Care and decision-making at the end of life of ALS patients

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Cover: Ward of the general hospital at the Catharijnesingel 15 (later number 101) in Utrecht in 1926, precursor of today's University Medical Center Utrecht (from The Utrecht Archives).

Care and decision-making at the end of life of ALS patients

Zorg en besluitvorming rond het levenseinde van ALS patiënten

(met samenvatting in het Nederlands)

Proefschrift

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Maud Maessen

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Contents

CHAPTER 1
GENERAL INTRODUCTION

Picture: Entrance of the general hospital at the Catharijnesingel 15 in Utrecht in 1911, the precursor of today's University Medical Center Utrecht. Patients and staff are waiting for the arrival of queen Wilhelmina and prince Hendrik.

1.1 INTRODUCTION

The research described in this thesis focuses on euthanasia and physician-assisted suicide (EAS) in the Dutch population of people with amyotrophic lateral sclerosis (ALS). National studies on end-of-life practices have revealed that the most frequently given reasons for a euthanasia request were: futile suffering, loss of dignity and fatigue. However, these studies consisted mostly of cancer patients.[1] While cancer patients form the majority of EAS cases in absolute sense, it is known that relatively, EAS occurs more frequently in ALS patients. Previous research showed that one in five ALS patients dies due to EAS in the Netherlands.[2] Before describing the general objectives of this thesis (1.4) and methods used in this thesis (1.5), the next two paragraphs of this chapter will address characteristics of the disease ALS (1.2), and end-of-life practices in ALS patients (1.3).

1.2 AMYOTROPHIC LATERAL SCLEROSIS

Amyotrophic lateral sclerosis (ALS) is an incurable neurodegenerative disease characterized by progressive degeneration of motor neurons in the brain and spinal cord leading to muscle weakness. Initial manifestations are weakness of limbs, or weakness in the bulbar region leading to abnormalities of speech, swallowing difficulties and facial weakness. Patients eventually become paralyzed and approximately 50% of the patients die within three years after onset of symptoms.[3] The etiology of ALS is largely unknown. Statistics show that males are more prone to suffer from ALS than females (1.8:1), an annual incidence of 2 per 100.000, and a median age of onset around sixty years.[4;5] Most ALS patients do not suffer from severe cognitive impairment. The impact of this disabling disease on the lives of the patients, their families and their caregivers is very high. The most important life threatening features of ALS are respiratory muscle weakness and dysphagia. Dysphagia can lead to the aspiration of food, liquids, or secretions which may cause pneumonia and may also lead to malnutrition and dehydration. These conditions can be minimized in patients who choose enteric feeding and with aggressive management of secretions.[6] Progressive neuromuscular respiratory failure is the most common cause of death in ALS.

1.3 END-OF-LIFE PRACTICES IN ALS

One treatment ALS patients can opt for to prevent neuromuscular respiratory failure is tracheostomy with mechanical ventilation. However, with mechanical ventilation the disease will progress with the risk of eventually becoming "locked in" in their own paralyzed body and only able to communicate with great difficulties or not at all. If a patient declines mechanical ventilation he or she will eventually suffer from respiratory failure. In some situations dyspnea or pain has to be treated with opioids in doses that might hasten death in patients with compromised pulmonary function.[7] When symptoms become untreatable and the suffering unbearable the physician may sedate the patient until his or her death or the patient may request the physician for euthanasia or physician-assisted suicide.[2;8] A retrospective study showed that 17% of the ALS patients died due to euthanasia and 3% due to physician-assisted suicide between 1994 and 1998 in the Netherlands.[2] Ninety-three percent of the deaths of these patients were classified as peaceful by physicians and all deaths occurred in an advanced stage of the disease. Of all 203 ALS patients in this study, 36% had given an advance directive indicating a desire for EAS.[2]

1.4 GENERAL OBJECTIVES OF THIS THESIS

The relative high percentage of EAS in ALS might be the result of inadequate supportive or palliative care, unrecognized depressions, patients feeling they were a burden on others or hopelessness.[9] In general, it is unclear whether the quality of palliative care in the Netherlands is insufficient and related to EAS,[10;11] but it has been reported that the supply of aids and appliances for ALS patients is sometimes suboptimal.[12;13] It is also known that depression is not always recognized by physicians.[14] In ALS patients it may even be harder to recognize a depression, as symptoms of depression overlap with symptoms of ALS. Although depression is a major consideration in the euthanasia procedure, referral to a psychiatrist is not mandatory.[15;16] Studies on end-of-life practices in specific diseases other than cancer are relatively rare, but could give valuable, more detailed information on possible shortcoming in palliative care of these terminally-ill patients. Therefore, this thesis examines the rate of EAS in ALS who died between 2000 and 2008 in the Netherlands and explores the characteristics

of the circumstances in the end-stage of ALS. Furthermore, it studies the determinants of requesting EAS among terminally ill ALS patients, focusing on symptoms of depression, palliative care characteristics and personal traits.

