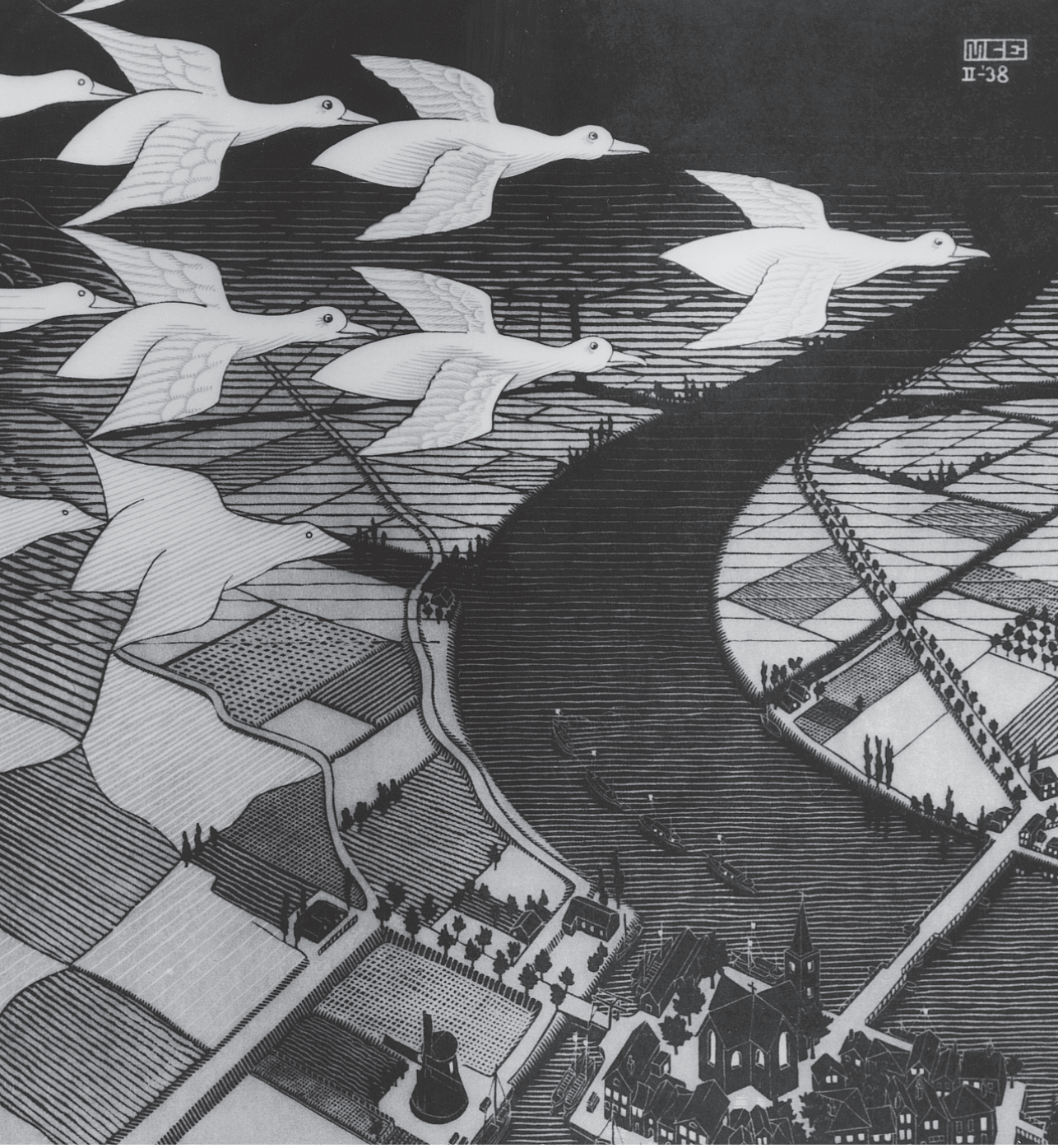

INEKE LOKKER

Acknowledging Different Perspectives

Burden and management of symptoms in the last phase of life

Acknowledging Different Perspectives

Burden and management of symptoms in the last phase of life

Martine Elizabeth Lokker

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Acknowledging Different Perspectives
Burden and management of symptoms in the last phase of life

Erkennen van verschillende perspectieven
Symptoomlast en -management in de laatste levensfase

Proefschrift

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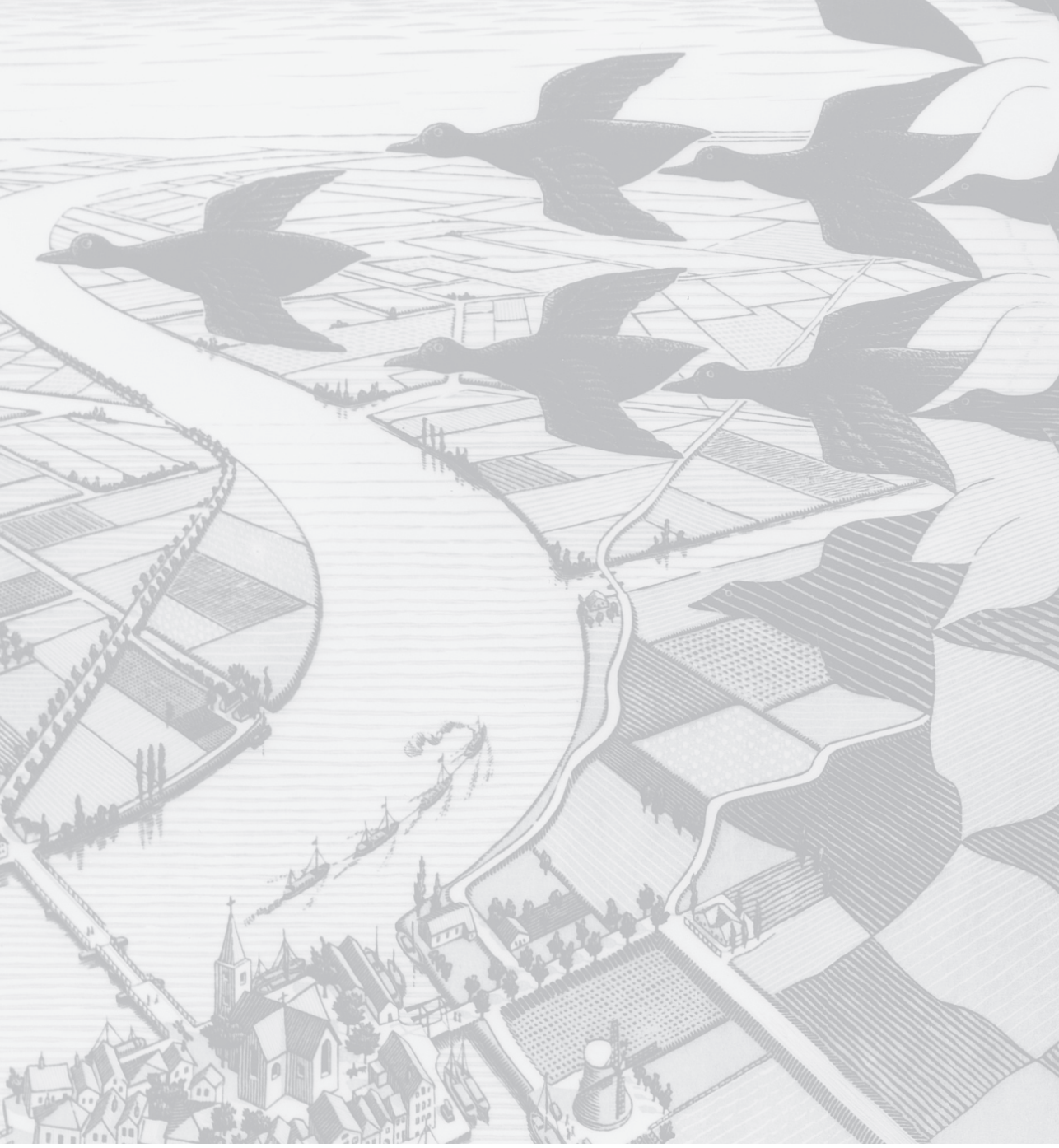
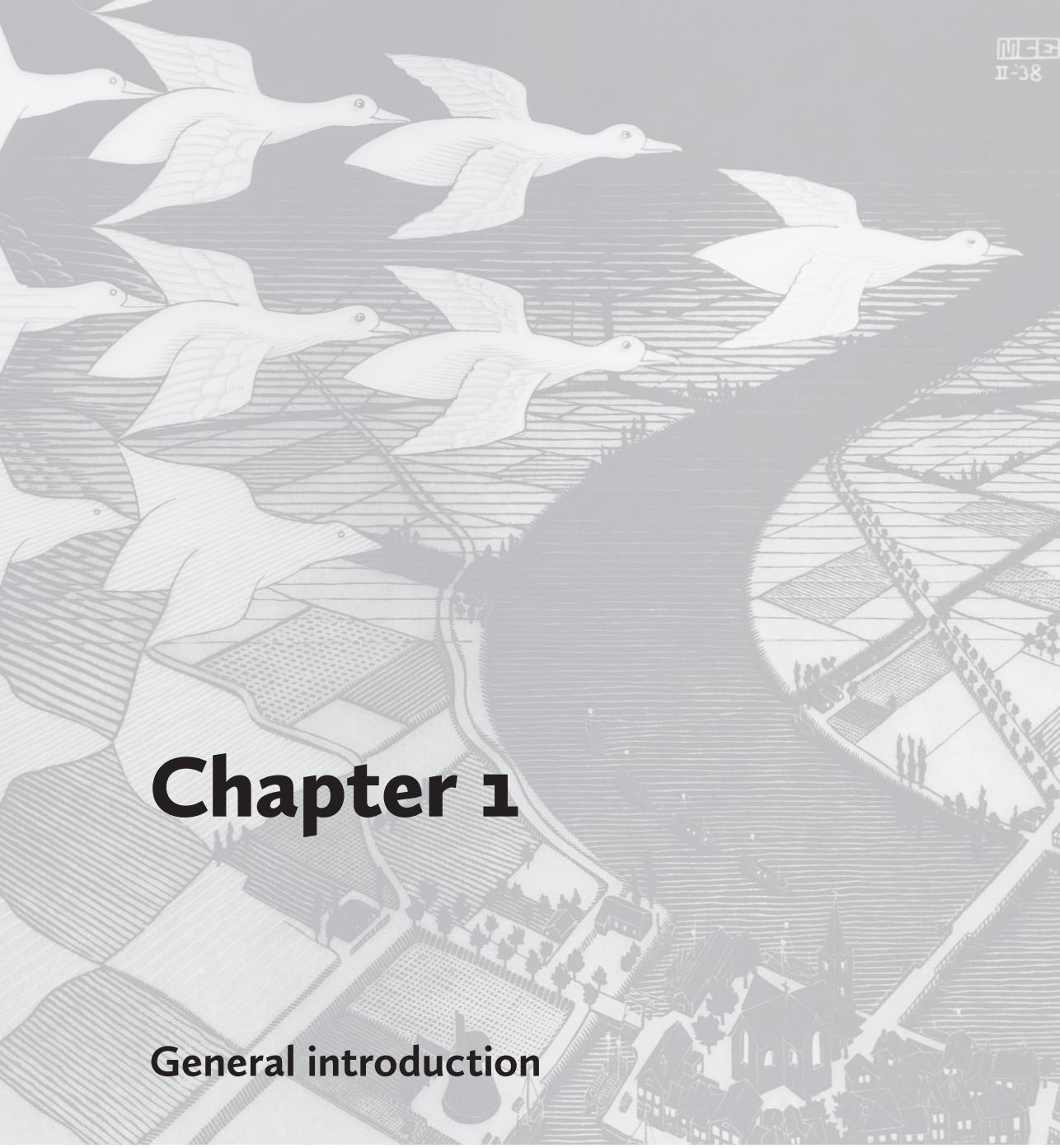
CONTENT





Chapter 1

General introduction

"Life is pleasant. Death is peaceful. It's the transition that's troublesome."
Isaac Asimov, American science fiction novelist & scholar (1920 – 1992)

Death comes to us all

At the beginning of the 20th century, death was often a sudden event, with infectious diseases, accidents and death in relation to childbirth as leading causes. Nowadays, sudden deaths are less common, especially in Western societies, where most people can anticipate death at an advanced age from a progressive illness which is preceded by a period of gradual decline[1,2]. Each year, 1.6 million patients in Europe will die from cancer and around 5.7 million from non-malignant chronic diseases[3]. In The Netherlands the total number of deaths in 2016 was approximately 149.000, of which 89.000 were non-sudden deaths[4,5]. Half of the patients (53%) die at home, 19% die in hospital and 28% in a nursing home[5].

Palliative care

As a chronic disease progresses, the emphasis in treatment goals shifts from prolonging life to preservation of quality of life[3]. This transition from curative care to palliative care is often a gradual process. The World Health Organization (WHO) defined palliative care in 2002 as "an approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual"[6]. It has been estimated that in high income countries, up to 82% of people who are approaching the end of life may benefit from palliative care[7].

Palliative care is mostly provided to patients suffering from advanced cancer, despite the fact that patients with a non-cancer diagnosis, like organ failure, neurological disease or dementia, may have the same palliative care needs as cancer patients[3,8]. Several studies have shown that early provision of palliative care can improve the quality of life of people with cancer or other life-threatening illnesses[9-11]. However, the start of palliative care is often delayed until the last weeks or days of life, when the disease is far advanced and disease focused treatments are no longer effective[12]. Three distinct trajectories of functional decline in patients with progressive chronic illness (see Figure 1[13]) have been described by Lunney et al, illustrating the characteristic dynamic patterns of patients with different underlying diseases[14]. The first trajectory, typically associated with cancer, involves a reasonably predictable decline in physical health over a period of weeks, months, or, in some cases, years, followed by a fast deterioration in the last few weeks. The second trajectory, typically associated with organ failure, features a gradual decline with intermittent severe symptomatic crises. Each exacerbation may result in death, but the patient may also survive several of such episodes. The third trajectory, typically associated with dementia or frailty, shows a

progressive erratic decline from an already low baseline of cognitive or physical functioning[13 14]. Insight into these trajectories can assist healthcare professionals in estimating when palliative care should commence. However, with multimorbidity, which has become the norm at the end of life, patients may present with a combination of one or more trajectories, making this estimation more complex[15].

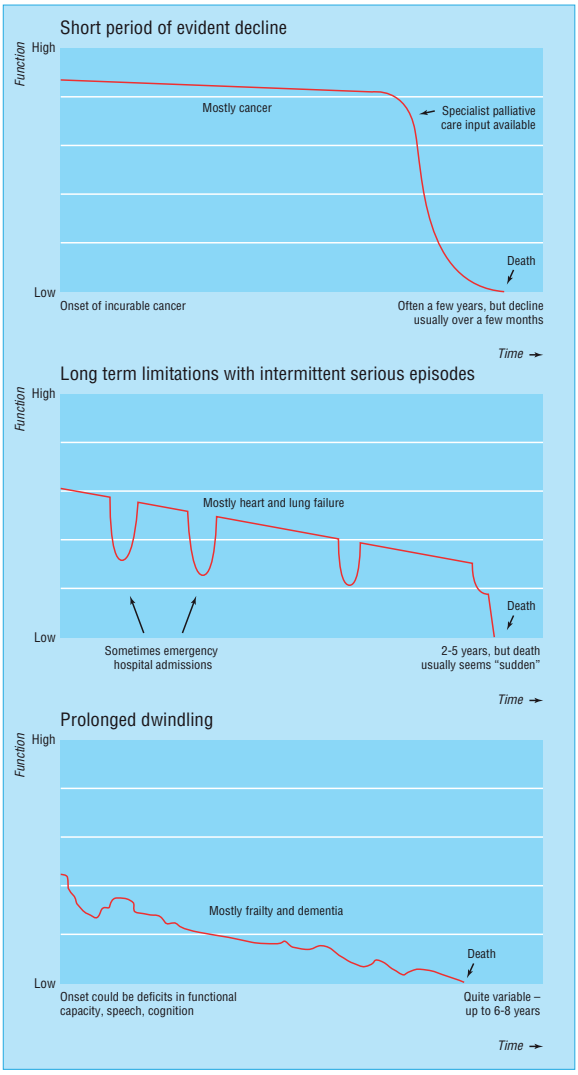


Figure 1, Typical illness trajectories for people with progressive chronic disease. From Murray et al., 2005

Symptoms

In order to deliver good palliative care it is important to know which symptoms may occur during a specific disease trajectory or disease phase and what their impact on daily

functioning is. The New Oxford Dictionary provides the following definition of a symptom: "A physical or mental phenomenon, circumstance or change of condition arising from and accompanying a disorder and constituting evidence for it." Symptom expression varies from patient to patient, depending on the individual patient's perception and on other factors, such as psychosocial issues. While symptoms are often addressed separately, patients frequently have multiple coexisting symptoms[16-18]. Moreover, when evaluating symptoms, it is important to be aware of their multidimensional nature. Evaluation of a symptom should not be limited to its mere presence but also includes its severity and/or impact. The mere presence of a symptom does not imply that it is distressing or that there is a need for action[16].

Symptoms in patients with advanced disease

The last 25 years, the number of studies focusing on symptoms in patients with advanced diseases has increased steadily (see figure 2). Symptom related aspects that are covered in these studies are the prevalence, burden (i.e. impact or distress) or management (i.e. symptom control or interventions) of symptoms; the development, validation or translation of tools for screening or assessment of symptoms; a focus on specific symptoms or specific diagnoses; symptom aspects in relation to specific locations of care, care providers, (palliative) care teams, countries or regions of the world; and comparisons between different symptom assessors (e.g. patients or proxies such as family members or healthcare professionals).

A number of systematic reviews on symptoms in patients with advanced diseases (i.e. cancer, chronic organ failure, dementia) have been published this last decade[19-21]. Teunissen et al. performed a review on symptom prevalence in patients with cancer which showed that during the palliative phase fatigue, pain, lack of energy, weakness and appetite loss were all highly prevalent symptoms, being present in more than 50% of patients[20]. Janssen et al. reviewed studies on the prevalence of symptoms in patients with advanced chronic organ failure and found that fatigue, dyspnoea, insomnia and pain were frequently reported in all patient groups[19]. Lastly, van der Steen showed that patients with advanced dementia are often reported as having pain, shortness of breath, discomfort, restlessness, and difficulty with swallowing[21]. There seems to be a certain degree of concordance when looking at highly prevalent symptoms in patients with different types of advanced disease.

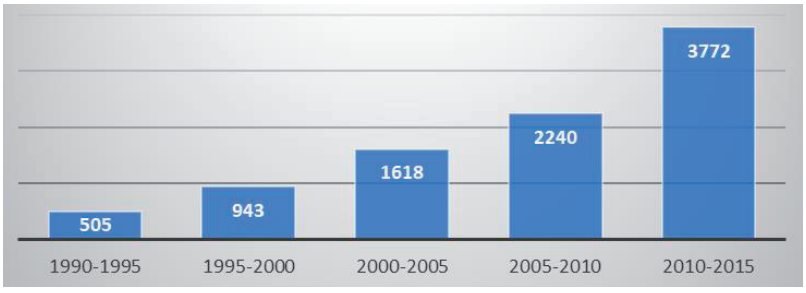


Figure 2 Number of published studies on symptoms in advanced diseases between 1990 and 2015 in English

Although the number of studies on symptoms in patients with advanced diseases increases, evidence remains scarce or lacking for some subgroups. Of the approximately 9000 studies published between 1990 and 2015 on symptoms in patients with advanced diseases, around 56% focused on symptoms in relation to cancer compared to 9% that focused on chronic organ failure (i.e. chronic heart failure, chronic obstructive pulmonary disease or chronic renal failure) and 2% that focused on dementia[22]. Furthermore, also in the studies in cancer, various cancer types were not evenly represented. Especially, patients with specific cancer types, as for example head and neck cancer, were barely studied. Moreover, almost all research has focused on patients in high-income countries[19 20 23 24], whether patients in developing parts of the world experience the same symptoms and functional limitations remains unclear.

Diagnosing dying and awareness of dying

Recognition of the dying phase (i.e. the phase when death is expected to occur within hours or days[25 26]) is an important prerequisite to enable patients and their families to prepare for their impending death and saying goodbye[27]. Being aware that death is imminent is often seen as one of the features of a good death in modern Western culture[28-31]. Awareness that a patient's death is imminent allows healthcare professionals to appropriately reset the goals of care to prevent possible harmful treatment. Diagnosing dying has been described as being partly 'art' and partly science[32]. On the one hand, it has been repeatedly shown that physicians are inaccurate in their prognoses for terminally ill patients. Mostly they overestimate patients' life expectancy, although more experienced physicians have shown to have greater prognostic accuracy[33 34]. On the other hand, nurses have been described as perceiving signs and symptoms of dying earlier than physicians do[35]. This seems to be related to the intensity, frequency and duration of their contact with patients. Besides spending more time with a patient, intuition or a 'sixth sense' have also been suggested to be part of nurses' assessment of imminent death[36 37]. Hence, a diagnosis of dying should preferably be established by physicians together with nurses, i.e. by an interdisciplinary team. It is not clear to what extent patients recognize their own dying.

Symptoms in the dying phase

Several studies have focused on the relation between symptoms and patients' impending death[38-41]. Rigorous scientific evidence on which signs or symptoms could indicate imminence of death is still lacking. Benedetti et al. performed a Delphi study to establish expert consensus on clinical phenomena indicating that a person will die within the next hours or days[42]. Death rattle, no food or fluid intake and changed breathing rhythm were judged by these experts as having the highest relevance.

A reduced oral intake is a common phenomenon at the end of life. This may be due to illness- or treatment-related symptoms or complications, such as dysphagia, nausea or vom-

iting, mechanical of functional obstruction in the digestive tract, generalized weakness, and in the last days of life by a decreased level of consciousness or a loss of desire to drink[43 44]. The evidence that artificial hydration may be beneficial when patients have a reduced oral intake at the end of life is limited and inconclusive[45-47]. Common arguments against artificial hydration are that it may increase the risk of complications such as oedema, ascites, and death rattle[43 48 49]. On the other side, artificial hydration has been suggested to reduce the risk of delirium or terminal restlessness[47 50 51]. To be able to provide good quality of care at the end of life it is important to know which symptoms or phenomena can occur, but also how symptoms or interventions interact.

Patients with an advanced disease (cancer or non-cancer) have been reported to experience many symptoms in their last week or days of life[52-62]. Pain (reported prevalence between 30%-60%)[20 52 56 58 60 62], shortness of breath (22%-62%)[20 52 56 58 60], restlessness (42%-51%)[52 62], dysphagia (16%-46%)[20 58], confusion (30%-68%)[56 57 60 62] and death rattle (39%-56%) [52 58] have all been reported to be common in the last week or days of life. Insight into commonly occurring symptoms in the dying phase enables healthcare professionals to be proactive in the care they provide and enables them to explain to patients and family members what they can expect during the dying phase.

AIM AND OVERVIEW OF THE THESIS

In this thesis, we focus on the impact of symptoms in the last phase of life. The studies described in this thesis were aimed at providing insight into various aspects of symptoms and symptom relief during the last phase of life. The following research questions will be addressed:

Research question 1 *What is the prevalence and impact of symptoms in two understudied patient groups: patients with incurable head and neck cancer and patients in a developing country with advanced heart failure?*

To answer this research question data were used from two survey studies.

To explore the prevalence and impact of symptoms in patients with incurable head and neck cancer, a cross-sectional descriptive study was performed at Erasmus MC. This study consisted of two parts. First, data from questionnaires filled in by patients between October 2006 and October 2008 as part of normal care were used to establish symptom prevalence for 30 symptoms, of which 9 psychosocial. Second, data were prospectively gathered from February 2009 up to May 2009 to establish the impact of those 30 symptoms for patients and potential discrepancies between the ratings from patients and their family caregivers (see chapter 2).

To explore the prevalence and burden of symptoms in patients with advanced heart failure in a developing region of the world, a cross-sectional observational study was performed at Groote Schuur Hospital in Cape Town, South Africa. Patients were recruited for this study between August and November 2012 from several inpatient facilities (i.e., an emergency unit, emergency ward, cardiology ward, and general medicine wards) and the outpatient cardiology clinic. Patients provided information on symptom prevalence of 28 physical and 4 psychological symptoms and the associated burden (see chapter 3).

Research question 2 *What is the prevalence and impact of death rattle and terminal restlessness and does fluid intake influence their occurrence?*

To answer this research question, first a systematic review focused on death rattle was performed in 2012. Several databases were searched for empirical studies on death rattle. We investigated which labels and definitions of death rattle were used, the prevalence of death rattle, the impact of death rattle on patients, relatives, and professional caregivers, and effects of medical and nonmedical interventions (see chapter 4).

As fluid intake is suggested to be related to the occurrence of death rattle and terminal restlessness, a multicentre prospective observational study was performed. Data were collected in 8 hospitals (one to three wards per hospital) and five hospices, including three palliative care units in nursing homes (PCUs), in the Netherlands. Data collection took place between November 2012 and November 2013 in patients who were, according to the multidisciplinary care team, likely to die within a few days. Data were collected using a digital version of the Care Program for the Dying (CPD), which was supplemented for this study with questions about death rattle, terminal restlessness, use of opioids and patients' fluid intake (see chapter 5). The CPD, a Dutch instrument for multidisciplinary care can be used to support care and symptom management during the last days of life. The CPD was originally based on the Liverpool Care Pathway for the dying patient[63] and adapted to the Dutch language and healthcare system. The CPD is started when the multidisciplinary team agrees that the patient is likely to die within a few days. The CPD is a template for multidisciplinary care in the last few days to hours of life and consists of three parts in which different data are recorded by doctors and nurses[64]. The care program assesses the physical, psychological, social, spiritual/religious and information needs of patients and relatives at 4 hourly intervals[59 64]. Between 2010 and 2012 a digital version of the CPD was developed in the Netherlands to comply with the need for digitalization in healthcare

Research question 3 *To what extent are patients aware of the imminence of their death?*

To answer this research question, we performed a secondary analysis of data that were collected in a study that investigated the effect of using the CPD on the care and quality of

life during the last 3 days of life. Patients were recruited from hospitals, nursing homes and home care services and data collection took place between November 2003 and February 2006. Nurses and family caregivers were requested to fill out a questionnaire with questions about the last 3 days of life. Both groups were asked whether a patient had been aware of the imminence of death. Also, medical records were screened for statements indicating that the patient had been informed of the imminence of death (see chapter 6).

Research question 4 *Do nurses experience moral distress in relation to the practice of palliative sedation?*

Patients who are nearing death sometimes experience symptoms that cannot be relieved with conventional therapeutic interventions, such as intractable pain, dyspnoea, and delirium[65 66]. Palliative sedation is a medical intervention used to alleviate unbearable and refractory suffering in the last phase of life by the deliberate lowering of a patient's level of consciousness to induce decreased awareness of symptoms[67-69]. Palliative sedation is a practice of last resort and is therefore often used in complicated cases, under stressful conditions and with time constraints, it has been linked to (emotional) burden for nurses[68 70-74]. To answer this research question, a secondary analyses of qualitative interview data was performed. Qualitative interviews with nurses were collected as part of a larger project about the practice of palliative sedation in the Netherlands after the introduction of a national guideline on palliative sedation. Nurses were interviewed between October 2008 and April 2009. Analyses were performed with the constant comparative method. (see chapter 7).

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nose specific we added (cancer OR neoplasms), ((heart OR organ OR kidney OR renal OR lung) AND failure) OR (CHF OR Copd OR CRF)) OR (Dementia).

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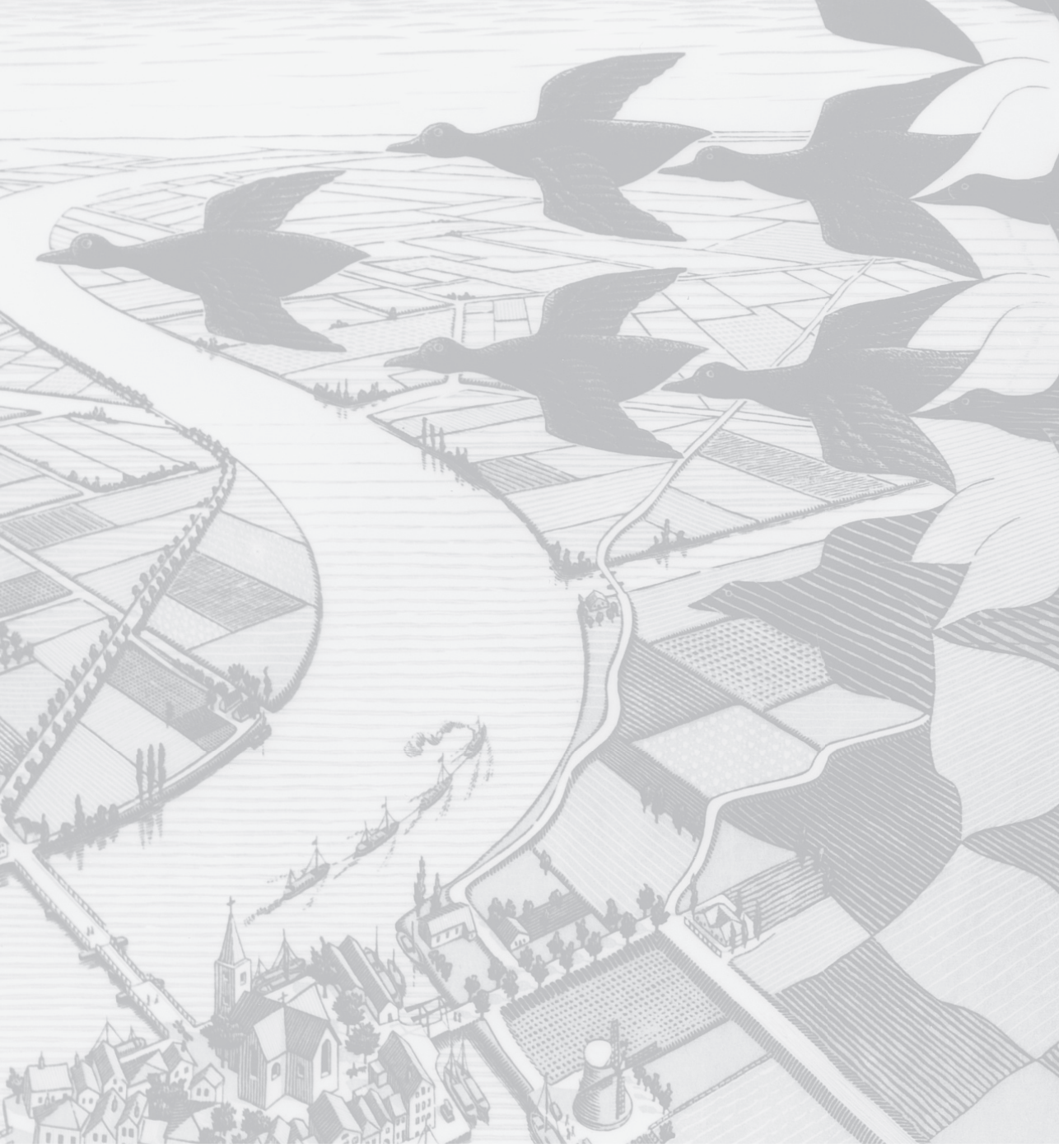

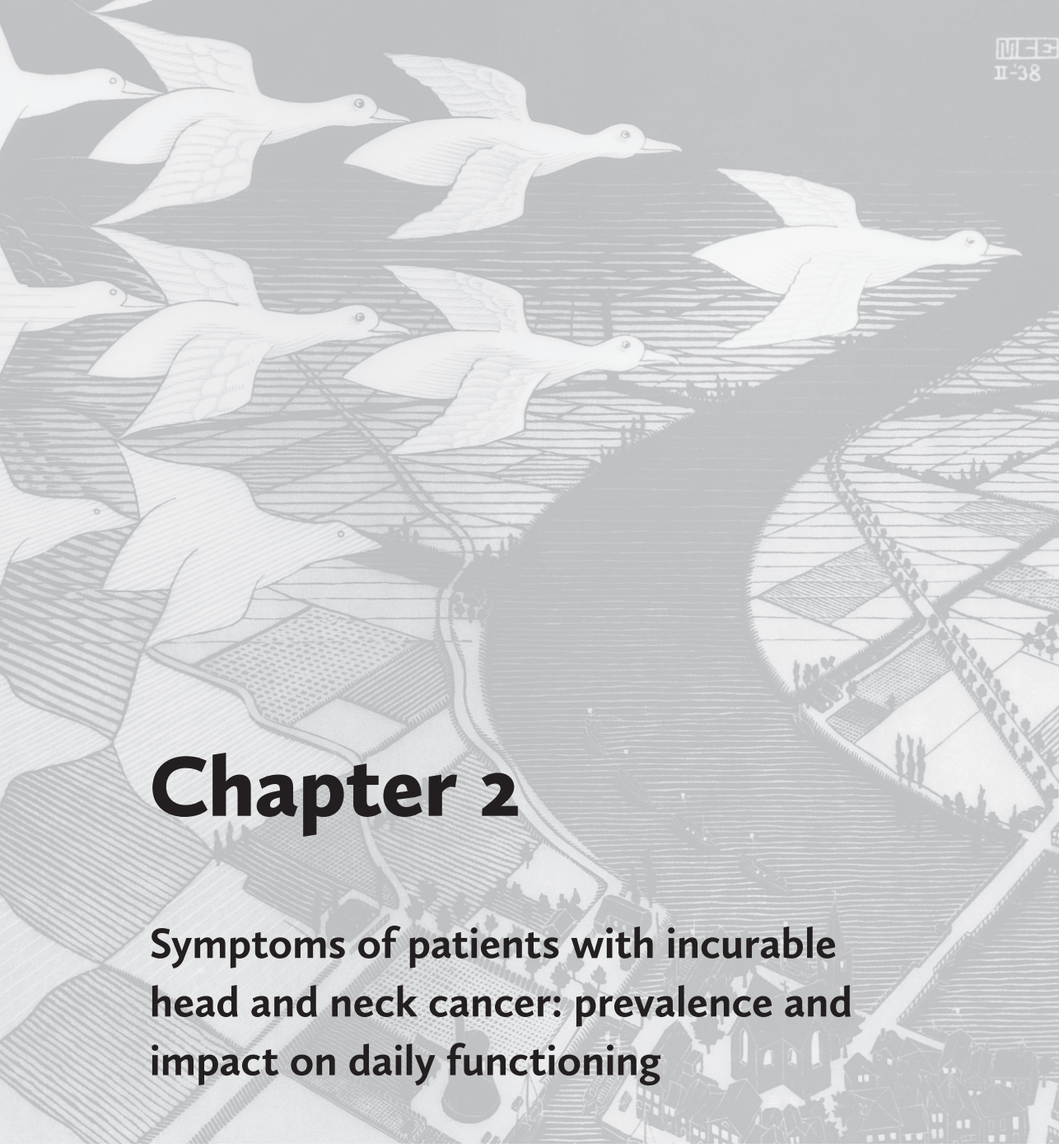

Chapter 2

Symptoms of patients with incurable head and neck cancer: prevalence and impact on daily functioning

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ABSTRACT

Background. There is lack of research on symptoms in patients with head and neck cancer in the palliative phase. The aim of this study was to explore symptom prevalence and the impact of these symptoms on daily functioning in patients with incurable head and neck cancer. Also, discrepancies between patients and family caregivers are described.

Methods. Questionnaires were used to collect data about symptom prevalence (N=124) and symptom impact (N=24).

Results. We discovered that the symptoms with a high prevalence were fatigue, pain, weakness, trouble with short walks outside, and dysphagia. The symptoms with the greatest impact on daily functioning were dyspnoea, voice changes, trouble with short walks outside, anger and weakness.

Conclusions. Patients with incurable head and neck cancer experience a great number of different symptoms. Focus on these symptoms by healthcare professionals could further optimize symptom management. In future research, we recommend further validation of the used questionnaires.

INTRODUCTION

Head and neck cancer is known as a psychological highly traumatic cancer type[1]. This is due to potential negative effects of the tumour itself and its treatment on various functions, such as swallowing, speaking, tasting, and smelling, as well as on the appearance of a patient. Head and neck cancer is the fifth most common cancer type worldwide and the most common neoplasm in central Asia[2]. In the United States, head and neck cancer accounts for 3% of malignancies; in The Netherlands, it accounts for nearly 5%[3 4]. The average age of patients affected with head and neck cancer is 63 years. More than two thirds of this patient group is men[4]. Significant risk factors for the occurrence of head and neck cancer are the use of tobacco and alcohol[5].

Approximately 25 to 30% of patients with head and neck cancer will at a certain moment reach the palliative phase[3 6]. Knowledge about experiences in the palliative phase of head and neck cancer is limited[7]. The palliative phase begins when cure is no longer possible or when curative treatment is refused and ends with the patient dying[8]. Earlier research among palliative patients with head and neck cancer showed a mean duration for the palliative phase of approximately 6 months[7]. During this phase, the number and intensity of symptoms can influence the quality of life of a patient negatively. Palliative care aims to improve the quality of life of patients and their family caregivers by adequately dealing with occurring symptoms, known as "symptom management"[9]. In this research, symptoms are defined as all complaints expressed by a patient as a result of a progressing disease or the consequences of the treatment for that disease. Patients with cancer in the palliative phase are frequently confronted with multiple and simultaneously occurring symptoms[10-15]. A systematic review of the literature (2007)[16] about symptom prevalence in patients with cancer in general during the palliative phase, revealed 5 somatic symptoms occurring in more than 50% of patients during the palliative phase. These somatic symptoms were: fatigue, pain, lack of energy, weakness and appetite loss. However, this research only included a very small group of patients (5%) suffering from a head and neck tumour Therefore, the possibility to generalize the results from this review to the entire population of patients with head and neck cancer patients is limited.

In another article (1997) [13] on symptom prevalence, patients with head and neck cancer were included, however, this research focused on somatic symptoms only in the terminal phase. The 5 most frequently reported symptoms were: weight loss, pain, feeding difficulties, dysphagia and cough. Symptoms in the very last part of the palliative phase (the terminal phase), however, are not fully representative for the entire palliative phase. This is confirmed by a review of patients with cancer in general[16], showing a difference between the prevalence of symptoms occurring in the last 2 weeks of living and symptoms that occur during the period prior to those weeks Research among patient with head and neck cancer in general also indicates that, besides somatic issues, more than one third of patients are

also confronted with psychological problems[17]. In a recent study of surviving relatives of patients with head and neck cancer, two thirds of the relatives claimed that the patient was depressed and had a need for better psychosocial support during the palliative phase[6]. When it comes to symptom report, earlier research suggests that family caregivers in comparison with patients often over-estimate patient symptoms[18-21]. These studies, however, did not include patients with head and neck cancer.

In order to deliver good healthcare, it is important to know which symptoms occur during a specific disease or disease phase, as well as the extent of their impact on daily functioning. In this article, "symptom impact" refers to: "the impact that symptoms have on daily functioning of an individual patient." The premise is that such an impact is either neutral or negative.

The current study focused on: (1) the prevalence of symptoms in patients with head and neck cancer during the palliative phase; (2) the impact of those symptoms on daily functioning of patients; and (3) discrepancies between patients and family caregivers with reference to how they individually score the occurrence of symptoms as well as their evaluation of the impact on daily functioning.

MATERIALS AND METHODS

Design

This cross-sectional descriptive study consists of a retrospective and a prospective element. The first research question was answered by making use of retrospectively collected data. The other 2 questions were answered by examining prospective data. This study was approved by the Medical Ethics Committee of the Erasmus Medical Centre Rotterdam.

Setting

At the Erasmus Medical Centre Rotterdam, a university medical centre in The Netherlands treating around 600 patients newly diagnosed with head and neck cancer every year, palliative care is given by a specialist palliative team for patients with head and neck cancer. This team consists of head and neck surgeons, specialized nurses, speech therapists, pain specialists, dietitians, social workers, and clergymen. Each year, approximately 130 new patients are registered by the palliative team. Since October 2006, as part of the standard working procedure, data is structurally gathered from patients with an head and neck tumour in the palliative phase. Since that date, all new patients are being requested by the specialized nurses to fill out a questionnaire, the Palliative Checklist (Pal-C), once during their palliative phase. In most cases, this happens shortly after receiving the diagnosis of their palliative status.

