen. Patiënten worden idealiter bij de NR-beslissing betrokken, waarmee patiëntautonomie wordt gewaarborgd. Als de behandelende arts besluit dat reanimeren op medische gronden zinloos is, moet de patiënt en zijn/haar naasten van deze beslissing op de hoogte worden gebracht.

Voor **hoofdstuk 2** onderzochten wij de frequentie van individuele NR-beslissingen en de mate van patiëntbetrokkenheid bij deze beslissingen in de afgelopen twintig jaar. Hiervoor maakten wij gebruik van het sterfgevallenonderzoek. Op basis van dit grootschalige vragenlijstonderzoek naar de praktijk van medische besluitvorming rond het levenseinde in Nederland vonden wij dat de frequentie van individuele NR-beslissingen bij patiënten die een niet-plotseling overlijden waren gestorven, was gestegen van 46% in 1990, naar 81% in 2010. Het percentage NR-beslissingen waarbij de patiënt betrokken was, steeg van 23% (1990) naar 45% (2001) en daarna naar 55% (2010). In de meeste gevallen waarin de NR-beslissing was gemaakt zonder betrokkenheid van de patiënt, werd deze beslissing genomen door de behandelende arts samen met de naasten. In alle gevallen in 1990 waarin er een NR-beslissing was gemaakt zonder patiëntbetrokkenheid, was 50% van deze patiënten incompetent voor het maken van beslissingen rond het levenseinde. Dit percentage steeg naar 72% in 2010. De belangrijkste redenen voor incompetentie waren dat de patiënt een verminderd bewustzijn had of buiten bewustzijn was, of dat de patiënt dementerend was.

Onze resultaten waren in overeenstemming met andere, kleinere onderzoeken, waarin de patiëntbetrokkenheid varieerde van 25 tot 82% en waarin ook de meeste patiënten incompetent bleken op het moment dat de NR-beslissing was gemaakt. Deze uitkomsten wijzen erop dat de NR-beslissing pas laat in het ziektetraject wordt gemaakt. Het is belangrijk dat artsen tijdig met patiënten praten over hun voorkeuren voor en verwachtingen over de zorg rond het levenseinde. Patiënten geven hun voorkeuren voor de zorg rond het levenseinde over het algemeen niet aan tot de behandelende arts een dergelijk gesprek aansnijdt. Met de toename van NR-beslissingen kan worden voorspeld dat het percentage succesvolle reanimaties zal stijgen omdat alleen patiënten met een hoge succeskans zullen worden gereanimeerd. Het is echter niet bekend wat het percentage succesvolle reanimaties in Nederland is en wat dit percentage in de afgelopen decennia is geweest. Een Amerikaans onderzoek heeft aangetoond dat het percentage succesvolle reanimaties in ziekenhuizen is gestegen van 13,7% in 2000 naar 22,4% in 2009, nadat het percentage in de decennia ervoor gelijk was gebleven. Omdat de reanimatietechniek in de periode 2000-2009 niet was gewijzigd, maar het bewustzijn om NR-beslissingen te nemen wel was toegenomen, zou de stijging van het percentage succesvolle reanimaties het gevolg kunnen zijn van een toename in NR-beslissingen.

Stoppen van medicijnen

Een andere medische interventie die in de laatste fase van het leven heroverwogen moet worden, is medicatiegebruik. Gedurende de laatste maanden en weken van het leven veranderen de behandeldoelen en lichaamsfuncties, waardoor medicijnen mogelijk niet meer zinvol zijn. In de praktijk vindt heroverweging van medicatiegebruik in de laatste fase van het leven onvoldoende plaats. In **hoofdstuk 3** onderzochten we of het aantal en het type medicijnen dat patiënten in de laatste fase van het leven gebruiken afhankelijk zijn van de plaats waar patiënten hun zorg krijgen. Hiervoor verrichtten we een retrospectief dossieronderzoek van de laatste levensweek van 179 patiënten die een verwacht overlijden stierven, van wie een derde was opgenomen in het ziekenhuis, een derde thuis zorg kreeg en een derde in een hospice verbleef. Dit retrospectieve dossieronderzoek maakte onderdeel uit van het MEDILAST-onderzoek: een multicentrisch, 'mixed methods'-onderzoeksproject dat als doel had om tot een beschrijving van de huidige praktijk te komen en om aanbevelingen te formuleren om het medicijngebruik in de laatste fase van het leven te optimaliseren. Het onderzoek werd uitgevoerd in een samenwerkingsverband tussen het VU medisch centrum, Radboudumc en Erasmus MC en werd verricht in de periode februari 2013-december 2015.

Uit het retrospectieve dossieronderzoek bleek dat patiënten gemiddeld negen medicijnen per dag gebruiken in de laatste week van het leven. Op de dag van overlijden gebruiken patiënten gemiddeld zes medicijnen. Gebruik van medicatie die

gericht is op verlichting van de symptoomlast nam in de laatste week van het leven toe, terwijl medicatie gericht op de preventie en behandeling van ziekten enigszins afnam. Het gebruik van symptoombestrijders was het grootst in het hospice. In alle drie de zorgsettings gebruikte een aantal patiënten een of meerdere medicijnen gericht op preventie tot aan overlijden, met name patiënten die thuis of in het ziekenhuis verbleven. Sommige van deze medicijnen hebben hun werking echter pas vele jaren na inname.

In de laatste jaren zijn er vele andere retrospectieve dossieronderzoeken verricht naar het gebruik van medicijnen in de laatste fase van het leven. Al deze onderzoeken hebben aangetoond dat veel patiënten potentieel overbodige medicijnen gebruiken in de laatste maanden van hun leven. Recentelijk zijn er verschillende systematische reviews verschenen naar het gebruik van preventieve medicijnen bij patiënten met een beperkte levensverwachting. Deze reviews onderstrepen de conclusie van ons dossieronderzoek, namelijk dat veel patiënten in de laatste fase van het leven preventieve medicijnen gebruiken.

Aangewakkerd door het bewustzijn van heroverweging van medicijnen die zijn gericht op de preventie en behandeling van ziekten, had ik als arts-assistent op de verpleegafdeling een gesprek met een patiënt met gemetastaseerd pancreascarcinoom. Zij was enkele jaren eerder gediagnosticeerd met diabetes mellitus type 2. Deze patiëntcasus is beschreven in **hoofdstuk 4**. De casus laat zien dat met het optimaliseren van het medicijngebruik er een gesprek kan ontstaan over de waarden, voorkeuren en behoeften van de patiënt in diens laatste fase van het leven. De casus laat ook zien dat dokters rekening moeten houden met de psychische en psychosociale effecten van het aanpassen en het stoppen van de behandeling.