1.5 METHODS

The current law on EAS came into force in 2002 in the Netherlands (i.e. the Termination of life on request and assisted suicide act). This act states that physicians are not prosecuted for performing EAS if the requirements of due care are met and the physicians inform the coroner. The requirements of due care include a voluntary and well-considered request from the patient to die; unbearable and hopeless suffering; the physician informing the patient about his/her situation and prospects; the absence of realistic alternatives for treatment; consulting a second independent physician and performing EAS with due medical care. One of the five regional euthanasia review committees determines whether the requirements of due care have been met. The review committees only forward cases to the legal prosecutor when the requirements of due care are not met.[15;16]

In this thesis, euthanasia (EUT) is defined as the administration of drugs by a physician with the explicit intention of ending the patient's life, at the patient's explicit request. Physician assisted-suicide (PAS) is defined as the prescription or supplying of drugs by a physician with the explicit intention of enabling the patient to end his or her own life. Continuous deep sedation (CDS) is defined as the administration of drugs to keep the patient in deep sedation or coma until death. End-of-life practices include euthanasia, physician-assisted suicide, ending of life without the patient's explicit request, withholding or withdrawing medical treatment with the possibility or explicit intention of hastening death, intensified alleviation of pain or symptoms while taking into account the possible hastening of death and continuous deep sedation.

In order to answer the research questions, data from five studies were analyzed:

I. A translation and validation study of a disease specific quality of life questionnaire.
II. A cross-sectional study on unbearable suffering of ALS, cancer and heart failure patients whom requested their physician for EAS.

III. A retrospective study among physicians and informal caregivers of deceased ALS patients on the rates of performed end-of-life practices and the circumstances before the patients' death.
IV. A prospective observational study among ALS patients and their physicians to determine if symptoms of depression, palliative care characteristics and personal traits were associated with a request for EAS.
V. A prospective observational study among ALS patients and their informal caregivers to explore their burden of care and quality of life.

In each chapter of this thesis the methods of the relevant study will be described in more detail.

1.6 OUTLINES OF THIS THESIS

In **chapter 2** the results of the validation of a Dutch version of the ALSAQ-40 are shown. This questionnaire examines the quality of life of ALS patients and is used in other chapters of this thesis. In **chapter 3** we define what specific kind of unbearable suffering ALS patients report according to physicians when they request EAS and compare this to patients with cancer and heart failure. **Chapter 4** reports on a retrospective study in informal caregivers and physicians of deceased ALS patients that shows the proportion of end-of-life practices in the Netherlands between 1998 and 2005. It also presents associations between disease, patients and health care characteristics and EAS and CDS. **Chapter 5** reports on a prospective study in ALS patients that shows associations between disease, patients and health care characteristics and the wish for EAS. The experienced burden of care on informal caregivers of ALS patients is described in **chapter 6**. **Chapter 7** discusses the conclusions of these studies. Furthermore, the strengths and limitations of the studies are described and recommendations for practice and future research are made. Finally, the findings presented in this thesis are summarized in **chapter 8**.

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CHAPTER 2
VALIDITY OF A QUALITY OF LIFE MEASURE

Picture: Residents and staff of City Poorhouse at the Doelenstraat12 in Utrecht in ±1925. Based on Maessen M, Post MW, Maillé R, Lindeman E, Mooij R, Veldink JH, van den Berg LH. Validity of the Dutch version of the Amyotrophic Lateral Sclerosis Assessment Questionnaire, ALSAQ-40, ALSAQ-5. Amyotroph Lateral Scler Other Motor Neuron Disord 2007;8 (2):96-100.

2.0 ABSTRACT

BACKGROUND To evaluate the effect of new treatments or therapies for ALS patients, a disease specific measurement of quality of life is important. The purpose of this study is to translate the 40-item and 5-item Amyotrophic Lateral Sclerosis Assessment Questionnaire (ALSAQ-40, ALSAQ-5) and to compare the psychometric properties of the Dutch versions to those of the original English version.