Follow-up of patients by the palliative team is done regularly, both in the outpatient clinic as well as by telephone. During about half of these medical telephone contacts, the family

caregiver speaks on the patient's behalf. This occurs because of issues such as difficulties with speech, pain and physical weakness of the patient.

Participants and procedure

Patients with a primary head and neck tumour in the palliative phase treated in the Erasmus Medical Centre Rotterdam were included. Patients who were younger than 18 years, unable to speak or write in Dutch, mentally incompetent or participating in another study at the same time were excluded. Participants were divided into 2 groups: the prevalence group and the symptom impact group.

The prevalence group

This group consists of all patients who completed a Pal-C (instrument described in detail below) between October 2006 and October 2008.

The symptom impact group

For this prospective part of our study, patient's main family caregivers were also included. Because of the limited number of available patients and the limited average life expectancy, a convenience sample was chosen. From February 2009 up to May 2009, patients were approached by the specialized nurses of the palliative team. After they had given written informed consent, participants were requested to separately fill out a questionnaire which is called the Palliative Symptom Impact list (Pal-SI), as mentioned below.

Data collection

The prevalence group

Sociodemographic data was gathered from the electronic patient file. Prevalence of symptoms was measured using the Pal-C. This questionnaire provides insight into the prevalence of 30 separate symptoms. The Pal-C was developed in 2006 by the Expert Centre of Palliative Care for Head and Neck Cancer of the department of Otorhinolaryngology and Head and Neck surgery of the Erasmus Medical Centre in Rotterdam. The instrument consists of 53 questions, of which the first 15 questions are from the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 15- Palliative (EORTC QLQ-C15-PAL)[22 23]. The remaining 38 questions of the Pal-C are based on the Integral Checklist[24]. The Integral Checklist is a questionnaire that was developed as an instrument for systematic screening of psychosocial and physical problems in ambulatory patients with cancer. The Pal-C is meant to obtain an impression of the situation as experienced by the patient during the past week. The Integral Checklist has been used previously in a study with patients with cancer in all phases of disease, including patients with head and neck cancer [24]. Completion of the questionnaire requires approximately 20 minutes The Pal-C, in its current form, has not been tested on validity and/or reliability. However, the Pal-C was primarily used to

support the gathering of information about the patient's health in a nonburdensome way and turned out to be a very practical instrument for that purpose and for referral to other specialists.

The symptom impact group

Sociodemographic data of patients was gathered from the electronic patient file. Caregivers sociodemographic data; sex, relationship to the patient, and age, were gathered by making use of questionnaires. Impact of symptoms was measured using the Pal-SI. This instrument was developed, for this study, by the Expert Centre of Palliative Care for Head and Neck Cancer of the department of Otorhinolaryngology and Head and Neck surgery of the Erasmus Medical Centre in Rotterdam. To enable comparison of data, the Pal-SI covers the same symptoms and uses equal formulation as in the Pal-C. The Pal-SI consists of 2 parts. Part A contains the 30 symptoms from the Pal-C. By answering "yes" or "no", the patient can indicate whether or not the specific symptom occurred in the previous week. In part B, the patient is asked to rate all symptoms present on an 11 point numeric scale (NMS), indicating the impact of a specific symptom on daily functioning. (0= "no impact", 10= "unbearable impact").

Specifically for family caregiver's, a family caregiver's version of the Pal-SI was available. This version differs from the original Pal-SI on 2 aspects: (1) to prevent missing values, the answer option "do not know" was added; and (2) all questions were formulated from the perspective of the family caregiver (i.e. instead of asking: "Have you had pain?", the family caregiver's version states "Do you think the patient had pain?". It took approximately 15 minutes to complete the Pal-SI.

Statistical analysis

The sociodemographic data, the prevalence of symptoms, and the impact of those symptoms were described by way of descriptive statistics. The sociodemographic data of patients from the prevalence group were statistically tested using the independent samples *t* test (age), chi-square test (sex, tumour location, and treatment) and the Mann-Whitney test (duration of palliative phase).

The sociodemographic data with reference to the patients from the symptom impact group were statistically tested using the Mann-Whitney test. In order to compare the prevalence and the symptom impact data of the patients and their family caregivers per pair, the Wilcoxon matched pairs test was performed.

Nonparametric tests were used when data was not normally distributed. With reference to the symptom impact group, this was the result of the limited number of cases. The significance level was set at 5%. For the analysis of the data, the statistics program SPSS version 14.0 was used.

RESULTS

Description of "prevalence group"

Between October 2006 and October 2008, 310 new patients were registered with the specialized nurses for palliative care. After exclusion, 220 patients were approached, of which 124 (56%) completed the Pal-C. Two percent of questions were not filled in. The reasons for exclusion and nonresponse are indicated in Figure 1.

Refer to Table 1 for sociodemographic data. Patients who completed a Pal-C (Pal-C+) were significantly different from those who did not complete a Pal-C (Pal-CΘ) on 3 aspects. The Pal-C+ group (1) consisted of more men; (2) were subjected to more extensive palliative treatment; (3) their duration of the palliative phase was longer, with a median discrepancy of more than 100 days.

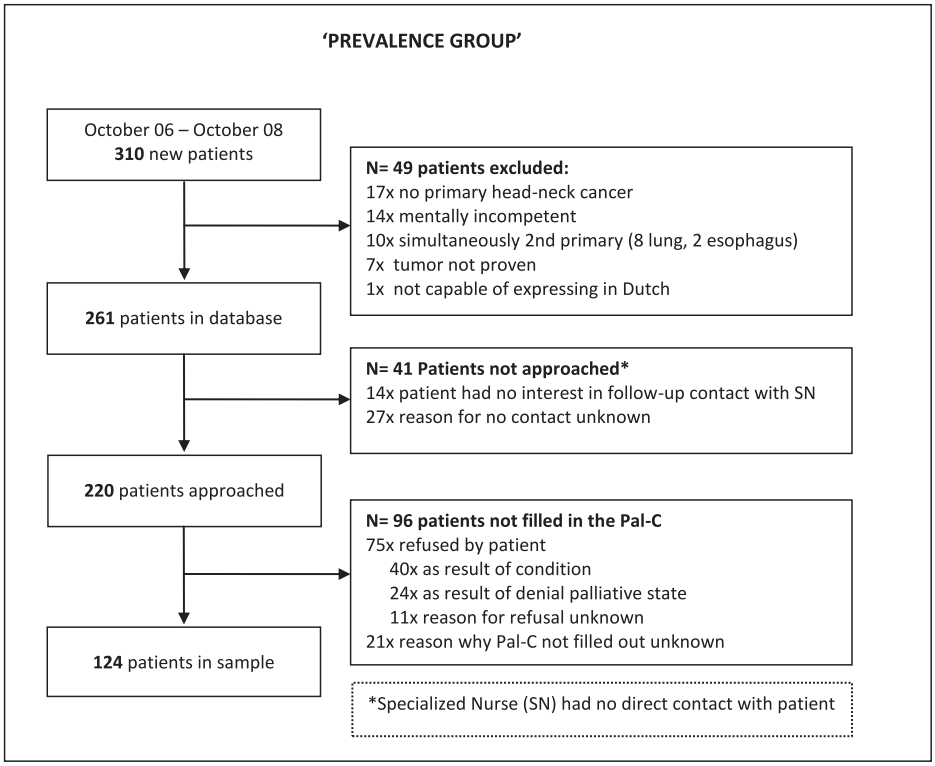

Figure 1. Prevalence Group

Description of "symptom impact group"

Between February 2009 and May 2009, 116 new patients were registered with the specialized nurses. Of the total of 56 patients who met all the inclusion criteria, 24 patients (43%)

Table 1. Socio-demographic data Prevalence Group

Characteristic	% (no. of patients) by group*				P value	
	Pal-C+ group (n=124)		Pal-CΘ group (n=137)			
Age, average (interval)	68 (39-90 y)		66 (28-98 y)		.203	
Sex						
Male	73 (91)		61 (83)		.019	
Female	27 (33)		39 (54)			
Location of Tumour						
Oral cavity	24 (30)		20 (28)		.724	
Oropharynx	26 (32)		30 (41)			
Larynx	11 (14)		13 (18)			
Hypopharynx	13 (16)		14 (19)			
Nasopharynx	2 (3)		2 (3)			
Nasal fossa	11 (14)		6 (8)			
Other †	12 (15)		15 (20)			
Treatment	All phases	Palliative phase	All phases	Palliative phase	A	P
No treatment	8 (10)	50 (62)	17 (23)	70 (96)	.067	.017
Surgery	2 (3)	2 (2)	3 (4)	0 (0)		
Radiotherapy (RT)	32 (39)	35 (43)	19 (26)	22 (30)		
Chemotherapy (CT)	0 (0)	7 (8)	0 (0)	6 (8)		
Surgery + RT	35 (43)	2 (2)	33 (45)	0 (0)		
Surgery + CT	1 (1)	0 (0)	0 (0)	1 (1)		
Surgery + RT + CT	7 (9)	1 (1)	15 (21)	0 (0)		
CT + RT	15 (19)	5 (6)	13 (18)	2 (2)		
Time interval between start of pall phase and Pal-C median (interval)	61 days (0-1682)		X			
Duration palliative phase	169 days (9-2621) ‡		62 days (1-652)§		.000	

Abbreviation: Pal-C, Palliative Checklist; CT, chemotherapy; RT, radiotherapy.

* Except as otherwise stated.

† Tumours of the skin, salivary glands, ear, and trachea.

‡ Based on 109 patients.

§ Based on 128 patients.

and 24 family caregivers completed a Pal-SI. For 3% of the questions, no answer was given. The reasons for exclusion and nonresponse are indicated in Figure 2.

Refer to Table 2 for sociodemographic data. Patients from the Pal-SI+ group were not significantly different from the patients of the Pal-SIΘ group. Family caregivers were, on average, 60 years old (32-77 years). Their relation to the patient was that of the husband/wife (17), daughter/son (5), friend (1) and brother (1).

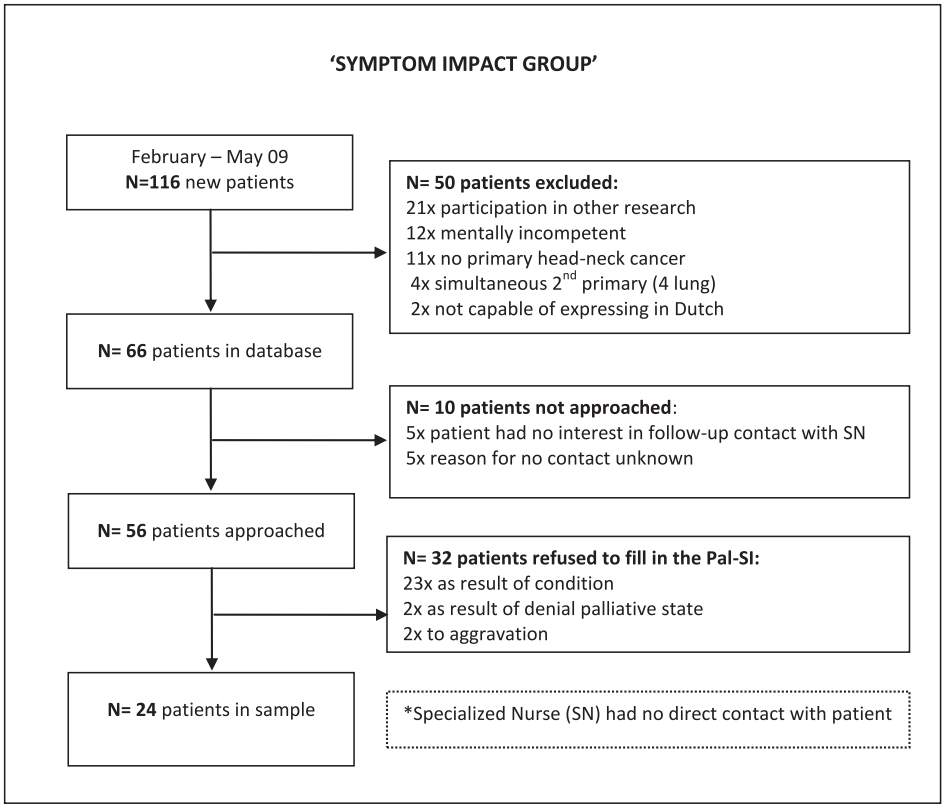

Figure 2. Symptom Impact Group

Prevalence of symptoms in "prevalence group"

All results obtained from the Pal-C are described in Table 3. Patients reported an average of 14 different symptoms (interval 0-26), of which there were 10 somatic symptoms and 4 psychosocial symptoms. Fatigue had the highest prevalence (81%), followed by pain (75%), weakness (75%), trouble with short walks outside (65%) and dysphagia (59%). Frequently reported psychosocial symptoms were worrying (61%), sadness (57%), tenseness (52%), depressed mood (52%) and powerlessness (50%).

Prevalence of symptoms in "symptom impact group"

All results obtained from the Pal-SI are described in Table 4. The patient and his/her family caregiver differed significantly from one another for the occurrence of 4 symptoms: difficulty sleeping (patient 29% vs caregiver 13%; p= .046), dyspnoea (21% vs 42%; p= .025), powerlessness (75% vs 46%; p= .046) and anxiety (29% vs 50%; p= .034).

Table 2. Socio-demographic data Symptom Impact Group

Characteristic	% (no. of patients) by group				P value	
	Pal-SI + group (n=24)		Pal-SIΘ group (n=42)			
Age, average (interval)	66 (29-90 y)		67 (38-98 y)		.957	
Sex						
Male	50 (12)		64 (27)		.260	
Female	50 (12)		36 (15)			
Tumour location						
Oral cavity	33 (8)		21 (9)		.823	
Oropharynx	17 (4)		19 (8)			
Larynx	8 (2)		14 (6)			
Hypopharynx	4 (1)		12 (5)			
Nasopharynx	0 (0)		5 (2)			
Nasal fossa	17 (4)		12 (5)			
Other *	21 (5)		17 (7)			
Treatment	All phases	Palliative phase	All phases	Palliative phase	A	P
No treatment	4 (1)	38 (9)	10 (4)	45 (19)	.797	.615
Surgery	4 (1)	4 (1)	2 (1)	2 (1)		
Radiotherapy (RT)	21 (5)	42 (10)	21 (9)	38 (16)		
Chemotherapy (CT)	0 (0)	13 (3)	0 (0)	10 (4)		
Surgery + RT	42 (10)	0 (0)	41 (17)	0 (0)		
Surgery + CT	0 (0)	0 (0)	2 (1)	0 (0)		
Surgery + RT + CT	17 (4)	4 (1)	12 (5)	0 (0)		
CT + RT	13 (3)	0 (0)	12 (5)	5 (2)		
Time interval between start of pall phase and Pal-SI, average (interval)	270 days (17-1024))		X			

Abbreviation: Pal-SI, Palliative Symptom impact list; CT, chemotherapy; RT, radiotherapy.
* Tumours of the skin, salivary glands, ear, and trachea

Impact on daily functioning from "symptom impact group"

According to the patients, dyspnoea, voice changes, trouble with short walks outside, anger, and weakness, all had, in decreasing order, a large impact on daily functioning. The score for the symptom impact on daily functioning of the patient differed significantly between the patients and their family caregivers on 5 symptoms: trouble with short walks outside (patient NMS 5,5 vs caregiver NMS 6,7 p= .047), difficulty sleeping (4,7 vs 5,3; p= .042), powerlessness (4,4 vs 3,8; p= .031), trouble expressing oneself (3,3 vs 4,9; p= .014) and anxiety (5,1 vs 4,5; p= .015).

Table 3. Prevalence of symptoms n=124 from the Pal-C

Symptoms	% of patients	(no./total no. of patients)	Symptoms	% of patients	(no./total no. of patients)
Fatigue	81	(101/124)	Dyspnoea	41	(51/123)
Pain	75	(93/123)	Coughing after eating/ drinking	38	(47/122)
Weakness	75	(93/123)	Need for help with everyday functioning	30	(37/123)
Trouble with short walks outside	65	(81/123)	Nausea	29	(36/121)
Dysphagia	59	(73/123)	Wound in neck or face	22	(27/124)
Difficulty speaking	57	(71/123)	Unpleasant smell/ stench	19	(24/123)
Difficulty sleeping	56	(70/124)	Worrying*	61	(75/118)
Head and Neck oedema	56	(69/122)	Sadness*	57	(71/118)
Daily activities restricted as result of pain	53	(66/121)	Depressed mood*	52	(65/123)
Weight loss	53	(66/124)	Tenseness*	52	(65/122)
Voice changes	52	(64/123)	Powerlessness*	50	(62/117)
Constipation	48	(60/123)	Anger*	39	(48/116)
Shortness of breath	48	(59/123)	Anxiety*	32	(39/117)
Need to stay in bed/ chair during day	48	(59/123)	Trouble expressing oneself*	24	(30/118)
Appetite loss	53	(66/119)	Feelings of shame*	12	(15/118)

Abbreviation: Pal-C, Palliative Checklist. * Psychosocial symptoms.

DISCUSSION

In the first part of this research, we explored symptom prevalence in 124 patients with incurable head and neck cancer. Within this sample, "fatigue" was the somatic symptom most prevalent (81%), followed by pain (75%), weakness (75%), trouble with short walks outside (65%) and dysphagia (59%). To our knowledge, no comparative figures are known for symptom prevalence in patients with incurable head and neck cancer. Prior studies among head and neck cancer survivors, a few years after their curative treatment, indicate diverging percentages for the prevalence of fatigue (33 to 48%)[25 26], pain (10 to 43%)[25-28], and dysphagia (17 to 76%)[25-28]. For the prevalence of weakness and trouble with short walks outside, no comparative figures were found. We hypothesize that symptoms experienced by patients in the palliative phase are not consistent with those experienced by cancer survivors because of the difference of disease phase, location/ presence of the tumour, and tumour treatments.

The 4 most prevalent symptoms experienced by patients with head and neck cancer in the palliative phase are consistent with the results of a systematic review in 25,074 patients with cancer in general, during the palliative phase.[16]. Despite a probable difference in aetiol-

Table 4. Results Symptom Impact Group n=24 from the Pal-SI

Symptoms	Prevalence, % (n)		P value	Symptom impact, average (interval)		P value
	Patients	Close relatives		Patients	Close relatives	
Somatic						
Trouble with short walks outside	25 (6/24)	38 (9/24)	.083	5,5 (2-9)	6,7 (3-9)	**.047**
Need to stay in bed/chair during day	21 (5/24)	25 (6/24)	.317	3,8 (1-6)	4,8 (1-8)	.102
Need for help with everyday functioning	13 (3/24)	13 (3/24)	1.00	4,0 (3-5)	5,0 (5)	.180
Shortness of breath	38 (9/24)	33 (8/24)	.705	3,4 (1-7)	4,5 (2-8)	.561
Pain	54 (13/24)	58 (14/23)	.317	4,9 (2-10)	5,5 (1-10)	.109
Difficulty sleeping	29 (7/24)	13 (3/24)	**.046**	4,7 (1-10)	5,3 (2-10)	**.042**
Weakness	42 (10/23)	50 (12/22)	.705	5,2 (1-1-0)	4,6 (1-10)	.476
Appetite loss	21 (5/23)	13 (3/23)	.059	5,0 (1-8)	6,0 (2-8)	.414
Nausea	25 (6/24)	17 (4/22)	.317	3,4 (1-5)	2,0 (1-3)	.223
Constipation	21 (5/24)	25 (6/22)	.564	4,8 (2-10)	4,8 (2-10)	.102
Fatigue	92 (22/24)	79 (19/23)	.317	4,5 (1-10)	4,8 (1-10)	.796
Daily activities restricted as result of pain	33 (8/24)	25 (6/23)	.317	5,0 (1-10)	4,5 (2-6)	.313
Head and Neck oedema	25 (6/23)	29 (7/22)	.655	4,3 (1-7)	4,9 (1-10)	.465
Wound in neck or face	13 (3/24)	17 (4/23)	.564	5,0 (5)	5,3 (3-9)	.102
Unpleasant smell/ stench	4 (1/24)	17 (4/24)	.083	5,0 (5)	4,3 (2-6)	.068
Dyspnoea	21 (5/24)	42 (10/24)	**.025**	7,0 (3-10)	4,6 (1-8)	.234
Difficulty speaking	54 (13/24)	54 (13/24)	1.00	4,9 (2-10)	4,7 (1-9)	.648
Dysphagia	54 (13/23)	42 (10/22)	.405	5,0 (1-10)	6,2 (3-10)	.813
Coughing after eating/drinking	33 (8/23)	42 (10/24)	.666	4,1 (1-7)	5,0 (1-10)	.055
Voice changes	38 (9/24)	50 (12/24)	.257	5,9 (1-10)	4,8 (1-10)	.698
Weight loss	25 (6/24)	29 (7/23)	.317	3,8 (1-8)	4,9 (1-8)	.131
Psychosocial						
Tenseness *	38 (9/24)	33 (8/23)	1.00	3,9 (1-10)	4,1 (2-6)	.858
Depressed mood *	46 (11/24)	38 (9/21)	.317	3,9 (2-7)	3,1 (2-5)	.088
Powerlessness *	75 (18/24)	46 (11/21)	**.046**	4,4 (1-10)	3,8 (2-7)	**.031**
Worrying *	63 (15/24)	63 (15/21)	.083	4,4 (1-8)	4,4 (1-8)	.368
Trouble expressing oneself*	25 (6/24)	42 (10/23)	.157	3,3 (2-7)	4,9 (2-8)	**.014**
Feelings of shame*	13 (3/24)	4 (1/24)	.317	2,3 (1-5)	2,0 (2)	.461
Anxiety *	29 (7/24)	50 (12/21)	**.034**	5,1 (2-8)	4,5 (2-8)	**.015**
Anger *	29 (7/24)	42 (10/23)	.180	5,3 (3-7)	4,2 (1-8)	.609
Sadness	71 (17/24)	54 (13/24)	.102	4,6 (1-9)	6,0 (2-9)	.338

Abbreviations: Pal-SI, Palliative Symptom impact list.

* Psychosocial symptoms.

ogy of various symptoms as a result of different primary diagnoses, it seems that the most prevalent symptoms during the palliative phase are independent of the primary diagnosis.

In this study, a distinction was made between somatic and psychosocial symptoms. Despite the assumption that psychosocial symptoms occur less frequently in palliative patients with cancer in general[17], it has been shown that these symptoms play an important role in the assessment of quality of life in patients with head and neck cancer[29-33]. The 5 most frequently reported psychosocial symptoms in our study were: worrying (61%), sadness (57%), tenseness (52%), depressed mood (52%) and powerlessness (50%). The prevalence figures for psychosocial symptoms found in our study are higher for the symptoms: worrying, sadness, tenseness, and anxiety compared to the findings of 2 other studies. The article by van den Beuken et al.[34] studied a subpopulation of 25 patients with incurable head and neck cancer during their treatment and found a prevalence of 25% for worrying, 17% for tenseness, and 8% for anxiety. In the overall incurable oncological population, Teunissen et al.[16] found a prevalence of 36% for worrying, 39% for sadness, and 30% for anxiety. These discrepancies between our findings compared with other studies could be explained by the use of different terminology, measuring instruments and sample selection. For example, van den Beuken (2009) included patients who were all still receiving some form of (palliative) treatment aimed at symptom control, such as surgery, radiotherapy, or chemotherapy during the palliative phase of their illness. Whereas we studied a group of patients of which only a small portion was receiving such treatment and the larger portion was not. Receiving treatment, even if this treatment is of a palliative nature, can place patients more in a fighting mode and less open to feelings and negative emotions such as worrying. Teunissen et al.[16] used a brought population of patients in the palliative phase, which could also lower the prevalence of these results because we know that patients with head and neck cancer psychologically suffer more[1] and have been associated with higher levels of depression and anxiety.

The least occurring psychosocial symptom (12%) was "feelings of shame". We find this remarkable because head and neck cancer and its treatment can lead to mutilations and disfigurement, and therefore one would expect a higher prevalence for this specific symptom. It could be possible that patients already coped with these consequences when they occurred earlier on during the curative phase. Another reason for the low prevalence of feelings of shame may be related to the specific characteristics of the majority of patients with head and neck cancer; men over 60 years of age, generally with a lower socioeconomic background. Especially sex and age might influence the importance of appearance. Our findings are consistent with a study of patients after a laryngectomy, in which 14% of patients reported experiencing feelings of shame[35].

In the second part of this research we explored the impact of symptoms on daily functioning of patients with incurable head and neck cancer. We also looked at discrepancies between patients and their family caregivers with respect to how they score symptom occurrence and symptom impact on daily functioning. The symptoms dyspnoea, voice

changes, trouble with short walks outside, anger, and weakness, all have, according to the patients in the symptom impact group, a significant impact on daily functioning.

Furthermore, we found that family caregivers of patients with head and neck cancer during the palliative phase frequently overestimate the occurrence of somatic symptoms as well as the impact from those symptoms on daily functioning of patients. In two thirds of cases, although not always significant, the prevalence and the symptom impact score for somatic symptoms were systematically estimated higher by the family caregivers compared to patients. However, when it comes to psychosocial symptoms, we see a reverse trend. Both symptom prevalence as well as symptom impact are underestimated by family caregivers. Approximately 50% of the symptom prevalence and the symptom impact score are indicated higher by the patients compared with family caregivers. These findings are not consistent with studies in patients receiving oncology treatment during the palliative phase, in which family caregivers more frequently overestimated psychosocial symptoms compared to somatic symptoms [19-21]. Research indicates that the degree of consistency between patients and their caregivers depends on the health condition of the patient in question. Just a slight consistency can be found when the health of the patient is very good or very bad[36]. A potential explanation for the discrepancy between patients and family caregivers could be underreporting of symptoms by patients. Patients do not wish to worry their caregivers and hence are very careful when communicating about their symptoms and/or the intensity of those symptoms[18 20 21 37]. Whether or not the discrepancy between patients and their family caregivers in our study can be explained by this is unclear and requires further investigation. It is remarkable that family caregivers indicated that dyspnoea was present, twice as often as the patients did. In case of a head and neck tumour, dyspnoea is a potentially realistic threat. It is likely that fear of suffocation makes the family caregivers more aware of possible signs of dyspnoea. In addition, a lot of patients with head and neck cancer trivialize their dyspnoea because the progression happens gradually. Our result is consistent with prior research among patients with lung cancer during the palliative phase[18].

Limitations

The cross-sectional method of current study is inapt to obtain a definite conclusion about the entire palliative phase. Practical achievability of a longitudinal approach within a palliative population, however, is limited, and hence very difficult to realize[38 39]. Despite the fact that the Pal-C and the Pal-SI are well used and practical instruments for gathering information in the least possible intrusive way, the lack of validation is a limitation. Another limitation was the 44% nonresponse within the prevalence group. Nonresponding patients had a significant shorter life expectancy and seemed to have a much worse condition than responding patients. Generalization of the results from the prevalence group should therefore be done carefully. The large number of nonresponse (more specifically, patients that dropped out because of their weak condition) within this group, however, also confirms

how vulnerable this specific cancer population group is. Finally, the option to work with an occasional random sample for investigating the symptom impact group means that patients were selected. The number of patients and caregivers is too limited to generalize results to the entire population. However, the gained insight has resulted in a number of discrepancies between patients with head and neck cancer and their caregivers, and patients suffering from other malignant dysfunctions.

CONCLUSION

Implications for clinical practice

This is the first study investigating the prevalence of symptoms in patients with head and neck cancer and their impact on daily functioning during the palliative phase reported by patients themselves and their family caregivers. These patients experience a large number of different symptoms. We found that most frequently reported somatic symptoms were: fatigue, pain, weakness, trouble with short walks outside, and dysphagia, which is consistent with research involving a wide palliative cancer population. In the psychosocial area, these are worrying, sadness, tenseness, depressed mood, and powerlessness. For these symptoms, there are no comparative prevalence figures yet available. The symptom with the greatest impact on daily functioning, according to patients, is dyspnoea. According to the caregivers, this is the symptom "trouble with short walks outside". For a number of symptoms, the mutual discrepancies between patients and their caregivers are significant.

These results were limited due to several aspects such as a relatively low accrual rate, mainly because of the condition of patients and the use of a non-validated questionnaire. Future research should, therefore, be focused on replication of our results with further validation of the used questionnaire. We do, however, believe that the results give valuable insight into symptoms experienced by patients with head and neck cancer in the palliative phase and their impact on daily functioning of those patients, a subject that is clearly underexposed in research.

Furthermore, we suggest that care for patients with head and neck cancer in the palliative phase should include targeted screening. This screening should focus on highly prevalent symptoms as fatigue and psychosocial symptoms which, because they are less visible, may now receive less attention. We also suggest that in the relationship between healthcare workers and patients and their caregivers, attention should be paid to the discrepancies between patients and caregivers found in this study. By making this difference in perception open for discussion, patients and caregivers can become more aware of this within their relationship. Insight regarding possible discrepancies may contribute to better and targeted healthcare and hence improve the quality of life of patients with head and neck cancer and their caregivers.

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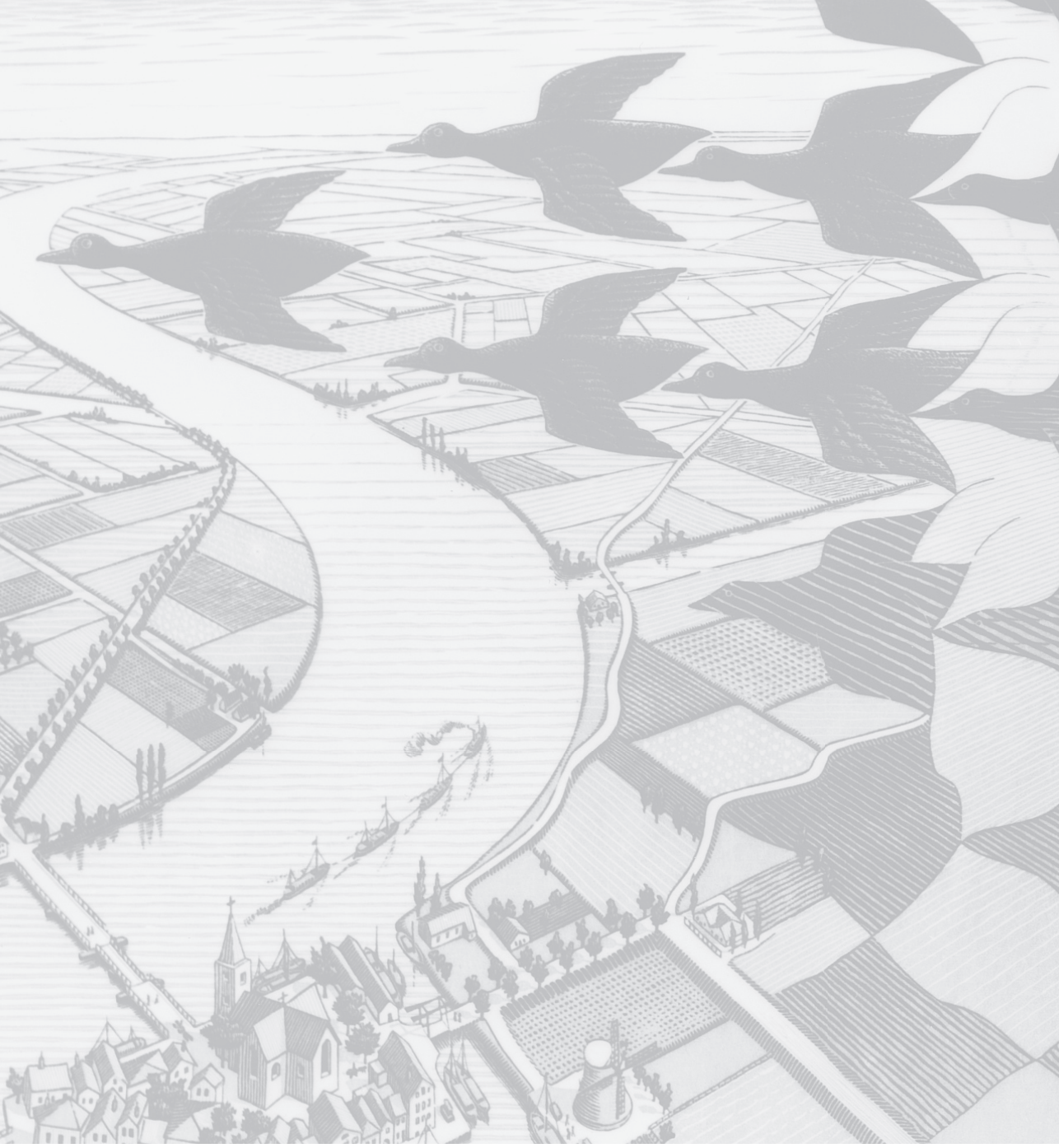

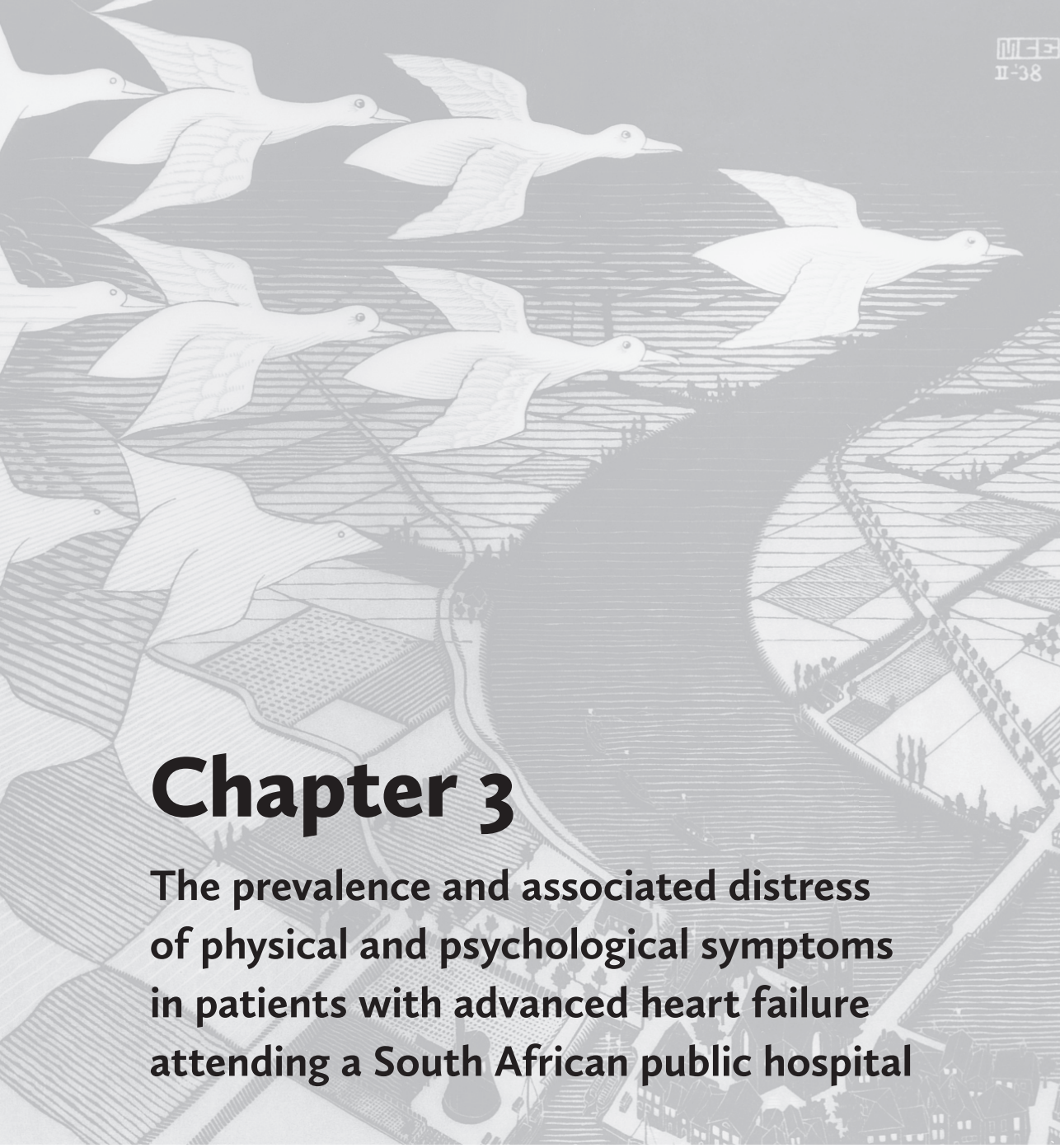

Chapter 3

The prevalence and associated distress of physical and psychological symptoms in patients with advanced heart failure attending a South African public hospital

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ABSTRACT

Background. Despite the high prevalence of heart failure in low- and middle-income countries, evidence concerning patient-reported burden of disease in advanced heart failure is lacking.

Objective. The aim of this study is to measure patient-reported symptom prevalence and correlates of symptom burden in patients with advanced heart failure.

Methods. Adult patients diagnosed with New York Heart Association (NYHA) stage III or IV heart failure were recruited from the emergency unit, emergency ward, cardiology ward, general medicine wards and outpatient cardiology clinic of a public hospital in South Africa. Patients were interviewed by researchers using the Memorial Symptom Assessment Scale-Short Form, a well-validated multidimensional instrument that assesses presence and distress of 32 symptoms.

Results. A total of 230 patients (response, 99.1%) 90% NYHA III and 10% NYHA IV (12% newly diagnosed), with a mean age of 58 years, were included. Forty-five percent were women, 14% had completed high school, and 26% reported having no income. Mean Karnofsky Performance Status Score was 50%. Patients reported a mean of 19 symptoms. Physical symptoms with a high prevalence were shortness of breath (95.2%), feeling drowsy/tired (93.0%), and pain (91.3%). Psychological symptoms with a high prevalence were worrying (94.3%), feeling irritable (93.5%), and feeling sad (93.0%). Multivariate linear regression analyses, with total number of symptoms as dependent variable, showed no association between number of symptoms and gender, education, number of healthcare contacts in the last 3 months, years since diagnosis, or co-morbidities. Increased number of symptoms was significantly associated with higher age (b=0.054, p=0.042), no income (b=-2.457, p=0.013) and fewer hospitalizations in the last 12 months (b=1.032, p=0.017).

Conclusions. Patients with advanced heart failure attending a medical centre in South Africa experience high prevalence of symptoms and report high levels of burden associated with these symptoms. Improved compliance with national and global treatment recommendations could contribute to reduced symptom burden. Healthcare professionals should consider incorporating palliative care into the care for these patients.

INTRODUCTION

Heart failure is a chronic progressive syndrome associated with high morbidity and mortality[1-3]. The prognosis of heart failure is as poor as, or even worse than, that of many cancers[4-10]. Community-based studies have reported mortality rates of 30% to 40% within 1 year of diagnosis and 60% to 70% within 5 years[1 11-13]. Progressive decrease in functional capacity and an increasing frequency of hospitalizations are common in patients who have advanced heart failure[14-16]. Among patients who are hospitalized, mortality rates are even higher[9]. However, when patients are optimized using evidence-based medication, mortality can be reduced[3 17-19].

Multiple investigators have shown that heart failure has a great impact on the health status and quality of life of patients, which can be directly attributed to their symptom burden (e.g., fatigue, shortness of breath, fluid retention) and functional limitations[4 9 20-28]. Unlike most cardiovascular conditions, heart failure is becoming more common[6 7 29 30]. At this moment, cardiovascular diseases account for about 30% of deaths worldwide, with 80% of deaths occurring in the developing world[31]. Heart failure has emerged as a dominant type of cardiovascular disease in Africa[31], and it is a leading cause of death in South Africa[32]. Common causes of heart failure in Africa, such as rheumatic heart disease, peripartum cardiomyopathy, and hypertensive heart disease, are most prevalent in the young[31 33-35]. This is in contrast with developed countries, where heart failure is a condition of the elderly, with a mean age of 76 years[31].