Zorg in de stervensfase

Als het naderend overlijden onomkeerbaar is, is het belangrijk dat de zorg wordt aangepast. In deze stervensfase dient zorg die is gericht op curatie en levensverlenging – die ellendig en onwaardig kan zijn – idealiter niet ingezet te worden. In **hoofdstuk 5** wordt een onderzoek beschreven waarin wij nagingen hoeveel en welke diagnostische en therapeutische interventies worden ingezet in het ziekenhuis bij patiënten met kanker in de laatste 72 uur van hun leven. Daarnaast onderzochten we of herkenning van de stervensfase door de behandelende arts van invloed is op de inzet van deze interventies.

We vonden dat in de laatste 72 uur 59% en in de laatste 24 uur van het leven 24% van de patiënten een of meer diagnostische interventies onderging. De interventies die het meest werden ingezet, waren bloedafname en radiologische onderzoeken. Therapeutische interventies werden bij 47% (in de laatste 72 uur), respectievelijk 31% (in de laatste 24 uur) van de patiënten toegepast. Dit betrof in de meeste gevallen

intraveneuze vochttoediening en sondevoeding. Gemiddeld kregen patiënten in de laatste 72 uur van het leven 7,2 verschillende medicijnen; op de dag van overlijden waren dit gemiddeld 5,8 medicijnen. Het bleek dat herkenning van de stervensfase tot gevolg had dat patiënten minder diagnostische interventies ondergingen. Ook gebruikten patiënten bij wie de stervensfase was herkend minder medicijnen in de laatste 24 uur voorafgaand aan het overlijden. Zowel patiënten bij wie de stervensfase was herkend als patiënten bij wie deze fase niet was herkend, gebruikten op de dag van overlijden preventieve medicijnen.

Ons onderzoek laat zien dat bij veel patiënten met kanker die in het ziekenhuis overlijden medische interventies worden ingezet in de laatste dagen van hun leven. Een aantal van deze interventies heeft als doel levensverlenging. De meeste interventies zijn potentieel schadelijk. Onze resultaten zijn in overeenstemming met die van eerder onderzoek naar de inzet van medische interventies in de laatste dagen van het leven. Het aantal medicijnen dat in de laatste dagen werd voorgeschreven, is vergelijkbaar met het aantal medicijnen dat patiënten uit het retrospectieve dossieronderzoek, beschreven in hoofdstuk 3, gebruikten.

Een van de voorgestelde opties om het aantal potentieel schadelijke medische interventies te verminderen is het vergroten van de herkenning van de stervensfase door artsen. Ons onderzoek laat inderdaad zien dat herkenning van de stervensfase leidt tot minder gebruik van diagnostische interventies en van medicijnen die gericht zijn op preventie en behandeling van ziekten. Het was wel opvallend dat ook bij patiënten van wie de behandelende arts de stervensfase had herkend, interventies werden ingezet waarvan de meerwaarde zeer twijfelachtig is in de laatste dagen van het leven.

Deel II Perspectieven op het stoppen van medicijnen

De perspectieven van patiënten, hun naasten en artsen op het gebruik van potentieel overbodige medicijnen in de laatste fase van het leven zijn vrijwel onbekend. Ook is het niet duidelijk wat de belemmeringen en overwegingen zijn die bijdragen aan het continueren van deze medicijnen. Om dit te analyseren hebben we een interviewonderzoek verricht, dat is beschreven in **hoofdstuk 6**. We namen diepte-interviews af bij 17 patiënten met een geschatte levensverwachting van minder dan 3 maanden en bij 12 van hun naasten. Ook interviewden we 20 medisch specialisten en 12 huisartsen die aan de geïnterviewde patiënten zorg verleenden.

Artsen gaven verschillende redenen voor waarom patiënten in de praktijk meestal niet stoppen met potentieel overbodige medicijnen: de mogelijkheid van stoppen wordt niet overwogen, stoppen heeft geen prioriteit en de gevolgen van stoppen zijn vaak onzeker. Patiënten en hun naasten gaven aan dat zij in principe openstaan

voor het stoppen van potentieel overbodige medicijnen. Ook kwam naar voren dat als artsen de mogelijkheid van stoppen van medicijnen bespreken met patiënten, zij vooral de nadruk leggen op de medische zinloosheid van het continueren, in plaats van op de zinvolheid van het stoppen.

Uit een eerder gepubliceerd onderzoek kwam naar voren dat artsen het liefst wachten met het stoppen van medicijnen totdat patiënten hun beperkte levensverwachting hebben geaccepteerd. Artsen zijn bezorgd om patiënten de indruk te wekken dat zij in de steek gelaten worden. Ons onderzoek laat echter zien dat patiënten en hun naasten openstaan voor het stoppen van medicijnen. Dit komt overeen met de resultaten van een vragenlijstonderzoek onder patiënten met multimorbiditeit, waaruit bleek dat vrijwel alle patiënten (> 90%) bereid zijn om medicijnen te stoppen. Een onderzoek naar het stoppen van statines bij patiënten met een levensverwachting van minder dan een jaar maakte daarnaast duidelijk dat minder dan 10% van de patiënten door het stoppen van potentieel overbodige medicijnen gevoelens van 'in de steek gelaten te worden' of 'dat het naderend einde in zicht is' ervaart. Een ander onderzoek liet ook zien dat de overgrote meerderheid van de patiënten met gevorderde kanker openstaat voor het stoppen van overbodige medicijnen.

In **hoofdstuk 7** beschrijven we de uitkomsten van een vragenlijstonderzoek dat als doel had om de opvattingen over en ervaringen met het stoppen van medicijngebruik in de laatste fase van het leven van artsen te achterhalen. Het vragenlijstonderzoek had daarnaast als doel om factoren te identificeren die van invloed zijn op het continueren van het gebruik van potentieel overbodige medicijnen aan het einde van het leven. De vragenlijst bestond uit een vignet over een patiënt met multimorbiditeit en uit verschillende stellingen over het stoppen van medicijnen bij patiënten met een beperkte levensverwachting. We stuurden de vragenlijst naar een aselecte steekproef van 500 huisartsen en 500 medisch specialisten (geriaters, cardiologen, longartsen, internisten-oncologen en neurologen). In totaal respondeerden 321 artsen. Omdat ruim 100 van de in totaal 1000 aangeschreven artsen niet (meer) werkzaam waren als zorgverlener of verhuisd waren en de vragenlijst dus niet hadden ontvangen, was het responspercentage 37%.