METHODS Eighty-one ALS patients participated in this cross-sectional study. The measures used were the ALSAQ-40, the ALSAQ-5, the MOS Short-Form-36 (SF-36) and the Revised ALS Functional Rating Scale (ALSFRS-r).

RESULTS The Dutch ALSAQ-40 was sensitive to differences in disease severity (all scales Kruskal-Wallis, $p<0.05$), had no floor and few ceiling effects (Communication, Eating and drinking scales), had excellent internal consistency reliability (all scales Cronbach's alpha >0.90, all item to subscale correlations above 0.40) and showed good construct validity as it correlated as expected with SF-36 and ALSFRS-r scores. The total and item scores of the ALSAQ-5 were strongly correlated with the corresponding total and subscale scores of the ALSAQ-40 (Spearman's rho >0.80). The ALSAQ-5 and ALSAQ-40 showed comparable correlations with the subscales of the SF-36 and the ALSFRS-r, except for ADL. All other results of the Dutch ALSAQ-40 and ALSAQ-5 were comparable to those of the original UK questionnaires.

CONCLUSION The psychometric properties of the Dutch version of the ALSAQ-40 and the ALSAQ-5 are good and similar to those of the original English version.

2.1 INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is a progressive disease and approximately 50% of the patients die within three years of onset.[1] Although there is currently no cure for ALS, treatment with riluzole does prolong survival by three to six months, albeit without affecting the quality of life.[2] Measurement of health-related quality of life, also called health status, is important when evaluating the effect of new treatments or therapies for ALS. A new disease-specific health status measure, the 40-item Amyotrophic Lateral Sclerosis Assessment Questionnaire (ALSAQ-40), has been introduced in the UK seemed better suited than a generic health status measure like the MOS Short-Form 36 (SF-36).[3;4] Several studies have since provided further evidence for its reliability and validity.[3-5] The ALSAQ-40 has also been summarized to a 5-item version (ALSAQ-5) to diminish the strain of completing the questionnaire.[6] The purpose of this study is to determine the psychometric properties of the Dutch translation of the ALSAQ-40 and ALSAQ-5 and to compare these to those of the original English version.

2.2 METHODS

Patients
Between May and December 2004, 86 patients were asked to participate in the study during their outpatient consultation at the national referral center, the University Medical Centrum in Utrecht. Four patients refused to participate; one patient did not finish the questionnaires, because the items evoked emotional distress. Thirty-five percent of the 81 participants needed help from the researcher to record their answers. All patients met the El Escorial diagnostic criteria for probable or definite ALS. Exclusion criteria were a pre-existing psychiatric disorder, insufficient knowledge of the Dutch language and cognitive disorders. Patients were asked to complete the SF-36 and the ALSAQ-40 in alternate order. In addition, the researcher completed the Revised ALS Functional Rating Scale (ALSFRS-r).

Instruments
Severity of ALS was measured by the ALSFRS-r. This is a 12-item scale, in which the patient's functioning for each item is rated on a scale from to 0

(unable to attempt the task) to 4 (normal function). The total score ranges from 0 to 48. The ALSFRS-r can be divided into four factors: fine motor, gross motor, bulbar and respiratory function.[7;8] The ALSAQ-40 is a disease-specific health status measure for use in studies of patients with ALS or other comparable motor neuron diseases. The ALSAQ-40 consists of 40 items referring to the patient's condition which the patient has to score on a five-point scale. Questions cover five dimensions of health status that are affected by the disease: Physical Mobility (containing ten items), Activities of Daily Living and Independence (ten items), Eating and Drinking (three items), Communication (seven items) and Emotional Functioning (ten items). Each dimension is assessed using a summary score ranging from 0 to 100, with 0 representing the best possible health status and 100 representing the worst possible health status.[3] Jenkinson et al. showed that the original English ALSAQ-40 had high internal consistency reliability (all scales Cronbach's alpha >0.90) and found evidence for construct validity as Spearman correlations between similar domains on the ALSFRS-r and the SF-36 were higher than 0.51.[3-5] The ALSAQ-40 showed good corrected item to scale total correlations (0.61 to 0.95) and was found to be in part sensitive to differences in self-reported health state.[3-5] To shorten the ALSAQ-40, 1 item out of each of the 5 dimensions of the ALSAQ-40 was selected to create the ALSAQ-5. The items selected produced results that closely resembled the scores of the former 5 dimensions and correlated with the SF-36 in the same magnitudes as the ALSAQ-40.[6] Each item was also recoded into a score ranging from 0 to 100, with 0 representing the best possible health status and 100 representing the worst possible health status.[6;9]