Despite the great burden of heart failure being present in low- and middle-income countries where formal health resources are limited, almost all research concerning advanced heart failure has focused on patients in high-income countries. It remains unclear whether patients with heart failure in developing parts of the world experience the same symptoms and functional limitations. The aims of this study are to measure the prevalence and associated burden of physical and psychological symptoms among patients with New York Heart Association (NYHA) stage III/IV heart failure attending a South African medical centre and to determine which characteristics are associated with the level of symptom burden.

METHOD

Design and population

This cross-sectional observational study is part of a longitudinal study investigating symptoms and care needs in patients with advanced heart failure. The Human Research Ethics Committee of the University of Cape Town reviewed and approved this study (HREC REF: 208/2012).

Patients were recruited for this study between August and November 2012 from several inpatient facilities (i.e. emergency unit, emergency ward, cardiology ward, general medicine

wards) and the outpatient cardiology clinic of a 900-bed tertiary academic medical centre in South Africa. Patients 18 years or older; able to communicate in English, Afrikaans or isiXhosa; and diagnosed with NYHA stage III/IV heart failure were included. Patients were recruited consecutively by the researcher (M.E.L.) after the attending physicians had indicated that a specific patient met the inclusion criteria. Informed consent was obtained from all participants. The questionnaires used in this study and the information and consent forms were translated from English (forward and back) into Afrikaans and isiXhosa (the main languages of the Western Cape of South Africa).

Data collection

The following patient demographic and clinical data were collected from the patient: age, gender, education level (primary school, some high school, high school completed, higher education), income (employed with/without payment, unemployed, disability grant, pension, living from private means), number of healthcare contacts during the last 3 months (outpatient visits, telephone contacts, other) and number of previous hospital admission within the past 12 months. The reason for the hospital visit, years since diagnosis, NYHA stage at the time of the interview, aetiology/ comorbidity, current medication, and presence of an implantable cardioverter defibrillator were collected from the medical record.

To describe the functional limitations of the population, functional status was measured with the Karnofsky Performance Status (KPS) scale[36]. The KPS consists of 11 percentage categories denoted in deciles from 100% (asymptomatic, normal function) to 0% (death), which combine information on the patient's ability to function at work and at home, the severity of symptoms, and the need for personal and medical care[37]. The KPS is regarded as the gold standard performance scale for patients with cancer, but use of the instrument has been reported in 3 studies in patients with advanced heart failure and 1 study in patients with acute myocardial infarction[38 39]. Recently, the KPS was described as adding clarification to the description of the heart failure population when used in studies together with the NYHA classification[39.] Interobserver reliability of the KPS varies between 0.66 and 0.97[40-42].

For a 2-dimensional assessment of symptom prevalence and associated burden, we used the Memorial Symptom Assessment Scale-Short Form (MSAS-SF)[43]. The MSAS-SF is a patient-rated instrument in which patients rate the presence of 28 physical symptoms and the frequency of 4 psychological symptoms during the past 7 days. In addition to the 7-day period prevalence, the MSAS-SF also measures the associated burden for each symptom recorded as prevalent. Distress of physical symptoms is rated on a 5-point (0–4) Likert scale (not at all, 0.8; a little bit, 1.6; somewhat, 2.4; quite a bit, 3.2; very much, 4.0). Frequency of psychological symptoms is rated on a 4-point (0-4) Likert scale (rarely, 1; occasionally, 2; frequently, 3; almost constantly, 4). If the symptom is not present, a value of 0 is assigned for the burden index. The MSAS-SF consists of 3 subscales: the global distress index (4 psychological symptoms: feeling sad, worrying, feeling irritable, and feeling nervous, and 6 physical symp-

toms: lack of energy, pain, lack of appetite, feeling drowsy, constipation, and dry mouth); the physical symptom distress score (12 prevalent physical symptoms: lack of energy, pain, lack of appetite, feeling drowsy, constipation, dry mouth, nausea, vomiting, change in taste, weight loss, feeling bloated, and dizziness), and the psychological symptom distress score (6 prevalent psychological symptoms: worrying, feeling sad, feeling nervous, difficulty sleeping, feeling irritable, and difficulty concentrating). The MSAS-SF has good psychometric properties, with subscale Cronbach's α coefficients of 0.76 to 0.87, and 1-day test-retest reliability correlation coefficients of 0.86 to 0.94[43]. Use of the MSAS-SF has been well reported among patients with heart failure and patients from sub-Saharan Africa with HIV and cancer[20 21 44-46].

Questionnaire items of the MSAS-SF were read aloud by researcher (M.E.L.), and patient's self-report response entered on their behalf. All patients were interviewed in the language of their choice (English, Afrikaans, or isiXhosa). Self-completion was not used because of potential limited literacy in this population. All data were then entered into LimeSurvey (online survey software that was used as data entry tool in this study) and subsequently imported into SPSS version 20.0 for analysis.

Analysis and statistics

The patient demographic and medical characteristics were described with descriptive statistics. When data were nonnormally distributed, median scores were presented. For each item within the MSAS-SF, prevalence and associated burden were calculated. Scores for the global, physical, and psychological subscales were calculated[47]. The total number of prevalent symptoms for each respondent and the mean number of prevalent symptoms for the sample were also calculated. A high level of symptom burden was defined as the sum of "quite a bit" and "very much" of distress associated with physical symptoms and the sum of "frequently" and "almost constantly" for the frequency of psychological symptoms. Education was measured using 4 groups (primary school, some high school, high school completed, and higher education). The high school completed and the higher education group both contained a very low number of patients, making a 3-group division (ie, lower, middle, and higher education) not possible. Therefore, education was divided into 2 groups of primary school versus more than primary school (including some high school, high school completed, and higher education). Income was measured using 6 groups (employed with payment, employed without payment, unemployed, disability grant, pension, living on own private means), but could not be categorized into levels of income (low, middle, and high); therefore, income was divided into no income (employed without payment and unemployed) versus income (employed with payment, disability grant, pension, and living on own private means).

Linear regression analyses were used to identify associations with symptom burden. Five models were constructed, with the following dependent variables: global distress (model 1), physical distress (model 2), psychological distress (model 3), total MSAS (model 4) and total number of symptoms (model 5). Univariate linear regression analyses were performed to test

the association of different patient characteristics with the dependent variables: age (continuous), gender (two levels of male/female), education (two levels of primary high school / > primary high school), income (two levels of yes/no), years since diagnosis (two levels of 0 / > 0 years), number of prior hospital admission within the past 12 months (continuous), number of healthcare contacts during the last three months (two levels of 0/>0) and number of co morbidities (continuous). Following each univariate regression, multivariate regression models were constructed. Independent variables were entered stepwise into the multivariate model if they were significant in univariate analyses at the conservative 25% level.[45] For each model, the 95% confidence interval of the unstandardized *b* coefficient was calculated.

RESULTS

Sample characteristics

A total of 232 patients met the inclusion criteria for this study, and of these, 2 patients declined participation. Therefore, a total of 230 patients (response 99.1%) were included in the study (Table 1). The mean (SD) age was 58 (16.7) years (median, 60 years; min-max, 18-90 years); 45% were women, 14% completed high school, and 26% reported having no income. Most patients included in this study had been admitted to the hospital because of an exacerbation of their illness. Eighty-eight percent had been diagnosed with heart failure before their hospital visit. The most prevalent stage of heart failure in this population was NYHA stage III (90%). Comorbidity was common; only 19 patients were reported having no other illnesses. The most prevalent comorbidities were hypertension (70%) and diabetes (38%). Mean KPS was 50% ("requires considerable assistance and frequent medical care"). On average, patients had been previously admitted to hospital on 1 occasion during the past year. Sixty-eight percent of all patients had not had any contact with a healthcare professional during the previous 3 months. According to the medical records, angiotensin-converting enzyme (ACE) inhibitors, were used by 57% of patients with an existing diagnosis; β-blockers, by 47%; angiotensin receptor blockers by 4%; mineralocorticoid receptor antagonists(MRA), by 12%; diuretics other than MRA, by 92%; and digoxin, by 11%. Five percent of patients had an implantable cardioverter-defibrillator (ICD).

Symptom prevalence and burden

The 7-day period symptom prevalence and associated burden are reported in Table 2. Patients reported a mean of 19 symptoms (not in table). Eighteen symptoms were reported by more than 50% of all patients. Physical symptoms with highest prevalence were shortness of breath (95.2%), feeling drowsy/tired (93.0%) and pain (91.3%). Psychological symptoms with highest prevalence were worrying (94.3%), feeling irritable (93.5%) and feeling sad (93.0%). Symptoms associated with highest burden were shortness of breath (93.1%), numbness/tingling in hands or feet (90.5%) and "I do not look like myself" (89.9%).

Table 1. Sample Characteristics (n=230)

Patient demographic characteristics			**Patient medical characteristics**		
Age median ± SD, y	60	± 16.7	Aetiology/ comorbidity cardiovascular diseases		
Gender			Hypertension	70%	161
Male	45%	103	Ischemic Heart disease	13%	30
Female	55%	127	Valvular heart disease	3%	7
Education level			Rheumatic heart disease	3%	6
Primary school	49%	112	Post-partum cardiomyopathy	1%	2
Some high school	37%	86	Congenital heart disease	1%	2
High school completed	11%	25	Hypertrophic obstructive cardiomyopathy	0,4%	1
Higher education	3%	7	Aetiology/ comorbidity other diseases		
Income			Diabetes type 2	24%	55
Employed with payment	22%	50	Diabetes type 1	14%	31
Employed without payment	2%	5	Renal Failure	12%	28
Unemployed	24%	55	COPD	8%	19
Disability grant	10%	24	Asthma	7%	16
Pension	41%	94	HIV	7%	15
Living on own private means	1%	2	Tuberculosis	4%	8
Patient medical characteristics			Cancer	1%	2
Heart failure diagnosis			Comorbidity per patient, mean (interval)	2	0-4
Years since diagnosis[a] median/ interval	1	0-18	Karnofsky Performance Score, mean (interval)	50% (90%-20%)	
Newly diagnosed	12%	27	Reason for hospital visit		
NYHA stage at time of interview			Acute admission	86%	197
III	90%	207	Outpatient clinic[b]	13%	29
IV	10%	23	Planned admission	2%	4
Contact with healthcare professionals			Medication use (patients with an existing diagnosis n=201)		
Prior hospital admissions last year (mean/interval)	1	0-4	ACE-inhibitors	57%	115
Prior healthcare contacts last 3 months			β-blockers	47%	94
0	63%	144	Angiotensin receptor blockers	4%	7
1	28%	64	Digoxin	11%	22
≥ 2	10%	22	MRA	12%	25
Implantable Cardioverter Defibrillator (ICD)	5%	11	Diuretics other than MRA	92%	184

Data are presented as percentage and number, unless otherwise indicated. Abbreviations: ACE, angiotensin-converting enzyme; COPD, chronic obstructive pulmonary disease; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association.

[a]Number of years since diagnosis missing for 2 patients.

[b]Includes patients following recent hospitalization and for scheduled follow-up.

Table 2. 7-day-Period Symptom Prevalence[a] and Associated Symptom Burden (N=230)[b]

Symptoms	Prevalence	Burden (Total 100%)				
		Not at All	A Little Bit	Somewhat	Quite a Bit	Very Much
Physical problems						
Shortness of breath	95.2% (n=219)	0.9% (n=2)	2.7% (n=6)	3.2% (n=7)	11.4% (n=25)	81.7% (n=179)
Feeling drowsy/ tired	93.0% (n=214)	0.5% (n=1)	3.7% (n=8)	6.5% (n=14)	23.4% (n=50)	65.9% (n=141)
Pain	91.3% (n=210)	1.4% (n=3)	2.4% (n=5)	12.4% (n=26)	24.8% (n=52)	59.0% (n=124)
"I don't look like myself"	90.4% (n=208)	1.4% (n=3)	2.4% (n=5)	6.3% (n=13)	15.9% (n=33)	74.0% (n=154)
Weight loss	84.8% (n=195)	5.6% (n=11)	12.3% (n=24)	21.5% (n=42)	20.0% (n=39)	40.5% (n=79)
Lack of energy	82.2% (n=189)	1.1% (n=2)	2.6% (n=5)	14.3% (n=27)	18.0% (n=34)	64.0% (n=121)
Swelling of arms or legs	81.3% (n=187)	2.1% (n=4)	2.7% (n=5)	9.1% (n=17)	32.6% (n=61)	53.5% (n=100)
Difficulty sleeping	77.0% (n=177)	1.1% (n=2)	2.3% (n=4)	13.6% (n=24)	28.8% (n=51)	54.2% (n=96)
Numbness/tingling in hands or feet	73.5% (n=169)	2.4% (n=4)	2.4% (n=4)	4.7% (n=8)	20.1% (n=34)	70.4% (n=119)
Changes in way food tastes	73.0% (n=168)	3.6% (n=6)	5.4% (n=9)	7.7% (n=13)	29.8% (n=50)	53.6% (n=90)
Lack of appetite	72.2% (n=166)	3.6% (n=6)	7.8% (n=13)	14.5% (n=24)	39.8% (n=66)	34.3% (n=57)
Difficulty concentrating	67.4% (n=155)	7.7% (n=12)	13.5% (n=21)	33.5% (n=52)	32.9% (n=51)	12.3% (n=19)
Difficulty swallowing	55.7% (n=128)	4.7% (n=6)	5.5% (n=7)	17.2% (n=22)	38.3% (n=49)	34.4% (n=44)
Problems with sexual interest/ activity	52.6% (n=121)	25.6% (n=31)	25.6% (n=31)	33.9% (n=41)	7.4% (n=9)	7.4% (n=9)
Cough	49.1% (n=113)	5.3% (n=6)	8.8% (n=10)	18.6% (n=21)	23.0% (n=26)	44.2% (n=50)
Nausea	42.2% (n=97)	6.2% (n=6)	15.5% (n=15)	24.7% (n=24)	25.8% (n=25)	27.8% (n=27)
Dizziness	41.3% (n=95)	4.2% (n=4)	24.2% (n=23)	24.2% (n=23)	17.9% (n=17)	29.5% (n=28)
Feeling bloated	36.1% (n=83)	6.0% (n=5)	7.2% (n=6)	33.7% (n=28)	25.3% (n=21)	27.7% (n=23)
Dry mouth	35.7% (n=82)	8.5% (n=7)	22.0% (n=18)	28.0% (n=23)	25.6% (n=21)	15.9% (n=13)
Problems urinating	32.2% (n=74)	2.7% (n=2)	14.9% (n=11)	32.4% (n=24)	24.3% (n=18)	25.7% (n=19)
Itching	28.3% (n=65)	13.8% (n=9)	29.2% (n=19)	29.2% (n=19)	15.4% (n=10)	12.3% (n=8)
Changes in skin	27.0% (n=62)	14.5% (n=9)	22.6% (n=14)	12.9% (n=8)	16.1% (n=10)	33.9% (n=21)

Table 2. 7-day-Period Symptom Prevalence[a] and Associated Symptom Burden (N=230)[b] (continued)

Symptoms	Prevalence	Burden (Total 100%)				
		Not at All	A Little Bit	Somewhat	Quite a Bit	Very Much
Constipation	26.1% (n=60)	1.7% (n=1)	20.0% (n=12)	21.7% (n=13)	28.3% (n=17)	28.3% (n=17)
Vomiting	25.7% (n=59)	6.8% (n=4)	15.3% (n=9)	27.1% (n=16)	33.9% (n=20)	16.9% (n=10)
Sweats	25.2% (n=58)	10.3% (n=6)	12.1% (n=7)	19.0% (n=11)	36.2% (n=21)	22.4% (n=13)
Hair loss	13.9% (n=32)	18.8% (n=6)	21.9% (n=7)	18.8% (n=6)	15.6% (n=5)	25.0% (n=8)
Mouth sores	12.6% (n=29)	27.6% (n=8)	20.7% (n=6)	17.2% (n=5)	17.2% (n=5)	17.2% (n=5)
Diarrhea	12.2% (n=28)	25.0% (n=7)	10.7% (n=3)	17.9% (n=5)	21.4% (n=6)	25.0% (n=7)
Symptoms	**Prevalence**	**Burden (total 100%)**				
		Rarely	**Occasionally**	**Frequently**	**Almost constantly**	
Psychological problems						
Worrying	94.3% (n=217)	31.3% (n=68)	35.9% (n=78)	24.9% (n=54)	7.8% (n=17)	
Feeling irritable	93.5% (n=215)	38.6% (n=83)	31.2% (n=67)	22.3% (n=48)	7.9% (n=17)	
Feeling sad	93.0% (n=214)	28.5% (n=61)	51.9% (n=111)	11.7% (n=25)	7.9% (n=17)	
Feeling nervous	92.2% (n=212)	25.0% (n=53)	20.8% (n=44)	31.1% (n=66)	23.1% (n=49)	

Distress of physical symptoms is rated on a 5-point (0-4) Likert scale (not at all, 0.8; a little bit, 1.6; somewhat, 2.4; quite a bit, 3.2; very much, 4.0). Frequency of psychological symptoms is rated on a 4-point
(0-4) Likert scale (rarely, 1; occasionally, 2; frequently, 3; almost constantly, 4). If the symptom is not present, a value of 0 is assigned for the burden index.

[a]Symptom prevalence in descending order of prevalence.

[b]Symptom prevalence presented for N = 230 without missing values.

Correlates of symptom burden

Univariate and multivariate regression analyses to determine associations with symptom burden are presented in Table 3. Age, income, and prior hospital admission were found to be consistent correlates for the multivariate models. In the multivariate analyses, age, income and prior hospital admission were correlated to global distress (model 1: b=0.007, *P*=0.030; b=-0.270, *P*=0.029 and b=-0.168, *P*<0.001 respectively), physical distress(model 2: b=0.007, *P*=0.037; b=-0.298, *P*=0.013 and b=-0.211, *P*<0.000 respectively), number of symptoms (model 5: b=0.053, *P*=0.038; b=-2.233, *P*=0.021 and b=-1.498, *P*<0.001 respectively), psychological distress (model 3: prior hospital admission only, b=-0.116, *P*=0.023) and total distress (model 4: prior hospital admission only, b=-0.168, *P*<0.001). In these models, a higher symptom burden was associated with having a higher age, having no income (dichotomous variable; having no income compared to income) and having fewer hospital admissions within the past 12 months. Multivariate analyses showed no association between the different models and the independent variables of gender, education, healthcare contacts, years since diagnosis, or comorbidities.

Table 3. Associations With Symptom Burden

Independent variables	Univariate analysis			Multivariate analysis		
	b	*P*	95% CI for b	b	*P*	95% CI for b
			Model 1: Global distress Subscale, r^2 =9,0%			
Age	0.002	0.449	-0.003, 0.008	**0.007**	**0.030**	**0.001, 0.014**
Gender	-0.102	0.280	-0.287, 0.083			
Education	-0.060	0.525	-0.244, 0.125			
Income	-0.157	0.140	-0.366, 0.052	**-0.270**	**0.029**	**-0.512, -0.028**
Years since diagnosis	-0.042	0.772	-0.326, 0.242			
Prior hospitalizations	**-0.172**	**<0.000**	**-0.264, 0.080**	**-0.168**	**<0.000**	**-0.260, -0.076**
Healthcare contacts	0.137	0.156	-0.053, 0.327	0.160	0.091	-0.026, 0.347
Co-morbidity	0.022	0.661	-0.077, 0.122			
			Model 2: Physical distress Subscale, r^2 = 13,0%			
Age	0.001	0.729	-0.005, 0.006	**0.007**	**0.037**	**0.000, 0.013**
Gender	-0.140	0.132	-0.322, 0.043	-0.112	0.204	-0.285, 0.061
Education	-0.021	0.823	-0.203, 0.161			
Income	**-0.221**	**0.035**	**-0.426, -0.016**	**-0.298**	**0.013**	**-0.532, -0.064**
Years since diagnosis	-0.088	0.534	-0.368, 0.191			
Prior hospitalizations	**-0.216**	**<0.000**	**-0.305, -0.128**	**-0.211**	**<0.000**	**-0.300, -0.122**
Healthcare contacts	0.074	0.438	-0.114, 0.262	0.106	0.247	-0.074, 0.286
Co-morbidity	-0.024	0.625	-0.123, 0.074			

Table 3. Associations With Symptom Burden (continued)

Independent variables	Univariate analysis			Multivariate analysis		
	b	*P*	95% CI for b	b	*P*	95% CI for b
			Model 3: Psychological distress Subscale r^2 = 2,8%			
Age	0.001	0.762	-0.005, 0.007			
Gender	-0.115	0.251	-0.311, 0.082	-0.116	0.247	-0.312, 0.081
Education	0.045	0.653	-0.151, 0.241			
Income	-0.121	0.284	-0.344, 0.101			
Years since diagnosis	-0.027	0.859	-0.332, 0.277			
Prior hospitalizations	-0.114	0.024	-0.214, -0.015	**-0.116**	**0.023**	**-0.215, -0.016**
Healthcare contacts	0.038	0.711	-0.164, 0.241			
Co-morbidity	0.008	0.885	-0.098, 0.144			
			Model 4: Total MSAS Score, r^2 =8,8%			
Age	0.001	0.749	-0.004, 0.005			
Gender	-0.122	0.119	-0.275, 0.032	-.0124	0.100	-0.271, 0.024
Education	-0.029	0.709	-0.182, 0.124			
Income	-0.159	0.072	-0.333, 0.014			
Years since diagnosis	-0.072	0.547	-0.308, 0.164			
Prior hospitalizations	**-0.171**	**<0.000**	**-0.246 -0.095**	**-0.168**	**<0.000**	**-.0243, -0.093**
Healthcare contacts	0.055	0.492	-0.103, 0.213			
Co-morbidity	-0.016	0.695	-0.099, 0.066			
			Model 5: Number of symptoms, r^2 =10,7%			
Age	0.010	0.666	-0.034, 0.054	**0.053**	**0.038**	**0.003, 0.104**
Gender	-1.391	0.061	-2.847, 0.066	-1.177	0.101	-2.584, 0.229
Education	-0.446	0.548	-1.91, 1.013			
Income	**-1.669**	**0.047**	**-3.316, -0.021**	**-2.233**	**0.021**	**-4.124, -0.341**
Years since diagnosis	-0.415	0.716	-2.661, 1.832			
Prior hospitalizations	**-1.530**	**<0.000**	**-2.250 -0.809**	**-1.498**	**<0.000**	**-2.218, -0.778**
Healthcare contacts	0.238	0.756	-1.270, 1.746			
Co-morbidity	-0.268	0.503	-1.056, 0.520			

Bold values correspond with significant outcomes (P = .05).
Abbreviations: CI, confidence interval; MSAS, Memorial Symptom Assessment Scale.

DISCUSSION

This study is the first to assess the prevalence, burden, and correlates of physical and psychological symptoms in patients with NYHA stage III and IV heart failure in a developing country. We found that these patients report a high prevalence of symptoms and high levels of burden associated with these symptoms. Higher symptom burden is associated with a higher age, having no income and fewer hospital within the past 12 months.

The prevalence figures reported in this study are high compared with findings of several other studies who used the MSAS[9 20 27 48]. Focussing on the most prevalent physical and psychological symptoms in this study, varying percentages have been reported for the prevalence of shortness of breath (95.2% vs 56.3%-85.0%[9 20 27 48]), feeling drowsy/tired (93.0% vs 52.0%-90.0%[9 20 27 48]), pain (91.3% vs 52,0%-56,0%[20 27]), worrying (94.3% vs 43.7%-61.5%[9 27]), feeling irritable(93.5% vs 33.0%-53.7%[9 27]) and feeling sad(93.0% vs 42.7%-54.7%[9 27]). The high prevalence figures found in the current study are striking, especially in this group, with a high rate of patients being diagnosed with NYHA stage III. The discrepancies in symptom prevalence between our findings and previous studies could be explained by several factors: Not all studies restricted their inclusion to NYHA stage III or IV but also included NYHA stage I and II, measurements were done at different locations (i.e. at home, during an outpatient clinic visit, during an hospital admission) and at different points in the course of the illness (during an exacerbation, during a chronic period), studies reported on patients with a higher average age (having a younger age has been associated with a higher symptom burden in patients with cancer[49 50]), and studies were carried out in developed parts of the world (i.e. Europe and North America). It is possible that the prevalence figures in the current study are higher compared with earlier findings because most patients in the current study were interviewed at the time of an exacerbation of their illness (86% of patients were at the hospital for an acute admission). Also, the KPS in our study was quite low compared with that in 3 other studies in patients with advanced heart failure (50% vs 69%-76%), which seems to confirm this hypothesis. Another possible explanation for the difference in prevalence figures is related to the prescription rates of recommended treatment. Treatment guidelines in South Africa[51 52] are in line with those for Europe and North America[53 54] in their recommendation for the use of ACE inhibitors, ß-blockers, and spironolactone as an important part of heart failure treatment. The reported levels of medication in our study are, however, lower than recommended and also low compared to other studies, in which ACE-inhibitors were used by 47% to 82% of patients[27 44 48 55-58] (vs 57% in our study); ß-blockers, by 34% to 88%[27 44 48 55-58] (vs. 47%); and MRAs, by 18% to 72%[44 48 56-58] (vs. 12%). Under-treatment has been reported as a problem in heart failure treatment and does not seem to be limited to developing counties[30 56].

The symptoms shortness of breath, numbness/ tingling in hands or feet and "I do not look like myself were considered most distressing by our study group. We found 2 previous studies

that reported on distress of symptoms in an advanced heart failure population. Blinderman et al.[9] studied a sample of 103 community-dwelling patients with NYHA stage III/IV heart failure in the United States. According to this sample, the most distressing symptoms were other pain (in this study, pain was differentiated into cardiac pain and other pain), problems with sexual interest/activity and lack of energy. Zambroski et al.[27] studied a sample of 53 patients with NYHA stage II to IV heart failure visiting a heart failure clinic in the United States. Patients in this study judged lack of energy, difficulty sleeping and shortness of breath to be the most distressing symptoms. Patients in the studies of Blinderman et al. and Zambroski et al. and the current study seem to disagree about which symptoms are most distressing to them. This discrepancy could be related to the differences in symptom prevalence and ranking of most prevalent symptoms. Numbness or tingling in hands or feet can be caused by swelling of the arms or legs or associated with peripheral neuropathy secondary to diabetes. Prevalences of the symptom swelling of the arms or legs and of diabetes were higher in the current study compared with the studies of Blinderman et al. and Zambroski et al (81.3% vs 32.0-47.2% and 38% vs 33-32%, respectively[9 27]). It could by hypothesized that patients who report feeling that they do not look like themselves do so because of the presence of disfiguring symptoms such as swelling of arms or legs and weight loss (84.8% vs 19.4%-32.1%[9 27]), which were both more prevalent in our study. To be able to focus care on the most distressing symptoms, communication about symptom-related distress is key.

Having a higher age, having no income, and having fewer hospital admissions within the past 12 months were associated with higher symptom burden. The association with age is in accordance with previous studies that have shown an increased risk of heart failure hospitalization with increasing age[15 59]. The association with income is in line with studies that have looked at the relationship between socioeconomic status (SES) and the risk of heart failure hospitalizations[59-61]. A lower SES is associated with a higher risk for heart failure and heart failure-related hospital admissions. Hospitalizations are usually due to an exacerbation of heart failure. The association of higher symptom burden with fewer hospital admissions is therefore rather surprising. It could be that patients who have been admitted have been well cared for, including receiving the recommended treatment, leading to lower symptom burden in the group with previous hospital admissions. Another explanation could be related to the association with no income. In South Africa, healthcare access for all is constitutionally enshrined, but great inequities in access to and the subsequent use of healthcare remain[62]. Studies have indicated that low-income groups in South Africa cannot "afford" to be ill and therefore underreport or "ignore" illness[62 63]. Also, no money for transport, out-of-pocket payments, delays due to a belief that the illness was not serious enough to warrant immediate care, or that care would be ineffective have been reported as access barriers for the low-SES group[62]. It is startling that the number of healthcare contacts was not associated with symptom burden; therefore, we can presume that pain and symptom burden are not adequately addressed in routine existing care.

Many of the symptoms that are being reported by patients with advanced heart failure are not generally thought of as being caused by heart failure[4 20]. Some symptoms may be related to medication used to treat heart failure, such as dry mouth or constipation, or with comorbidities, which are highly prevalent in this population[20 64 65]. Although the causes of various symptoms, such as pain[5 8 66], remain unclear, these diverse symptoms together are responsible for a major portion of the decrease in quality of life associated with heart failure[20]. Advanced heart failure has been described as having one of the largest effects on quality of life of any advanced disease[20 28]. To optimally treat patients with heart failure, attention needs to be paid to all symptoms that are present , irrespective of their aetiology. Several authors have emphasized the need for incorporating palliative care in advanced heart failure care[4 8 53 67-69]. Palliative care is care tailored to the needs of patients; it is a holistic approach to the care for patients and their families who are facing the problems associated with a life-threatening illness.

There are some limitations to this study. First, concerning generalizability of the results, the patients were recruited from 1 medical centre and may therefore not be representative for the total population with heart failure residing in community settings; although patients were recruited consecutively during an inclusion period of 3 months, most patients who were included in the study were diagnosed with stage III heart failure. It is therefore possible that our results are not completely generalizable to patients with stage IV heart failure. We hypothesize that patients with stage IV heart failure are often too ill to visit the hospital and are taken care of at home. Second, concerning reliability and completeness of data collected from the medical record, it is not clear to what extent these medical records were complete and thus completely reflected the medical history and current health status of the patient. We did not collect data on ejection fraction, and therefore, we cannot fully reflect on the reported levels of medication in this study. Third, the cross-sectional design provides us with a "snapshot" of the symptom burden experienced by patients with advanced heart failure. Symptom burden is expected to change during the course of the disease. A longitudinal follow-up is needed to know how symptom burden changes over time in patients with advanced heart failure, and these longitudinal data will follow in subsequent reporting. The strength of this study lies in the use of patient-reported data, instruments with good psychometric properties and multiple language options, the high response rate, and multiple recruitment points throughout the medical centre.

In conclusion, patients with advanced heart failure attending an academic medical centre in South Africa experience a high prevalence of symptoms and report high levels of burden associated with these symptoms. Current treatment seems not to be in accordance with national and global recommendations. Improved compliance with national and global treatment recommendations could contribute to reduced symptom burden. Attention should be paid to high prevalent symptoms, symptoms associated with high distress, and symptoms

that are not generally thought of as being caused by heart failure. Incorporating palliative care into the care for these patients could contribute to the provision of tailored care.

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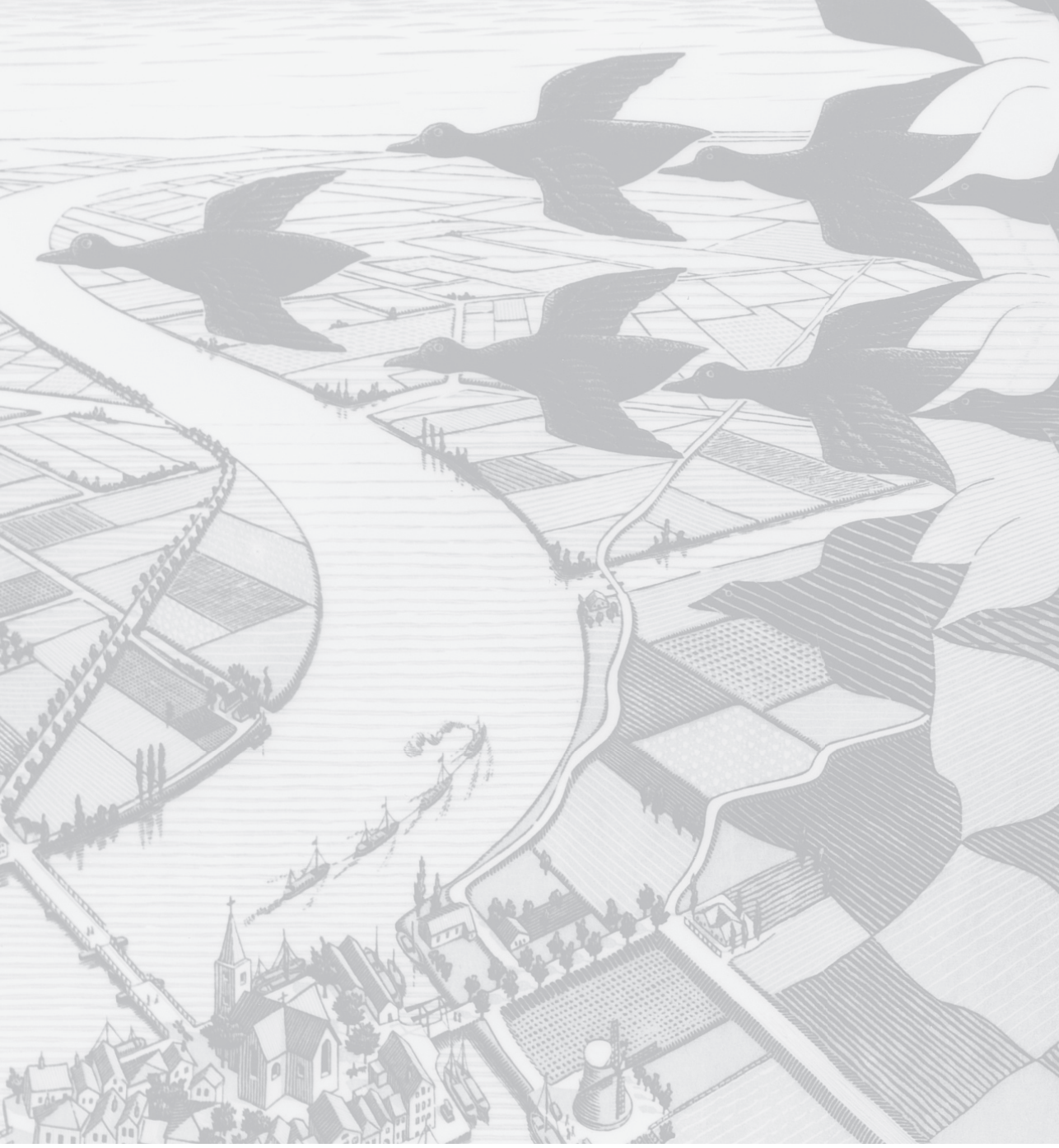

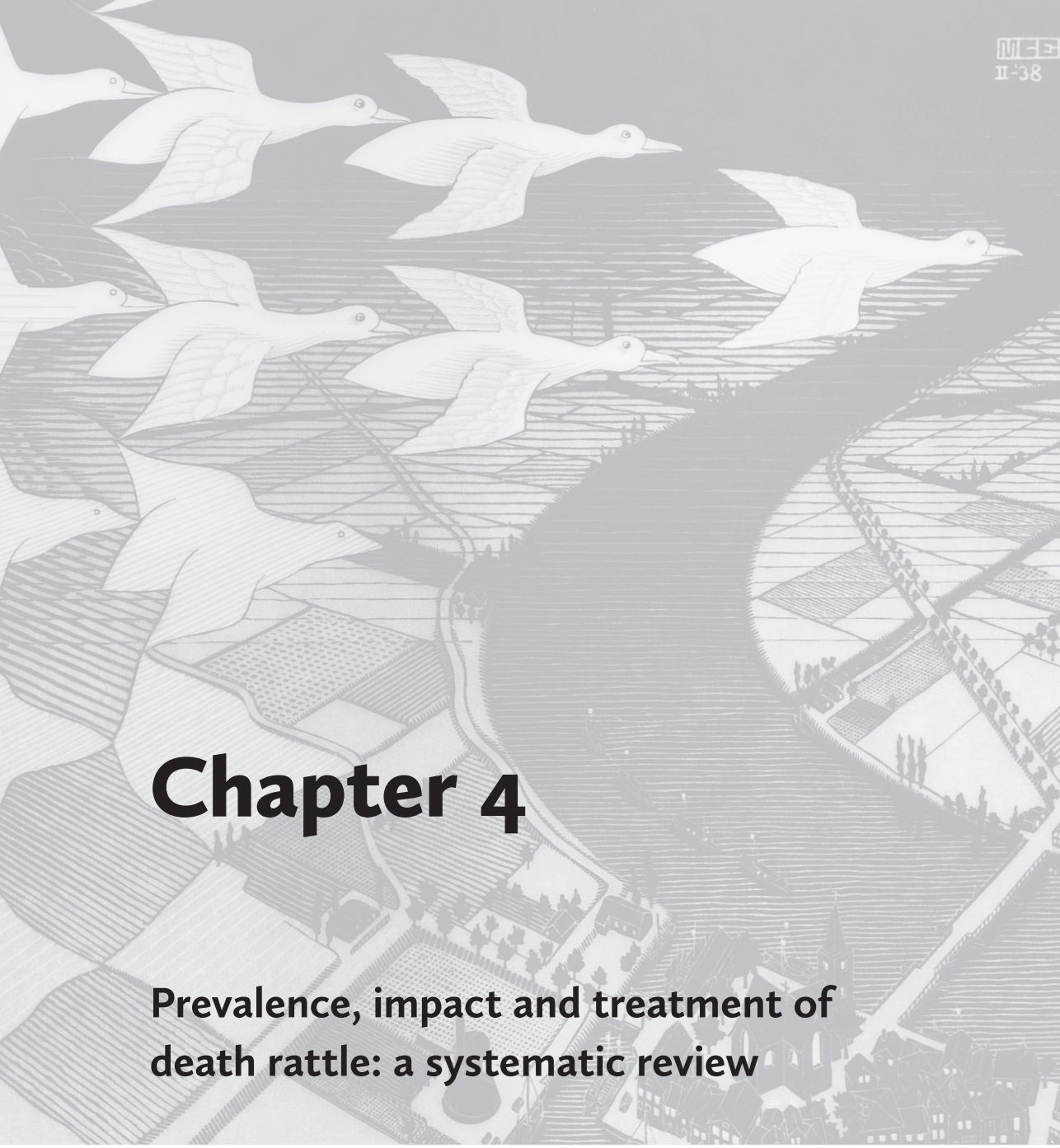

Chapter 4

Prevalence, impact and treatment of death rattle: a systematic review

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J Pain Symptom Manage. 2014;47(1):105-22

ABSTRACT

Context. Death rattle, or respiratory tract secretion in the dying patient, is a common and potentially distressing symptom in dying patients. Healthcare professionals often struggle with this symptom because of the uncertainty about management.

Objectives. To give an overview of the current evidence on the prevalence of death rattle in dying patients, its impact on patients, relatives, and professional caregivers, and the effectiveness of interventions.

Methods. We systematically searched the databases PubMed, Embase, CINAHL, PsychINFO and Web of Science. English-language articles containing original data on the prevalence or impact of death rattle or on the effects of interventions were included.

Results. We included 39 articles, of which 29 reported on the prevalence of death rattle, eight on its impact, and 11 on the effectiveness of interventions. There is a wide variation in reported prevalence rates (12-92%; weighted mean, 35%). Death rattle leads to distress in both relatives and professional caregivers, but its impact on patients is unclear. Different medication regimes have been studied, that is, scopolamine, glycopyrronium, hyoscine butylbromide, atropine and/or octreotide. Only one study used a placebo group. There is no evidence that the use of any antimuscarinic drug is superior to no treatment.

Conclusions. Death rattle is a rather common symptom in dying patients, but it is doubtful if patients suffer from this symptom. Current literature does not support the standard use of antimuscarinic drugs in the treatment of death rattle.

INTRODUCTION

Care for the dying has received growing attention over the past decade, in both healthcare research and practice. Although several challenges of performing research in end-of-life care have been reported[1-5], the demand for evidence-based guidelines is increasing. Until now, for many symptoms associated with the dying phase, research has been scarce, as is the case for death rattle. Death rattle or respiratory tract secretion in the dying patient, is a common symptom in dying patients, although reported prevalences vary considerably[6-10]. Death rattle is thought to be caused by an accumulation of secretions in the airways[11]. It is unclear whether or to what extent it represents discomfort for the patient, and whether nursing and medical interventions to reduce its prevalence are needed or effective. Even when the patient does not appear to be disturbed by the symptom, treatment is often initiated because of distress in the attending relatives[12-14]. Treatment modalities include nursing interventions, for example, repositioning of the patient and suction of secretions and pharmacologic interventions. The use of antimuscarinic drugs is recommended in several palliative care textbooks[11, 15-18].