De meerderheid van de respondenten zou stoppen met het gebruik van preventieve middelen bij de patiënt beschreven in het vignet. De respondenten waren veel verdeelder over of en wanneer medicijnen gericht op het behandelen van chronische ziekten gestopt kunnen worden. Slechts een kleine minderheid van de respondenten herkende zich in de voorgestelde factoren die van invloed kunnen zijn op het continueren van medicijnen aan het einde van het leven. Voorbeelden van deze potentiele factoren waren: onduidelijke gevolgen van het stoppen van medicijnen en het gevoel hebben dat patiënten zich in de steek gelaten voelen als medicijnen worden gestopt.

Onze resultaten kwamen overeen met die van de retrospectieve dossieronderzoeken, waaruit bleek dat artsen over het algemeen het gebruik van potentieel overbodige medicijnen continueren in de laatste fase van het leven. Toekomstig onderzoek naar de gevolgen van het stoppen van medicijnen is noodzakelijk, met name van medicijnen gericht op het behandelen van chronische ziekten, zoals diabetes mellitus en hypertensie. Het was opvallend dat slechts een klein percentage van de respondenten zich kon vinden in de voorgestelde factoren die van invloed kunnen zijn op het continueren van medicijnen. Het is hierdoor mogelijk dat een gebrek aan bewustzijn om medicijnen te stoppen een belangrijke oorzaak is van het continueren van medicijnen in de dagelijkse praktijk, zoals ook naar voren kwam uit het interviewonderzoek (hoofdstuk 6).

Deel III Oplossingen

In deel III zijn oplossingen beschreven die de zorg aan het einde van het leven kunnen helpen optimaliseren. In **hoofdstuk 8** staan aanbevelingen voor het optimaliseren van het medicijngebruik aan het einde van het leven, naar aanleiding van een internationaal Delphi-onderzoek. Een Delphi-onderzoek is een gestructureerd proces dat als doel dient om consensus onder experts te bereiken op een specifiek thema. In ons Delphi-onderzoek, dat uit twee ronden bestond, maakten we gebruik van een lijst met 58 mogelijke oplossingen om het medicijngebruik aan het einde van het leven te optimaliseren. In totaal waren 42 experts, uit 13 verschillende landen, bereid om mee te doen aan het onderzoek.

In de eerste ronde was er een hoge mate van overeenstemming tussen de experts voor een groot deel van de voorgestelde oplossingen (gemiddelde: 87%; bereik: 62-100%). De belangrijkste oplossingen die in de tweede ronde door de experts werden aangegeven, betroffen de centrale rol die artsen moeten hebben in het medicijngebruik aan het einde van het leven, de noodzaak het bewustzijn onder artsen om het medicijngebruik te optimaliseren te vergroten, het belang van onderwijs in medicijngebruik aan zorgverleners en het belang van een open en eerlijk gesprek met de patiënt en familie. De experts stelden tevens voor om een lijst te ontwikkelen met medicijnen die afgebouwd of gestopt kunnen worden.

Tot op heden is er slechts één gerandomiseerd onderzoek verricht naar het stoppen van medicijnen bij patiënten met een beperkte levensverwachting. Hierin werd de veiligheid van het stoppen van statines onderzocht bij patiënten zonder recente cardiovasculaire gebeurtenis en met een levensverwachting tussen een maand en een jaar. Dit onderzoek toonde dat statines veilig gestopt kunnen worden bij deze patiëntcategorie. Het stoppen van het medicijn was zelfs geassocieerd met een betere kwaliteit van leven dan het continueren ervan.

Hoofdstuk 9 bevat een ingezonden brief waarin we de onderzoeksmethode die was gebruikt in dit 'stoponderzoek' bekritiseren. Deze methode was een zogenoemd conventioneel blok-gerandomiseerd klinisch onderzoek. Bij dit type onderzoek dient voorafgaand aan de randomisatie 'informed consent' aan de patiënt gevraagd te worden. Dit heeft als gevolg dat zowel de patiënten in de controlegroep als hun behandelende artsen zich bewust zijn van de interventie die wordt onderzocht. Dit kan problematisch zijn bij zogenaamde 'stoponderzoeken', waarin contaminatie, dat wil zeggen dat deelnemers in de controlegroep de interventie overnemen, op de loer ligt. De belangrijkste boodschap van onze brief is dat onderzoekers de juiste onderzoeksmethoden moeten gebruiken om te voorkomen dat de uitkomsten van toekomstige 'stoponderzoeken' suboptimaal zijn. We stelden het 'Zelen's design' voor als mogelijk alternatief. Met deze onderzoeksmethode wordt pas na randomisatie aan patiënten om informed consent gevraagd. Hierdoor worden de deelnemers in de controlegroep niet geïnformeerd over de interventie en is de kans op contaminatie veel kleiner.

Hoofdstuk 10 bevat een persoonlijk verhaal over de laatste dagen van het leven van mijn vader. In dit verhaal staan enkele redenen waardoor te veel mensen onwaardig sterven, namelijk: niet herkennen dat een patiënt stervende is en ontoereikende communicatie met de patiënt en diens naasten over de mogelijkheid van het naderend overlijden. Het verhaal over mijn vader onderstreept bovendien dat er voortdurend medische interventies werden aangeboden, waardoor valse hoop over zijn toekomstperspectieven werd gecreëerd. Bovendien werden deze interventies aangeboden zonder dat de voors en tegens van deze interventies werden besproken. Bij mijn vader betrof het interventies, zoals een echo abdomen, die normaal gesproken relatief weinig schadelijke effecten tot gevolg hebben. Door de zeer zwakke conditie van mijn vader hadden deze in andere situaties beperkte negatieve effecten echter grote invloed op zijn welzijn. In plaats van medische interventies bij patiënten met een beperkte levensverwachting aan te bieden, zouden veel vaker de voor- en nadelen van deze interventies besproken moeten worden.