The SF-36 is a generic health status measure. It contains 36 items across eight multi-item scales: physical functioning (PF), role limitations due to physical health problems (RP), role limitations due to emotional problems (RE), social functioning (SF), bodily pain (BP), vitality (VT), mental health (MH) and general health perceptions (GH). All raw scale scores are linearly converted to a 0 to 100 scale, with higher values indicating a more favorable health status.[10;11] The SF-36 is a valid health status measure in persons with ALS.[12]

Translation
Two independent translations of the ALSAQ-40 from English to Dutch were made by two translators from different backgrounds but with Dutch mother tongue. These two translations were carefully synthesized and back-translated into English by a professional interpreter, native English speaker. The English translations were compared with the original English version by an expert committee and checked for inconsistencies. Thereafter the questionnaire was pilot tested by five patients, which did not lead to essential changes.

Data analysis
Usual baseline data and ALS characteristics (including time since onset, time since diagnosis, vital capacity) were evaluated. ALSAQ-40 data were evaluated for floor and ceiling effects and sensitivity to disease severity (Kruskal-Wallis test). Floor and ceiling effects were considered to be present if 20% or more scored in answering categories reflecting the respectively worst possible or the best possible health status. Internal consistency was studied with Cronbach's alpha. An alpha of 0.70 was considered sufficient for studies at population level and 0.90 at individual level.[13] For the item to scale correlations, corrected for overlap, a Spearman's rho correlation of 0.40 was considered the required minimum. To test construct validity, the ALSAQ-40 subscales were compared to scales measuring the same construct from the SF-36 and the ALSFRS-r. Non-parametric Spearman correlation coefficients were used and it was hypothesized that scales with similar content would correlate strongly (0.60 or higher).
Spearman's rho was also used to compare the items of the ALSAQ-5 with the subscales of the ALSAQ-40. A correlation of 0.80 was considered the required minimum. Finally, a Fisher Z-transform of the correlations between identical subscales of the ALSAQ-40 and the ALSAQ-5 and the ALSFRS-r and the SF-36 was used to test whether the correlations were significantly different ($p<0.05$).[14]

2.3 RESULTS

Score distribution

The characteristics of the total cohort of patients are shown in Table 1. Median and floor and ceiling effects of the ALSAQ-40 subscale scores were determined (Table 2). A ceiling effect was seen in the Communication and the Eating and Drinking subscales. This ceiling effect decreased when only the severely ill patients were selected (11.1% and 33.3%, respectively) and disappeared (5.6% and 11.1%, respectively) when only the bulbar ALS patients were selected.

Table 1: Patients' characteristics.

Patients' characteristics	**n=81**
Age (years), mean (SD)	57.2 (10.8)
Male, n (%)	52 (64.2)
Time since onset (months), mean (SD) (range)	35, (34) (7-246)
Time since diagnosis (months), mean (SD) (range)	19, (25) (1-162)
Familial ALS, n (%)	7 (8.6)
Site of onset: Spinal, n (%)	63 (77.8)
VC, mean (SD)	86.7 (20.2)
ALSFRS-r, mean (SD)	33.0 (7.9)
Disease severity, n (%)	
Severe (ALSFRS-r ≤ 28)	27 (33.3)
Moderate (ALSFRS-r 28-37)	25 (30.9)
Mild (ALSFRS-r >38)	29 (35.8)

SD = Standard deviation
VC= Vital capacity
ALSFRS-r= Revised Amyotrophic Lateral Sclerosis Functional Rating Scale

Internal consistency
Cronbach's alpha values were 0.90 or greater for all dimensions of the ALSAQ-40 and for the total score of the ALSAQ-40 (Table 2).

Table 2: Score distribution and internal consistency of ALSAQ-40 (n=81).

Subscale	Median	Ceiling %	Floor %	Means corrected item to subscale correlations (range)	Alpha
Mobility	52.5	8.6	16.0	0.79 (0.68-0.86)	0.95
ADL	52.5	2.5	7.4	0.75 (0.66-0.84)	0.94
Eating and drinking	0.0	51.9	2.5	0.83 (0.80-0.85)	0.91
Communication	25.0	34.6	3.7	0.90 (0.72-0.96)	0.97
Emotional functioning	25.0	6.2	1.2	0.65 (0.50-0.78)	0.90
Total	40.6	0.0	0.0	0.56 (0.29-0.71)	0.94

Floor= Score = 100 (worst health status)
Ceiling= Score = 0 (best health status)
Alpha = Chronbach's α values
ADL = Activities of daily living and independence

Corrected item to subscale correlations were all above 0.40 ($p<0.01$). Item and total score correlations were all but 4 above 0.40 and significant. All means of corrected item to subscale correlations were higher for the 'own' scale than for the other scales (data not shown).