A recent Cochrane review focusing on interventions for death rattle concluded that there is no evidence that any intervention, pharmacologic or nonpharmacologic, was superior to placebo in the treatment of noisy breathing in dying patients[19]. This Cochrane review was based on four articles (two English, two German) and only included level A evidence studies, that is, randomized controlled trials and high-quality prospective controlled studies. Randomized controlled trials among patients who are in the dying phase are rare, mainly because of ethical and practical considerations related to randomization, informed consent, the use of placebo, and follow-up[1-5]. Studies with a lower level of evidence can also provide useful information on care for dying patients. We performed a systematic search of the scientific literature with the aim of giving a comprehensive overview of empirical studies on the prevalence of death rattle, its impact on patients, relatives and professional caregivers, and the effectiveness of interventions.

METHODS

We conducted a systematic search of the databases PubMed, Embase, CINAHL, Web of Science and PsychINFO. All the databases were searched for articles published up to August 2012 in English on the prevalence, impact and treatment of death rattle. Fig. 1 presents a detailed overview of the search strategy. The search strategy was not restricted to recent publications to retrieve all the relevant literature. In addition, we hand-searched reference lists of included articles and relevant literature reviews.

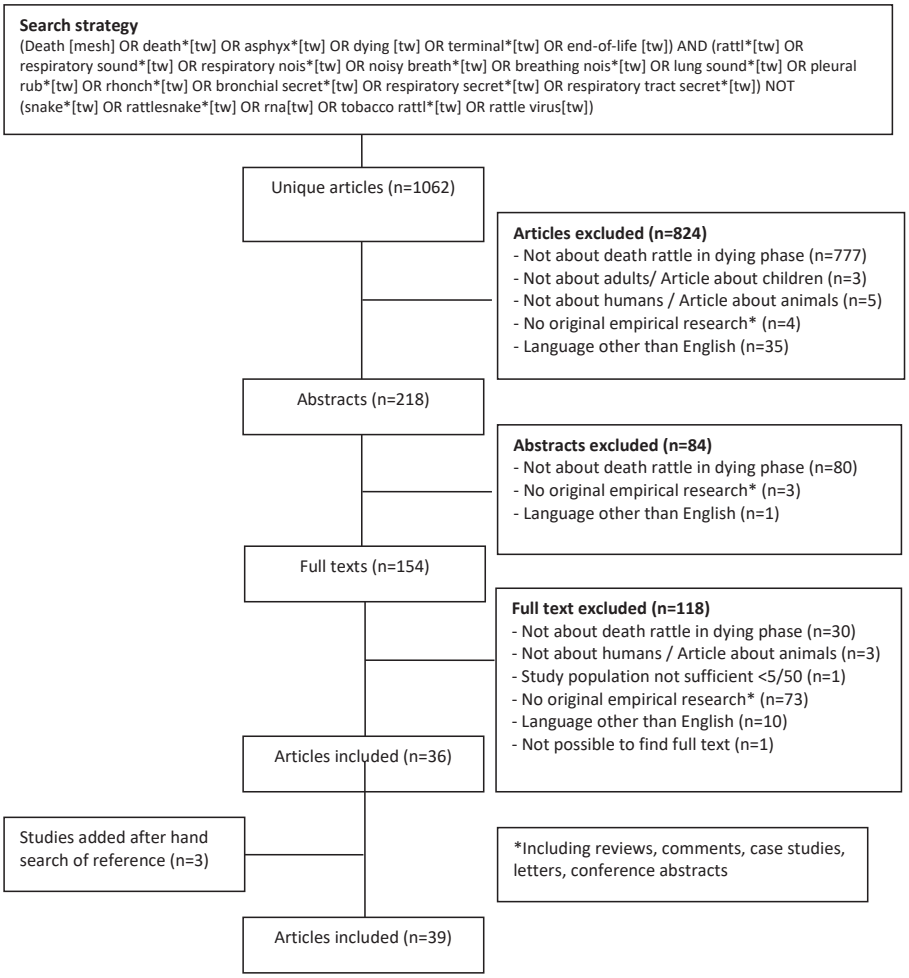

Figure 1. Search strategy and selection of articles

Study selection

Studies were included when they met the following inclusion criteria: the study described original empirical research about death rattle in the dying phase of human adults and the study included data about the prevalence of death rattle, experiences of patients, relatives, or professional caregivers with death rattle, or the effectiveness of interventions. Studies on the prevalence of death rattle had to include at least 50 subjects. Reviews, comments, case studies, letters, and conference abstracts were excluded. All duplicates were removed. Articles were selected in a stepwise procedure. First, all titles were assessed as possibly relevant or not relevant; titles that were not relevant were excluded. In the second step, the abstracts of the remaining articles were screened on the selection criteria. If the abstracts met these criteria, the full text were assessed in step 3.

Titles of 10% of the articles were independently assessed by two reviewers (M.E.L. and A.v.d.H.). Cohen's Kappa was calculated to determine the level of agreement: κ=0.78, indicating a substantial agreement[20]. Differences in scoring were discussed until consensus was reached. The remaining titles were assessed by M.E.L. This procedure was repeated for the assessment of abstracts (κ=0.77) and full texts (κ=0.90). For all the studies that did not pass the selection process, the reasons for non-inclusion were registered.

Data extraction

We collected information on general characteristics of the studies and results related to our research questions, using a standardized extraction form. Extracted data included the number of patients studied, study setting, study design, source of information, frequency of measurements, measurement method, primary diagnosis (cancer or noncancer), and general patient characteristics. We also extracted data on the prevalence of death rattle, assessments of the impact of death rattle on patients, relatives, and professional caregivers, and effects of medical and nonmedical interventions.

Quality assessment

The quality of the selected studies was assessed using the multimethod assessment tool devised by Hawker et al[21]. This tool can be used to evaluate studies with quantitative and qualitative designs. All studies were assessed on nine different aspects: abstract and title; introduction and aims; methods and data; sampling; data analysis; ethics and bias; results; transferability or generalizability; and implications and usefulness. For each aspect, a score was given on a four-point scale, from 1, very poor, to 4, good. Summing the different area scores results in a total score, from 9, very poor, to 36, good.

RESULTS

Selection of articles

Our search yielded 1062 unique articles. In the first step, 824 articles were excluded because the articles' titles were assessed as not relevant. In the second step, 84 articles were excluded because their abstracts did not meet the selection criteria. This resulted in 154 remaining articles, of which 36 articles could be included after assessment of the full texts (Figure 1). A manual search of references identified three other studies, for a total of 39 studies (Table 1).

The studies were published between 1988 and 2012. Eight studies were performed in Asia, of which seven were done in Japan; two in Australia; one in New Zealand; 24 in Europe, of which 16 were done in the U.K.; and four in North America. The 39 studies included three randomized controlled trails[22-24], two prospective comparative studies[25-26], eight prospective observational studies[7-8, 10, 27-31], two cross-sectional surveys[32-33], two retrospective surveys[34-35], 18 medical record reviews[6, 9, 36-51], three qualitative interview studies[12, 14, 52], and one qualitative focus group study[13].

Table 1 General characteristics of included studies (n=39)

Author/Country	Year of publication	Setting	Sample size	Design	Quality Assessment[a]
Asia					
Yamaguchi et al.,[27] Japan	2012	Hospital, PCU, home care	161	Prospective observational study	28
Morita et al,.[29] Japan	2005	Hospital, PCU, home care	226	Prospective observational study	29
Seah et al.,[48] Singapore	2005	Hospital	189	Medical records review	27
Morita et al.,[28] Japan	2004	Hospital, PCU, home care	310	Prospective observational study	29
Morita et al.,[34] Japan	2004	PCU	195	Retrospective survey	20
Morita et al.,[8] Japan	2000	Hospital	245	Prospective observational study	26
Morita et al.,[31] Japan	1999	Hospice	350	Prospective observational study	26
Morita et al.,[30] Japan	1998	Hospice	100	Prospective observational study	23
Australia					
Sheehan et al.,[50] Australia	2011	PCU	199	Medical records review	28
Clark et al.,[22] Australia	2008	Hospital	10	Randomized controlled trail	29
Lichter et al.,[10] New Zealand	1990	Hospice	200	Prospective observational study	21
Europe					
Lundquist et al.,[49] Sweden	2011	Hospital, home-care, PCU, residential care	2382	Medical records review	31
Mercadante et al.,[35] Italy	2011	Home-care	181	Retrospective survey	29
Bradley et al.,[52] UK	2010	Hospital, hospice	15	Qualitative interviews	29
Pace et al.,[45] Italy	2009	Home-care	169	Medical records review	23
Wildiers et al.,[23] Belgium	2009	PCU	333	Randomized controlled trail	32
Jakobsson et al.,[42] Sweden	2008	Residential care, home care	229	Medical records review	30
Wee et al.,[13] UK	2008	Hospice	41	Qualitative focus groups	27
Wee et al.,[12] UK	2006	Hospital, hospice, home care	12	Qualitative interviews	31
Wee et al.,[14] UK	2006	Hospital, hospice, home care	17	Qualitative interviews	30
Hugel et al.,[41] UK	2006	PCU	165	Medical records review	25

Table 1 General characteristics of included studies (n=39) (continued)

Author/Country	Year of publication	Setting	Sample size	Design	Quality Assessment[a]
Grogan et al.,[38] UK	2005	Hospice/ PCU	68	Medical records review	21
Kass et al.,[43] UK	2003	PCU	202	Medical records review	26
Fowell et al.,[37] UK	2002	Hospital, hospice, PCU, home care	500	Medical records review	28
Wildiers et al.,[9] Belgium	2002	Hospital	107	Medical records review	20
Back et al.,[25] UK	2001	PCU	504	Prospective comparative study	26
Ellershaw et al.,[36] UK	2001	PCU	168	Medical records review	25
Hughes et al.,[26] UK	2000	Hospice, PCU	111	Prospective comparative study	20
Watts et al.,[32] UK	1999	Not specified	23	Cross sectional survey	17
Pautex et al.,[46] Switserland	1997	Hospital	100	Medical records review	20
Watts et al.,[33] UK	1997	PCU	23	Cross sectional survey	23
Bennett et al.,[6] UK	1996	Hospice	96	Medical records review	22
Ellershaw et al.,[7] UK	1995	Hospice	82	Prospective observational study	28
Power et al.,[47] Ireland	1992	Hospice	100	Medical records review	19
Hoskin et al.,[40] UK	1988	Hospital	158	Medical records review	20
North-America					
Heisler et al.,[24] USA	2012	PCU	137	Randomized controlled trail	31
Protus et al.,[51] USA	2012	Hospice	147	Medical records review	23
Hall et al.,[39] Canada	2002	Long term care facilities	185	Medical records review	27
Lindley-Davis et al.,[44] USA	1991	Home care	11	Medical records review	24

PCU= palliative care unit

[a] Quality assessment: 9 = very poor, 18 = poor, 27 = fair, 36 = good.

Quality assessment

The total scores for quality of the included articles are presented in Table 1. One article was rated between "very poor" and "poor;" 20 articles were rated between "poor" and "fair;" and 18 articles were rated between "fair" and "good."

Labels and definitions of death rattle

Various labels were used to describe death rattle: bronchial secretion, (troubling/noisy/terminal) respiratory (tract) secretions, increasing secretions, noisy-retained secretions, terminal secretions, pulmonary rattles, noisy (rattling/moist) breathing (at the end of life), or respiratory symptoms. In addition, definitions of death rattle varied between studies. Twenty-two articles provided a definition of death rattle. Elements included in these definitions were the noise or sound associated with death rattle[6-9, 12-14, 22-26, 28-31, 33, 41, 43, 50-52], the movement of (accumulated) secretions[7-9, 22-23, 28-31, 41, 43, 50-51], location in the hypopharynx, bronchial tree[7-8, 25, 28-31, 41, 43, 51] or upper airways[9, 23, 50], the relation with respiration[6-9, 12-14, 22-23, 25, 28-31, 33, 41, 43, 50, 52], its occurrence in the terminal phase of an illness[6, 9, 12, 14, 22-23, 25, 41], its relation with weakness and/or inability to cough or clear the airways[6, 9, 22-23, 25, 51], and the idea that it can be distressing for those involved[6, 8, 22, 25, 41, 50-51].

Prevalence of death rattle

Data on the prevalence of death rattle were reported in 29 articles (Table 2). Sample sizes ranged between 68 and 2382 patients. Studies were performed in hospitals (34%), palliative care units (45%), home care (28%), hospices (34%), or long term care facilities (7%); some studies concerned more than one type of setting. Sixteen studies were performed in a population of patients with a diagnosis of primary cancer, eight in a mixed population (cancer and noncancer combined) and in five studies, the diagnosis of patients were not specified.

The prevalence of death rattle varied between studies. The lowest and highest percentages reported were 12%, in a retrospective study of 169 patients with a brain tumors[45], and 92%, in a prospective study of 82 patients with various forms of cancer[7]. The weighted mean for these 29 studies was 35% The reported median time from the onset of death rattle until death was between 11 and 28 hours[23-25, 30, 41, 43, 51].

Six studies[23-25, 27-29] used a scoring scale as proposed by Back et al.[25] to assess the severity of death rattle. This scoring scale records the volume of noise associated with death rattle: 0, inaudible; 1, audible only very close to the patient; 2, clearly audible at the end of the bed, in a quiet room; 3, clearly audible at about 20 ft (9.5 m) (at the door of the room), in a quiet room. Of these six studies, four presented data about the severity of death rattle: 6-17% of all patients had death rattle score 1, 19-26% had score 2 and 5-11% had a score 3[23-25, 28].

Patient characteristics that were found to be significantly associated with the presence of death rattle were disoriented cognitive function[42], male gender[43], lung cancer[8, 28, 43], a tumor

Table 2 Studies reporting on prevalence of death rattle (n=29)

Author/country/ year	Setting	Symptom label	Measurement method	Design	Sample size	Diagnosis	Prevalence
Pace et al.[45] Italy, 2009	Home care	Death rattle	Death rattle presence as listed in medical record	Retrospective	169	Cancer (brain tumors)	12%
Seah et al.[48] Singapore, 2005	Hospital	Troubling respiratory secretions	Death rattle presence as listed in medical record	Retrospective	189	Mixed (cancer and various non-cancer)	15%
Mercadante et al.[35] Italy, 2011	Home care	Death rattle	Death rattle presence during last two hours of patient's life as determined by relatives	Retrospective	181	Cancer (various tumors)	16%
Lundquist et al.[49] Sweden, 2011	Hospital, PCU, home care, residential care	Respiratory tract secretions	Death rattle presence as listed in medical record	Retrospective	2382	Cancer (various tumors)	17%
Wildiers et al.[9] Belgium, 2002	Hospital	Death rattle	Death rattle presence as listed in medical record	Retrospective	107	Cancer (various tumors)	23%
Protus et al.[51] USA, 2012	Hospice	Terminal respiratory secretions	Death rattle presence as listed in medical record	Retrospective	147	Mixed (cancer and various non-cancer)	27%
Jakobsson et al.[42] Sweden, 2008	Residential care, home care	Pulmonary rattles	Death rattle presence as listed in medical record	Retrospective	229	Diagnosis not specified	30%
Morita et al.[34] Japan, 2004	PCU	Bronchial secretion	Death rattle frequency during last week of patient's life as rated by relatives: 'not at all,' 'sometimes,' 'often,' 'very often.' *Prevalence based on grouping together 'often' and 'very often'*	Retrospective	195	Cancer (not specified)	33%
Hoskin et al.[40] UK, 1988	Hospital	Respiratory symptoms	Death rattle presence based on anti-muscarinic drugs use as listed in medical record	Retrospective	158	Cancer (various tumors)	34%

Table 2 Studies reporting on prevalence of death rattle (n=29) (continued)

Author/country/ year	Setting	Symptom label	Measurment method	Design	Sample size	Diagnosis	Prevalence
Morita et al.[30] Japan, 1998	Hospice	Death rattle	Death rattle presence observed by professional caregivers	Prospective	100	Cancer (various tumors)	35%
Pautex et al.[46] Switserland, 1997	Hospital	Death rattle	Death rattle presence as listed in medical record	Retrospective	100	Mixed (cancer and various non-cancer)	38%
Hall et al.[39] Canada, 2002	Hospice	Noisy breathing	Death rattle presence as listed in medical record	Retrospective	185	Mixed (cancer and various non-cancer)	39%
Morita et al.[28] Japan, 2004	Hospital, PCU, home care	Bronchial secretion	Death rattle scoring scale Back et al.[25]	Prospective	310	Cancer (lung/abdominal)	41%
Back et al.[25] UK, 2001	PCU	Death rattle	Death rattle scoring scale Back et al.[25]	Prospective	504	Cancer (various tumors)	41%
Yamaguchi et al.[27] Japan, 2012	Hospital, PCU, home care	Bronchial secretion	Death rattle scoring scale Back et al.[25]	Prospective	151	Cancer (abdominal)	43%
Heisler et al.[24] USA, 2012	PCU	Death rattle	Death rattle scoring scale Back et al.[25]	Prospective	404	Mixed (cancer and various non-cancer)	44%
Morita et al.[8] Japan, 2000	Hospital	Death rattle	Death rattle presence as observed by professional caregivers	Prospective	245	Cancer (various tumors)	44%
Morita et al.[31] Japan, 1999	Hospice	Death rattle	Death rattle presence as observed by professional caregivers	Prospective	350	Cancer (various tumors)	44%
Power et al.[47] Ireland, 1992	Hospice	Respiratory secretions	Death rattle presence based on use of anti-muscarinic drugs as listed in medical record	Retrospective	100	Diagnosis not specified	44%
Morita et al.[29] Japan, 2005	Hospital, PCU, home care	Bronchial secretion	Death rattle scoring scale Back et al.[25]	Prospective	226	Cancer (abdominal)	45%
Ellershaw et al.[36] UK, 2001	PCU	Respiratory tract secretion	Death rattle presence as listed in medical record	Retrospective	168	Diagnosis not specified	
Bennett et al.[6] UK, 1996	Hospice	Death rattle	Death rattle presence as listed in medical record	Retrospective	96	Mixed (cancer and various non-cancer)	45%

Table 2 Studies reporting on prevalence of death rattle (n=29) (continued)

Author/country/ year	Setting	Symptom label	Measurment method	Design	Sample size	Diagnosis	Prevalence
Kass et al.[43] UK, 2003	PCU	Respiratory tract secretions	Death rattle presence as listed in medical record	Retrospective	202	Cancer (various tumors)	49%
Fowell et al.[37] UK, 2002	Hospital, hospice, PCU, home care	Respiratory tract secretions	Death rattle presence as listed in medical record	Retrospective	500	Mixed (cancer and various non-cancer)	50%
Lichter et al.[10] New Zealand, 1990	Hospice	Noisy and moist breathing	Death rattle presence as observed by professional caregivers	Prospective	200	Diagnosis not specified	56%
Grogan et al.[38] UK, 2005	Hospice, PCU	Respiratory secretions	Death rattle presence as listed in medical record	Retrospective	68	Diagnosis not specified	59%
Sheehan et al.[50], Australia, 2011	PCU	Noisy respiratory secretions	Death rattle presence based on anti-muscarinic drugs use as listed in medical record	Retrospective	199	Mixed (cancer and various non-cancer)	60%
Hugel et al.[41] UK, 2006	PCU	Respiratory tract secretions	Death rattle presence as listed in medical record	Retrospective	165	Cancer (various tumors)	80%
Ellershaw et al.[7] UK, 1995	Hospice	Respiratory tract secretion	Death rattle presence observed by professional caregivers or anti-muscarinic drug administered	Prospective	82	Cancer (various tumors)	92%

Abbreviations: PCU = Palliative care unit

[a] Number of patients in the study on which prevalence was based

located in bone, liver, intestinal tract[8] or brain[6, 8] , pneumonia[28] and a duration of stay in a hospice of more than nine days[6] (see appendix).

Impact of death rattle

Data on the impact of death rattle on patients, relatives and professional caregivers were reported in eight studies: four quantitative studies[32-34, 44] and four qualitative studies[12-14, 52] (table 3). Sample sizes in the four quantitative studies ranged between 11 and 65 respondents. Respondents were nurses[32-33, 44] or bereaved relatives[34]. Sample sizes in the four qualitative studies ranged between 12 and 41 respondents. Respondents were professional or informal caregivers (nurses, physicians and volunteers)[13, 52] or bereaved relatives[12, 14].

Impact on patients

In a study among nurses, 87% indicated that they felt that death rattle does not distress the dying patient[32]. A qualitative study among physicians, nurses and volunteers suggested that patients may feel distressed because of the sound of death rattle of other patients in the same ward[13].

Impact on relatives

Eight studies provided information on the impact of death rattle on relatives. According to one study, relatives perceived death rattle as 'not so distressing' in 5%, as 'slightly distressing' in 15%, as 'distressing' in 26%, and as 'very distressing' in 52%[34]. In two studies among nurses, 100% of them indicated that death rattle causes distress for all those involved, but particularly for relatives[32-33]. Such distress is, according to one study among nurses, related to relatives experiencing that patients were 'gagging' and 'drowning' in secretions (no percentage mentioned)[44].

The qualitative studies suggested that, although death rattle was regarded as distressing for most relatives[12-14, 52], some relatives found it reassuring to hear the patient breathe, or regarded death rattle as a helpful warning sign of impending death[12, 14, 52].

Impact on professional caregivers

One quantitative and two qualitative studies reported on the impact of death rattle on professional caregivers. In a cross-sectional survey, 79% of nurses regarded death rattle as distressing[32]. Focus groups with hospice staff and volunteers and interviews with physicians and nurses showed that for them, death rattle may be distressing[13, 52]. Interviewed nurses and physicians mentioned that they themselves possibly benefited from interventions to diminish death rattle. This benefit is related to being able to do something for the patient and family[52].

Table 3 Studies reporting on impact of death rattle (n=8)

Author/ country	Year of publication	Setting	Design	Source	Sample size[a]	Description of impact
Quantitative studies						
Morita et al.,[34] Japan	2004	PCU	Retrospective survey of relatives	Relatives of patient with death rattle	65	**Impact (of death rattle) on relatives** Relatives' reports on the impact of death rattle: 'not distressed at all' (n=0 / 0%), 'not so distressed' (n=3 / 5%), 'slightly distressed' (n=10 / 15%), 'distressed' (n= 17 / 26%), or 'very distressed' (n= 34 / 52%).
Watts et al.,[32] UK	1999	Not specified	Cross sectional survey of nurses	Nurses	23	**Impact (of death rattle) on patients** Death rattle does not distress the dying person (n=30 / 87%) **Impact (of death rattle) on relatives** Death rattle distresses relatives (n=23 / 100%). Relatives mention to nurse that the death rattle in particular had caused them distress (n=12 / 52%) **Impact (of death rattle) on caregivers** Death rattle distresses nurses (n=18 / 79%), some thought that suction is appropriate (n=6 / 26%)
Watts et al.,[33] UK	1997	PCU	Cross sectional survey of nurses	Nurses	23	**Impact (of death rattle) on relatives** Death rattle causes distress to all parties, but particularly to relatives (n=23/100%)
Lindley-Davis et al.,[44] USA	1991	Home care	Medical records review	Nurses	11	**Impact (of death rattle) on relatives** Relatives' distress with death rattle: Relatives had high levels of anxiety as the client began 'gagging' and 'drowning' in secretions. (n=not mentioned in article).

Table 3 Studies reporting on impact of death rattle (n=8) (continued)

Author/ country	Year of publication	Setting	Design	Source	Sample size[a]	Description of impact
Qualitative studies						
Bradley et al.,[52] UK	2010	Hospital, hospice	Qualitative interviews with physicians and nurses	Physicians and nurses	15	**Impact (of death rattle) on relatives** Death rattle can cause family distress. Some families find a positive side to the presence of death rattle (it gives them reassurance to hear them breathe). Respondents believe that families may benefit from their management choices. **Impact (of death rattle) on caregivers** Nurses and other staff are likely to be distressed by death rattle; some respondents suggest that death rattle has little to no impact. The impact is described as feeling uncomfortable, feeling frustrated or unpleasant, or as death rattle being distressing or hard to bear. Caregivers may benefit from management decisions, because doing something feels more comfortable than doing nothing
Wee et al.,[13] UK	2008	Hospice	Qualitative focus groups with staff and volunteers	Physicians, nurses and volunteers	41	**Impact on patients** Patients in the same ward may feel distressed because of the sound of death rattle of other patients. **Impact (of death rattle) on relatives** Death rattle is believed to distress relatives. **Impact (of death rattle) on caregivers** Hospice staff and volunteers have largely negative feelings about death rattle. Doctors and nurses were divided about why they intervened The way in which they themselves make sense of the sound influences both their response to relatives and the actions they take.
Wee et al.,[12] UK	2006	Hospital, hospice, home care	Qualitative interviews	Relatives of patient with death rattle	12	**Impact (of death rattle) on relatives** Some have explicit negative feelings about the sound of death rattle. This was sometimes associated with their concerns about the patient's suffering. Others are not distressed; some even found it helpful, as a warning sign of impending death.

Table 3 Studies reporting on impact of death rattle (n=8) (continued)

Author/ country	Year of publication	Setting	Design	Source	Sample size[a]	Description of impact
Wee et al.,[14] UK	2006	Hospital, hospice, home care	Qualitative interviews	Relatives of patient with death rattle	17	**Impact (of death rattle) on relatives** Most are distressed by the sound of death rattle. Others are not particularly bothered, regard it as a useful warning sign that death was imminent or are more distressed by other issues surrounding the dying process. Relatives may take their cue from the patient's appearance, being concerned if the patient looks distressed, but less so if the patient is not obviously disturbed.

PCU= palliative care unit

[a] People in the study that reported on impact of death rattle

Table 4 Studies reporting on interventions for death rattle and their effectiveness (n=11)

Author / county / year/ design	Setting	Diagnosis	Interventions for death rattle		
			Description of intervention [a]	Outcome measure	Effectiveness of intervention
Two or more study groups (medication)					
Heisler et al.[24] USA, 2012 *Randomized controlled trail*	PCU	Mixed (cancer & various non-cancer)	1) **Atropine (n=74)** 1 mg sublingually (2 drops 1% solution) 2) **Placebo (n=63)** 2 drops of placebo (saline) solution	Reduction of score with ≥ 1 point *Death rattle score Back et al[25]*	**No difference between groups** Effectiveness after two hours; 38%, 41% (p = 0·73) Effectiveness after four hours; 40%, 52% (p = 0·21)
Wildiers et al.[23] Belgium, 2009 *Randomized controlled trail*	PCU	Cancer (various tumors)	1) **Atropine (n=115)** 0,5 mg sc bolus, followed by 3 mg/24h 2) **Scopolamine (n=112)** 0,25 mg sc bolus, followed by 1,5mg/24h 3) **Hyoscine butylbromide (n=106)** 20 mg sc bolus, followed by 60 mg/24h	Lowering of score to 0 or 1 *Death rattle score Back et al[25]*	**No difference between groups** Effectiveness after one hour; 42%, 37%, 42% (p = 0·72) Effectiveness after 24 hours; ; 76%, 68%, 60% (ns; p unknown)
Clark et al.[22] Australia, 2008 *Randomized controlled trail*	Hospital	Cancer (various tumors)	1) **Octreotide (n=5)** 0,2 mg bolus , if death rattle persisted ≥ 1h 0,4 mg **Scopolamine** was administered 2) **Scopolamine (n=5)** 0,4 mg bolus, if death rattle persisted ≥ 1h 0,2 mg **Octreotide** was administered	A decrease in the level of death rattle *Level categorized into 5 points: none, mild, moderate, severe, very severe*	**No difference between groups** Overall effectiveness; 40%, 40%
Back et al.[25] UK, 2001 *Prospective comparative study*	PCU	Cancer (various tumors)	1) **Scopolamine (n=108)** 0,4 mg sc bolus, if the noise was still unacceptable ≥30 min. 0,4 mg sc repeated. Optionally followed by 1,2 – 2,4 mg/ 24 h sc 2) **Glycopyrronium (n=62)** 0,2 mg sc bolus, if the noise was still unacceptable ≥30 min 0,2 mg sc repeated. Optionally followed by 0,8 mg/ 24h sc	Death rattle scores at 30 min, 1 h and final score before death were compared with the initial score, and categorized as better, the same or worse. *Death rattle score Back et al[25]*	**Scopolamine group responded more often than Glycopyrronium group (p = 0·002)** at t= 30 minutes Effectiveness after 30 min; 56%, 27% (p = 0·002) Effectiveness after one hour; 57%, 40% (p=0·09) Symptom-free at death; 51%, 42% (p=0·12)

Table 4 Studies reporting on interventions for death rattle and their effectiveness (n=11) (continued)

Author / county / year/ design	Setting	Diagnosis	Interventions for death rattle		
			Description of intervention [a]	Outcome measure	Effectiveness of intervention
Hughes et al.[26]. UK, 2000 *Prospective comparative study*	Hospice, PCU, hospice	Diagnosis not specified	1) **Scopolamine (n=37)** 0,4 mg bolus, after 30 min with no result 0,6 mg bolus and 2,4 mg/ 24h after 30 min with no result 0,6 mg **scopolamine** # 2) **Hyoscine butylbromide (n=37)** 20 mg bolus, after 30 min with no result 20 mg bolus and 20 mg/24h after 30 min with no result 0,2 mg **glycopyrronium** # 3) **Glycopyrronium (n=37)** 0,2 mg bolus, after 30 min with no result 0,4 mg bolus and 0,6 mg/24h after 30 min with no result 0,4 mg **glycopyrronium** #	Level of relief of death rattle noise and of relatives' distress. Baseline levels - Intensity of death rattle noise: mild, moderate or severe - Relatives' distress: not at all, a little, quite a bit, very much Level of change - Absent, much better, slightly better, same, slightly worse or much worse	**No difference between groups** Effectiveness after 30 min; 35%, 54%, 46% (p unknown) Symptom-free at death; 54%, 65%, 65% (ns; p unknown)
Two or more study groups (medication)					
Hugel et al[41]., UK, 2006 *Medical records review*	PCU	Cancer (various tumors)	1) **Glycopyrronium (n=36)** 0,2 mg sc bolus, followed by 0,6mg/24h (+ p.r.n. 0,2 mg). ≥2 p.r.n. doses/24h =>continuous dose increase to 1,2mg/24h 2) **Scopolamine (n=36)** 0,4 mg sc bolus, followed by 1,2mg/24h (+ p.r.n. 0,4 mg) ≥2 p.r.n. doses/24h => continuous dose increased to 2,4 mg/24h	Response was determined grouping together immediate, late, and transient response, and comparing it to no response *Response categorized* $	**Glycopyrronium group responded more often than scopolamine group (p = 0·01)** Overall response: group 1) 100%, group 2) 78% (p = 0·01) Symptom-free at death: group 1 72%, group 2 58% (p unknown)
Two or more study groups (non-medication)					
Morita et al.[29] Japan, 2005 *Prospective observational study*	Hospital, PCU home care	Cancer (abdominal)	1) **Hydration group (n=59)** ≥ 1 l/day at 1 week & 3 weeks before death 2) **Non-hydration group (n=167)** < 1 l/day at 1 week & 3 weeks before death	Symptom severity in the last 3 weeks of the patients with and without hydration *Death rattle score Back et al*[25]	**No difference between groups** Difference in death rattle score ≥ 1 (p = 0·79) Difference in death rattle score ≥ 2 (p = 0·74)

Table 4 Studies reporting on interventions for death rattle and their effectiveness (n=11) (continued)

Author / county / year/ design	Setting	Diagnosis	Interventions for death rattle		
			Description of intervention [a]	Outcome measure	Effectiveness of intervention
Yamaguchi et al.[27] Japan, 2012 *Prospective observational study*	Hospital, PCU, home care	Cancer (abdominal)	1) **Large volume hydration group (n=80)** ≥ 1 l/day at study inclusion 2) **Small volume hydration group (n=56)** < 1 l/day at study inclusion	Symptom severity 48 hours before death *Death rattle score Back et al*[25]	**No difference between groups** Difference death rattle prevalence (p = 0·073)
One group					
Protus et al.[51] USA, 2012 *Medical records review*	Hospice	Mixed (cancer & various non-cancer)	1) **Atropine (n=22)** 2 drops 1% solution sublingually (0,5mg/drop) every 2 h as needed	The reduction or resolution of death rattle	Overall effectiveness; 86%
Kass et al.[43] UK, 2003 *Medical records review*	PCU	Cancer (various tumors)	1) **Scopolamine (n=59)** 0,4 mg bolus, followed by 1,2 mg/24h if no result after 24 hours => continuous dose increased to 2,4 mg/24h	The presence or absence of death rattle	Effectiveness within four hours; 31%· Overall effectiveness/ symptom-free before death; 64%
Wildiers et al.[9] Belgium, 2002 *Medical records review*	Hospital	Cancer (various tumors)	1) **Scopolamine (n=25)** 0,25 mg/4h bolus or iv dose between 1 - 2,5 mg/24h	Medication was effective when there was no evidence for persisting disturbing rattle (as well for relatives as for the caregivers).	Overall effectiveness; 72%

PCU = palliative care unit; SC = subcutaneous; NS, nonsignificant; prn = pro re nata (as needed medication); IV = intravenous.

[a] is the number of patients in the intervention group.

[b] Treatment schedule continued: after 30 minutes with no result, 0.4 mg of glycopyrronium, after 30 minutes with no result, 0.4 mg of glycopyrronium.

[c] A response included immediate (within four hours), late (after more than four hours), transient (symptom-free episodes after treatment but not symptom free at death), no response (no symptom-free episode).

Interventions for death rattle

Eleven studies reported on the effectiveness of interventions for death rattle (table 4). Sample sizes ranged between 5 and 167 respondents per study group. Nine studies described medical interventions and two studies described the association between the hydration level and death rattle. No studies were found on the effectiveness of other interventions, for example, repositioning of the patient, explanation of the symptom to relatives, or suctioning of secretions. Eight studies had a comparative design, comparing two or three interventions[22-27, 29, 41]. Three studies were not controlled[9, 43, 51].

Six studies compared two or three medication regimes. Medications studied included scopolamine[22-23, 25-26, 41], glycopyrronium[25-26, 41], hyoscine butylbromide[23, 26], atropine[23-24] and octreotide[22]. Three studies found no differences in the effectiveness of the different v regimes[22-23, 26]. One randomized controlled trail found no differences in the prevalence of death rattle between patients receiving atropine and patients receiving a placebo[24]. One comparative but uncontrolled study found that scopolamine was significantly more effective than glycopyrronium in reducing the severity of death rattle as recorded by nurses 30 minutes after administration of the medication, but no difference was found one hour after administration and at the final measurement before death[25]. A retrospective study using medical records found contrasting results: patients who received glycopyrronium were significantly more often reported as having a response to treatment than patients receiving scopolamine[41].Two studies compared two groups with different hydration regimes (<1 liter/day versus ≥1 liter/day)[27, 29]. A reduced level of hydration was found not to change death rattle prevalence.

DISCUSSION

The prevalence of death rattle was found to vary widely. Several characteristics of studies that assessed prevalences may explain this variance. First, there is a wide variety of labels and definitions used to describe death rattle, with the noise or sound as a constant element in all definitions. Whether the various labels all represent the exact same phenomenon is, however, not clear. Second, different study designs were used: 34% were prospective studies, 64% were retrospective studies. The weighted mean for the prevalence of death rattle in the prospective studies was 45%, compared to 30% in the retrospective studies. Third, few studies reported the exact point in time during the dying process at which the presence of death rattle was assessed. The natural course of death rattle is not clear. Kass and Ellershaw suggest that the prevalence of death rattle typically increases when death approaches[43]. However, Heisler et al. performed a placebo controlled trial and found an decrease of death rattle scores over time in the placebo group[24]. Fourth, studies reporting on prevalences were often restricted to patients with cancer, but some studies also included noncancer patients. Whether specific diseases are associated with the prevalence of death rattle is

unclear. Only patients with cerebral or lung malignancies were found to have a higher risk of death rattle[6, 8, 28, 43]. More studies are needed to give insight into specific relationships between underlying disease and death rattle prevalence rate. Fifth, measurement methods to determine death rattle prevalence varied between the different studies. Validated instruments, such as the death rattle scoring scale[25] were not used by most studies.

The impact of death rattle on patients remains unclear and can only be based on subjective reports of others. It is often assumed by healthcare professional that patients are not distressed by this symptom, because they are generally unconscious when death rattle develops. Many professional caregivers assume that death rattle is distressing for relatives[13]. Whether relatives experience distress seems to be related to their judgment whether a patient is comfortable. For some relatives the symptom can also be helpful because it either demonstrates that the patient is still alive or is seen as a sign of impending death. Professional caregivers themselves may also be distressed by the noise of death rattle, which often results in a medical intervention. Wee et al.[13] and Heisler et al.[24] suggest that the way in which professional caregivers interpret the symptom can influence their response and actions, which could also affect relatives' perceptions. Professional caregivers should be aware of this effect.

A number of different interventions for the treatment of death rattle are included in guidelines and palliative care textbooks: repositioning of the patient, explanation of the symptom to relatives, suctioning of secretions, reduction of artificial hydration, administration of antimuscarinic drugs and sedation. Only reducing the level of hydration and treatment with antimuscarinic drugs have been studied for their effectiveness. Two studies among patients with abdominal cancer found no relation between the level of hydration and the prevalence of death rattle. There is no evidence that the use of any antimuscarinic drug is superior to no treatment. This finding is in line with the previous Cochrane review focusing on interventions for death rattle[19]. However, studies on the effect of pharmacologic interventions are limited by their lack of a placebo group. Well-designed studies to assess the relation between hydration and death rattle, and studies on the effects of non-pharmacologic interventions for death rattle, are still lacking. More prospective randomized controlled studies on the effectiveness of medical therapy and other interventions are urgently needed to confirm these findings.

We conclude that death rattle is a common symptom in dying patients. Approximately one-third of dying patients will present with this symptom. Current evidence does not support the standard use of antimuscarinic drugs in the treatment of death rattle. More high-quality studies are needed to give insight into the effects of interventions, both pharmacologic and non-pharmacologic. Until then, care should focus on communication about the symptom with relatives and others involved in the care of these patients. Regarding the symptom as being part of the normal dying process could contribute to the lowering of distress levels of those involved.