Algemene discussie

De resultaten in deel 1 laten zien dat patiënten met een beperkte levensverwachting worden blootgesteld aan potentieel overbodige en zelfs schadelijke medische interventies. Dit betreffen veelal medische interventies die oorspronkelijk op de markt zijn gekomen voor heel andere indicaties en voor andere patiëntcategorieën. In de loop van de tijd is de indicatiestelling steeds verder verruimd, zonder dat hierbij de meerwaarde is bewezen. Een voorbeeld is reanimatie. Na de introductie van de reanimatietechniek in de jaren 60 was reanimeren voorbehouden aan voorheen

gezonde patiënten die een hartstilstand doormaakten als gevolg van bijvoorbeeld een acuut myocardinfarct, anesthesiologische complicaties, een operatie of een ernstige bijwerking van medicatie. Al snel werd de indicatiestelling verruimd en werd het gemeengoed om iedere patiënt met een hartstilstand te reanimeren, ook patiënten met zeer slechte gezondheidstoestand. Het is gebleken dat het percentage succesvolle reanimaties bij deze patiënten zeer laag is.

Ook medicijnen zijn in de loop van de tijd voorgeschreven voor hele andere indicaties en bij andere patiëntcategorieën dan oorspronkelijk zijn onderzocht. Wat de waarde van medicijnen is bij patiënten met een beperkte levensverwachting, is veelal niet bekend. Vanwege alle nadelige effecten die het gebruik van medische interventies met zich mee kan brengen en de positieve gevolgen van het optimaliseren van het medische beleid (hoofdstuk 4), zouden zorgverleners meer stil moeten staan bij de toepassing van medische interventies bij patiënten met een beperkte levensverwachting. De overwegingen om bepaalde interventies wel of niet in te zetten zouden tijdig met patiënten met een beperkte levensverwachting besproken moeten worden.

Een specifieke vorm van deze vroege communicatie is anticiperende besluitvorming ('advance care planning'). Anticiperende besluitvorming kan worden gezien als een ontmoeting tussen de patiënt en diens behandelende arts rond de levensdoelen van die patiënt. Hierdoor kan worden vastgesteld wat passende zorg is voor de korte termijn en wordt richting gegeven aan passende zorg in toekomstige scenario's. Anticiperende besluitvorming moet vooral niet worden gezien als één gesprek tussen zorgverleners en patiënten en hun naasten, maar als een continu proces van communicatie die veelal uit meerdere gesprekken bestaat. Het is gebleken dat anticiperende besluitvorming onder andere de kwaliteit van zorg aan het einde van het leven kan verbeteren. Het beste moment waarop een gesprek over anticiperende besluitvorming kan plaatsvinden is als er een mijlpaal in het beloop van het leven van de patiënt is, zoals tijdens of kort na een ziekenhuisopname of bij ziekteprogressie.

Een reanimeerbeslissing is een voorbeeld van anticiperende besluitvorming. In de afgelopen jaren is er enige ophef ontstaan over de reanimeerbeslissing, met name in de ziekenhuissetting. In de huidige praktijk is het noodzakelijk dat voor elke patiënt die in het ziekenhuis wordt opgenomen, een beleid is afgesproken met betrekking tot het wel of niet reanimeren van deze patiënt op het moment dat hier een indicatie voor is.

Sommige experts zijn van mening dat dit beleid niet met elke patiënt die wordt opgenomen afgesproken moet worden. Zij zien een gesprek over reanimatie als ingrijpend en iets wat veel inbreuk maakt op de privésfeer van de patiënt. Bovendien is de mening van de patiënt over reanimatie ook lang niet altijd van belang voor de betreffende ziekenhuisopname. Daarnaast kan een gesprek over reanimeren patiënten veel onrust geven omdat zij het idee kunnen krijgen dat zij nog maar zeer kort te leven hebben. Een reanimeerbeslissing zou alleen gemaakt moeten worden met patiënten die daadwerkelijk een risico lopen op respiratoir of cardiaal falen. Dit beleid zou hiermee

in overeenstemming zijn met het beleid dat in andere landen, zoals Engeland, geldt. Met het voorstel om een reanimeerbeslissing alleen te nemen bij mensen met een risico op respiratoir of cardiaal falen ligt er een belangrijk gevaar op de loer omdat artsen de levensverwachting overschatten en zij vooral gefocust zijn op het genezen van ziekten en het uitstellen van het overlijden. Dit kan ervoor zorgen dat reanimeerbeslissingen, in het bijzonder het besluit om niet te reanimeren, in een nog later stadium – of helemaal niet – zullen worden genomen dan nu het geval is (hoofdstuk 2).

Een aannemelijke reden voor de inzet van medische interventies tot vlak voor het overlijden die in hoofdstuk 5 is beschreven, is dat zorgverleners volharden in hun dagelijkse werkroutine. Om te voorkomen dat zorgverleners dit blijven doen en om de symptoombehandeling voor patiënten in de stervensfase te optimaliseren, kunnen zorgverleners gebruikmaken van het Zorgpad Stervensfase. Dit zorgpad, dat is gebaseerd op de 'Liverpool Care Pathway', geeft handvatten voor multidisciplinaire zorg aan patiënten in de stervensfase. Het betreft een kwaliteitsinstrument dat bijdraagt aan de kwaliteit van zorg aan stervende patiënten. Vanwege verkeerd gebruik is de 'Liverpool Care Pathway' in Engeland controversieel geworden. In Nederland, en in veel andere landen, is echter gebleken dat afgeleiden van de 'Liverpool Care Pathway', zoals het Zorgpad Stervensfase, meerwaarde laten zien voor de zorg aan stervenden. Daarom is het Zorgpad Stervensfase in veel zorginstellingen in Nederland geïmplementeerd.

De resultaten in deel II van het proefschrift laten zien dat een gebrek aan bewustzijn om medicijnen te stoppen een belangrijke oorzaak lijkt te zijn van het gebruik van potentieel overbodige medicijnen in de laatste fase van het leven. De resultaten in hoofdstuk 6 tonen dat artsen onvoldoende de mogelijkheid en – wellicht – de noodzakelijkheid van het stoppen van medicijnen overwegen. Deze bewustwording zou moeten worden vergroot door (na)scholing aan artsen, maar ook door specifieke aandacht te besteden aan het stoppen van medicijnen in richtlijnen en protocollen. Hierdoor zouden artsen zichzelf de standaardvraag moeten stellen of een bepaald medicijn, in overleg met de patiënt, gestopt kan worden, waardoor de zorg kan worden geoptimaliseerd.