Construct validity
Strong correlations ($r_s>0.60$) with the ALSFRS-r were found between Mobility and Gross Motor, between ADL and Gross and Fine Motor, between Communication and Bulbar and between Eating & Drinking and Bulbar and Respiratory with the ALSFRS-r (table 3).
Strong correlations with the SF-36 subscales were found between Mobility and Physical Functioning, between ADL and Physical Functioning and between Emotional Functioning and Mental Health.

Table 3: Construct validity: Non-parametric (Spearman) correlation coefficients between subscales of ALSAQ-40, ALSFRS-r and SF-36 (n=81).[a]

	ALSAQ-40[b]					
	Mob	**ADL**	**Com**	**ED**	**EF**	**Total**
Alsfrs-r Subscales						
Gross Motor	0.90**	0.67**	0.16	0.05	0.25*	0.74**
Fine Motor	0.53**	0.78**	0.06	0.07	0.24*	0.59**
Bulbar	0.03	0.15	0.85**	0.78**	0.25*	0.47**
Respiratory	0.19	0.28*	0.50**	0.61**	0.31**	0.45**
SF-36 Subscales[c]						
PF	0.85**	0.68**	0.14	0.04	0.28*	0.72**
RP	0.16	0.24*	0.04	0.10	0.32**	0.20
RE	0.08	0.10	0.06	0.09	0.35**	0.02
SF	0.24*	0.24*	0.22*	0.27*	0.50**	0.40**
BP	0.30**	0.27*	0.15	0.15	0.28*	0.36**
VT	0.29**	0.41**	0.17	0.33**	0.49**	0.45**
MH	0.07	0.18	0.24*	0.13	0.75**	0.34**
GH	0.16	0.15	0.23*	0.25*	0.43**	0.31**

[a] All correlations raw (negative) correlations are inverted, because high ALSAQ-40 scores correspond with low ALSFRS-r and SF-36 scores.

[b] MOB= Mobility, ADL= Activities of daily living and independence, COM= Communication, ED= Eating and drinking, EF= Emotional functioning,

[c] PF=Physical functioning, RP=Role limitations due to physical health problems, RE=Role limitations due to emotional problems, SF=Social functioning, BP=Bodily pain, VT=Vitality, MH=Mental health, GH=General health perceptions

* $p < 0.05$ ** $p < 0.01$

Face validity

All patients were asked to give their opinion concerning the ALSAQ-40 and the SF-36. All patients thought the questions on the ALSAQ-40 were easy to answer and it took all patients less time to complete this than the SF-36. Both patients and researchers thought that some questions of the SF-36 (e.g. 'I am as healthy as anybody else') were inappropriate for people with ALS. With regard to the ALSAQ-40, 14 people noted that there is a

difference between 'always found it difficult to walk' and 'not able to walk at all', which in the ALSAQ-40 is combined into the same category. Six patients missed items, for instance questions about cramps, losing weight, problems with sleeping, pain in general and shortness of breath.

ALSAQ-5

The mean total score of the Dutch ALSAQ-40 correlated strongly with the mean total score of the ALSAQ-5 (0.89). The mean ALSAQ-5 scores were: Mobility 51.9, ADL 58.3, Eating and Drinking 22.5, Communication 39.2, Emotion 38.0. The ALSAQ-5 items correlated strongly with the 5 subscale scores of the ALSAQ-40 from which they were derived: Mobility (0.80), ADL (0.81), Eating and Drinking (0.90), Communication (0.97), and Emotion (0.86), (all p's<0.01). However, in our study population, only the Communication and Emotion subscales, the item selected for the ALSAQ-5, were the items that showed the strongest item to subscale correlation. For the other 3 subscales, another item (Tired when walking, Difficulty getting dressed, Difficulty swallowing) correlated slightly higher with the subscale score (maximum difference 0.07). Correlations between the ALSAQ-5 items and the corresponding subscales of the ALSFRS-r and the SF-36 were mostly similar or somewhat lower compared to the correlations between ALSAQ-40 scales and the ALSFRS-r and the SF-36. Only seven correlations were significantly lower using the ALSAQ-5 than using the ALSAQ-40: (ALSFRS-r: Gross Motor with Mobility (r=0.73)/ADL (r =0.40)/Total (r =0.51) and Fine Motor with ADL(r =0.62), SF-36: PF with Mobility (r =0.73)/ADL (r =0.38)/Total(r =0.51)). However, these differences disappeared in the ADL subscale if the 3 items of the ALSAQ-5 were replaced by the 3 items that showed the strongest item to subscale correlation.