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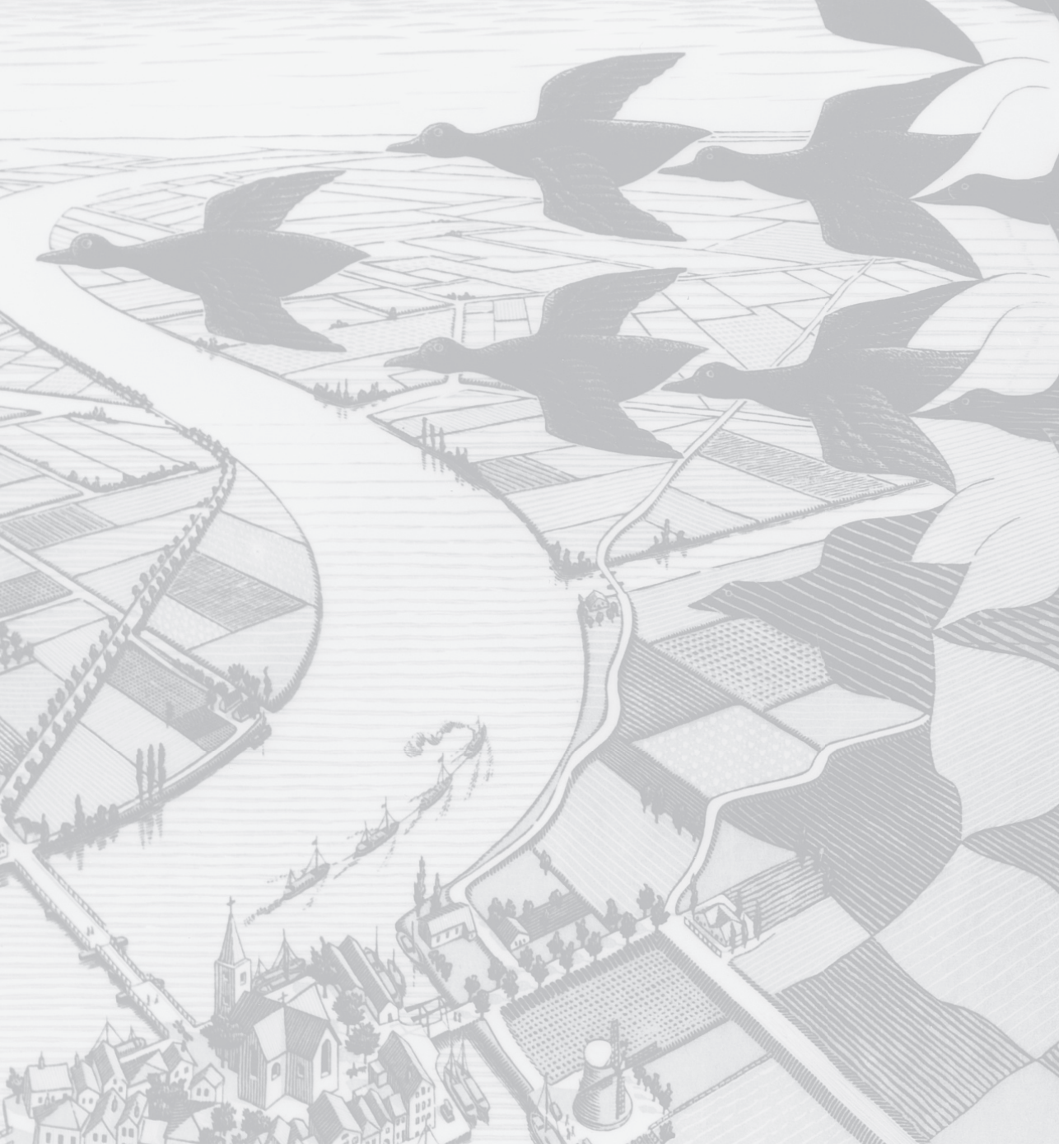
Appendix Table 1. Prevalence in subgroups

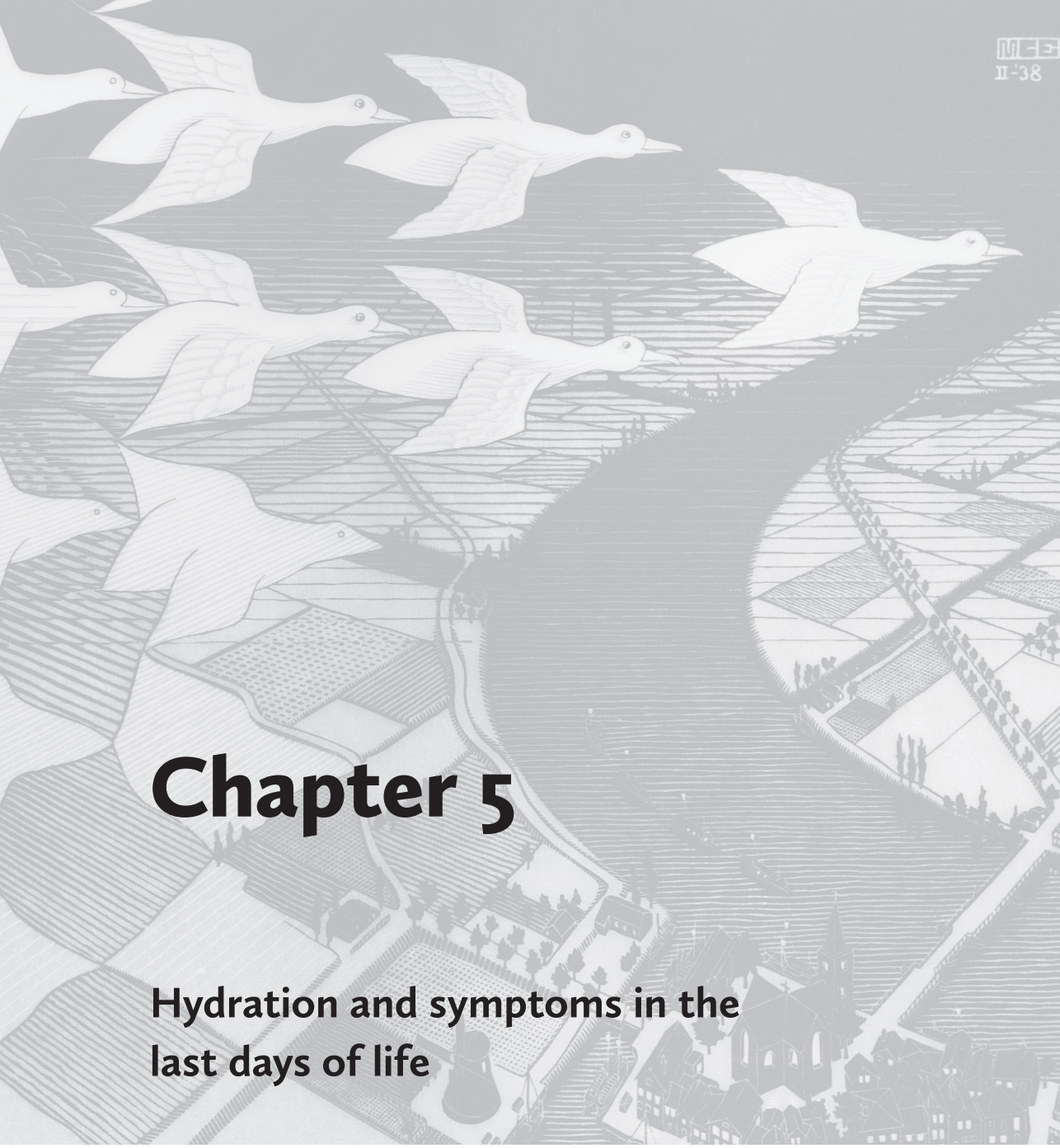
Author / country, year of publication	Setting	Diagnosis	Sample size[a]	Prevalence in subgroups	
Jakobsson et al[42]., Sweden, 2008	Residential care, home care	Diagnosis not specified	229	Physical function	
				• Adl-independent	28%
				• Adl-dependent	32% (p > 0·05)
				Cognitive function	
				• Oriented	25%
				• Disoriented	41% (p = 0·022)
Morita et al[29]., Japan, 2005	Hospital, PCU, home care	Cancer (abdominal)	226	Hydration status	
				Prevalence of secretion score ≥ 1[b]	
				• Hydration + [(c)]	44%
				• Hydration – [(d)]	46% (p > 0·05)
				Prevalence of secretion score ≥ 2[b]	
				• Hydration +	19%
				• Hydration –	17% (p > 0·05)
Morita et al[28]., Japan, 2004	Hospital, PCU, home care	Cancer (lung + abdominal)	310	**Primary tumor site**	
				• Abdominal	67%
				• Lung	46% (p = 0·001)
				Brain metastases	
				• Present	56%
				• Absent	51% (p > 0·05)
				Lung metastases	
				• Present	58%
				• Absent	47% (p > 0·05)
				Pneumonia	
				• Present	68%
				• Absent	46% (p = 0·002)
				Dysphagia	
				• Present	
				• Absent	75%
				No correlation with age and gender	49% (p > 0·05)

Appendix Table 1. Prevalence in subgroups (continued)

Author / country, year of publication	Setting	Diagnosis	Sample size[a]	Prevalence in subgroups	
Kass et al[43]., UK, 2003	PCU	Cancer (various tumors)	202	Tumor locations	
				• Lung cancer	68%
				• GI cancer	42%
				• Hepatobiliary & pancreatic ca	40%
				• Breast	46%
				• Gynecological cancer - breast	35%
				• Urological, renal & prostatic ca	29%
				• Musculoskeletal & skin cancer	43%
				• Brain cancer	75%
				• Other ca or unknown primary	50%
				• non-cancer	50%
				Risk factors for development	
				• Age	(p > 0·05)
				• **Male gender**	(p = 0·034) RR 1,35
				• **Lung cancer**	(p = 0·003) RR 1·58
Morita et al[8]., Japan, 2000	Hospital	Cancer (various tumors)	245	**Tumor in brain**	
				• Present	21%
				• Absent	9% (p <0·01)
				Tumor in lung	
				• Present	63%
				• Absent	34% (p < 0·01)
				Tumor in bone	
				• Present	46%
				• Absent	29% (p < 0·01)
				Tumor in liver	
				• Present	32%
				• Absent	51% (p<0·01)
				Tumor in intestinal tract	
				• Present	27%
				• Absent	40% (p <0·05)
Pautex et al[46]., Switserland, 1997	Hospital	Mixed (cancer and various non-cancer)	100	Dementia	
				• Yes	46%
				• No	30% (p > 0·05)
Bennett et a[6]l., UK, 1996	Hospice	Mixed (long, liver, brain tumors, COPD, heart failure)	96	**Duration of stay > 9 days**	p = 0·048
				Cerebral malignancy	p = 0·048
				No correlation with pulmonary malignancies or pulmonary diseases	

PCU = palliative care unit; GI = gastrointestinal; RR = relative risk; COPD = chronic obstructive pulmonary disease; ADL = activities of daily living.
[a]Number of patients in the study on which prevalence was based. [b]Death rattle score25: 'inaudible' (score 0), 'audible only very close to the patient' (score 1), 'clearly audible at the end of the bed in a quiet room' (score 2) and 'clearly audible at about 6m or at the door of the room' (score 3).
[c]Artificial hydration ≥ 1 l/day. [d]Artificial hydration < 1 l/day.





Chapter 5

Hydration and symptoms in the last days of life

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Submitted

ABSTRACT

Background. At the end of life oral fluid intake is often reduced. Consensus about the most appropriate management for terminally ill patients with limited oral fluid intake is lacking. The debate about (artificial) hydration has mostly focused on two distinct symptoms in particular; death rattle, which has been linked to over-hydration at the end of life, and terminal restlessness, which has been linked to under-hydration at the end of life. The aim of this study is to investigate to what extent the amount of fluid intake, preceding and during the dying phase, is related to the occurrence of death rattle and terminal restlessness.

Methods. We performed a multicentre prospective observational study in eight hospitals and five hospices/palliative care units (PCU's). We collected data on the occurrence of death rattle and terminal restlessness, fluid intake and opioid use of patients who were expected to die within a few days or hours.

Results In total, 371 patients were included (59% of all deaths during the study period). Death rattle was reported at least once in 40% (n=149) of patients during the dying phase, and in 35% (n=130) of patients during the last 24 hours of life. The prevalence of death rattle increased with death coming nearer and was not associated with the amount of fluid intake during the days before dying. Terminal restlessness was reported in 26% of patients (n=96) during the dying phase and in 13% (n=49) of patients during the last 24 hours of life. Terminal restlessness occurred almost evenly throughout the dying phase and was not associated with a lower amount of fluid intake during the days before dying. Terminal restlessness during the last 24 hours of life was associated with a higher amount of fluid (i.e. > 250ml/day) during 48-25 hours before death.

Conclusions. Caution with fluid intake to prevent development of death rattle does not seem to be necessary. Our study suggests that a higher amount of fluid intake during 48-25 hours before death may be associated with the occurrence of terminal restlessness during the last 24 hours of life. Actively providing dying patients with artificial fluid therefore does not seem to be beneficial.

INTRODUCTION

Most patients with a deteriorating chronic illness have a reduced oral intake at the end of life. This may be due to illness- or treatment-related symptoms or complications, such as dysphagia, nausea or vomiting, generalized weakness, and, in the last days of life, to a decreased level of consciousness or a loss of desire to drink[1 2]. The evidence that artificial hydration (AH) may be beneficial when patients have a reduced oral intake in the last days of life is limited and inconclusive[3-5]. Common arguments against AH are that it may increase the risk of complications such as oedema, ascites, and death rattle[1 6 7]. On the other side, the most commonly mentioned benefits of AH are that hydration may alleviate patients' feelings of thirst and reduce the risk of delirium or terminal restlessness[1 5 6 8-10]. Opinions vary on whether or not AH prolongs the dying process[1 5 11 12]. As a result of these opposing arguments, attitudes whether or not AH should be used at the end of life vary among professional caregivers[5-7 13]. Professional caregivers working in palliative care tend to be more reserved about the benefits of AH than other professionals: most of them do not believe that hydration contributes to the alleviation of symptoms or prolongs survival[10 13]. Moreover, many of them are concerned about the additional burden of AH in the last week of life[10 13].

The debate about possible benefits of AH has focused especially on two distinct symptoms in particular; death rattle and terminal restlessness. Death rattle due to respiratory tract secretion is a common symptom with a prevalence of 35% among dying patients and has been linked to over-hydration at the end of life[5 14 15]. Terminal restlessness, an agitated delirium at the end of life, is a common indication for palliative sedation and has been linked to under-hydration at the end of life[5 7 8 16-18]. The aim of this study is to investigate to what extent the amount of fluid intake, preceding and during the dying phase, is related to the occurrence of death rattle and terminal restlessness. The dying phase is defined as the phase when death is expected to occur within hours or days[19 20].

METHOD

Study design and population

We performed a multicentre prospective observational study in patients, 18 years or older, who were, according to the multidisciplinary care team, likely to die within a few days. Data were collected in 8 hospitals (one to three wards per hospital) and five hospices, including three palliative care units in nursing homes (PCUs), in the Netherlands. Data collection took place between November 2012 and November 2013. The study was approved by the Medical Ethics Research Committee of the Erasmus MC, University Medical Centre Rotterdam.

Data collection

Anonymous data were collected using a digital version of the Care Program 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[21]. It was adapted to the Dutch language and healthcare system. The CPD is started when the multidisciplinary team agrees that the patient is likely to die within a few days and consists of three parts in which different data are recorded by nurses and physicians. For this study, the CPD was supplemented with questions about death rattle, terminal restlessness, patients' fluid intake and use of opioids. We used the following data from the first part of the CPD, reflecting patient characteristics and the patient's situation at the start of the CPD: diagnosis (cancer, non-cancer), gender, date of birth, date and time of the start of the CPD, level of consciousness (conscious, semi-conscious, unconscious) and prevalence of restlessness, confusion and respiratory tract secretions. Further, we used data from questions that were added to part 1, about patients' opioid use during the last day before the start of the CPD, and their total fluid intake (oral, intravenous (IV) and via feeding tube) during the last week and during the last day before the start of the CPD. Questions that were added to the second part of the CPD, reflecting the patient's situation from the start of the CPD until death, concerned total fluid intake, opioid use, occurrence of death rattle and terminal restlessness, all per 4 hourly intervals. From the third part of the CPD, reflecting the situation after the patient's death, we used data about the date and time of the patient's death and the provision of sedation during the dying phase. See the appendix for a detailed description of the variables that were used for this study.

Analysis and statistics

Patients were excluded from the study if data were missing on the date and time of the start of the CPD, the date and time of death or for more than 6 consecutive measurements (CPD, part 2).

Duration of the dying phase was calculated using the start date and time of the CPD and the date and time of the patient's death. *Total fluid intake* was based on the intake of oral fluid, IV fluid as well as fluid intake via a feeding tube. Nurses estimated patient's oral intake during the week before the start of the CPD; during the last day before the start of the CPD, and during the dying phase. The fluid intake by different routes was added per period of time and scored into 3 categories: 0-499 millilitres (ml) per day, 500-999ml per day, ≥1000ml per day for the periods preceding the start of the CPD; and 0-249ml per day, 250-499ml per day, ≥500ml per day during the dying phase. *Opioid doses* were recalculated to the morphine equivalent daily dose (MEDD) (mg/d) according to published equianalgesic dose tables[22 23]: oral morphine 60 mg/day = parental morphine 20 mg/day = transdermal/parenteral fentanyl 25 µg/hour = oral oxycodone 40 mg/day = parental hydromorphone 4 mg/day = transdermal buprenorphine 26 µg/ hour.

In case the dying phase had a duration longer than 48 hours, *fluid intake and opioid dose during 48-25 hours before death* (i.e. the last day preceding the last 24 hours of life) were calculated using the 4 hourly consecutive measurements from part 2 of the CPD. In case the dying phase had a duration between 24 and 48 hours, fluid intake and opioid dose were calculated using data concerning the intake/dose during the last day before the start of the CPD and the 4 hourly information from the consecutive measurements from part 2 of the CPD. In case the dying phase had a duration shorter than 24 hours, fluid intake and opioid dose were based on the data concerning the intake/dose during the last day before the start of the CPD (figure 1). *Death rattle* occurrence was assessed by the attending nurse using the scoring scale as proposed by Back et al.[24]. This scoring scale records the experienced volume of death rattle: 0. inaudible; 1. audible only very close to the patient; 2. clearly audible at the end of the bed, in a quiet room; 3. clearly audible at the door of the room (about 20

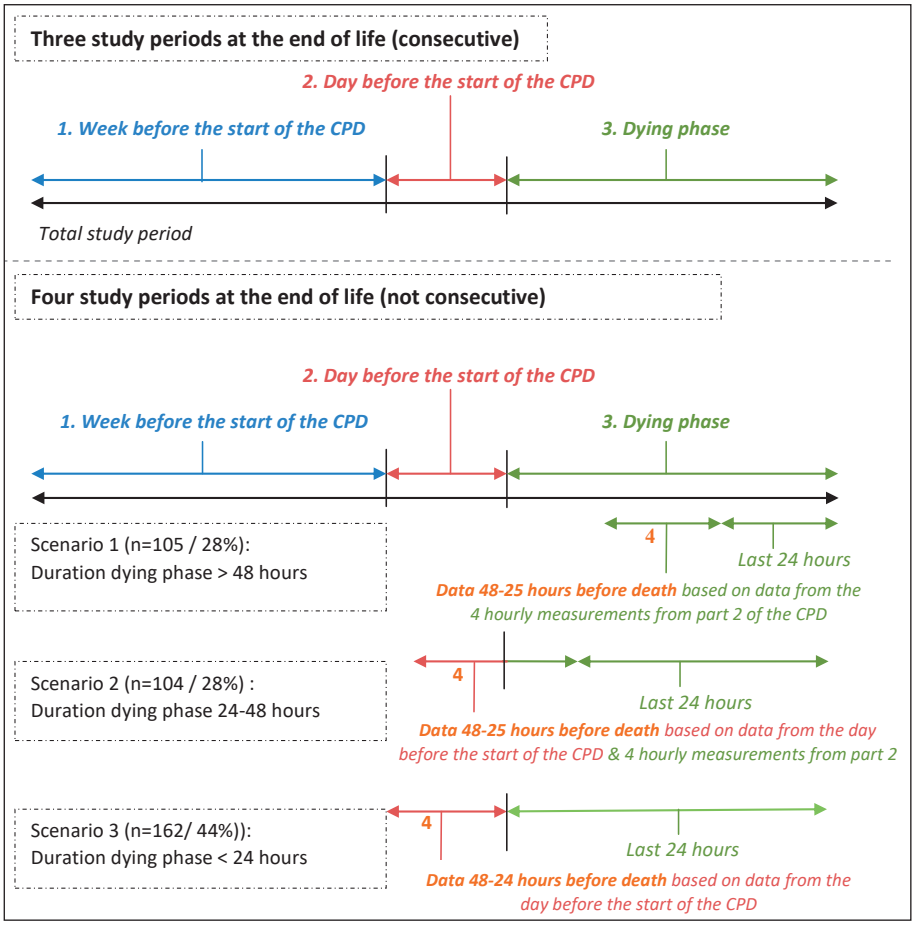

Figure 1. Data collection in relation to the moment of dying

feet/ 10 meter), in a quiet room. In this study a patient was considered to have death rattle when there was a score of ≥2 on at least one 4 hourly measurement during the dying phase. *Terminal restlessness* occurrence was assessed by the attending nurse using the calmness scale of the Vancouver Interaction and Calmness Scale (VICS)[25]. The calmness scale consists of five items: 1. patient appears calm; 2. patient appears restless; 3. patient appears distressed; 4. patient is moving around uneasily in bed; 5. patient is pulling at lines/tubes. Each item is scored on a 6-point Likert-scale (strongly agree, agree, mildly agree, mildly disagree, disagree, strongly disagree). In this study, a patient was considered to experience terminal restless when, focusing on statements 2-5, two statements were scored with 'strongly agree' or 'agree' on at least one 4 hourly measurement, or when at least one statement was scored with 'strongly agree' or 'agree' on at least two consecutive measurements.

Associations between the occurrence of symptoms and patients' fluid intake (i.e. during the week and day before the start of the CPD and during 48-25 hours before death) and other characteristics, including patients' gender, age at death, diagnosis, place of death, duration of the dying phase, level of consciousness at the recognition of the dying phase and opioid use (i.e. during the day before the start of the CPD and during 48-25 hours before death) were analysed using Chi-Square or Mann-Whitney tests, where appropriate. All analyses were performed using SPSS for Windows version 22.0 (SPSS, Inc. Chicago, IL).

RESULTS

Patient characteristics

During the study period 631 patients died in the participating care settings. The CPD was initiated for 476 patients (75% of all deaths), 371 of whom were included in this study (59% of all deaths). One hundred and five patients could not be included; 49 due to missing data about the date and time of the start of the CPD and/or death and 56 due to missing data for more than 6 consecutive 4 hourly measurements (part 2 of the CPD).

The included patients had a mean age of 72 years, almost half of them were male and 79% had been diagnosed with cancer (table 1). Forty-four percent of patients died in the hospital, 56% in the hospice. The median duration of the dying phase was 25 hours for all patients, 23 hours for patients dying in a hospital and 29 hours for patients dying in a hospice. Twenty-eight percent of patients had a duration of the dying phase longer than 48 hours, 28% had a duration between 24-48 hours and 44% had a duration shorter than 24 hours. At the start of the CPD, 22% of the patients were unconscious, 36% were restless, 24% were confused and 19% presented with respiratory tract secretions. Seventy-six percent of the patients used opioids during the last day before the start of the CDP and 93% during the dying phase.

Table 1. Patient characteristics (n=371)

	N (%)	
Gender		
Male	181 (49%)	
Female	190 (51%)	
Age at death (years: mean, SD)		72 (14)
Diagnosis		
Cancer	289 (79%)	
Non-cancer	76 (21%)	
Place of death		
Hospital	164 (44%)	
Hospice	207 (56%)	
Duration of the dying phase (hours: median, range)		25, 0-279
Symptoms at the start of the CPD		
Level of consciousness		
Conscious	112 (30%)	
Semi- conscious	175 (47%)	
Unconscious	80 (22%)	
Restlessness	132 (36%)	
Confusion	86 (24%)	
Respiratory tract secretions	68 (19%)	
Treatment		
Opioid use during the last day before the start of the CPD	282 (76%)	
Morphine equivalent daily dose (mg/24h) (median, range)		75 (2-4200)
Opioid use during the dying phase	345 (93%)	
Morphine equivalent daily dose (mg/24h) (median, range)		108 (0-10790)
Use of palliative sedation during the dying phase	162 (44%)	
Fluid intake		
Total daily fluid intake last week before start of the CPD (ml) (median, range)		625 (125-3375)
0-499ml per day	74 (22%)	
500-999ml per day	117 (35%)	
≥1000ml per day	144 (43%)	
Total daily fluid intake last day before start of the CPD (ml) (median, range)		625 (125-2875)
0-499ml per day	187 (55%)	
500-999ml per day	70 (21%)	
≥1000ml per day	81 (24%)	
Total daily fluid intake during the dying phase (ml) (median, range)		250 (6-2250)
0-249ml per day	257 (69%)	
250-499ml per day	61 (16%)	
≥500ml per day	53 (15%)	
Total daily fluid intake 48-25 hours before death (ml) (median, range)		334 (42-2500)
0-249ml per day	190 (51%)	
250-499ml per day	44 (12%)	
≥500ml per day	121 (33%)	

Table 2. Detailed information concerning fluid intake during the last period of life

	Total (n=371)	Hospital (n=164)	Hospice (n=207)
Week before the start of the CPD			
Orally			
N (%) Yes	302 (81%)	121 (74%)	181 (87%)
median-range	625ml (125-1000ml)	625ml (125-1000ml)	625ml (125-1000ml)
IV			
N (%) Yes	90 (24%)	85 (52%)	5 (2%)
median-range	1250ml (250-1500mlL)	1250ml (250-1500mlL)	750ml (750-750ml)
Tube			
N (%) Yes	23 (6%)	18 (11%)	5 (2%)
median-range	750ml (250-1500ml)	750ml (250-1500ml)	750ml (250-1500ml)
Day before the start of the CPD			
Orally			
N (%) Yes	255 (69%)	106 (65%)	149 (72%)
median-range	125ml (125-1000ml)	625ml (125-1000ml)	125ml (125-1000ml)
IV			
N (%) Yes	94 (25%)	90 (55%)	4 (2%)
median-range	750ml (250-1500ml)	750ml (250-1500ml)	750ml (250-750ml)
Tube			
N (%) Yes	19 (5%)	17 (10%)	2 (1%)
median-range	750ml (250-1500ml)	750ml (250-1500ml)	500ml (250-750ml)
During the dying phase			
Orally			
N (%) Yes	152 (41%)	66 (40%)	86 (42%)
median-range	250ml (25-1650ml)	250ml (25-1650ml)	220ml (27-1038m)
IV			
N (%) Yes	125 (34%)	121 (74%)	4 (2%)
median-range	179ml (6-1500ml)	179ml (6-1500ml)	297ml (31-719ml)
Tube			
N (%) Yes	12 (3%)	9 (6%)	3 (1%)
median-range	21ml (4-107ml)	31ml (5-107ml)	9ml (4-11ml)

Fluid intake

Patients' total fluid intake decreased during the last phase of life (table 1). During the week before the start of the CPD, 78% of patients had a total fluid intake of ≥ 500 ml/day, which decreased to 45% of patients during the last day before the start of the CPD and 15% during the dying phase. Fluid intake mainly involved oral intake, which decreased during the last days of life. During the week before the start of the CPD, 81% of patients had an oral intake of fluid, which decreased to 69% of patients during the last day before the start of the CPD

and 41% during the dying phase. Twenty-four percent of patients had IV hydration during the week before the start of the CPD, 25% during the last day before the start and 34% during the dying phase. IV hydration was predominantly prescribed in the hospital. Intake via a feeding tube involved 6% of patients during the week before the start of the CPD, 5% during the last day before the dying phase, and 3% during the dying phase. Detailed information concerning fluid intake per care setting is described in table 2.

Prevalence of death rattle and terminal restlessness

Figure 1 shows the percentages of patients with death rattle or terminal restlessness per period of 4 hours before death. Overall, death rattle was reported at least once in 40% (n=149) of patients during the dying phase, and in 35% (n=130) of patients during the last 24 hours of life. Death rattle scores of ≥2 were often reported more than once; 62% of patients with death rattle had 2 or more death rattle scores of ≥2 and 35% of these patients had 3 or more of such episodes. The prevalence of death rattle increased with death coming nearer. Terminal restlessness was reported at least once in 26% of patients (n=96) during the dying phase and in 13% (n=49) of patients during the last 24 hours of life. For most patients with terminal restlessness (61%), terminal restlessness was only reported once; 19% had terminal restlessness at ≥3 measurements. Terminal restlessness occurred almost evenly throughout the dying phase.

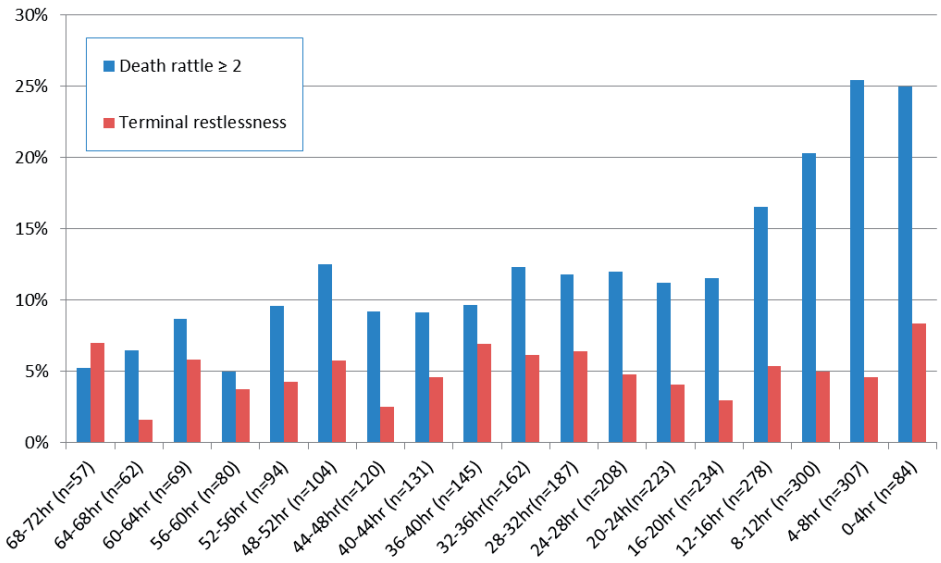

Figure 2. Percentage of patients with death rattle or terminal restlessness score per four-hourly measurement during the last 72 hours of life

Table 3. Associations between death rattle or terminal restlessness with fluid intake and other patient characteristics (n=371)

	N	Symptom present somewhere during the dying phase				Symptom present during the last 24h of life			
		Death rattle score ≥2 (n=149)	P Value	Terminal restlessness (n=96)	P Value	Death rattle score ≥2 (n=130)	P Value	Terminal restlessness (n=49)	P Value
		N (%)		N (%)		N (%)		N (%)	
Gender			0.361		0.323		0.575		0.342
Male	181	77 (43%)		51 (28%)		66 (36%)		27 (15%)	
Female	190	72 (38%)		45 (24%)		64 (34%)		22 (21%)	
Age (years)			0.51		0.12		0.084		0.159
<65	102	44 (43%)		33 (32%)		40 (39%)		19 (19%)	
65-75	116	36 (31%)		28 (24%)		31 (27%)		12 (10%)	
>75	152	68 (45%)		35 (23%		58 (38%)		18 (12%)	
Diagnosis			0.830		0.643		0.970		0.640
Cancer	289	118 (41%)		76 (26%)		102 (35%)		36 (12%)	
Non-cancer	76	30 (39%)		18 (24%)		27 (36%)		11 (14%)	
Place of death			0.977		0.117		0.748		0.679
Hospital	164	66 (40%)		49 (30%)		56 (34%)		23 (14%)	
Hospice	207	83 (40%)		47 (23%)		74 (36%)		26 (13%)	
Duration of the dying phase (hours)			0.458		**0.003**		0.416		0.138
< 24	169	62 (37%)		30 (18%)		62 (37%)		16 (9%)	
24–48	104	45 (43%)		31 (30%)		39 (38%)		18 (17%)	
>48	98	42 (43%)		35 (36%)		29 (30%)		15 (15%)	
Level of consciousness at the start of the CPD			0.153		**0.001**		0.350		0.159
Conscious	112	39 (35%)		34 (30%)		34 (30%)		19 (17%)	

Table 3. Associations between death rattle or terminal restlessness with fluid intake and other patient characteristics (n=371) (continued)

	N	Symptom present somewhere during the dying phase				Symptom present during the last 24h of life			
		Death rattle score ≥2 (n=149)	P Value	Terminal restlessness (n=96)	P Value	Death rattle score ≥2 (n=130)	P Value	Terminal restlessness (n=49)	P Value
Semi- conscious	175	78 (45%)		53 (30%		67 (38%)		23 (13%)	
Unconscious	80	29 (36%)		8 (10%)		26 (32%)		6 (8%)	
Opioid use during the last day before the start of the CPD			0.820*		0.221*		0.378*		0.233*
1st quartile (<29 mg/24h)	67	26 (39%)		16 (24%)		23 (34%)		10 (15%)	
2nd quartile (29 mg - 74 mg/24h)	64	26 (41%)		20 (31%)		25 (39%)		11 (17%)	
3rd quartile (75 mg – 179 mg/24h)	69	23 (33%)		15 (22%)		22 (32%)		7 (10%)	
4th quartile (≥180 mg/24h)	72	34 (47%)		23 (32%)		29 (40%)		13 (18%)	
Opioid use during the period 48-24 hrs before death			NA		NA		0.332*		0.132*
1st quartile (<8 mg/24h)	91	NA		NA		25 (27%)		7 (8%)	
2nd quartile (8 mg - 57 mg/24h)	94	NA		NA		37 (39%)		14 (15%)	
3rd quartile (58 mg – 143mg/24h)	91	NA		NA		29 (32%)		11 (12%)	
4th quartile (≥144 mg/24h)	95	NA		NA		39 (41%)		17 (18%)	
Total daily fluid intake during the week before the start of the CPD			0.186*		0.074*		0.324*		0.265*
0-499ml per day	74	26 (35%)		14 (19%)		23 (31%)		7 (9%)	
500-999ml per day	117	47 (40%)		33 (28%)		42 (36%)		16 (14%)	
≥1000ml per day	144	64 (44%)		45 (31%)		55 (38%)		22 (15%)	
Total daily fluid intake during the last day before the start of the CPD			0.065*		0.384		0.435*		0.398*
0-499ml per day	187	70 (37%)		46 (25%)		65 (35%)		22 (12%)	
500-999ml per day	70	28 (40%)		24 (34%)		24 (34%)		11 (16%)	
≥1000ml per day	81	41 (51%)		22 (27%)		33 (41%)		12 (15%)	

Table 3. Associations between death rattle or terminal restlessness with fluid intake and other patient characteristics (n=371) (continued)

	N	Symptom present somewhere during the dying phase				Symptom present during the last 24h of life			
		Death rattle score ≥2 (n=149)	P Value	Terminal restlessness (n=96)	P Value	Death rattle score ≥2 (n=130)	P Value	Terminal restlessness (n=49)	P Value
Total daily fluid intake during the period 48-24 hours before death			NA		NA		0.130*		**0.049***
0-249ml per day	190	NA		NA		74 (39%)		19 (10%)	
250-499ml per day	44	NA		NA		15 (34%)		8 (18%)	
≥500ml per day	121	NA		NA		37 (31%)		21 (17%)	

Statistics: Chi-Square; *Mann-Whitney
NA = not applicable

Associations between death rattle or terminal restlessness with fluid intake and other patient characteristics

No significant association between death rattle and the amount of fluid intake was found (Table 3). A higher amount of fluid intake during the week and day before the start of the CPD tended to be associated with an increased occurrence of death rattle. Terminal restlessness was not associated with a lower amount of fluid intake during the days before dying. Terminal restlessness during the last 24 hours of life was statistically significant associated with a higher amount of fluid during the time period 48-25 hours before death (p=0.049). Patients' level of consciousness at the start of the dying phase and the duration of the dying phase were also associated with terminal restlessness. Being conscious or semi-conscious at the start of the dying phase was associated with a higher occurrence of terminal restlessness during the dying phase (p=0.004). A longer duration of the dying phase was also associated with a higher occurrence of terminal restlessness (p=0.003).

DISCUSSION

We found no significant association between the amount of fluid intake and the occurrence of death rattle. We did not find an association between a lower amount of fluid intake and terminal restlessness either. Terminal restlessness during the last 24 hours of life was however associated with a higher amount of fluid intake during the time period 48-25 hours before death.

Three previous studies have assessed death rattle occurrence and its association with AH7 9 14. Morita et al.14 performed a multicentre, prospective, observational study of patients dying from cancer. Patients were divided in two groups: those who received 1 liter or more of AH per day both 1 week and 3 weeks before death (hydration group n=59) and those who did not (non-hydration group n = 167). During the last 3 weeks of life, 44% of patients in the hydration group and 46% of patients in the non-hydration group were recorded as presenting with death rattle (p=0.79). Yamaguchi et al.9 also performed a prospective observational study of patients dying from cancer. A comparison was made between patients who received more than 1liter of AH a day (large-volume hydration group n=76) and patients who received less than 1 liter a day (small-volume hydration group n=75). However, this classification was made on the basis of their intake of AH at inclusion in the study, not taking into account any change in fluid intake closer to death. In total, 43% of patients were recorded as presenting with death rattle during 48 hours before death, 51% in the large-volume group and 35% in the small-volume group (p=0.07). Fritzson et al.[7] performed a medical record review in which he studied patients who died in hospital and compared patients who had received parenteral fluid (PF group) to matched control patients who had not received parenteral fluid (non-PF group). During the last week of life 60% of all patients presented with death rattle, 63% in the PF group and 50% in the non-PF group (p=0.07). During the last 24 hours of life 46% of

all patients presented with death rattle, 50% in the PF group and 33% in the non-PF-group (p=0.02). Morita[14] and Fritzson[7] both reported on an AH intake of 1liter during the last 24 hours before death, not taking into account any oral intake. These intakes of AH are high compared to the median fluid intake in our study; 334 ml during the day preceding the last 24 hours.

We did not find an association between a lower amount of fluid intake during the days before dying and the occurrence of terminal restlessness. Terminal restlessness during the last 24 hours of life was however associated with a higher amount of fluid during the time period 48-25 hours before death. Previous studies on the relation between fluid intake and occurrence of terminal restlessness or delirium showed diverse results. Morita et al.[14] failed to show a difference in delirium occurrence between hydrated and non-hydrated patients with a prevalence of 12% in the hydration group and 13% in the non-hydration group (= 0.80). Bruera et al.[11] performed a randomized controlled trial in 129 patients with advanced cancer. Patients were divided in two groups: those who received 1 liter of AH per day for the duration of a week (hydration group), and those who received 110 ml of AH per day (placebo group). No differences were found between the two groups in the occurrence of delirium. Yamaguchi et al.[9] found a higher occurrence of delirium in patients who received less than 1 liter of fluid a day compared to patients who received more than 1 liter (17% vs 5%, p=0.01) and proposed hydration as an intervention to treat delirium. Our finding of an association between more fluid intake and more terminal restlessness is in line with the study by Fritszon et al.[7] who also found a higher occurrence of terminal restlessness in patients receiving AH during the last 24 hours of life as compared to patients without AH.

This study has some limitations. Firstly, the optimal design to study the effects of fluid intake would be a randomized controlled trial, which would however pose ethical challenges. We conducted a prospective observational study to explore variations in fluid intake in daily practice. Secondly, the patient's oral intake was based on nurses' estimation. It would have been more reliable if we had used a fluid balance measure. However a fluid balance measure would lead to medicalizing the dying phase and is therefore not a common practice at the end of life. Thirdly, at the start of this study no instrument to measure terminal restlessness was available. Because of the close connection between restlessness and calmness, we decided to use the calmness scale of the Vancouver Interaction and Calmness Scale. We did not use any other instrument to validate the calmness scale and it is possible that patients were misclassified. However, the prevalence reported in this study is in line with other studies focusing on terminal restlessness and delirium at the end of life. Fourthly, we collected information on fluid intake at three moments in time; the week before the start of the CPD, the day before the start of the CPD and, 4 hourly, during the dying phase. Information on symptom occurrence was measured, 4 hourly, during the dying phase. Relating the total fluid intake during the dying phase to symptom occurrence during the dying phase could mean relating a symptom occurring at the start of the dying phase to an average level of

fluid intake based on the entire dying phase. Therefore we calculated a separate variable concerning the fluid intake during the time period 48-25 hours before death. Whereas terminal restlessness occurred almost evenly throughout the dying phase and often only once, it is possible that patients in the non-symptom group during the last 24 hours of life actually presented with terminal restlessness before the last 24 hours of life but were successfully treated (i.e. sedated). We found no evidence that patients with terminal restlessness were more often sedated compared to patients who were not terminal restless (p=0.23, not in table). Fifthly, the high percentage of missings for the measurement period 4-0 hours before death could mean that we over- or underestimated the occurrence of death rattle and terminal restlessness during that 4 hourly period. From daily practice we know that completing the measurement for this time period is often forgotten by nurses because completion is required after the patient has died. However, the terminal restlessness percentage is in line with what we would expect based on the other measurements and daily practice. Looking at the increase in death rattle occurrence during the 4 previous measurements, it is possible that the actual percentage for death rattle would have been higher. Consensus about the natural course of death rattle, whether it increases or decreases closer to death, is still lacking. Kass and Ellershaw suggest that the prevalence of death rattle typically increases when death approaches[26]. Yet, Heisler et al.[27] performed a placebo controlled trial and found an decrease of death rattle scores over time in the placebo group. Sixthly, we did not make a distinction between types of opioids and added up opioids with different opioid metabolisms. It is possible that by combining opioids we lost the ability to show associations between specific opioid use and occurrence of symptoms on the one hand and/or specific opioid use and level of hydration of the other hand.