Het interviewonderzoek (hoofdstuk 6) heeft duidelijk gemaakt dat artsen angst hebben dat het bespreken van stoppen van medicijnen patiënten het idee kan geven dat zij 'opgegeven' zijn en dat 'de handdoek in de ring is gegooid'. Om te voorkomen dat patiënten deze gedachten krijgen is het van belang om juist de positieve kanten van het stoppen te benadrukken, zoals het verminderen van het risico op bijwerkingen en van de last van het innemen van medicijnen, in plaats van de negatieve kanten van het continueren. Deze 'positieve' communicatiestijl zou ook meerwaarde kunnen hebben bij het bespreken van het stoppen of niet-starten van andere behandelingen, zoals reanimatie.

Andere redenen om potentieel overbodige medicijnen niet te stoppen die uit ons interviewonderzoek naar voren kwamen, waren onvoldoende prioriteit en onduidelijkheid over de negatieve gevolgen van het stoppen. Onduidelijkheid over het stoppen lijkt de belangrijkste oorzaak te zijn waarom artsen onderling sterk verschillen in het stoppen van medicijnen aan het einde van het leven (zie hoofdstuk 7). Dit geldt met name voor medicijnen gericht op het behandelen van chronische ziekten, zoals anticoagulantia en bloedglucoseverlagende medicijnen, waarbij stoppen directe negatieve gevolgen kan hebben voor patiënten.

Tot op heden zijn er nauwelijks ondersteunende middelen om artsen te ondersteunen bij het stoppen van medicijnen. Onlangs zijn twee richtlijnen ontwikkeld die gebruikt kunnen worden bij het stoppen van medicijnen bij patiënten met een beperkte levensverwachting. De eerste richtlijn is de 'OncPal-stoprichtlijn'. Deze richtlijn is ontwikkeld en gevalideerd om artsen te ondersteunen bij het stoppen van medicijnen bij patiënten met gevorderde kanker. De tweede richtlijn is de 'STOPPFrail', die 27 verschillende medicijnen bevat die potentieel overbodig zijn bij kwetsbare ouderen met een beperkte levensverwachting. Deze richtlijn is ontwikkeld in een Delphi-onderzoek. De effecten en veiligheid van de 'OncPal-stoprichtlijn' en de 'STOPPFrail' zijn nog niet geëvalueerd. Naast deze twee richtlijnen is een richtlijn verschenen voor de zorg aan patiënten met diabetes mellitus en een beperkte levensverwachting. In deze richtlijn staat onder andere dat als de levensverwachting enkele weken tot maanden is metformine gestopt kan worden, omdat het de glucosespiegel nauwelijks verlaagt en met name bedoeld is om langetermijncomplicaties te voorkomen.

De resultaten in deel III tonen aan dat er grote behoefte is aan onderzoek om na te gaan wat de gevolgen zijn van het stoppen van medicijnen aan het einde van het leven, maar dat voor het verrichten van dergelijk onderzoek er nog wel belangrijke methodologische horden te nemen zijn. Onderzoek bij patiënten in de laatste fase van het leven wordt bemoeilijkt doordat er sprake is van een zeer kwetsbare patiëntpopulatie. Het onderzoek naar de gevolgen van het stoppen van statines bij patiënten met een levensverwachting van minder dan een jaar is een 'landmark-onderzoek' geweest, dat het begin is van meer 'stoponderzoeken'. Deze 'stoponderzoeken' vragen echter om onderzoeksmethoden waarbij de kans op contaminatie wordt geminimaliseerd.

In hoofdstuk 9 deden wij de suggestie om bij toekomstig onderzoek gebruik te maken van het 'Zelen's design', waarbij informed consent pas na randomisatie wordt gevraagd. Omdat alleen de patiënten in de experimentele groep om consent wordt gevraagd, is het 'Zelen's design' bekritiseerd. Een andere onderzoeksopzet waarmee contaminatie kan worden voorkomen, is de 'cohort multiple randomized controlled trial'. De basis van de 'cohort multiple randomized controlled trial' is een observationeel cohort van patiënten bij wie uitkomstmaten op vaste tijdstippen worden gemeten. Binnen dit cohort kunnen voor een interventie geschikte patiënten

worden geïdentificeerd. Patiënten die gerandomiseerd worden om de interventie te krijgen, worden geïnformeerd over deze interventie, die zij kunnen accepteren of weigeren. Patiënten die niet worden gerandomiseerd om de interventie te krijgen, zullen niet benaderd worden en de standaardbehandeling ondergaan. Dit proces kan voor meerdere interventies gelijktijdig herhaald worden. In het geval van een *cluster* 'cohort multiple randomized controlled trial', waarin bijvoorbeeld zorginstellingen gerandomiseerd worden, zullen zowel patiënten in de controlegroep als hun behandelende artsen niet op de hoogte zijn van de interventie, waardoor de kans op contaminatie nog kleiner wordt.

Methodologische overwegingen

De onderzoeksmethoden die zijn gebruikt in dit proefschrift, hebben enige beperkingen. De eerste beperking betreft het matige responspercentage van de vragenlijstonderzoeken. Het responspercentage van het vragenlijstonderzoek beschreven in hoofdstuk 7 bleef steken op 37%, ondanks dat we zeer actief waren om 'non-responders' te vragen de vragenlijst alsnog in te vullen. Een belangrijk argument waarom artsen de vragenlijst niet invulden was dat zij geen tijd en behoefte hadden om de lijst in te vullen, vooral omdat zij al zo vaak gevraagd worden om een vragenlijst in te vullen. Het responspercentage van de PalTec-H-vragenlijstonderzoek, beschreven in hoofdstuk 5, was 45%. Zelden haalt een grootschalig vragenlijstonderzoek onder artsen een responspercentage van 70% of hoger. Dit percentage wordt veelal gezien als de grens waarmee wordt verondersteld dat de onderzoeksresultaten generaliseerbaar zijn. Bij alle lagere percentages is de kans op 'non-response bias' vergroot. In onze vragenlijstonderzoeken was het mogelijk dat vooral artsen met affiniteit voor levenseindezorg de vragenlijst invulden en retourneerden.

In de afgelopen jaren is onderzocht op welke manier het responspercentage van vragenlijstonderzoeken onder artsen te verhogen is. Geen van de interventies, zoals het verkorten van de vragenlijst of het digitaliseren van de lijst, had echter grote invloed. Een interventie die er mogelijk wel voor zorgt dat de respons hoger wordt, is de respondent een geldbedrag te overhandigen.

De tweede beperking is dat we niet kunnen uitsluiten dat er in het interviewonderzoek, beschreven in hoofdstuk 6, sprake is geweest van selectiebias omdat de geïnterviewde patiënten wisten dat zij op korte termijn zouden komen te overlijden en zij bereid waren om geïnterviewd te worden.

Een derde beperking is dat de vragenlijstonderzoeken en het interviewonderzoek mogelijk beïnvloed zijn door zogenaamde 'sociale wenselijkheidbias', dat wil zeggen dat respondenten op specifieke vragen een sociaal wenselijk antwoord hebben gegeven.

Een vierde beperking is dat 'recall bias' mogelijk van invloed is geweest op de resultaten van het PalTec-H-vragenlijstonderzoek (hoofdstuk 5) omdat artsen na

het overlijden van de patiënt werd gevraagd om de vragenlijst in te vullen. Omdat de vragenlijst al binnen een week na het overlijden naar de behandelende arts werd gestuurd, is de kans dat er daadwerkelijk sprake was van 'recall bias' klein.

Aanbevelingen voor de praktijk

Bewustzijn

Er moet een algemeen besef bij artsen komen dat iedere patiënt met een niet te genezen ziekte op een zeker moment in het ziekteproces komt te overlijden. Het overlijden komt veelal veel eerder dan artsen verwachten. In de huidige zorgverlening neigen artsen ernaar zorg te geven die is gericht op genezing en levensverlenging. Dit heeft tot gevolg dat de zorg in de laatste fase van het leven gepaard gaat met overbehandeling. De focus op genezing en levensverlenging staat een goede dood van de patiënt in de weg. Zolang het overlijden wordt gezien als een medische fout, zal de zorg aan stervende patiënten ondermaats blijven.

Artsen moeten zich ook bewuster worden van het gegeven dat de inzet van medische interventies niet altijd in het belang is van patiënten. De inzet van minder of geen interventies die als doel genezing en levensverlenging hebben, is in specifieke situaties beter. Hiervoor is het van belang dat artsen openlijk met patiënten spreken over de voors en tegens van in te zetten medische interventies, in plaats van dat de volgende medische interventie die ingezet kán worden, voorgesteld wordt. Patiënten moeten tegenwoordig soms hun behandelende arts overtuigen dat niet kiezen voor levensverlengende behandeling de beste keuze is. Het is van belang dat artsen afstappen van het credo 'we hebben er alles aan gedaan' om het overlijden te voorkomen, en streven naar 'we hebben voorkomen dat we te veel hebben gedaan' om het onvermijdelijke overlijden te voorkomen.

In de afgelopen jaren zijn verschillende initiatieven ontplooid om het besef dat minder zorg soms betere zorg is onder artsen te vergroten. Zo is in 2013 een rapport verschenen van de artsenfederatie KNMG om te bereiken dat patiënten in de laatste fase van het leven passende zorg krijgen. Deze bewustwording moet ook meer in de medische curricula naar voren komen.

Het gebeurt ook dat patiënten en hun naasten eisen dat behandelingen ingezet of gecontinueerd worden die in de laatste fase van het leven als medisch zinloos worden gezien. Een belangrijke reden hiervoor is dat zij een onrealistische verwachting hebben over de effectiviteit van de betreffende medische interventie. Zo wordt het succespercentage van reanimaties in ziekenhuizen door patiënten geschat op iets meer dan 60%, een schatting die drie keer hoger ligt dan het daadwerkelijke percentage. Als patiënten informatie krijgen over het daadwerkelijke percentage

succesvolle reanimaties, willen sommige hun reanimeerbeleid wijzigen in een niet-reanimeerbeleid.

Een andere belangrijke reden om behandelingen te eisen die als medisch zinloos worden gezien, is de blijvende hoop die patiënten hebben op genezing en levensverlenging. Hoewel wordt verondersteld dat het behouden van een vorm van hoop goed is voor patiënten in de laatste fase van hun leven, betekent dit niet dat artsen de waarheid niet moeten vertellen en bepaalde, medisch zinloze, behandelingen dienen in te zetten. Er zijn ook andere – realistischere – vormen van hoop, zoals de hoop om geen pijn te hebben en om goed afscheid te kunnen nemen.

Besluitvorming en communicatie

De uiteindelijke behandelbeslissing is de verantwoordelijkheid van de behandelende arts. Deze beslissing moet gebaseerd zijn op het medische nut van de interventie en de waarden en doelen van de patiënt. Artsen zijn nooit verplicht om interventies in te zetten die als medisch zinloos worden gezien. De vorm van medische besluitvorming waarbij de behandelende arts de behandelbeslissing bepaalt, wordt het paternalistische beslismodel genoemd. Dit beslismodel was in de jaren 50 gemeengoed.

Tegenwoordig is 'shared decision-making' (gezamenlijke besluitvorming) het basismodel van medische besluitvorming. Bij deze vorm van besluitvorming besluiten de patiënt en de behandelende arts samen over de medische behandeling. Gezamenlijke besluitvorming is met name van toepassing bij zogenaamde 'preference-sensitive decisions', wanneer er meer dan één behandeloptie is en het afwegen van voor- en nadelen dilemma's kan geven. In een onderzoek bij patiënten met gemetastaseerd niet-kleincellig longcarcinoom, werd aangetoond dat patiënten die actief betrokken waren in de medische besluitvorming minder vaak agressieve therapieën ondergingen dan patiënten die minder of niet actief waren betrokken. Dit laat zien dat als patiënten actief worden geïnformeerd over behandelopties zij minder vaak voor agressieve opties kiezen. Het was opvallend dat niet alleen de kwaliteit van leven van patiënten die actief betrokken waren in de besluitvorming toenam, maar ook de tijd tot overlijden.

Een Nederlands vragenlijstonderzoek onder patiënten en naasten toonde dat als de zorg in de laatste fase van het leven als ongepast wordt gezien, dit meestal geassocieerd is met overbehandeling. Hetzelfde vragenlijstonderzoek liet echter ook zien dat het continueren van een behandeling die (mogelijk) levensverlengend is door zowel patiënten als naasten als gepast wordt gezien als die behandeling leidt tot zeer veel bijwerkingen en uiteindelijk niet tot levensverlenging.