In conclusion, we found that a higher amount of fluid intake (i.e. possible over-hydration), preceding and during the dying phase, was not associated with the occurrence of death rattle. Further, a lower amount of fluid intake (i.e. possible under-hydration), preceding and during the dying phase, was not associated with the occurrence of terminal restlessness. Caution with fluid intake to prevent development of death rattle does not seem to be necessary. Our study suggests that a higher amount of fluid intake during the period 48-25 hours before death may be related to occurrence of terminal restlessness during the last 24 hours of life. Actively providing dying patients with artificial fluid therefore does not seem to be beneficial.

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APPENDIX

Variables used in this study

Part 1 of the CPD, *reflecting the patient's situation at the start of the dying phase*

- Diagnosis (cancer, non-cancer)
- Gender (male, female)
- Date of birth
- Date and time of the start of the CPD
- Level of consciousness (conscious, semi-conscious, unconscious)
- Prevalence of restlessness (yes, no)
- Prevalence of confusion (yes, no)
- Prevalence of respiratory tract secretions (yes, no)

Questions added to part 1 of the CPD specifically for this study

- Has the patient used opioids in the last 24 hours? (yes/no)
  - Indicate route (transdermal, oral, rectal, oral, nasal), type (morphine,...) and the total dose during the past 24 hours
- Total fluid intake during the week preceding the recognition of the dying phase
  - Oral intake (1 cup is approximately 250 ml)
  - None
  - Sibs
  - Between 1-4 cups/ day
  - More than 4 cups/ day
- Intravenous infusion
  - None
  - Less than 0,5 l/day
  - 0,5-1 l/day
  - 1-1,5 l/day
  - 1,5 l/day and more
- Feeding tube
  - None
  - Less than 0,5 l/day
  - 0,5-1 l/day
  - 1-1,5 l/day
  - 1,5 l/day and more
- Total fluid intake during the last 24 hours preceding the recognition of the dying phase
  - Oral intake (1 cup is approximately 250 ml)
  - None

  - Sibs
  - Between 1-4 cups/ day
  - More than 4 cups/ day
- Intravenous infusion
  - None
  - Less than 0,5 l/day
  - 0,5-1 l/day
  - 1-1,5 l/day
  - 1,5 l/day and more
- Feeding tube
  - None
  - Less than 0,5 l/day
  - 0,5-1 l/day
  - 1-1,5 l/day
  - 1,5 l/day and more

Part 2 of the CPD, *reflecting the patient's situation from the start of the dying phase until death*

Questions added to part 2 of the CPD specifically for this study

- Total fluid intake, per four hourly intervals, until death
  - Oral intake (1 cup is approximately 250 ml)
    - None
    - Sibs
    - 1 cup
    - More than 1 cup
  - Intravenous infusion
    - None
    - Less than 0,5 l/day
    - 0,5-1 l/day
    - 1-1,5 l/day
    - 1,5 l/day and more
  - Feeding tube
    - None
    - Less than 0,5 l/day
    - 0,5-1 l/day
    - 1-1,5 l/day
    - 1,5 l/day and more
- Has the patient used opioids in the last 4 hours? (yes/no)

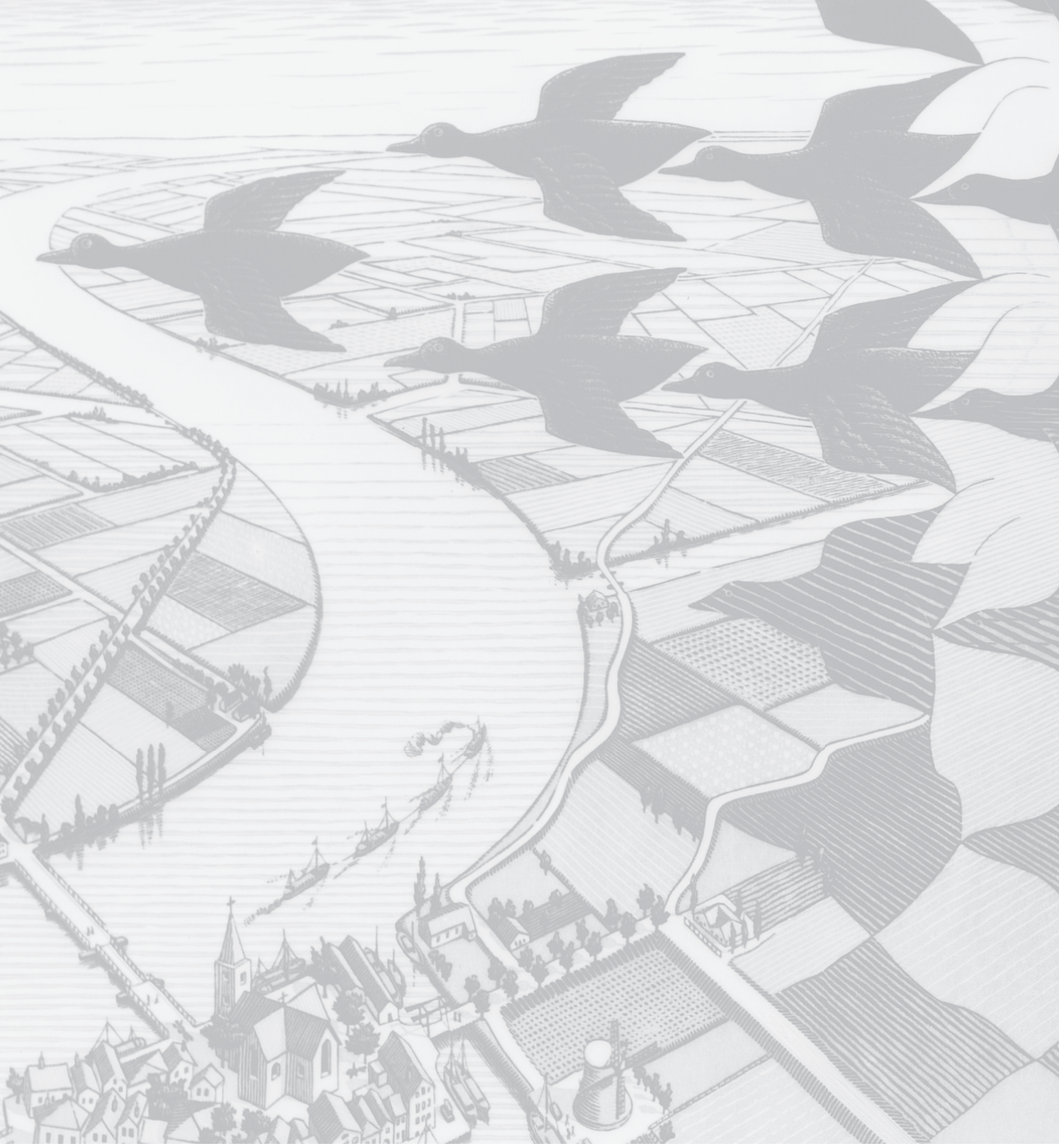
    - Indicate route (transdermal, oral, rectal, oral, nasal), type (morphine,...) and the total dose during the past 24 hours
- Has the patient had death rattle in the last 4 hours? (yes/no)
    - 0, inaudible
    - 1, audible only very close to the patient
    - 2, clearly audible at the end of the bed, in a quiet room
    - 3, clearly audible at the door of the room (about 20 feet / 10 meter), in a quiet room.
- Please indicate to what extend you agree (strongly agree, agree, mildly agree, mildly disagree, disagree, strongly disagree) with the following statements
    - 1, patient appears calm
    - 2, patient appears restless
    - 3, patient appears distressed
    - 4, patient is moving around uneasily in bed
    - 5, patient is pulling at lines/tubes.

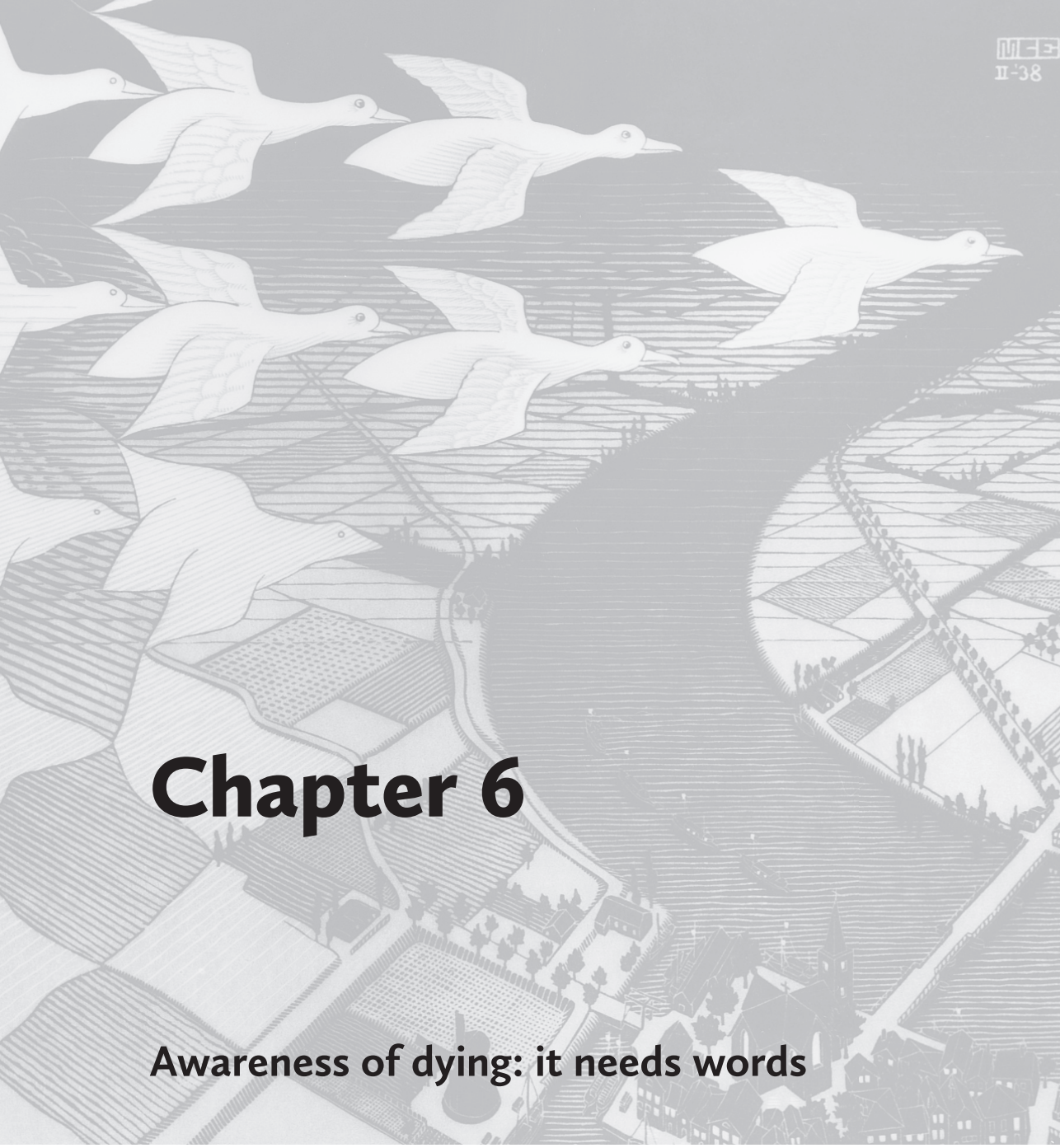
Part 3 of the CPD, *reflecting the situation after death*

- Date and time of death

Questions added to part 3 of the CPD specifically for this study

- Did the patient receive palliative sedation (yes/no)





Chapter 6

Awareness of dying: it needs words

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ABSTRACT

Purpose. The purpose of this research is to study to what extent dying patients are aware of the imminence of death, whether such awareness is associated with patient characteristics, symptoms and acceptance of dying, and whether medical records and nurses' and family caregivers' views on patients' awareness of dying agree.

Methods. Nurses and family caregivers of 475 deceased patients from three different care settings in the southwest Netherlands were requested to fill out questionnaires. The two groups were asked whether a patient had been aware of the imminence of death. Also, medical records were screened for statements indicating that the patient had been informed of the imminence of death.

Results. Nurses completed questionnaires about 472 patients, family caregivers about 280 patients (response 59%). According to the medical records, 51% of patients had been aware of the imminence of death; according to nurses, 58%; according to family caregivers, 62%. Patients who, according to their family caregiver, had been aware of the imminence of death were significantly more often in peace with dying and felt more often that life had been worth living. Inter-rater agreement on patients' awareness of dying was fair (Cohen's Kappa= 0,23-0,31).

Conclusions. Being aware of dying is associated with acceptance of dying, which supports the idea that open communication in the dying phase can contribute to the quality of the dying process. However, views on whether or not patients are aware of the imminence of death diverge between different caregivers. This suggests that communication in the dying phase of patients is open for improvement.

INTRODUCTION

Being aware that death is imminent is often seen as one of the features of a good death in modern Western culture[1-4]. However, until the early 1970's the issue of death was rarely open for discussion in healthcare[3 5]. Not confronting terminally ill patients openly with their upcoming death was a generally accepted code of conduct for physicians. Physicians were encouraged to give patients hope on a serious chance of recovery. The belief within the medical world was that dashing someone's hope for recovery implied heavy emotional burden and therefore could lead to an unbearable end. Nowadays, in modern Western society this view is no longer commonly present. In accordance with currently often mentioned attributes of a good death[6], communication and openness about the situation of a patient who is approaching death is increasingly seen as preferable[3]. But even in this age, which is characterized by an emphasis on "informed consent" and "open communication", the course of a disease and its fatal conclusion are not always communicated explicitly by physicians[7]. Furthermore, there seems to be a relation between hope and the extent to which people are aware of the prognosis that they are going to die soon. McGrath suggests that the challenge of accepting the reality of a terminal diagnosis is so emotionally difficult that patients often oscillate between acceptance and hopeful denial[8]. It can be questioned to what extent this also holds for the dying phase, when death is expected within hours or days.

Awareness that a patient's death is imminent allows healthcare professionals to appropriately reset the goals of care to prevent possible harmful decisions. A prerequisite for such a reset is adequate communication. When there is shared agreement among members of the healthcare team that a patient is dying, the process of decision making can be better coordinated[9]. This is confirmed by a study on whether recognition of the dying phase had impact on the number of medical interventions. That study showed that patients with a recognized dying phase received significantly less diagnostic interventions as compared to patients in whom the dying phase was not recognized[10]. Several instruments to support and promote clear communication around the dying and death of the patient have been developed, such as the Liverpool Care Pathway for the dying patient (LCP) [11-13]. Open awareness of the onset of the dying phase among physicians, nurses, and patients and their family caregivers is an important element of the LCP[10 14 15].

In this study we define the concept of *awareness of dying* as knowing that death is imminent within hours or days. This definition is in concordance with the definition of the dying phase by Ellershaw and Ward[12] which states that the dying phase means having only hours or days to live. We studied to what extent dying patients are aware of the imminence of death and whether such awareness is associated with patient characteristics, use of the LCP, symptoms and acceptance of dying (also defined as a central element of a good death[3]). In addition we investigated the level of agreement on patients' awareness of dying between medical records, nurses and family caregivers.

PATIENTS AND METHOD

Design and population

We performed a secondary analysis of data that were collected in the context of an intervention study that investigated the effect of using the LCP on the care and quality of life during the last 3 days of life of 475 patients[16-19]. Data collection took place between November 2003 and February 2006. Halfway this period, the LCP was introduced and subsequently used for each patient for whom the multidisciplinary team agreed that the dying phase had started.

For this study, patients were recruited from hospitals, nursing homes and home care services in the southwest of the Netherlands[19]. Patients aged 18 years or older were included when they had died during the study period in either one of these institutions. The Medical Ethical Research Committee of the Erasmus MC approved the study.

About 2 months after the death of a patient, a relative, who had been 'contact person' for the patient, received a letter from the institution that had provided terminal care. In this letter, he/she was asked for consent to be approached by the research team to fill in a written questionnaire. A reminder was sent to nonresponding relatives after 2 and 6 weeks, respectively. Only relatives who gave their consent were mailed a questionnaire. Within 1 week after the death of an eligible patient, a nurse who had been closely involved with caring for the patient during the last 3 days of life completed a questionnaire. In total, 472 nurses (response 99%) participated. Of the relatives, 280 consented and completed a questionnaire (response 59%).

Data collection

Within each institution, a member of the care team (mostly a nurse) collected data on age, gender, diagnosis, use of LCP and place of dying, from the medical and nursing records. A question related to whether a patient had been aware of the imminence of death was included in the nurses' and family caregivers' questionnaires. Nurses were asked whether the patient had been informed about the onset of the dying phase ('yes', 'more or less', 'no'). Family caregivers were asked whether, during the last 3 days of life, it had been clear to the patient that he/she would die within a couple of days ('yes', 'more or less', 'no', 'unknown'). For the purpose of this study, 'yes' and 'more or less' were combined to represent 'yes'. In addition, medical records were screened for information indicating whether or not the patient was aware of the dying phase ('yes', 'no').

From the family caregivers' questionnaires, we also used a question concerning the consciousness of the patient 72 hours before death, a question about whether the patient was in peace with dying and a question about the relationship of the family caregiver with the patient. Nurses were asked if they had the impression that patients during the last 3 days of their lives had felt that life had been worth living. Nurses were also asked to assess the presence of 28 symptoms during the last 3 days of life. Questions about 16 symptoms (shortness

of breath, pain, fatigue, lack of appetite, need of rest, trouble sleeping, weakness, nausea, vomiting, constipation, diarrhoea, difficulty concentrating, tenseness, worrying, depressed mood and difficulty remembering) originated from the EORTC QLQ-C30 questionnaire[20]. Questions about the remaining 12 symptoms were added to the questionnaire (mouth problems/dysphagia, coughing, agitation, troublesome mucus production, poor vision, restlessness, involuntary movements, itching, incontinence, pressure ulcers, confusion and anxiety), because these symptoms are common in the last phase of life[14 21-24]. All questions concerning symptoms were scored on a 4-point Likert scale. Answer options were: 'not at all', 'a little', quite a bit' or 'very much'. For the purpose of this study, these answers were recoded: 'quite a bit' and 'very much' were added up to represent 'symptom present', 'not at all' and 'a little' were added up to represent 'symptom not present'.

Analysis and statistics

Associations between awareness of dying and 4 patient characteristics (diagnosis, age, gender, place of dying), use of LCP, 2 aspects of acceptance of dying (peace with dying, life worth living) and the 28 symptoms were statistically tested, using Chi-square tests. Family caregivers' rating whether a patient was aware of the imminence of death was used as reference in these analyses. Patients were excluded from these analyses when they had been unconscious during the last 72 h before dying. The agreement on patients' awareness of dying between medical record, nurse and family caregiver was determined for each pair (i.e. medical record-nurse, medical record-family caregiver, nurse-family caregiver) by calculating Cohen's Kappa's. These scores were interpreted using the Landis and Koch criteria where kappa values are associated with the following levels of agreement: <0.00 = poor, 0.00 to 0.20 = slight; 0.21 to 0.40 = fair; 0.41 to 0.60 = moderate; 0.61 to 0.80 = substantial; 0.81 to 1.00 = almost perfect[25]. The significance level was set at 5%. For the analysis of the data, we used SPSS version 17.0.

RESULTS

Patients were on average 76 years old (range 34-100) at the time of death (Table 1). The majority (71%) had cancer as their primary diagnosis. A small majority of the patients were female. Of all patients 42% died in hospital, 24% in a nursing home and 29% at home. According to the medical records, 52% of all patients had been aware of the imminence of death, according to nurses 58% and according to family caregivers 62%. The LCP, introduced halfway during the study period, was used in a third of all patients. Patients were reported to have had an average of 8 different symptoms (interval, 0-20). Symptoms most prevalent during the last three days of life were related to lack of energy (need of rest, fatigue, weakness 74-85%), lack of appetite (73%), difficulty concentrating (47%) and shortness of breath (44%).

Table 1. Characteristics of patients (N=280)

Characteristic		
Age category	N	%
≤75 years	128	46
>75 years	149	54
Gender		
Male	131	47
Female	149	53
Diagnosis		
Cancer	189	71
Non-cancer	78	29
Place of Dying		
At home	82	29
Nursing home	67	24
Hospital	117	42
Elsewhere	14	5
Awareness of dying		
According to the medical record patient was aware	145	52
According to nurse patient was aware	163	58
According to family-caregiver patient was aware	173	62
Relationship with family-caregiver/ proxy		
Partner	106	38
Parent/child	122	44
Sibling	12	4
Other family	28	10
Other non-family	11	4
Use of LCP		
No	179	64
Yes	101	36
Symptom prevalence during the last 3 days of life	N^1/ N^2	%
In need of rest	224 / 265	85
Fatigue	215 / 264	81
Weakness	195 / 263	74
Lack of appetite	191 / 263	73
Difficulty concentrating	118 / 251	47
Shortness of breath	116 / 266	44
Incontinence	110 / 266	41
Pain	106 / 271	39
Mouth problems / dysphagia	77 / 207	37
Restlessness	100 / 269	37
Worrying	86 / 250	34

Table 1. Characteristics of patients (N=280) (continued)

Characteristic		
Difficulty remembering	83 / 253	33
Tenseness	68 / 252	27
Troublesome mucus	73 / 271	27
Confusion	68 / 263	26
Anxiety	67 / 260	26
Trouble sleeping	64 / 266	24
Depressed mood	58 / 247	23
Poor vision	45 / 252	18
Coughing	37 / 214	17
Involuntary movements	43 / 268	16
Nausea	41 / 266	15
Constipation	38 / 261	15
Pressure ulcers	36 / 270	13
Vomiting	29 / 267	11
Agitation	25 / 256	10
Diarrhoea	23 / 261	9
Itching	12 / 265	5

N^1 number of patients in whom the symptom was present, N^2 number of patients for whom the nurse answered the item

Different variables were assessed on their association with awareness of dying. Of four patient characteristics tested, only place of dying was significantly associated with awareness of dying (p= 0.012) (Table 2). Of patients dying at home, 83% were aware of the imminence of death, compared to 68% of patients dying in a hospital and 62% of patients dying in a nursing home.

Patients who were aware of the imminence of death were more often in peace with dying (p= 0.000) and felt more often that life had been worth living (p= 0.009), compared to patients who were not aware (Table 3). No clear association between symptoms and awareness was found, except for two symptoms. Patients aware of dying more often experienced a lack of appetite (p= 0.049) and less often experienced tenseness (p= 0.014) compared to patients not aware of dying (not in table).

The percentage of patients that, according to the family caregivers, had been aware of the imminence of death was stable before and after introduction of the LCP (63% before, 62% after, p = 0.474). For nurses, the percentage of patients that they thought had been aware of the imminence of death was 54% before and 62% after introduction (p =0.143). The percentage of patients for whom a statement was found in the medical record indicating that he or she was aware of the dying phase was 38% before and 64% after the introduction of the LCP (p = 0.000) (not in table). The level of agreement, as assessed by Cohen's kappa,

Table 2. Patients' characteristics and awareness of the imminence of death (n=213[a])

	Patient aware of the imminence of death [b]		P-value [c]
	Yes	No	
Diagnosis			
Cancer (n=134)	72%	28%	0.477
Non-cancer (n=43)	70%	30%	
Age			
≤75 years (n=82)	72%	28%	0.560
>75 years (n=103)	72%	28%	
Gender			
Male (n=87)	69%	31%	0.328
Female (n=100)	73%	27%	
Place of dying			
At home (n=53)	83%	17%	**0.012**
Nursing home (n=87)	62%	38%	
Hospital (n=38)	68%	32%	
Elsewhere (n=9)	100%	0%	

[a] Excluding unconscious patients (n=67)
[b] Excluding patients for whom awareness was unknown (N=25)/ missing (n=1)
[c] Chi square test

on whether or not the patient had been aware of the imminence of death, was 0.23 for the medical records and family caregivers, 0.28 for nurses and caregivers, and 0.31 for the medical records and nurses (table 4). The inter-rater agreement was not related to patient characteristics, such as age, gender, diagnosis, use of the LCP or place of death (not in table).

DISCUSSION

According to the medical records, nurses and caregivers, 51% to 62% of patients had been aware of the imminence of death in the last days of life. Patients dying at home were more often aware of the imminence of death compared to patients who died in a hospital or in a nursing home. Whether a patient was aware of dying was not clearly associated with symptoms. Finally, awareness turned out to be associated with acceptance of dying; patients who were aware of the imminence of death were more often in peace with dying and felt more often that life had been worth living than patients who were not aware.

In 1965, Glaser and Strauss described four categories of 'awareness of dying', used for deaths expected within hours, days, weeks or months of a patient's life. These categories

Table 3. Awareness of the imminence of death and acceptance of dying (n=213[a])

		Patient aware of the imminence of death [b]				P-value [c]
		Yes		No		
		N	%	N	%	
		118		36		
Patient in peace with dying	Yes		85		56	**0.000**
	No		15		44	
		120		44		
During the last 3 days, patient felt that life had been worth living	Yes		72		50	**0.009**
	No		28		50	

[a] Excluding unconscious patients (n=67)

[b] Excluding patients for whom awareness was unknown (N=25)/ missing (n=1)

[c] Chi square test

ranged from *closed awareness* (the patient does not recognize his impending death even though everyone else does) through *suspicion awareness* (the patient suspects what the others know and therefore attempts to confirm of invalidate his suspicion) and *mutual pretence* (each party defines the patient as dying, but each pretends that the other has not done so') to *open awareness* (caregivers and patient both are aware that the patient is dying, and act on this awareness relatively openly)[26]. In 1997 Seale et al.[27] argued that 'a preference for open awareness of dying is now well established in terminal care settings and amongst the general population in the UK, USA and other Anglophone countries'. It is plausible that this is also true for the Netherlands. However, the percentage of cases in our study in which dying patients were openly aware of the imminence of death within days was only 51-62%, depending on whether it was assessed through the medical record, the nurse or a family member.

Studies on awareness of dying and its determinants are scarce[2 7 27]. The fact that over one third of patients was not considered being aware of the imminence of death probably reflects, at least partly, the difficulty of diagnosing dying, even in settings where death is a relatively common event. The natural course of a lethal disease is typically not a straightforward matter of steady or stepwise decline from diagnosis to death. Consequently it can be difficult to distinguish a decline in the patient's condition due to an acute reversible problem, from a decline due to the progression of a life-limiting illness towards death[9]. This seems to be even more complex for non-malignant diseases, because these often have 'entry–re-entry' death trajectories, involving episodic, acute exacerbations, frequent hospitalisation, stabilisation and subsequent further decline, making determination of the end of life phase more problematic[28 29]. Our analyses however did not reveal a relation between awareness of dying and malignant or non-malignant diseases. Previous research has also shown that prognostication at the end of life is difficult, although predictions become more accurate when

Table 4. Patients' awareness of the imminence of death: Inter-rater agreement between medical records, nurses and family caregivers (n=250[a])

	Medical record			Nurse			Caregiver			
Rating of awareness										
Was the patient aware that he was going to die?	Yes	No	Missing	Yes	No	Missing	Yes	No	Missing	Unknown
	51%	21%	28%	58%	33%	9%	62%	25%	1%	12%
Inter-rater agreement										
Medical record and Nurse			K = 0.31[b]							
Medical record and Caregiver						K = 0.23[c]				
Nurse and Caregiver							K = 0.28[b]			

Interpretation of Cohen's Kappa; Poor agreement ≤0,00, Slight agreement 0,00-0,20, Fair agreement 0,21-0,40,
Moderate agreement 0,41-0,60, Substantial agreement 0,61-0,80, Almost perfect agreement 0,81-1,0[25]

[a] Excluding patients for where not all three sources answered this question (n=30)

[b] p=0,000

[c] p=0,003

patients are closer to death, a finding which has been referred to as the 'horizon effect'[30-32]. The finding that age and gender were not associated with awareness of dying is in agreement with a study by Seale et al[27]. In Seale's study awareness of dying was more common among younger family caregivers and among patients who died from non-cancer diseases. Comparisons were however limited to patients in 'full open awareness' (where there is not only knowledge of dying, but also a value commitment towards openness) and patients in 'closed awareness', leaving all possible other types of awareness and a large proportion of patients in more limited types of open awareness, out of the analyses. This could perhaps explain why in our study we did not find this same association. Our finding that patients dying at home were more often aware of the imminence of death than patients dying in a hospital or nursing home is probably related to the selection of patients who die in these settings. Severely ill patients in the Netherlands are often admitted to the hospital with the aim of addressing complications or relieving complex symptoms, in the expectation that they will be discharged to go home. Additionally, in the nursing home, a higher percentage of patients with dementia probably resulted in a lower percentage of patients being aware of dying. Our finding is consistent with previous research by Seale et al.[27] who also found higher frequencies of awareness of dying among patients dying at home. They hypothesise that patients who are aware of their imminent death have a greater tendency to control the circumstances of death, including their place of death. Patients who were aware of the imminence of death were, compared to patients who were not aware, significantly more often in peace with dying and felt more often that life had been worth living. Whether awareness of dying leads to acceptance of dying or acceptance leads to awareness remains unclear.

The medical record and nurses' and family caregivers' perspectives on whether or not patients had been aware of the imminence of death differed in a substantial number of cases. Deviating perspectives on awareness of dying were also found by Rich et al.[33] in a study concerning the experiences of medical staff and family of deceased patients. These authors also found only fair agreement between medical staff and family on the question 'did you know that death was imminent'? Apparently, communication between physician, nurses and family in the dying phase is not optimal in a substantial number of cases. The percentage of cases in which, according to the medical record, the patient had been aware increased significantly after the introduction of the LCP. However, the agreement between the three groups did not increase accordingly. Although use of the LCP seems to improve the knowledge of physicians and nurses about patients' awareness of dying, the alignment between all parties involved is not optimal. The use of the LCP in this study was limited to a particular period and physicians and nurses were new in using this instrument. More extended use of the instrument may lead to more communication and mutual knowledge about patients in the dying phase.

Our study had some limitations. Firstly, all data were collected after the death of a patient. It was therefore not possible to obtain information from the patient. In addition, family caregivers and nurses provided information retrospectively and a certain degree of recall bias can therefore not be precluded. Secondly, the cross-sectional design of the study makes inferences about causality not possible. Finally, our study population is not completely representative for the Dutch population. In our study the mean age of death was lower (76) than in the Dutch population (80)[34] and the proportion of cancer patients (71%) was higher than the proportion of cancer deaths in the Dutch population (30%)[35]. Moreover, the place of dying of the patients in this study was not fully comparable with the distribution in the Netherlands. In our study the distribution was, 29% of patients dying at home, 24% in a nursing home and 42% in a hospital, compared to the distribution in the Dutch population which is 38%, 23% and 33%[36].

In conclusion, our finding that being aware of the imminence of death is associated with acceptance of dying supports the idea that open communication in the dying phase between physicians, nurses, patients and family caregivers can contribute to the quality of the dying process. Communication about all potentially relevant aspects of the situation of a patient in the dying phase is a requirement for adequate patient-centred care and also an important focus of the LCP. Findings of the current study suggest that the communication in the dying phase of patients is not yet optimal and open for improvement. The most suitable time and strategy to enhance open communication about the dying phase cannot be concluded from our data, and should be a topic in future research.

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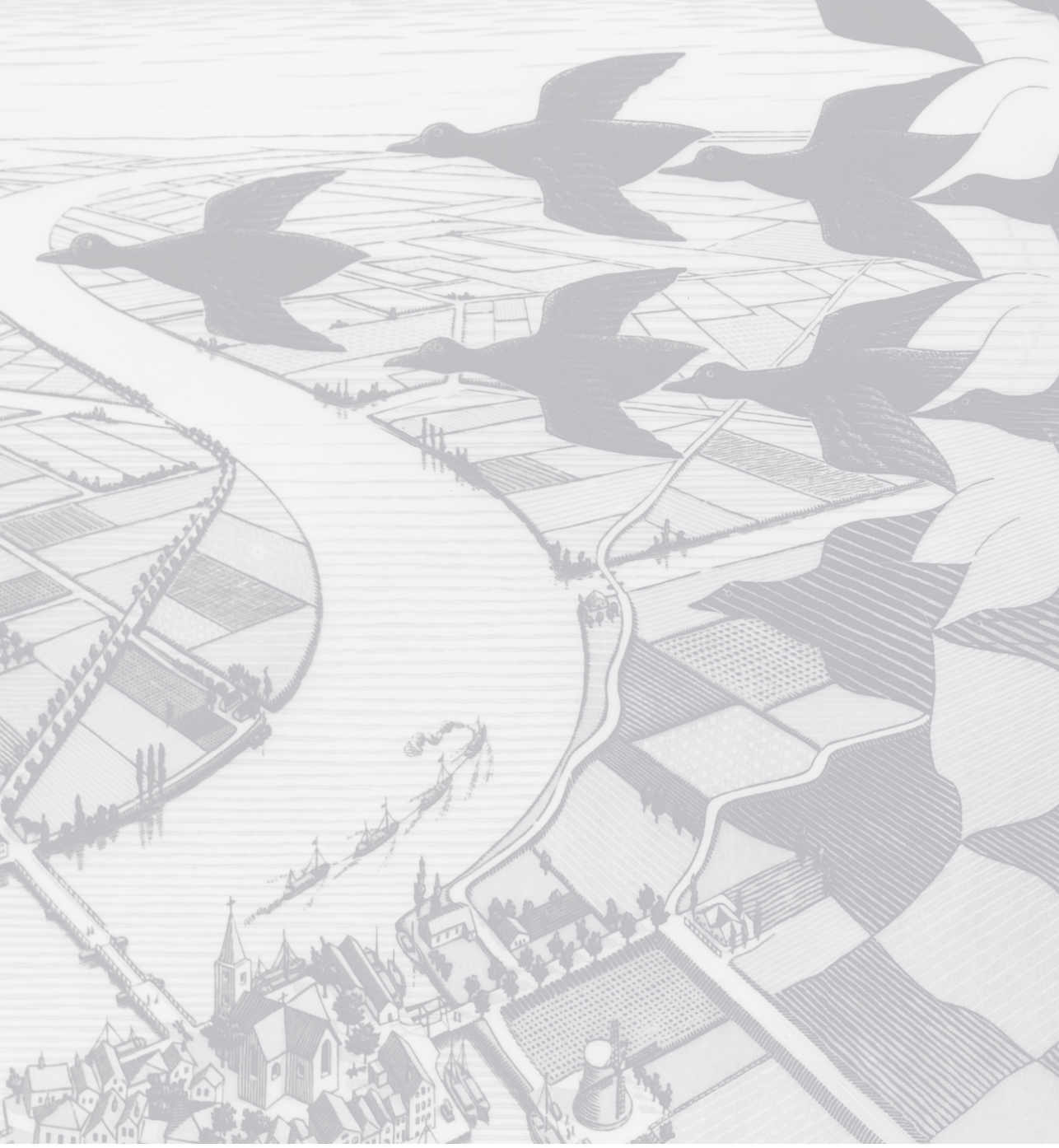

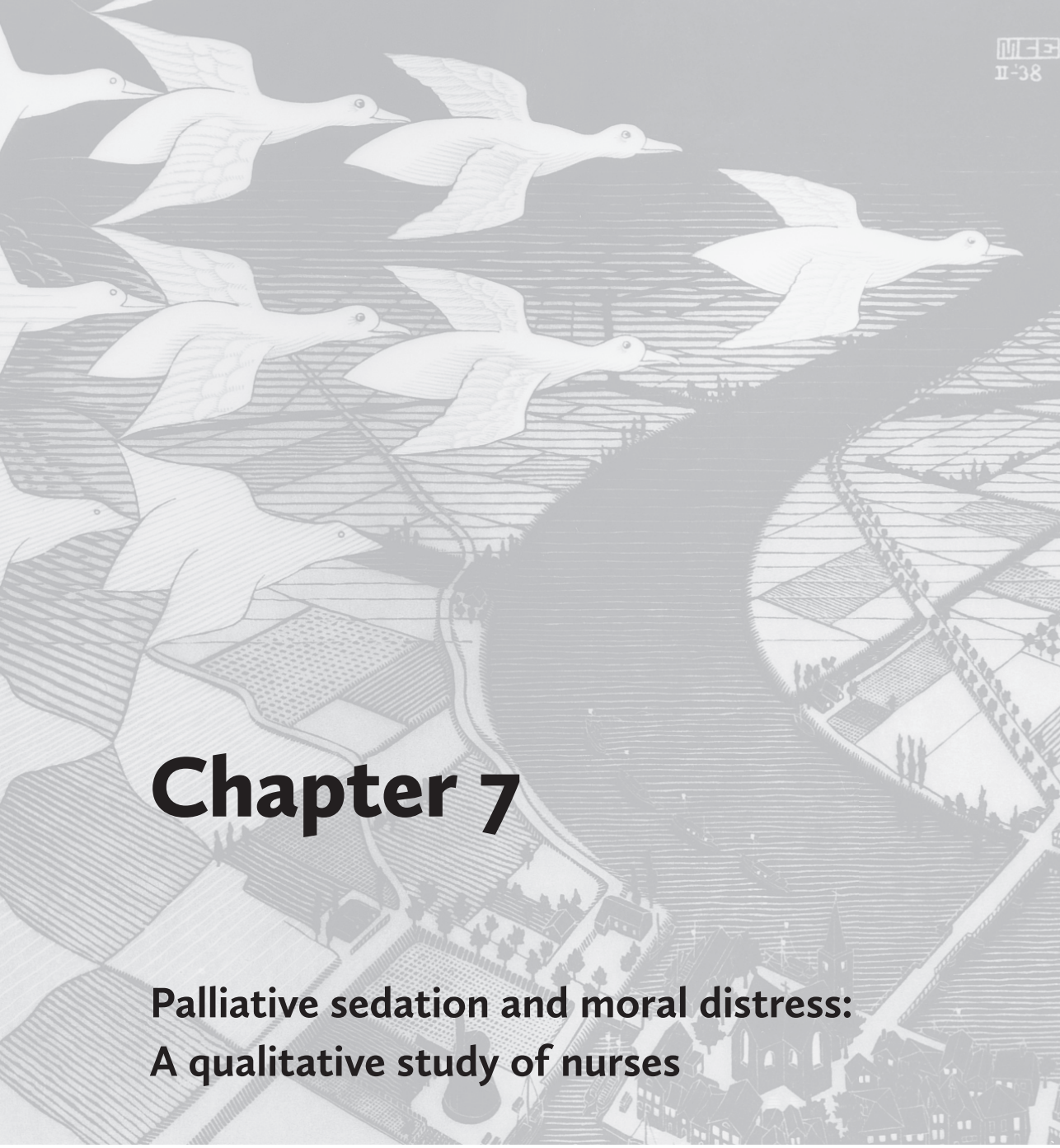

Chapter 7

Palliative sedation and moral distress: A qualitative study of nurses

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ABSTRACT

Background. Clinical nursing practice may involve moral distress, which has been reported to occur frequently when nurses care for dying patients. Palliative sedation is a practice that is used to alleviate unbearable and refractory suffering in the last phase of life and has been linked to distress in nurses.

Aim. The aim of this study was to explore nurses' reports on the practice of palliative sedation focusing on their experiences with pressure, dilemmas and morally distressing situations.

Methods. In-depth interviews with 36 nurses working in hospital, nursing home or primary care.