Critici hebben aangegeven dat de gezondheidszorg is doorgeslagen in het centraal stellen van de keuzevorming van de patiënt. Zij geven aan dat patiënten niet altijd in staat zijn keuzes te maken, bijvoorbeeld omdat zij op het moment van keuze te ziek zijn om een beslissing te nemen. Het is ook gebleken dat de meerderheid

van de patiënten de voordelen van medische interventies overschat en de nadelen ervan onderschat. Een ander punt van kritiek is dat patiënten met een beperkte levensverwachting en hun naasten het gevoel kunnen krijgen dat zij een keuze tussen leven en dood moeten maken, of dat zij kiezen voor een vroegtijdige dood als zij niet kiezen voor de levensverlengende behandeling.

In het laatste decennium is het libertair paternalisme geïntroduceerd. In dit beslismodel fungeert de behandelende arts als keuzearchitect, door de patiënt aan te sporen om voor de optie te kiezen die door het medische team als zinvolst wordt gezien, waarbij patiënten nog steeds vrij zijn om voor een andere behandeloptie te kiezen. Deze manier van keuzebeïnvloeding wordt ook wel 'nudging' genoemd, omdat de persoon die kiest in een (juiste) richting wordt geduwd. Met libertair paternalisme wordt keuzevrijheid behouden, maar worden de nadelen van gezamenlijke besluitvorming beperkt.

Onafhankelijk van het beslismodel dat wordt gebruikt, is het belangrijk dat medische beslissingen in een zo vroeg stadium worden bediscussieerd. Hiermee wordt de kans aanzienlijk vergroot dat patiënten mee kunnen denken met deze besluitvorming en in staat worden gesteld om te gaan met de gevolgen van de beslissing.

Aanbevelingen voor toekomstig onderzoek

Om goede voorlichting te kunnen geven aan patiënten over de voors en tegens van behandelingen in de laatste fase van het leven, is het van belang te weten wat de gevolgen zijn van het stoppen of continueren ervan. De beschikbare cijfers over reanimaties in het ziekenhuis komen vrijwel allemaal uit de VS; de Nederlandse situatie is tot op heden onbekend. Het is dan ook goed dat er recent een onderzoek is gestart naar de gevolgen van reanimatie in Nederlandse ziekenhuizen. Hierin wordt gekeken naar de 1-jaarsoverleving, de kwaliteit van leven en de functionele status van patiënten die in het ziekenhuis worden gereanimeerd. Er is daarnaast vrijwel niets bekend over wat de ervaringen en gedachten van patiënten en hun naasten zijn over de reanimatievraag in het ziekenhuis. De beperkte literatuur laat zien dat patiënten deze vraag vooral zien als een keuze tussen leven en dood. Meer onderzoek naar de ervaringen en gedachten van patiënten en hun naasten is noodzakelijk.

Een belangrijke reden voor het continueren van potentieel overbodige medicijnen is dat nauwelijks bekend is wat de gevolgen zijn van het stoppen ervan. Het is noodzakelijk dat er meer onderzoek wordt verricht naar de gevolgen van het stoppen van medicijnen in de laatste fase van het leven die zijn gericht op de preventie en behandeling van ziekten. Resultaten van deze onderzoeken kunnen in richtlijnen worden verwerkt, waarmee artsen kunnen worden ondersteund om het gebruik van medicijnen in de laatste fase van het leven te optimaliseren.

In ons onderzoek naar medische interventies in de laatste dagen van het leven (hoofdstuk 5) viel op dat de stervensfase bij ongeveer 50% van de patiënten was herkend. Toekomstig onderzoek moet trachten het stervensproces te ontrafelen, zodat artsen het naderend overlijden nog beter herkennen en de zorg geoptimaliseerd kan worden.

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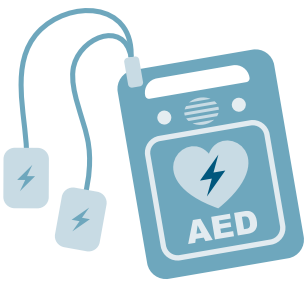
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Appendices

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Books

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Book contributions

1. Pro-choice versus pro-life. In: New life (Dutch). Tijdstroom Uitgeverij. September 2012.
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Reports

1. Second evaluation of the termination of life on request and assisted suicide act. December 2012. Author of: chapter 8 and 9.

PhD portfolio

Name PhD student:	**Eric C.T. Geijteman**
PhD period:	**February 2013-December 2018**
Erasmus MC Departments:	**Public Health, Medical Oncology**
Promotors:	**Prof. dr. A. van der Heide**
	Prof. dr. C.C.D. van der Rijt
	Prof. dr. T. van Gelder
Supervisor:	**Dr. L. van Zuylen**

1. Courses	Year	Workload	
		Hours	ECTS
Biostatistical Methods I: Basic Principles	2013		2
Qualitative research (working with AtlasTi)	2013		1
Biomedical English Writing and Communication	2014		3
Research Integrity	2014		0.3
Methods of Clinical Research	2014		1
Basic Course for Clinical Investigators	2014		2
Teach the Teacher	2014		1
Pharmaco-epidemiology	2015		1
Principles of Clinical Pharmacology	2015		2

2. Presentations	Year	Workload	
		Hours	ECTS
Oral presentations			
End of life care and decision making, 'post-EAPC symposium', Arnhem, the Netherlands	2013	10	
Medication management in the last phase of life, 'interne geneeskunde-bespreking', Rotterdam, the Netherlands	2014	10	
Medication management in the last phase of life, symposium 'gewoon goed gegaan: zorg rond het levenseinde', Delft, the Netherlands	2014	10	
Medication treatment at the end of life, 'symposium over ouderenzorg, goede zorg voor de oudste ouderen', Noordwijk, the Netherlands	2015	10	

Information transfer between care providers, 'het ziekenhuis en de dood', Rotterdam, the Netherlands	2015	10	
Withholding treatment at the end of life, 'wetenschapsdag interne oncologie', Rotterdam, the Netherlands	2015	10	
Information transfer between care providers, 'de dokter en de dood, Medisch Contact', Utrecht, the Netherlands	2015	10	
Information transfer between care providers, '4de regiosymposium palliatieve zorg 's-Hertogenbosch-Bommelerwaard', 's-Hertogenbosch, the Netherlands	2015	10	
Sense and nonsense of medication treatment at the end of life, 'de dokter en de dood, Medisch Contact', Utrecht, the Netherlands	2015	10	
Medication management in the last phase of life, 'scholingsdag consulenten palliatieve zorg', Rotterdam, the Netherlands	2015	10	
Medication treatment at the end of life, 'zuster en de dood', Ede, the Netherlands	2016	10	
'Sense and nonsense of treatment of comorbid diseases in te last phase of life, 'congres feest aan zee', Middelburg, the Netherlands	2016	10	
Opinions of physicians on discontinuation of medications at the end of life: a questionnaire study, 'preventing overdiagnosis conference', Barcelona, Spain	2016		1
Sense and nonsense of treatment in the last phase of life, 'ROIG-bijeenkomst palliatieve zorg', Rotterdam, the Netherlands	2016	10	
Medication use in the last phase of life, 'zuster en de dood', Ede, the Netherlands	2017	10	
Medication management in the last phase of life, 'congres 25 jaar Kuria en afscheid prof. dr. Zuurmond', Amsterdam, the Netherlands	2017	10	
Medication use in the last phase of life, Vught, the Netherlands, '5de regiosymposium palliatieve zorg 's-Hertogenbosch-Bommelerwaard', Vught, the Netherlands	2017	10	
Interventions in the last days of life of hospitalized patients with cancer, 'compassion, care and clinical excellence in hospital palliative care conference', Liverpool, United Kingdom	2017		1
Optimizing medication use at the end of life, symposium 'doelmatigheid van zorg', Leiden, the Netherlands	2018		1
Medication use at the end of life, 'NIV-dagen' (annual meeting for internists), Maastricht, the Netherlands	2018	10	
Medication use at the end of life, 'PRISMA symposium' (annual meeting for (hospital) pharmacists), Amersfoort, the Netherlands	2018	10	
Medication use at the end of life, 'research meeting public health' (Erasmus MC), Rotterdam, the Netherlands	2018	10	

Poster presentations		
Trends in do-not-resuscitate decisions in the Netherlands over the past 20 years, EAPC, Prague, Czech Republic	2013	5
Oromandibular dystonia: a serious side effect of capecitabine, NVKFB, Leiden, the Netherlands	2014	5
Sense and nonsense of treatment of comorbid diseases in terminally ill patients, EACPT, Madrid, Spain	2015	5
Understanding continuation of potentially inappropriate medications at the end of life: perspectives from patients, their relatives, and physicians, EAPC, Dublin, Ireland	2016	5

3. Educational activities and lecturing	Year	Workload	
		Hours	ECTS
Tutoring first year students curriculum Medicine, Erasmus MC	2014-2015		2
Lecture 'practical pharmacotherapy in the elderly patient', 5th year curriculum Medicine, Erasmus MC	2014-2015		2
Supervising Marlies Tempelman, research internship curriculum Medicine, Erasmus MC	2015-2016		2
Checking essays, 3th year curriculum Medicine, Erasmus MC	2015		1
Lecture 'discontinuation of drugs at the end of life', general practitioners, Renesse, Alkmaar, Purmerend, Santpoort	2016		2
Lecture 'pharmacodynamics and pharmacokinetics', bachelor 3, Erasmus MC	2014	10	
Lecture 'fatique', clinical reasoning, bachelor 1, Erasmus MC	2015	10	
Lecture 'medication use at the end of life, 'kennisdag palliatieve aandachtsvelders', Erasmus MC	2015	10	

Reviewing for scientific journals
Plos ONE, CMAJ, BMC Medical Ethics, Journal of Gerontology, Journal of Palliative Medicine, International Journal of Chronic Obstructive Pulmonary Disease, Dutch Journal of Medicine (NTvG), Dutch Flemish Journal of Palliative Care (NVTPZ)

Grants writing (co-author)		
Death rattle in the dying phase: is prophylactic treatment effective?	2015	5
Prudent medication management in the last phase of life	2018	3
Living well, dying well. A research programme to support living until the end	2018	3

Workgroup		
Workgroup 'treatment decisions', Reinier de Graaf Gasthuis, Delft, the Netherlands	2018	1
Workgroup 'treatment decisions', Nederlandse Internisten Vereniging (NIV)	2018	1
Module 'deprescribing' (part of guideline polypharmacy in the elderly people), Nederlandse Internisten Vereniging (NIV)	2018	1

Organising committee		
Symposium 'zuster en de dood' (two times), Ede, the Netherlands	2015-2016	2
Symposium 'grenzen aan de (ic-)zorg, Delft, the Netherlands	2018	1

Awards	
Best oral presentation at the 'compassion, care and clinical excellence in hospital palliative care conference' (Liverpool)	2017
Best initiative within theme 'risk management and ethics' at the annual Dutch efficiency conference (Leiden)	2018

Other		
Member editorial board, Dutch Flemish Journal of Palliative Care	2017-2018	1
Writing news items, Dutch Journal of Medicine (NTvG)	2015-2018	1

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Janneke, je bent mijn alles. Mijn drang om te excelleren is niet altijd gemakkelijk voor jou. En al helemaal niet in een periode waarin wij aan *baby bunching* hebben gedaan. Vanaf de eerste keer dat we elkaar ontmoetten ben ik zo verliefd op je. Ik hoop dat we met elkaar nog ontzettend veel plezier mogen beleven!

About the author

Eric Geijteman was born on October 7th 1982 in Alkmaar, the Netherlands. After graduating from the Petrus Canisius College in Alkmaar in 2001, he studied Human Movement Sciences and Nursing. From 2004 he studied Medicine at the VU University Medical Center, Amsterdam. During his study he worked as student assistant at the section Pharmacotherapy, part of the department Clinical Pharmacology and Pharmacy, at the VU University Medical Center. In 2010, he obtained his qualification as a Medical Doctor with cum laude honor. From July 2010 until July 2011, he worked as a resident at the department of Internal Medicine at the Medical Center Alkmaar. Next, he became involved in the research project 'second evaluation of the termination of life on request and assisted suicide act'. In February 2013, he started his PhD trajectory under supervision of Prof. dr. A. van der Heide, Prof. dr. C.C.D. van der Rijt, Prof. dr. T. van Gelder, and dr. C. van Zuylen. During his PhD trajectory he did a fellowship in Clinical Pharmacology under the supervision of Prof. dr. T. van Gelder. In the second half of 2015, he worked as a resident scientific editor at the Dutch Journal of Medicine (Nederlands Tijdschrift voor Geneeskunde). As of January 2016, he started with his medical specialist training at Reinier de Graaf Hospital, Delft (program director dr. H. Boom), and Erasmus MC University Medical Center, Rotterdam (program directors dr. S.C.E. Klein Nagelvoort-Schuit and dr. A.A.M. Zandbergen).