Results. Several nurses described situations in which they felt that administration of palliative sedation was in the patient's best interest, but where they were constrained from taking action. Nurses also reported on situations where they experienced pressure to be actively involved in the provision of palliative sedation, while they felt this was not in the patient's best interest. The latter situation related to (1) starting palliative sedation when the nurse felt not all options to relieve suffering had been explored yet; (2) family requesting an increase of the sedation level where the nurse felt that this may involve unjustified hastening of death; (3) a decision by the physician to start palliative sedation where the patient had previously expressed an explicit wish for euthanasia.

Conclusions. Nurses experienced moral distress in situations where they were not able to act in what they believed is the patient's best interest. Situations involving moral distress require nurses to be well informed and able to adequately communicate with suffering patients, distressed family and physicians.

INTRODUCTION

When being confronted with challenges in clinical practice, nurses and other healthcare professionals can experience moral distress[1]. Moral distress is defined as "the pain or anguish affecting the mind, body or relationships in response to a situation in which the person is aware of a moral problem, acknowledges moral responsibility, and makes a moral judgment about the correct action; yet, as a result of real or perceived constraints, participates, either by act or omission, in a manner he or she perceives to be morally wrong"[2 3]. Morally distressed nurses experience burnout and have a high tendency to leaving the profession[3-6]. A growing number of studies have reported on moral distress among nurses, but until now these are mainly restricted to intensive and acute care[7-9].

Moral distress has been reported to occur frequently when nurses care for dying patients. In a survey study of 47 critical care nurses, 79% reported that they had experienced moral distress[1]. Nurses play an important role in care at the end of life, as they are often the frontline caregivers for patients nearing the end of life[10]. Care at the end of life is often complex, nurses working in this field have to deal on a daily basis with difficult symptoms of terminal illnesses, distressed patients and families, suffering and death[11]. Moral distress among nurses working in end-of-life care seems to be inextricably bonded to the distress that is experienced by patients[1 12 13]. A study focusing on end-of-life care among 222 geriatric nurses showed that 8% of the nurses actually left their job and 12% considered quitting their job because of discomfort with the way patient care was handled[14].

A common practice at the end of life, which has been described as something nurses struggle with, is palliative sedation[15]. Patients who are nearing death sometimes experience symptoms that cannot be relieved with conventional therapeutic interventions, such as intractable pain, dyspnoea, and delirium[16 17]. Palliative sedation is a medical intervention used to alleviate unbearable and refractory suffering in the last phase of life by the deliberate lowering of a patient's level of consciousness to induce decreased awareness of symptoms[18-20]. Palliative sedation includes several subtypes: intermittent and continuous sedation, as well as deep and superficial sedation. Continuous deep sedation until death is the most far-reaching subtype[20]. In the Netherlands, the Royal Dutch Medical Association has issued a guideline on palliative sedation that states that continuous deep sedation until death can only be considered for patients who have a life expectancy of one to two weeks at most[20]. Palliative sedation is frequently used in end-of-life care, most often in hospitals and for patients with cancer[21-23]. Studies have indicated that palliative sedation was used in 12%-18% of dying patients in the UK, Belgium (Flanders), and the Netherlands[24-26].

Palliative sedation is a practice of last resort and is therefore often used in complicated cases, under stressful conditions and with time constraints[19 27 28 29]. In addition, a number of studies reported on experiences of physicians with pressure related to palliative sedation. Blanker performed a study among general practitioners (GP's) and found that one in six GPs

had experienced pressure during a decision making process on the use of palliative sedation, from patients, relatives or other persons[30]. Also, pressure to increase the level of sedation as a means to hasten death has been described in other studies focusing on physicians[31]. Palliative sedation has been linked to (emotional) burden for nurses[5 32]. A study among 2607 nurses in Japan showed that 12% of nurses experienced emotional burden related to palliative sedation[5]. A qualitative study among 26 home care nurses and 25 (GPs) focusing on their collaboration, roles, and responsibilities during the process of palliative sedation showed that some nurses found performing sedation "burdensome"[32].

The aim of this study was to explore nurses' reports on the practice of palliative sedation focusing on their experiences of pressure, dilemmas and morally distressing situations by performing a secondary data analysis of an interview study among nurses.

METHOD

Participants

In this study we analysed data from qualitative interviews with nurses that were collected as part of a larger project about the practice of palliative sedation in the Netherlands after the introduction of a national guideline on palliative sedation[33]. The project focused on physicians' and nurses' experiences with continuous palliative sedation. The first part of the project was a questionnaire study; 185 nurses working in general practice, nursing homes, hospices and hospitals completed a questionnaire about their most recent case of continuous palliative sedation. Details of the study have been described elsewhere[33-35]. In the questionnaire, respondents were asked if they were willing to participate in an additional qualitative interview. In total, 36 nurses indicated willingness and were subsequently interviewed.

Procedures

A semi structured interview scheme was developed with open-ended questions that were based on themes from the questionnaire: refractory symptoms, decision-making and communication, the practice of palliative sedation, and experiences with the palliative sedation guideline from the Royal Dutch Medical Association[20]. Questions partly pertained to the case that respondents had described in the questionnaire, but also concerned other experiences with the practice of palliative sedation. Nurses who had stated willingness to participate in an interview were approached via telephone and the study aims and methods were explained to them. An interview was arranged and they were interviewed at a location of their choice. Participants consented to the audiotaping of their interview. The interviews were conducted during a 7-month period (October 2008 - April 2009) by four interviewers with a medical or health science background. Consistency among interviewers was ensured through the use of the interview scheme, a one-day training, and monthly meetings to discuss findings and interim analyses. The interviews lasted between 30 and 65

minutes. Information about the nurses' age, gender and work setting was obtained from the questionnaire. This study was exempt from review by a research ethics committee under Dutch law.

Analysis

The recordings were transcribed verbatim by a professional agency and anonymized. Analyses were performed with the constant comparative method[36]. Themes and subthemes were independently derived from a subset of five interviews by MEL and SJS. These (sub)themes were compared and organized in an initial coding tree which was discussed in depth by MEL, SJS and AvdH on several occasions after which the coding tree was adjusted. The final version was used for coding all interviews. Another five interviews were coded by MEL and SJS independently and differences in coding were discussed until consensus was reached. The final version was used for coding all interviews. The remaining interviews were coded by MEL, interview fragments that raised questions while coding were discussed in depth between MEL and SJS. The codes used in the interviews were connected to the main theme ´pressure´, with several subthemes. The coded fragments were discussed in depth by MEL, SJS and AvdH. Quotes were selected by MEL and AvdH to illustrate the arguments.

RESULTS

Table 1 shows the characteristics of the 36 interviewed nurses.

In the interviews, several nurses described that interacting with physicians and family members is an important part of their work in palliative care. Whether or not a patient is experiencing unbearable suffering can be judged differently by the family, the physician or the nurse. Nurses described situations in which they felt that providing palliative sedation was in the patient's best interest, but experienced (real or perceived) constraints that prevented them from taking action. They also described situations in which they experienced pressure to be involved in the administration of palliative sedation, but felt that their action was not in the patient's best interest.

Table 1 Nurses' characteristics (n=36)

Age	
< 40 yrs	14
40-49 yrs	13
50-59 yrs	9
>60 yrs	0
Gender	
Female	34
Male	2
Worksetting	
General practice/ home care	11
Nursing home/ Hospice	10
Hospital	15

Experiencing constraints preventing action.

Several nurses described situations in which they felt that starting palliative sedation was necessary to alleviate the patient's suffering, whereas the physician thought that it was too early to start. These situations related to differences in the assessment of the patient's situation leading to a discrepancy in opinion about the

severity of the patient's suffering. The hierarchical difference between physicians and nurses in situations where such disagreement is present was also mentioned as distressing.

> *"A young person still, and it was clear that he couldn't go on like that any longer. It had already been discussed that when the situation would become unbearable sedation could be started. And the physician just refused. He thought it was not yet necessary... Clearly a case of "you're just a nurse, I'm the physician and I decide what 's going to happen". Not listening to your observations and your experience. Well that's it, you have to accept that. And that's really awful." R931 hospital*

Nurses are often the caregivers that spend the most time with the patient and his family, usually more than physicians. Explaining or justifying on behalf of the physician to the patient why it was not yet time to start palliative sedation when nurses themselves thought it was, was experienced as very troublesome.

> *"Talking, talking, talking, and of course you try to explain [to the patient and his relatives] why the physician isn't willing to start [the sedation]. Of course the need should be there, but I had the feeling that the physician's reluctance was not right; that it was perfectly okay to start with [the sedation]." R822 nursing home*

Differences in opinions between nurses and physicians seemed to occur relatively often during out of office hours or in the absence of a pro-active care plan.

> *"It happened during the night shift (....) it was obvious that the situation couldn't go on like that, and it had been agreed upon already that when the situation would not be under control anymore that sedation could be initiated. And the physician just refused. He did not find it necessary." R931 hospital*

Experiencing pressure to act

Feeling pressured to act but not being convinced that this act is in the best interest of the patient was a frequently reported theme in the interviews. Feeling pressure to act was described as occurring at two points in time, i.e. before the start of sedation and during the sedation process, and coming from different sources, i.e. the physician and the family.

Pressure before the start of palliative sedation

Several nurses reported on situations where they felt that the family was requesting action, i.e. the initiation of palliative sedation, but where the nurse did not feel that it was indicated or appropriate yet. Watching a close relative nearing the end of life can be a heavy burden for family members, sometimes an even greater burden than it seems to be for the patient himself.

"Sometimes the relatives say: "we can't bear the sight [of our suffering relative] anymore" or "when will it end?" While you don't observe this feeling in the patient. Sometimes you do, but not always. Sometimes I get the feeling that the relatives suffer most, more than the patient." R869 nursing home

Nurses indicated that intensive and careful communication with the family is needed to explain why their request may come too early. The Dutch guideline states that a life expectancy of one to two weeks at most is a necessary condition for starting palliative sedation. Nurses however seem to have a narrower view: they seem to consider the start of the dying phase, that is the moment at which it is recognized that the patient will very likely die within hours or days, as the only appropriate moment to start palliative sedation.

"(...) What we always try to do, if possible, together with the GP is to keep the situation as stable as possible until we can establish someone has entered the dying phase. (...) I have rarely seen... I can't remember I've ever seen that a GP failed to resist the pressure [of family to start sedation]. But still a lot of communication with the relatives is needed. "R712 home care

A decision by the physician to start palliative sedation can also be experienced by nurses as coming too early. Sometimes nurses felt that not all options to relieve the patient's suffering had been discussed or explored yet and that therefore not all requirements to start palliative sedation had been met.

"Sometimes you doubt if the physician has done enough to address the symptoms. And if he has adequately judged whether or not the patient is in the dying phase" A863 home care

Dealing with this situation required a lot of deliberation and the nurse sometimes felt a need to provide the physician with alternative options to relieve the patient's symptoms. To be able to engage fully in these discussions, nurses require adequate knowledge about clinical and ethical aspects of palliative sedation. When the physician was receptive to the arguments of the nurse the decision to start palliative sedation was sometimes postponed, but this was not always the case.

"When he [the physician] wants to start continuous sedation, while you yourself aren't convinced yet that that is necessary or useful at that moment, this sometimes led to the whole thing not taking place. (.....) [If you want to have an impact as a nurse,] you have to have alternatives available. When I don't have an alternative, I can't start the conversation." R878 nursing home

Several nurses stressed the difference between palliative sedation and euthanasia. Some of them described a situation in which a patient had expressed an explicit wish for euthanasia (i.e. active ending of life, a legal practice in the Netherlands as long as it is performed by a physician who acts in accordance with the legal criteria of due care), but where the physician decided to provide palliative sedation, either because the euthanasia procedure was judged

as too time consuming or because of a conscientious objection of the physician to perform euthanasia. Nurses indicated that they felt distressed by the disregard of the patient's wish in such a situation.

> *"We've had a case of a man who had been ill for a long time, he had expressed a clear wish for euthanasia but his GP didn't want to cooperate. In the end these people were somewhat pressured into the direction of palliative sedation. Eventually he was sedated, but it took several days, and he even regained consciousness and was distressed. Afterwards, when I went there for a house call, his wife told me "this wasn't how he had wanted it". I feel bad about that." R706 home care*

Pressure during the sedation process

Nurses described experiencing distress when family members, after the goodbyes had been said and palliative sedation had been started, explicit or implicitly requested for expediting the patient's dying trajectory because it was taking longer than they had expected.

> *"Well sometimes the relatives are tired of waiting and they think: how long will this go on? Do we really have to sit here for another three days? We don't want that. That's when you sometimes feel pressured." A773 hospital*

> *About continuous sedation, I think about the phase when a patient is sedated and relatives fairly soon start to ask if the pump can be turned up some more, they've had enough of it, they're all there now, so they think if the pump is turned up, their relative will die sooner, and that would suit them." A863 home care*

Nurses and family members may disagree upon whether a patient is comfortable while being sedated. Family members were reported to sometimes having a preference for a deep level of sedation and requesting an increase of the sedative drug dosage to suppress moves or noises from the patient, such as death rattle, while nurses indicated that these phenomena are part of the normal dying process.

> *"With every little movement or sound a patient makes, they want the pump to be turned up. And just after it has been turned up a little, they want it to be turned up some more. You can try to explain that the effect should be awaited, but then they may manage to pressure you in a way that makes you feel very ill at ease in the end. That's when you think, "I'm now doing something I don't feel comfortable with" R990 hospital*

DISCUSSION

Nurses described two distinct situations involving distress while working together with physicians in caring for patients in the last phase of life for whom palliative sedation is

considered: (1) the nurse felt that palliative sedation was needed to alleviate the suffering of a patient, whereas the physician thought that it was not (yet) indicated; 2) the physician decided to start palliative sedation whereas the nurse viewed this as not indicated because not all requirements to start palliative sedation had been met (yet). Nurses' feelings of distress in both these situations can be characterized as feelings of powerlessness. The feeling of powerlessness as a cause of moral distress was also identified by Oberle et al[13] who studied acute care nurses' and doctors' perceptions of ethical dilemmas in end of life care decisions. In that study, moral distress as experienced by nurses was related to their 'lower' hierarchical position: not being listened to by doctors; being expected to remain silent even when witnessing choices they consider wrong; being unable to have an impact on decisions despite their professional assessment and detailed understanding of the patient's condition. In our interviews nurses described difficult situations when having to deal with physicians who are on duty and do not know the patient, physicians who are inexperienced in end-of-life care or in providing palliative sedation and situations in which a pro-active care plan was absent. Preferably the decision to start palliative sedation does not come as a 'surprise' to the involved healthcare professionals; instead, it should be the anticipated potential outcome of a process of efforts to control symptoms near the end of life.

It is obvious that nurses and physicians can have different interpretations of what the appropriate indication and time to start palliative sedation are. Nurses experienced their inability to alleviate the patient's suffering in situations where the physician disagrees with providing palliative sedation as evoking stress. Such stress can in turn result in suffering for themselves[13]. On the other hand, nurses judged recognition that the dying phase has started as an important prerequisite to start palliative sedation. Recognizing the start of the dying phase most often occurs hours or days before death. The Dutch guideline on palliative sedation states that continuous sedation can only be administered when a patient's 'life expectancy is less than one to two weeks[20]. This prerequisite is included to make clear that continuous sedation can only be used when there is no or a very limited possibility that it hastens death. There seems to be a discrepancy between the criterion on life expectancy in the guideline and nurses' views, where nurses appear to prefer a more limited life expectancy than the guideline. This may be related to nurses' concerns that sedation might hasten death, a concern previous reported by Anquinet et al. in a qualitative study of home care nurses and their experiences with palliative sedation[32]. In addition, adequately predicting patients' remaining life expectancy remains difficult, although such predictions have been shown to become more accurate when patients are closer to death[37-39].

Nurses may also feel uncomfortable when the course of sedation is not in line with expectations or preferences of patients. Especially waking up during continuous sedation can cause distress[40]. A protracted and seemingly disquiet dying process can also be very burdening for family. This may lead to implicit or explicit requests to increase the level of the sedation, either or not with the purpose of hastening the patient's death. A decision of the

physician to grant such requests may evoke the feeling that the patient receives unnecessary or arguable treatment. Providing medical treatment and care that is perceived as not serving the patient's best interest has been described before as evoking moral distress[41-44].

Feelings of powerlessness and the experience of patients receiving unnecessary treatment have also been described as causes of moral distress by Hamric et al[42]. They distinguished different root causes of moral distress, including internal worker factors, such as perceived powerlessness, and factors related to the immediate clinical situation, such as the experience of patients receiving unnecessary treatment. Nurses seem to feel that they are very capable of estimating dying patients' needs, because of their experience and nearness to the patient, without having the authority to make decisions on care and treatment. In our study, we did not find other causes of moral distress as suggested by Hamric et al., such as lacking situational knowledge (an internal worker factor); a lack of truth-telling; a lack of patient consent to be treated (factors related to the immediate clinical situation); or external factors, such as inadequate staffing and lack of administrative support.

According to Epstein and Hamric[45] addressing moral distress is not a matter of analysing single cases. Instead, multidisciplinary interventions aimed at the organization of care are needed. Based on our interviews we feel that several actions may be needed to support nurses in dealing with stressful situations that may result from the use of palliative sedation. These actions may be focused on nurses as individuals or on a group-level. The first action would be education about the guideline and decision making process that precedes palliative sedation. When nurses are well educated they will better understand the procedure and considerations of the physician and more adequately discuss their concerns or feelings with physicians. A second action would be to focus on the communication between nurses and physicians. Epstein suggests to design and use forums for interdisciplinary problem solving such as interdisciplinary rounds[45]. When both physicians and nurses are included in discussions about the use of palliative sedation this could lead to a better understanding of each other's roles, thoughts and reasoning. A third action is related to the content of the Dutch guideline for palliative sedation. This guideline[20] describes the different steps in the decision making process and acknowledges dilemma's that can arise when palliative sedation is prescribed. However the guideline is not very specific about the roles and tasks of the physician and the nurse and could benefit from more explicit guidance in that area. A fourth action would be to investigate to what extent physicians experience moral distress related to the provision of palliative sedation. Insights from physicians could further substantiate strategies to support nurses in dealing with stressful situations related to palliative sedation.

Using interviews from a rather large group of nurses increased the validity of this qualitative interview study. However, our study also has some limitations. Due to the fact that the original data collection was not aimed at achieving saturation of information on the topics studied here, we cannot be sure that we have not missed any relevant information. Further,

due to the retrospective design of the study we cannot preclude recall bias, which was however limited by asking about specific and recent cases.

To conclude, the nurses in this study described various situations in which they experienced moral distress when being involved in the practice of palliative sedation. Their main concern was that they felt that they were not able to act in the patient's best interest. To deal with these situations, nurses need to be able to adequately communicate with suffering patients, distressed family members and physicians and to have adequate knowledge about clinical and ethical aspects of palliative sedation. Empowering nurses in up taking their professional role seems to serve the best interest of both patients and nurses themselves.

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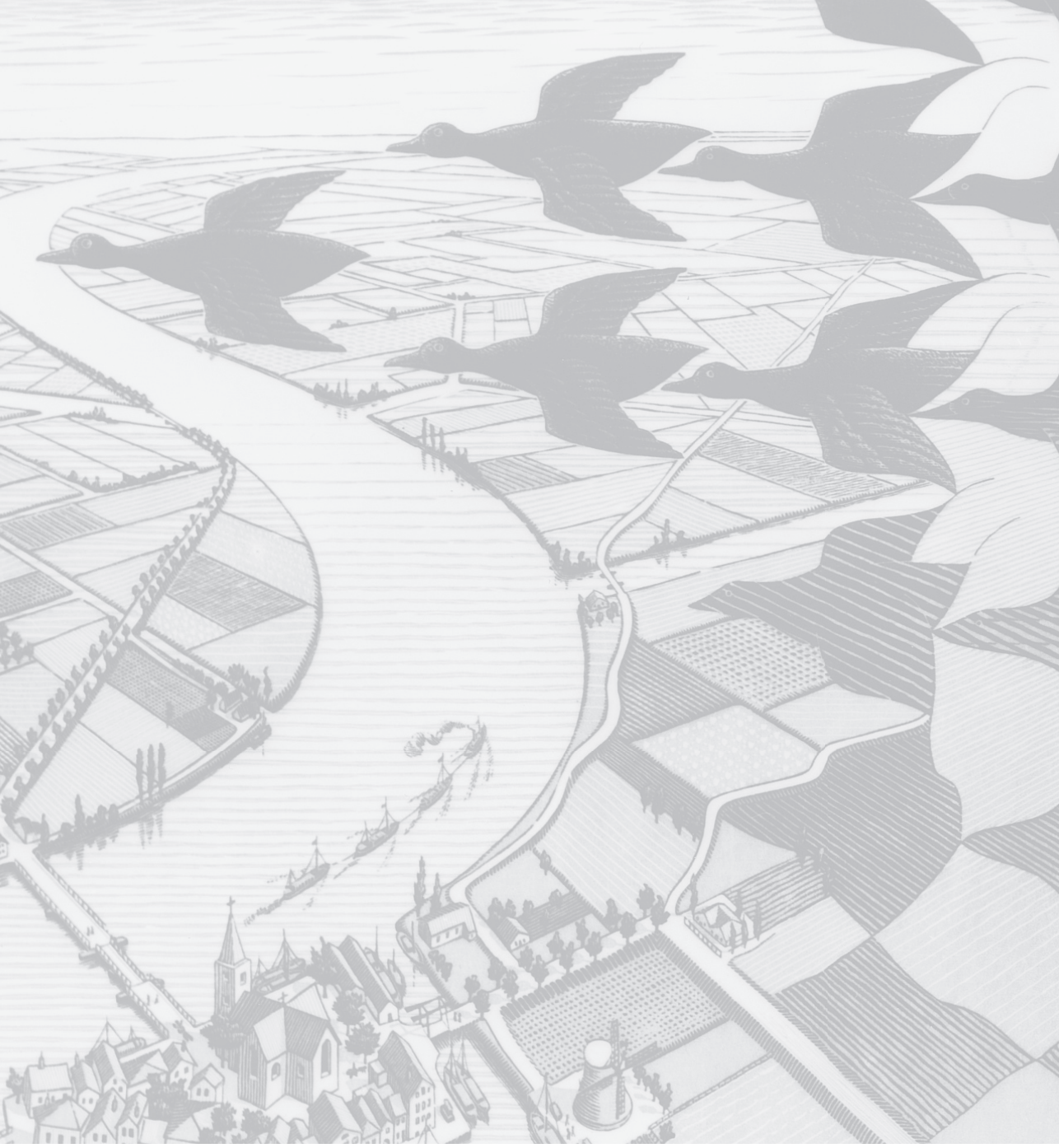

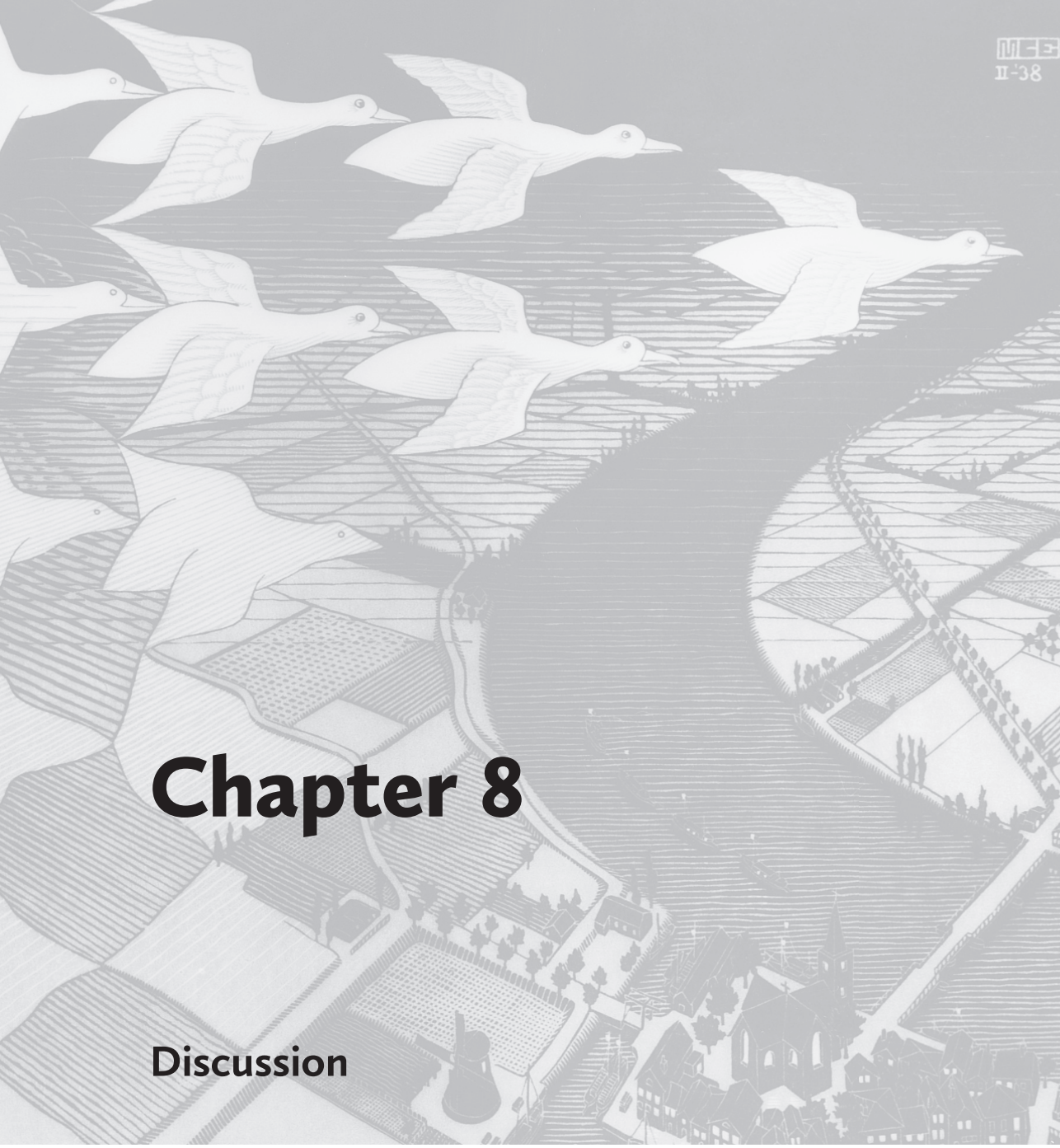

Chapter 8

Discussion

The studies described in this thesis concern various aspects of symptoms and symptom relief during the last phase of life of patients with advanced diseases. This chapter presents the key findings of the studies, followed by methodological considerations and a general discussion focusing on two important emerging themes in these studies, i.e. acknowledging different perspectives and communication. Finally some implications and recommendations for clinical practice and future research will be discussed.

KEY FINDINGS

In order to deliver good healthcare, it is important to know which symptoms occur during a specific disease or disease phase, as well as their impact on patients' daily functioning and quality of life. We studied the prevalence and impact of symptoms in two understudied patient groups (chapter 2 & 3). First, we focused on patients with incurable head and neck cancer (chapter 2) and found that these patients reported an average of 14 different symptoms (interval 0–26), of which 10 somatic symptoms and 4 psychosocial symptoms. The most frequently reported somatic symptoms were 'fatigue', 'pain' and 'weakness'. In the psychosocial area, these were 'worrying', 'sadness' and 'tenseness'. The symptom with the greatest impact on daily functioning, was 'dyspnoea'. We compared the reporting of patients and family members and found that in two thirds of cases, although not always significant, the occurrence rates and impact scores of physical symptom as estimated by family members were higher than those estimated by patients. For about 50% of the psychosocial symptoms we found a reverse trend. Second, we studied patients with advanced heart failure in South Africa (chapter 3). We found that patients, of whom 14% had completed high school and 26% had no income, reported a mean of 19 symptoms. Physical symptoms with the highest occurrence were 'shortness of breath', 'feeling drowsy/tired' and 'pain' . Psychological symptoms with the highest occurrence were 'worrying', 'feeling irritable' and 'feeling sad'. Symptoms with the highest burden were 'shortness of breath', 'numbness/ tingling in hands or feet' and 'I do not look like myself'. Higher symptom burden was associated with a higher age, having no income and fewer hospital admissions within the previous 12 months.

As death comes nearer, patients with advanced illness have been reported to experience many symptoms in their last week or days of life[1-11]. However, until now, research on the occurrence and impact of several symptoms in the dying phase has been scarce. This also holds for death rattle. We performed a systematic search of scientific literature concerning the prevalence of death rattle, its impact on patients, relatives and professional caregivers, and the effectiveness of interventions (chapter 4). We found that death rattle is a common symptom in dying patients. Approximately a third of patients will present with this symptom during the dying process. Death rattle leads to distress in both family members and professional caregivers, but it is doubtful if patients suffer from this symptom. Different

medication regimes for the treatment of death rattle have been studied. Current evidence does not support the use of antimuscarinic drugs in the treatment of death rattle.

At the end of life, oral fluid intake is often reduced. Whether it is beneficial for patients to substitute decreasing oral intake with artificial hydration has been debated frequently[12-14]. This debate has mostly focused on two distinct symptoms: death rattle, which has been linked to over-hydration, and terminal restlessness, which has been linked to under-hydration. To investigate whether the amount of fluid intake, preceding and during the dying phase, is related to the occurrence of death rattle and terminal restlessness, we performed a multicentre prospective observational study in patients who were, according to their multidisciplinary care team, likely to die within a few days (chapter 5). We found that death rattle was reported at least once in 40% of patients during the dying phase, and in 35% of patients during the last 24 hours of life. The occurrence of death rattle increased with death coming nearer. Terminal restlessness was reported in 26% of patients during the dying phase and in 13% of patients during the last 24 hours of life. Terminal restlessness occurred almost evenly throughout the dying phase. We found no association between fluid intake and the occurrence of death rattle. Terminal restlessness during the last 24 hours of life was associated with a higher intake of fluid during the period 48-25 hours before death.

Being aware that death is imminent is often seen as one of the features of a good death in modern Western culture[15-19]. We studied to what extent patients are aware of the imminence of their death by performing a secondary analysis of data from questionnaires filled in by nurses and bereaved family members, and data from patients' medical record (chapter 6). We found varying reports on whether patients were aware of the imminence of their death. According to the medical records, 51% of patients had been aware of the imminence of death, according to nurses this was true for 58% and according to family members for 62% of patients. Inter-rater agreement on patients' awareness of dying was fair. Whether a patient was aware of the imminence of dying was not clearly associated with the occurrence of symptoms that are common in the last days of life, such as fatigue, shortness of breath, pain, dysphagia or restlessness. Patients dying at home were more often aware of the imminence of death than patients who died in a hospital or in a nursing home. We also found that awareness of imminent death was associated with acceptance of dying: patients who were aware of the imminence of death were more often in peace with dying and more often felt that life had been worth living, than patients who had not been aware according to the family member.

Sometimes the symptoms which patients who are nearing death experience cannot be relieved with conventional therapeutic interventions. Palliative sedation is used to alleviate unbearable and refractory suffering in the last phase of life and has been linked to distress in nurses[20 21]. To explore the extent to which nurses experience distress when being involved in the practice of palliative sedation, we performed a secondary analysis of data from qualitative interviews with nurses (chapter 7). We found that whether or not a patient is

experiencing unbearable suffering can be judged differently by the family, the physician or the nurse. Nurses described morally distressing situations in which they felt that providing palliative sedation was in the patient's best interest, but experienced (real or perceived) constraints from physicians that prevented them from taking action. In these situations nurses felt that starting palliative sedation was necessary to alleviate the patient's suffering, whereas the physician thought that it was too early. Nurses also described situations in which they experienced pressure from physicians or family members to be actively involved in the provision of palliative sedation, but felt that this was not in the patient's best interest. The latter situation was related to (1) starting palliative sedation when the nurse felt not all options to relieve suffering had been explored; (2) family requesting an increase of the sedation level where the nurse felt that this may involve hastening of death; (3) a decision by the physician to start palliative sedation where the patient had previously expressed an explicit wish for euthanasia.

METHODOLOGICAL AND OTHER CONSIDERATIONS

We used different methods in the studies described in this thesis: cross-sectional surveys among patients and family members; a systematic literature review; a prospective observational study; secondary analyses of (1) cross-sectional data collected through questionnaires and from the medical record, and (2) data from qualitative interviews. Methodological and other considerations will be discussed per study.

Cross-sectional surveys - Prevalence & impact of symptoms in 2 understudied patient groups

A cross-sectional study is an observational study that provides a snapshot of a certain population. For the data collection in the head and neck-study (chapter 2) we used instruments (i.e. Pal-C and Pal-SI) that were judged by the healthcare professionals as practical for gathering information on symptom prevalence in the least possible intrusive way. However, these instruments did not undergo a formal psychometric evaluation. In this study, data were provided by two separate groups: the first group consisted of 124 patients who provided information on symptom presence, the second group consisted of 24 patient and family member couples who both provided information on the impact of symptoms. The 44% non-response within the group that provided information on symptom prevalence is a limitation. Non-responding patients had a significantly shorter life expectancy and seemed to have a much worse condition than responding patients. The large nonresponse (more specifically, patients who did not respond because of their weak condition) within this group confirms how vulnerable this specific cancer population is. The number of patients and family members in the group that provided information on the impact of symptoms was small which limits the possibility to generalize results.

In the heart failure study (chapter 3), we used the Memorial Symptom Assessment Scale (MSAS), a widely used and well validated instrument. Patients were recruited over the course of a month at multiple wards of the hospital and the questionnaire was available in different languages. Although we had a high response rate, most patients who were included in the study were diagnosed with stage III heart failure. It is therefore possible that our results are not generalizable to patients with stage IV heart failure.

Systematic review - Death rattle prevalence, impact and interventions

We conducted a systematic review to synthesize current evidence concerning the symptom death rattle (chapter 4). We found that the reported death rattle prevalence varied widely between studies. This variation might be explained by several factors. First, there is a wide variety of labels used to describe death rattle, and whether various labels all refer to the exact same phenomenon is not clear. Second, different study designs were used. 34% were prospective studies and the weighted mean occurrence of death rattle in these studies was 45%. Sixty-four percent of the studies were retrospective studies and the weighted mean occurrence of death rattle in these studies was 30%. Third, methods to determine the prevalence of death rattle varied between the studies. Few studies used validated instruments, such as the death rattle scoring scale[22].

The most optimal study design to evaluate the effectiveness of medical therapy and other interventions for death rattle is a controlled study. We found no studies that included a placebo group. Further, randomized controlled trials among patients who are in the dying phase are rare, mainly because of ethical and practical considerations related to randomization, informed consent, use of placebo and follow-up[1-5.]

Prospective observational study - Hydration and symptoms in the last days of life

A randomized controlled trial would also be the most optimal design to study the effects of fluid intake on the occurrence of symptoms, but would pose ethical challenges. In the Netherlands, healthcare professionals tend to be reserved about prescribing artificial hydration at the end of life.[23] In daily practice, fluid intake and administration of hydration vary. Therefore, we conducted a prospective observational study, to explore whether there is a relation between fluid intake in daily practice and the occurrence of death rattle and terminal restlessness (chapter 5). We prospectively collected information on fluid intake at three moments in time: the week before the start of the Care Program for the Dying (CPD), the day before the start of the CPD and 4 hourly during the dying phase, i.e. after the CPD was started. The occurrence of symptoms was also measured 4 hourly during the dying phase. To avoid mixing cause and effect, we calculated the total amount of fluid intake during the time period 48-25 hours before death and related this to occurrence of death rattle and terminal restlessness during the last 24 hours of life. Whereas terminal restlessness occurred almost evenly throughout the dying phase and often only once, it is possible that patients who were

classified as having no terminal restlessness during the last 24 hours of life actually presented with terminal restlessness before the last 24 hours of life but were successfully treated, e.g. by providing them with palliative sedation. However, we found no evidence that patients with terminal restlessness were more often sedated than patients without terminal restlessness. At the start of this study no instrument to measure terminal restlessness was available. We therefore decided to use the calmness scale of the Vancouver Interaction and Calmness Scale. Whereas the value of this instrument to measure terminal restlessness has not been assessed, it is possible that patients were misclassified. The prevalence found in our study is however in line with other studies on restlessness in the terminal phase of life. Occurrence of death rattle was measured using the validated Death rattle scoring scale by Back et al[22].

Secondary analyses – Awareness of dying & Palliative sedation and moral distress

An advantage of secondary analyses of research data is that it is a form of efficient use of research data. Especially for research in palliative care with its potentially fragile patients it is an advantage when data can be used as efficient as possible. However, when using data from qualitative studies, (chapter 7) it is unclear if the number of interviews was sufficient to achieve saturation of information on the researched topic. It is possible that relevant information is missed. In both secondary analyses, (chapter 6 & 7) data were used that were collected after the death of a patient. A certain degree of recall bias can therefore not be precluded. For the qualitative interviews, we tried to limit this bias by focusing on specific and recent cases.

INTERPRETATION OF THE FINDINGS

Acknowledging different perspectives

The studies in this thesis cover various aspects of the burden and management of symptoms during the last phase of life of patients with an advanced illness. A recurrent theme in the studies in this thesis is the presence of different perspectives. A specific situation can be viewed upon differently by different observers. Also, 'what you see is not always all there is to see'. In palliative care, this was already suggested when Dame Cicely Saunders in 1964 introduced the concept of 'total pain', which includes the physical, emotional, social, and spiritual dimensions of distress and thus encompasses more than might be expected when discussing pain[24].

In several specific situations studied in this thesis different perspectives appeared to be present: symptom prevalence and burden in patients with head and neck cancer may vary according to patients and family members (chapter 2), awareness of dying of a patient may vary according to healthcare professionals and family members (chapter 6) and what is in the best interest of a patient may vary according to nurses, physicians and family members in our study on palliative sedation (chapter 7).

A patient's assessment is often seen as the gold standard source to collect information about their health status. But even a patient's rating may not always be in accordance with reality, because patients may e.g. underreport symptoms because they do not want to be a burden, or prefer not to worry their family members[25-29]. At the end of life and especially in after-death research, so called proxy-ratings are often used, i.e. a healthcare professional or a family member is asked to provide information on the patient's situation. Studies have shown that patients' ratings of e.g. symptoms may differ from proxy ratings[25 30]. It does not seem to matter in this respect who the proxy is (i.e. healthcare professional or family member)[25]. Proxies have been shown to reliably report on the more objectively observable symptoms. Agreement is poorer when the reporting is about more subjective symptoms, such as pain, feelings and thoughts, anxiety and depression[30]. This is in line with the results in our study in patients with head and neck cancer, in which we saw overreporting by family members of dyspnoea and underreporting of powerlessness and anxiety (chapter 2). The level of patient-proxy agreement appears to be dependent, to a certain degree, on the health status of the patient. Several studies have suggested a U-shaped relationship, meaning that agreement is better when the patient's health status is either very good or very poor[25]. However, views on whether or not patients are aware of the imminence of death diverged between different caregivers (chapter 6). In our study on palliative sedation, the nurse, the physician and the family members appeared to potentially have different views on whether or not a patient was experiencing unbearable suffering (chapter 7). Nurses, physicians and family members usually differ on their level of knowledge and they have different roles and responsibilities when it comes to end of life care and decision making. We found in our study that nurses feel that they are very capable of estimating dying patients' needs, because of their experience and nearness to the patient. They however do not have the authority to make decisions on medical care and treatment, only physicians are legally responsible for making such decisions[31 32].

In our study on symptoms in patients with advanced heart failure, we found that patients reported more symptoms than expected (chapter 3). Many of the reported symptoms are not generally thought of as being caused by heart failure[33 34]. These symptoms might be related to treatment, but the causes of symptoms such as pain remain unclear. Two reviews have focused on symptoms in the last year of life and compared patients with cancer to those with other diagnoses[35 36]. They found that irrespective of the primary diagnosis, commonalities in the prevalence of symptoms were evident. The recommendation following that conclusion is that healthcare professionals should be aware that patients with life-limiting illnesses may exhibit problems and needs that are not strictly associated with their specific diagnosis. This suggests that there is a need for broad symptom screening, also because multimorbidity is currently becoming the norm at the end of life[37].

It is evident that different perspectives exist in the last phase of life. These different perspectives may result from a different appreciation of a phenomenon, a lack of evidence

on what the most beneficial intervention would be, or from a lack of communication among those involved. Evidence and communication are to a certain extent within our reach to tackle, but some causes of different perspectives will remain. It is important to be aware of the potential presence of these different perspectives, to acknowledge them and to make them part of the continuous communication about the patients' health status, with patients, family members and within the healthcare team.

'Acknowledging different perspectives: it needs words.'

Communication

Honest and sensitive communication has been identified by patients and family members as one of the most important elements of care during the last phase of life[38-40]. Care during the last phase of life is often delivered by a multidisciplinary team, which requires continuous communication and shared insights within the team and regular conversations between team members, patients, and family members[41].

A systematic review on the preferences for end-of-life communication of patients with advanced diseases and their family members showed their need for clear information at all stages of the illness trajectory, about the illness itself, prognosis and symptom management[40]. It is important to inform the patient and family members about what can be expected during the last phase of life. This information should be repeated regularly and tailored to existing or expected symptoms. Also, discussions about what is experienced by the patient and family members are important. Being a family member of someone who is in the last phase of life is often an intense and difficult experience. It can be the family member's first actual encounter with dying and death[42]. Even if family members are aware of the imminence of death, this does not mean that they are prepared for it[43]. A death from a chronic illness that is expected by healthcare professionals may be experienced as unexpected and traumatic by family members who are focusing on caregiving rather than on preparing themselves for bereavement[44-47]. In our study on palliative sedation (chapter 7) nurses described requests from family members to start palliative sedation or to expedite the patient's dying trajectory after palliative sedation had been started, which were from the perspective of the nurse not indicated or appropriate yet. Watching how a close relative is dying can be a heavy burden for family members, sometimes an even greater burden than for the patient him- or herself, which may result in such requests. It is important for healthcare professionals to listen to the family members, acknowledge their experiences and to communicate with the distressed family members to explain why their request may not be appropriate yet.

When focusing on two distinct symptoms of the dying phase, death rattle and terminal restlessness (chapter 4 and 5), there are different perspectives on how these symptoms should be addressed. For death rattle, this seems to be related to whether this symptom is

seen as a normal phenomenon at the end of life. When death rattle is seen as a distressing symptom which should be managed, communication and actions are most likely different from situations where the symptom is seen as a normal and non-burdening phenomenon of the dying phase[48 49].

When healthcare professionals communicate within the healthcare team, and with patients and their family members during the last phase of life, it is important to be sensitive about what is said and about how and when and by whom it is said. In addition, they need to listen to what patients and family members say, but also 'hear' what they do not (explicitly) say. Being sensitive to non-verbal cues and 'reading between the lines' is sometimes necessary to 'hear' what worries patients, family, or other healthcare professionals have, and what questions or fears for the near future.

IMPLICATIONS AND RECOMMENDATIONS

For clinical practice

Systematic screening of common symptoms is needed for patients with advanced illness, to be able to address the symptoms that are most distressing or burdensome for a patient. Screening of symptoms should not be limited to their presence, but should include a measure of the extent to which they cause distress or impact on daily functioning. For this screening, many (generic) symptom assessment instruments are available[50 51]. Bearing in mind the deteriorating condition of the patient, the length of such screening instruments should be kept to a minimum. Digital tools like computerized adaptive testing should be considered where possible. For care during the dying phase, the Care Program for the Dying can be used as a clinical instrument, because it includes systematic screening of the most common symptoms during the dying phase.

Care during the last phase of life should include continuous communication about the patients' health status, with patients and family members to identify potential differences in perspectives and appreciations of the patient's situation. The expected course of the illness, which symptoms could occur and the available treatment options should be discussed regularly. Palliative care is interdisciplinary care in which the complementary competences from different healthcare professionals are combined[52]. Ongoing communication within the healthcare team should be an integral part of palliative care. By doing so, physicians and nurses should be better able to understand each other's viewpoints and argumentation.

Proactive care planning and anticipatory prescription of medication are of the essence. Decisions to start palliative sedation for patients with refractory and unbearable suffering should not come as a 'surprise' to the involved health care professionals; instead, it should be the anticipated potential follow-up of efforts to control symptoms near the end of life.

For research

The number of studies focusing on symptoms in patients with advanced diseases has increased during the last decades. Future research should focus on understudied non-cancer groups and effectiveness of interventions for certain understudied symptoms during the last phase of life, such as death rattle. Our systematic review showed that death rattle leads to distress in both family members and professional caregivers, and that there is a lack of evidence for the effectiveness of any antimuscarinic medication in the treatment of death rattle (chapter 4). From a pharmacological perspective, antimuscarinic medications are unable to reduce existing secretions[53]. There are however indications that antimuscarinic medication might have a prophylactic effect[53-55]. Studies on the effectiveness of prophylactic prescription of antimuscarinic medication on the development of death rattle are therefore needed. Studies are also needed on the effectiveness of nursing interventions to address death rattle, such as repositioning of the patient and suctioning of secretions. The effectiveness of nursing interventions also needs to be investigated for many other symptoms, as the medical interventions often have limited results in the last phase of life[56-58].

Our findings on awareness of dying suggest that communication during patients' dying phase is not yet optimal (chapter 6). The optimal time and strategy to enhance open communication about the dying phase cannot be concluded from our data and should be a topic in future research.

In this thesis, various aspects of symptoms and symptom relief during the last phase of life of patients with advanced diseases have been discussed. To be able to provide good quality of care during the last phase of life, we need to systematically screen for common symptoms, acknowledge different perspectives, communicate continually and tailor our care to the needs of the individual patient and their family members.

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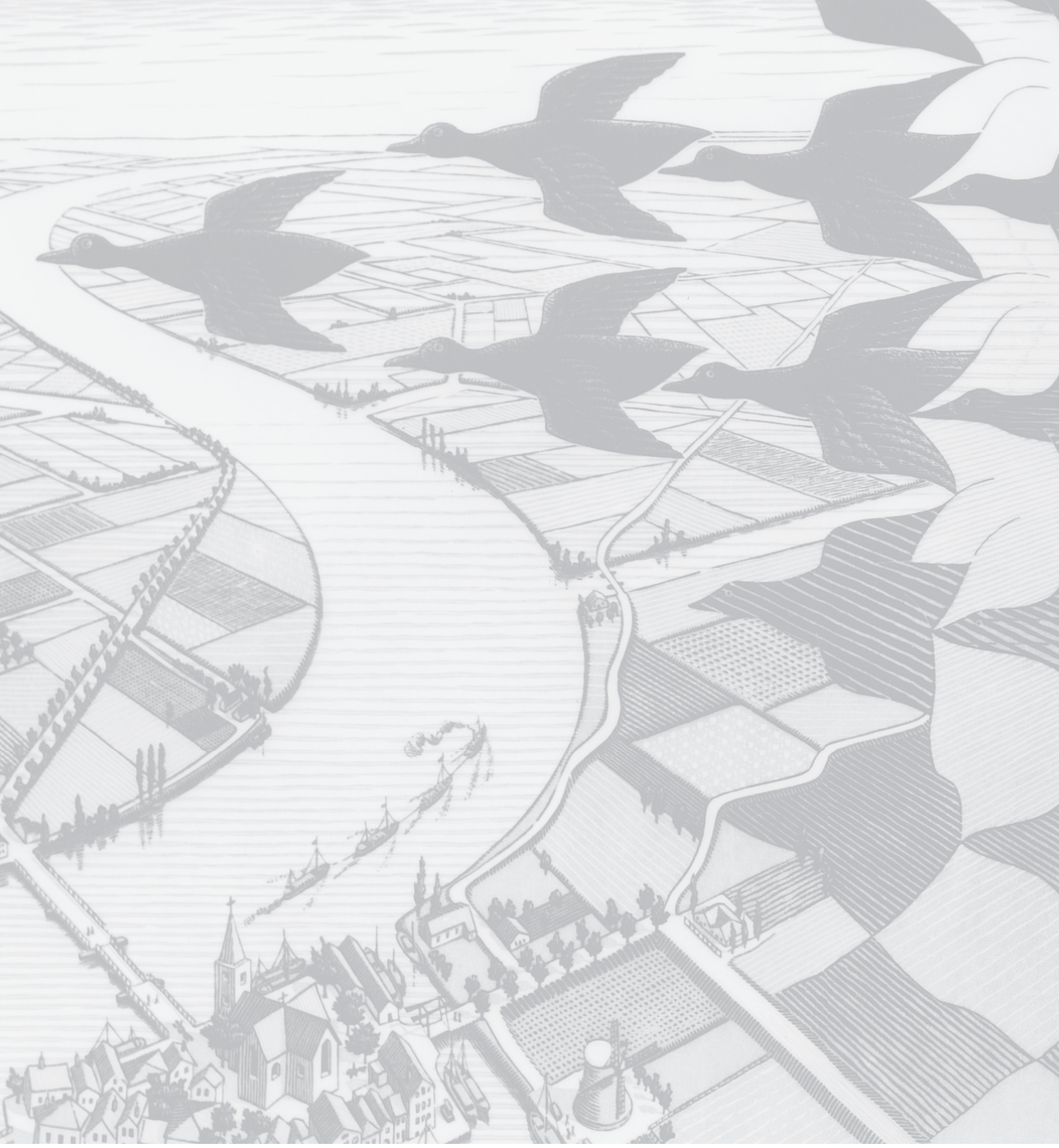

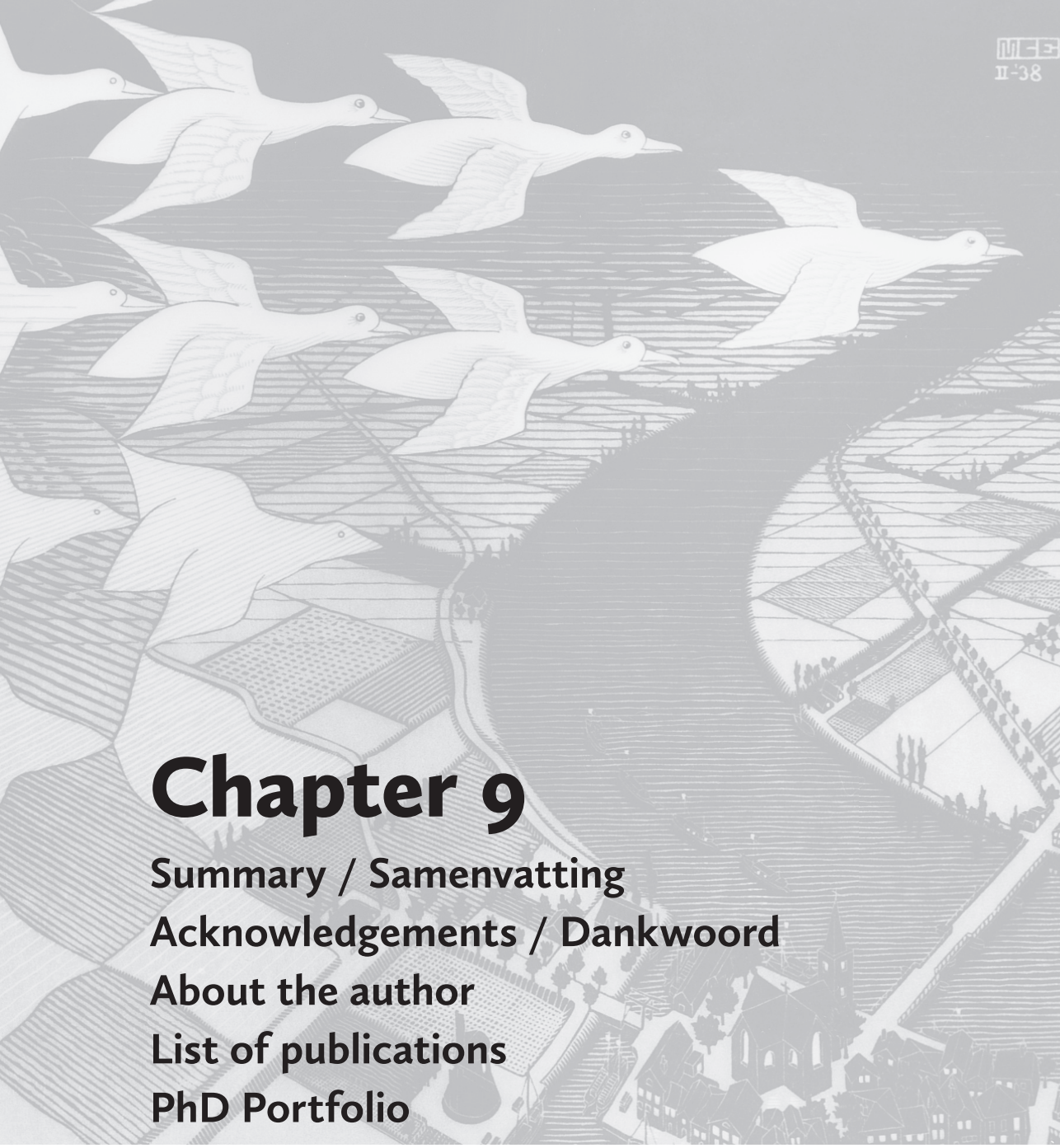

Chapter 9

Summary / Samenvatting
Acknowledgements / Dankwoord
About the author
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PhD Portfolio

SUMMARY

In the introduction (**chapter 1**), the background and aim of this thesis are described.

In order to deliver good palliative care it is important to know which symptoms may occur during a specific disease trajectory or disease phase and what their impact on daily functioning is. The last 25 years, the number of studies focusing on symptoms in patients with advanced diseases has increased steadily, however evidence remains scarce or lacking for some subgroups, such as patients with a specific type of cancer, non-cancer diseases and patients in developing parts of the world.

The aim of this thesis was to providing insight into various aspects of symptoms and symptom relief during the last phase of life.

Chapter 2 describes the results of a cross-sectional descriptive study into prevalence and impact of symptoms in patients with incurable head and neck cancer. Patients were included from the department of Otorhinolaryngology and Head and Neck Surgery. This study consisted of two parts, first data from questionnaires that were gathered between October 2006 and October 2008 as part of normal care was used to establish symptom prevalence for 30 symptoms, of which 9 psychosocial. For the second part, data were prospectively gathered from patients and family members between February 2009 up to May 2009 to establish the impact of those 30 symptoms and discrepancies between the ratings from patients and their family caregivers. We found that patients with incurable head and neck cancer reported an average of 14 different symptoms (interval 0–26), of which 10 somatic symptoms and 4 psychosocial symptoms. The most frequently reported somatic symptoms by the patients were 'fatigue', 'pain' and 'weakness'. In the psychosocial area, these were 'worrying', 'sadness' and 'tenseness'. The symptom with the greatest impact on daily functioning is 'dyspnoea'. We compared the reporting of patients and family members and found that in two thirds of cases, although not always significant, the occurrence rates and the impact score of somatic symptoms were systematically estimated higher by the family members compared to the patients. However, when it comes to psychosocial symptoms, we found a reverse trend. About 50% of the symptom prevalence and the symptom impact score are indicated higher by the patients compared with family members.

Chapter 3 describes the results of a cross-sectional descriptive study into prevalence and burden of symptoms in patients with advanced heart failure at Groote Schuur Hospital in Cape Town South Africa. Patients were recruited for this study between August and November 2012 from several inpatient facilities (i.e., emergency unit, emergency ward, cardiology ward, general medicine wards) and the outpatient cardiology clinic. Patients provided information on symptom prevalence of 28 physical and 4 psychological symptoms and the associated burden for each symptom recorded as prevalent. We found that the patients in our study, of

which 14% completed high school and 26% reported having no income, reported a mean of 19 symptoms of which 18 symptoms were reported by more than 50% of all patients. Physical symptoms with highest occurrence were 'shortness of breath', 'feeling drowsy/tired' and 'pain'. Psychological symptoms with highest occurrence were 'worrying', 'feeling irritable' and 'feeling sad'. Most symptoms were associated with high burden, symptoms with the highest burden were 'shortness of breath', 'numbness/ tingling in hands or feet' and 'I do not look like myself'. Higher symptom burden is associated with a higher age, having no income and fewer hospital admissions within the past 12 months.

In **chapter 4** the results of a systematic literature review on the prevalence of death rattle in dying patients, its impact on patients, relatives, and professional caregivers, and the effectiveness of interventions are presented. Several databases were searched for empirical studies in 2012. We investigated various labels and definitions of death rattle, the prevalence of death rattle, the impact of death rattle on patients, relatives, and professional caregivers, and effects of medical and nonmedical interventions. We found that death rattle is a common symptom in dying patients. Approximately a third of the patients will present with this symptom during the dying process. Death rattle leads to distress in both relatives and professional caregivers, but it is doubtful if patients suffer from this symptom. Different medication-regimes for the treatment of death rattle have been studied. There is no evidence that the use of any antimuscarinic drug is superior to no treatment.

Chapter 5 describes a multicentre prospective observational study we performed to study whether the amount of fluid intake, preceding and during the dying phase, is related to the occurrence of death rattle and terminal restlessness. Data were collected in 8 hospitals (one to three wards per hospital) and five hospices, including three palliative care units in nursing homes (PCUs), in the Netherlands. Data collection took place between November 2012 and November 2013 in patients who were, according to the multidisciplinary care team, likely to die within a few days. Data were collected using a digital version of the Care Program for the Dying (CPD), a Dutch instrument for multidisciplinary care for patients in the dying phase. For this study, the CPD was supplemented with questions about death rattle, terminal restlessness, use of opioids and patients' fluid intake. We found that death rattle was reported at least once in 40% of patients during the dying phase, and in 35% of patients during the last 24 hours of life. The prevalence of death rattle increased with death coming nearer. Terminal restlessness was reported in 26% of patients during the dying phase and in 13% of patients during the last 24 hours of life. Terminal restlessness occurred almost evenly throughout the dying phase. We found no association between fluid intake and prevalence of death rattle. We also did not find an association between low fluid intake and terminal restlessness. Terminal restlessness during the last 24 hours of life was associated with a higher intake of fluid during the period 48-25 hours before death.

Chapter 6 reports on the results of a secondary analysis of data from questionnaires filled in by nurses and bereaved family members, and data from the medical record we performed to investigate to what extent patients are aware of the imminence of their death. For the original study, patients were recruited from hospitals, nursing homes and home care services in the southwest of the Netherlands. Data collection took place between November 2003 and February 2006. Halfway this period, the LCP was introduced and subsequently used for each patient for whom the multidisciplinary team agreed that the dying phase had started. Within 1 week after the death of an eligible patient, a nurse who had been closely involved with caring for the patient during the last 3 days of life completed a questionnaire. About 2 months after the death of a patient, a relative, who had been 'contact person' for the patient, received a letter from the institution that had provided terminal care. In this letter, he/she was asked for consent to be approached by the research team to fill in a written questionnaire. A reminder was sent to nonresponding relatives after 2 and 6 weeks, respectively. Only relatives who gave their consent were mailed a questionnaire. We found varying reports whether patients were, according to the nurse, family member or reporting in the medical record, aware of the imminence of their death. According to the medical records 51% of patients had been aware of the imminence of death, according to nurses 58% and according to family members this was the case for 62% of patients. Inter-rater agreement on patients' awareness of dying was fair. Whether a patient was aware of dying was not clearly associated with common symptoms in the last days of life. Patients dying at home were more often aware of the imminence of death compared to patients who died in a hospital or in a nursing home. We also found that awareness was associated with acceptance of dying; patients who were aware of the imminence of death were more often in peace with dying and felt more often that life had been worth living than patients who were not aware according to the family member.

To explore nurses' reports on the practice of palliative sedation focusing on their experiences with pressure, dilemmas and morally distressing situations we performed a secondary data analysis of an interview study among nurses which we presented in **chapter 7**. Qualitative interviews with nurses were collected as part of a larger project about the practice of palliative sedation in the Netherlands after the introduction of a national guideline on palliative sedation. The project focused on physicians' and nurses' experiences with continuous palliative sedation. The first part of the project was a questionnaire study; nurses working in general practice, nursing homes, hospices and hospitals completed a questionnaire about their most recent case of continuous palliative sedation. In the questionnaire, respondents were asked if they were willing to participate in an additional qualitative interview. In total, 36 nurses indicated willingness and were subsequently interviewed between October 2008 and April 2009. Analyses were performed with the constant comparative method. The codes used in the interviews were connected to the main theme ´pressure´, with several

subthemes. Subthemes related to pressure were: (1) the nurse pressuring the physician, (2) the physician pressuring the nurse, (3) the family pressuring the nurse/physician. We found that whether or not a patient is experiencing unbearable suffering can be judged differently by the family, the physician or the nurse. Nurses described morally distressing situations in which they felt that providing palliative sedation was in the patient's best interest, but experienced (real or perceived) constraints from physicians that prevented them from taking action. These situations related to nurses feeling that starting palliative sedation was necessary to alleviate the patient's suffering, whereas the physician thought that it was too early to start. They also described situations in which they experienced pressure from physicians or family members to be actively involved in the provision of palliative sedation, but felt that their action was not in the patient's best interest. The latter situation related to (1) starting palliative sedation when the nurse felt not all options to relieve suffering had been explored yet; (2) family requesting an increase of the sedation level where the nurse felt that this may involve unjustified hastening of death; (3) a decision by the physician to start palliative sedation where the patient had previously expressed an explicit wish for euthanasia.

Finally, in **chapter 8** (general discussion) the key findings of the studies are summarizes and integrated. We concluded that it is important to acknowledge the presence of different perspectives concerning symptoms and symptom relief during the last phase of life. To establish this, improvement of communication within the healthcare team and with patients and family members is needed. Communication related to symptoms should preferably be a continuous process. The chapter concludes with implications for clinical practice and recommendations for future research.

SAMENVATTING

In de introductie (**hoofdstuk 1**), worden de achtergrond en doelstelling van dit proefschrift beschreven. Om goede palliatieve zorg te kunnen leveren is het belangrijk te weten welke symptomen tijdens een ziektetraject of ziektefase kunnen optreden en wat de impact van die symptomen is op het dagelijks functioneren. De laatste 25 jaar is het aantal studies naar symptomen bij patiënten met een vergevorderde ziekte gestaag toegenomen, maar bepaalde groepen zijn nog onderbelicht, zoals patiënten met bepaalde vormen van kanker, andere diagnoses dan kanker en patiënten in ontwikkelingsgebieden.

Het doel van dit proefschrift is om inzicht te geven in het voorkomen, de impact en de behandeling van symptomen tijdens de laatste levensfase.

Hoofstuk 2 beschrijft de resultaten van een cross-sectioneel beschrijvend onderzoek naar de prevalentie en impact van symptomen bij patiënten met een ongeneeslijke vorm van hoofd-hals kanker. Patiënten werden geïncludeerd op de afdeling keel-, neus- en oorheelkunde. Het onderzoek bestond uit twee delen. In het eerste deel werd de prevalentie vastgesteld van 30 symptomen, waarvan 9 psychosociaal, gebaseerd op vragenlijsten die tussen oktober 2006 en oktober 2008 onder patiënten werden afgenomen als onderdeel van de reguliere zorgverlening. In het tweede deel werd de impact van deze 30 symptomen bestudeerd en werden eventuele discrepanties tussen de antwoorden van patiënten en familieleden onderzocht in vragenlijsten die tussen februari 2009 en mei 2009, specifiek voor dit onderzoek, waren verzameld onder patiënten met een ongeneeslijke vorm van hoofd-hals kanker en hun familieleden. Wij vonden dat patiënten met een ongeneeslijke vorm van hoofd-hals kanker gemiddeld 14 symptomen rapporteerden (range 0–26), waarvan 10 somatisch en 4 psychosociale symptomen. Somatische symptomen die het vaakst gerapporteerd werden waren vermoeidheid, pijn en zwakte. Vaak voorkomende psychosociale symptomen waren 'zich zorgen maken', bedroefdheid en gespannenheid. Het symptoom met de grootste impact op het dagelijks functioneren was benauwdheid. We vergeleken de antwoorden van patiënten en familieleden en vonden dat in tweederde van de gevallen, hoewel niet altijd significant, familieleden de prevalentie en impact voor somatische symptomen systematisch hoger hadden gescoord dan de patiënten zelf. Ten aanzien van de psychosociale symptomen zagen we een tegengestelde trend: in ongeveer 50% van gevallen hadden de patiënten de prevalentie en de impact van de betreffende psychosociale scores hoger beoordeeld dan de familieleden.

Hoofdstuk 3 beschrijft de resultaten van een cross-sectioneel beschrijvend onderzoek naar symptoomprevalentie en symptoomlast bij patiënten met hartfalen in een vergevorderd stadium in het Groote Schuur Ziekenhuis in Kaapstad, Zuid-Afrika. Patiënten werden geïncludeerd voor dit onderzoek tussen augustus en november 2012 op verschillende klinische

afdelingen in het ziekenhuis (spoedeisende hulp, spoedeisende zorgafdeling, cardiologie afdeling, interne geneeskunde afdeling) en de polikliniek cardiologie. Patiënten gaven informatie over het voorkomen van 28 fysieke en 4 psychologische symptomen en de bijbehorende symptoomlast. De patiënten, van wie 14% de middelbare school had doorlopen en 26% geen inkomen had, rapporteerden gemiddeld 19 symptomen; 18 symptomen werden door meer dan 50% van alle patiënten gerapporteerd. Fysieke symptomen die het vaakst voorkwamen waren benauwdheid, slaperigheid/vermoeidheid, en pijn. Veel voorkomende psychologische symptomen waren 'zich zorgen maken', geïrriteerdheid, en bedroefdheid. Bijna alle aanwezige symptomen gingen gepaard met een grote symptoomlast; symptomen met de grootste symptoomlast waren benauwdheid, gevoelloosheid/tintelingen in handen of voeten, en 'ik lijk niet op mezelf'. Een hogere symptoomlast was geassocieerd met een hogere leeftijd, geen inkomen en minder ziekenhuisopnames gedurende de 12 maanden voorafgaande aan het onderzoek.

In **hoofdstuk** 4 zijn de resultaten beschreven van een systematische literatuurreview naar het voorkomen van reutelen in de stervensfase, de impact ervan op patiënten, familieleden en professionele zorgverleners, en de effectiviteit van interventies. Verschillende databases zijn in 2012 doorzocht op empirische studies. Reutelen komt veel voor. Bij ongeveer eenderde van alle patiënten wordt dit symptoom gerapporteerd tijdens de stervensfase. Reutelen wordt door zowel familieleden als professionele zorgverleners ervaren als hinderlijk, maar in hoeverre patiënten last ervaren van reutelen is onduidelijk. Er zijn verschillende klinische studies uitgevoerd naar het effect van anti-cholinerge medicatie op de ernst van reutelen. Daarin is geen bewijs gevonden voor de effectiviteit van anti-cholinerge middelen.

Hoofdstuk 5 beschrijft een multicenter prospectief observationeel onderzoek waarin bestudeerd is of de hoeveelheid vocht die voorafgaand aan en tijdens de stervensfase werd gebruikt gerelateerd is aan het optreden van reutelen en terminale onrust. Gegevens zijn verzameld in acht ziekenhuizen (een tot drie afdelingen per ziekenhuis) en vijf hospices, inclusief drie palliatieve zorg units in verpleeghuizen (PCU's). Dataverzameling vond plaats tussen november 2012 en november 2013 onder patiënten van wie, volgens het multidisciplinaire zorgteam, verwacht werd dat zij binnen een aantal dagen zouden overlijden. Data werden verzameld met een digitale versie van het Zorgpad Stervensfase (ZS), een Nederlands instrument voor multidisciplinaire zorg voor patiënten in de stervensfase. Specifiek voor dit onderzoek werd het ZS aangevuld met vragen over reutelen, terminale onrust, gebruik van opioïden en vochtgebruik. Reutelen werd minimaal eenmaal gerapporteerd bij 40% van de patiënten gedurende de stervensfase; voor de laatste 24 uur van het leven was dit bij 35% van de patiënten het geval. De prevalentie van reutelen nam toe naarmate het sterven dichterbij kwam. Terminale onrust werd tijdens de stervensfase bij 26% van de patiënten gerapporteerd; gedurende de laatste 24 uur van het leven trad dit bij 13% van de stervenden

op. Het voorkomen van terminale onrust was over het algemeen gelijk verdeeld over de hele periode van de stervensfase. We vonden geen associatie tussen de mate van vochtgebruik en het voorkomen van reutelen. We vonden ook geen associatie tussen een laag vochtgebruik (≤ 500 ml) en het voorkomen van terminale onrust. Terminale onrust gedurende de laatste 24 uur van het leven was wel geassocieerd met een hoger vochtgebruik gedurende de periode 48-25 uur voor het overlijden.

Hoofdstuk 6 beschrijft een onderzoek waarin bestudeerd is of patiënten zich bewust waren van hun naderend overlijden. Voor dit onderzoek is een secundaire analyse uitgevoerd van gegevens van een vragenlijstonderzoek onder verpleegkundigen en nabestaanden en gegevens vanuit de respectievelijke medisch dossiers. Dit onderzoek betrof patiënten die overleden waren in ziekenhuizen, verpleeghuizen en thuiszorgorganisaties in zuidwest-Nederland. Gegevens werden tussen november 2003 en februari 2006 verzameld. Halverwege deze periode werd het Zorgpad Stervensfase geïntroduceerd. Binnen een week na het overlijden werd door een verpleegkundige die nauw betrokken was geweest bij de zorg gedurende de laatste drie dagen van het leven van de patiënt een vragenlijst ingevuld. Ongeveer twee maanden na het overlijden ontving het familielid dat de 'contactpersoon' voor de patiënt was geweest een brief met de vraag of hij/zij toestemming wilde geven om benaderd te worden door het onderzoeksteam om een vragenlijst in te vullen. Een reminder werd verstuurd als na twee en zes weken nog geen reactie was ontvangen. Volgens de rapportage in het medisch dossier was 51% van de patiënten zich bewust geweest van hun naderend overlijden, volgens verpleegkundigen gold dit voor 58% en volgens nabestaanden voor 62% van de patiënten. De interbeoordelaarsbetrouwbaarheid was redelijk. Of een patiënt zich bewust was geweest van het naderend overlijden was niet geassocieerd met veel voorkomende symptomen in de stervensfase. Patiënten die thuis stierven waren zich vaker bewust van het naderend overlijden dan patiënten die in het ziekenhuis of verpleeghuis overleden. Patiënten die zich bewust waren van hun naderende overlijden hadden vaker vrede met het sterven en gaven vaker aan dat hun leven de moeite waard was geweest dan patiënten die zich volgens de nabestaanden niet bewust waren geweest van het naderend overlijden.

Om de ervaringen van verpleegkundigen met de praktijk van palliatieve sedatie en situaties waarin druk, dilemma's en gewetensnood voorkwamen te exploreren werd een secundaire analyse uitgevoerd op data vanuit een kwalitatief onderzoek onder verpleegkundigen; de resultaten zijn beschreven in **hoofdstuk 7**. Het onderzoek betrof 36 verpleegkundigen werkzaam in de eerste lijn, verpleeghuis, hospice of ziekenhuis Analyses werden uitgevoerd met behulp van de constant vergelijkende methode. De gebruikte coderingen waren gerelateerd aan het hoofdonderwerp ' het uitoefenen van druk', met verschillende sub-thema's: (1) de verpleegkundige oefent druk uit op de arts, (2) de arts oefent druk uit op de verpleegkundige, (3) de familie oefent druk uit op de verpleegkundige/arts. Verpleegkundigen gaven aan dat

de mate waarin een patiënt ondraaglijk lijdt verschillend wordt ingeschat door familieleden, de arts of de verpleegkundige. Verpleegkundigen beschreven situaties waarin ze morele last ervoeren omdat zij vonden dat op basis van de situatie van de patiënt palliatieve sedatie gestart zou moeten worden, maar de arts het daarvoor nog te vroeg achtte. Aan de andere kant beschreven verpleegkundigen situaties voorafgaand aan en tijdens sedatie waarbij zij druk ervoeren van de arts of familie om mee te werken aan palliatieve sedatie terwijl zij dit te vroeg of niet nodig achtten. Deze laatste situaties betroffen (1) het starten van palliatieve sedatie op een moment dat de verpleegkundige het gevoel had dat nog niet alle opties om het lijden te verlichten waren geëxploreerd; (2) familieleden die een ophoging van de sedatie verzochten terwijl de verpleegkundige vond dat daarmee het overlijden zou worden bespoedigd; (3) een besluit van de arts om met palliatieve sedatie te starten bij een patiënt die eerder een verzoek om euthanasie had gedaan.

In **hoofdstuk 8** worden de belangrijkste bevindingen van de in het proefschrift beschreven onderzoeken samengevat en geïntegreerd. We concluderen dat het belangrijk is om te onderkennen dat er verschillende perspectieven ten aanzien van symptomen en symptoomverlichting gedurende de laatste levensfase bestaan en van belang zijn. Bij de communicatie binnen het behandelteam en met de patiënt en zijn familieleden dient daar rekening mee gehouden te worden. Communicatie over symptomen is bij voorkeur een continu proces. Het hoofdstuk wordt afgesloten met implicaties voor de klinische zorgpraktijk en aanbevelingen voor vervolgonderzoek.

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Last, but certainly not least:
Onno, Mirre en Stije.
You are my sky full of stars 🩶

ABOUT THE AUTHOR

Ineke Lokker is geboren in Dirksland op 17 maart 1981. In 1999 behaalde zij haar HAVO diploma aan de Rijks Scholen Gemeenschap in Middelharnis. In datzelfde jaar startte zij met de studie HBO-Verpleegkunde (duaal) aan de Hogeschool Rotterdam, waar zij in 2004 afstudeerde. Tussen 2004 en 2007 werkte zij als (oncologie-) verpleegkundige op verschillende afdelingen van het Erasmus MC. Van 2007 tot april 2010 werkte zij als senior verpleegkundig consulent hoofd-hals oncologie op de afdeling KNO-Heelkunde van het Erasmus MC. Naast haar werk als verpleegkundige volgde zij tussen 2005 en 2006 de specialistische vervolgopleiding oncologieverpleegkundige aan de Zorgacademie van het Erasmus MC en studeerde tussen 2006 en 2009 Verplegingswetenschap aan de Universiteit van Utrecht. In mei 2010 startte zij als promovendus bij de afdelingen Maatschappelijke Gezondheidszorg en Interne Oncologie van het Erasmus MC. Hier voerde zij tot januari 2015 het onderzoek uit dat is beschreven in dit proefschrift over het voorkomen en de behandeling van symptomen tijdens de laatste levensfase. Gedurende haar onderzoeksaanstelling werkte zij van augustus 2012 tot februari 2013 als onderzoeker bij de Department of Public Health and Family Medicine, University of Cape Town, Zuid Afrika. Daarnaast voltooide zij tussen 2010 en 2012 de Master in Health Sciences, specialisatie Epidemiologie aan de Erasmus Universiteit Rotterdam en tussen 2013 en 2015 de leadership course van de European Palliative Care Academy. Gedeeltelijk tijdens en na haar onderzoeksaanstelling werkte zij van 2008 tot 2016 als docent bij de Zorgacademie van het Erasmus MC waar zij les gaf over Evidence Based Care en Palliatieve Zorg aan studenten die een verpleegkundige vervolgopleiding volgen. Van 2013 tot 2016 werkte zij als onderzoeker palliatieve zorg bij het Integraal Kankercentrum Nederland wat zij vanaf 2014 tot 2016 combineerde met het werk als verpleegkundige in Hospice Laurens Cadenza in Rotterdam. Tussen 2008 en 2016 is zij naast haar werk en studie actief geweest in verschillende nevenfuncties (VIP^2, V&VN Oncologie; V&VN Palliatieve Zorg; EONS; College Kwaliteitsregister V&V/RZ; Alumnivereniging Verplegingswetenschap NL; CDA).

Sinds april 2016 is zij werkzaam als Coördinator Kwaliteitsregistraties en Uitkomsten van Zorg/Waardegedreven Zorg bij de afdeling Kwaliteit en Patiëntenzorg van het Erasmus MC.

Ineke is getrouwd met Onno Geelof en is moeder van Mirre (2014) en Stije (2017).

LIST OF PUBLICATIONS

In this thesis

- **M.E. Lokker**, A. van der Heide, W.H. Oldenmenger, C.C.D. van der Rijt, L. van Zuylen, Hydration and symptoms in the last days of life (submitted)
- **M.E. Lokker**, S.J. Swart, J.A.C. Rietjens, L. van Zuylen, R.S.G.M. Perez, A. van der Heide. Palliative sedation and moral distress: A qualitative study of nurses. Appl Nurs Res. 2018 Apr; 40:157-161.
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- **M.E. Lokker**, L.A. van der Velden, M.P.J. Offerman, C. Gamel, M.F. de Boer, H.M. Vrehen, J.F.A. Pruyn, S.C.C.M. Teunissen. Symptomen bij hoofd-hals kankerpatiënten in de palliatieve fase. Prevalentie en invloed op dagelijks functioneren. Nederlands Tijdschrift voor Palliatieve Zorg, 2010; 2, 11-21.
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- **M.E. Lokker**. Wel of geen TPV. Oncologica, 2006; 23 (3), 38-44.

PHD PORTFOLIO

Name PhD student:	Ineke Lokker
Erasmus MC Department:	Public Health
PhD period:	2010-2018
Promotors:	Prof.dr. A. van der Heide & Prof.dr. C.C.D. van der Rijt
Supervisor:	Dr. L. van Zuylen

1. PhD training

	Year	Workload (ECTS)
General academic skills		
Scientific writing course, Erasmus MC	2010	0.5 ECTS
Computer course/ Literature search, Erasmus MC	2011	0.2 ECTS
Research skills		
Master Epidemiology, NIHES	2010-2012	70 ECTS
In depth courses		
Basiscursus regelgeving en organisatie voor klinisch onderzoekers (BROK)	2011	1 ECTS
Advanced European Bioethics course Suffering, Death & Palliative Care, IQ Healthcare, UMC St Radboud, Nijmegen, the Netherlands	2012	1 ECTS
Leadership Course, European Palliative Care Academy	2013-2015	27 ECTS
Oral presentations		
International Reference group LCP, the Netherlands	2010	1 ECTS
European Oncology Nursing Society Conference, the Netherlands	2010	1 ECTS
V&VN Oncology, The Netherlands	2010	1 ECTS
National conference on palliative care, the Netherlands	2010	1 ECTS
Paramedical Working group Head and Neck Tumours, the Netherlands	2010	2 ECTS
International Collaborative for End-of-Life Care Research	2010	1 ECTS
International LCP Conference, United Kingdom	2010	1 ECTS
Flemish-Dutch research forum Palliative Care, Belgium	2012	2 ECTS
Medilex congress, the Netherland	2012	1 ECTS
Comprehensive Cancer Center, the Netherlands	2013	1 ECTS
Cardio Vascular Care Congress, the Netherlands	2013	1 ECTS
Presentations at Erasmus MC 2009-2012 3 ECTS	2010-2014	2 ECTS
Presentations at Groote Schuur Hospital South Africa	2012-2013	2 ECTS
Conferences		
European Oncology Nursing Society conference	2010	1 ECTS
Society for Medical Decision Making, Annual Meeting	2011	1 ECTS
National conference on palliative care	2010-2012	2 ECTS
European Association of Palliative Care conference	2011-2013	3 ECTS
European Society of Cardiology, Heart Failure Conference	2013	1 ECTS
Seminars and Workshops		
Seminars department of Public Health, Erasmus MC	2010-2014	3 ECTS
Flemish-Dutch research forum Palliative Care	2012	1 ECTS

2. Teaching

Lecturing		
Specialistische verpleegkundige vervolgopleiding palliatieve zorg. Voeding en vocht aan het einde van het leven (Erasmus MC)	2010-2016	1.5 ECTS
Supervising practicals and excursions		
Supervising medical students theme 3.C.4 (community project)	2011	0.5 ECTS
Supervising Master's theses		
Milou van Belzen, MSc Health and Society	2014	1.5 ECTS