2.4 DISCUSSION

The results of this study show that the Dutch ALSAQ-40 and ALSAQ-5 are useful measures of health status in persons with ALS and that their psychometric properties are comparable to those of the original UK version.

The distributions of sex and disease onset (bulbar/spinal) in this study were similar to previous reports.[1] The time since onset and diagnosis and the

ALSAQ-40 figures suggest that the respondents of this study were less ill compared to those in the validation studies of the original ALSAQ-40.[3;4] Floor and ceiling effects were to be expected due to the well-known disproportionate distribution of symptom development with time in ALS. The ceiling effect in the Eating and Drinking and Communication subscales is probably due to the fact that bulbar involvement is generally absent in a large number of general ALS patients in the early stage of the disease. The original English ALSAQ-40 also showed a ceiling effect in the Eating and Drinking and Communication subscales.[3]

The internal reliability coefficients of each scale score of the ALSAQ-40 were excellent in both the English and the Dutch version.[3-5] Also the corrected item to scale correlations were high and of the same magnitude as the English ALSAQ-40.[3;4]

The Dutch ALSAQ-40 showed high correlations between similar domains on the ALSFRS-r and the SF-36. The English and Dutch ALSAQ-40 showed more or less similar correlations between domains on the ALSFRS-r and the SF-36. The Dutch ALSAQ-40 however showed more significant correlations than the UK version, probably due to the larger sample size in the Dutch study.

The short ALSAQ-5 seems to be a satisfactory substitute for the ALSAQ-40, especially in situations where ALS patients are too ill to complete a 40-item measure or in large scale trials where data reduction has advantages in response rate and data quality.[6] This study showed strong correlations between the Dutch ALSAQ-40 and ALSAQ-5, similar to the UK version.[6] The Dutch ALSAQ-5 and ALSAQ-40 correlated equally well with most similar subscales of the ALSFRS-r and the SF-36. The ADL item selected by Jenkinson et al.[6] for the ALSAQ-5 did perform moderately well in this study, but not as well as the 'best' item (Difficulty getting dressed). This might be due to the lower disease severity in this study. For future use of the Dutch ALSAQ-5, a choice has to be made between the best performing item or the item that allows best for international comparisons. Further studies of other language versions will show whether or not the UK item selection for the ALSAQ-5 is the optimal choice. In conclusion, the results of this study indicate that the Dutch ALSAQ-40 and ALSAQ-5 are valid instruments for the measurement of health status in Dutch patients with ALS.

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CHAPTER 3
ORIGIN OF SUFFERING

Picture: Women's ward of the general hospital at the Catharijnesingel 101 in Utrecht in ± 1927, the precursor of today's University Medical Center Utrecht.
Based on Maessen M, Veldink JH, van den Berg LH, Schouten HJ, van der Wal G, Onwuteaka-Philipsen BD. Requests for Euthanasia: Origin of Suffering in ALS, Heart failure and Cancer Patients, submitted.

3.0 ABSTRACT

OBJECTIVES In the Netherlands, relatively more patients with amyotrophic lateral sclerosis (ALS) (20%) die due to euthanasia or physician-assisted suicide (EAS) compared to patients with cancer (5%) and heart failure (0.5%). We wanted to gain insight into the reasons for ALS patients requesting EAS and compare these with the reasons of cancer and heart failure patients. Knowing disease-specific reasons for requesting EAS may improve palliative care in these vulnerable patients.

METHODS The data used in the present study were derived from the Support and Consultation in Euthanasia in the Netherlands (SCEN) evaluation study. This study provided consultation reports and questionnaires filled out by the attending physicians from 3337 consultations conducted by SCEN physicians in situations where a patient requested EAS. For this study we selected data on all ALS patients (n=51), all heart failure patients (n=61) and a random sample of 73 cancer patients.

RESULTS The most frequently reported reasons for unbearable suffering are in ALS patients; fear of suffocation (45%), and dependency (29%), in cancer patients; pain (46%), and fatigue (28%) and in heart failure patients; dyspnea (52%), and dependency (37%). Somatic complaints were reported more frequently as a reason for EAS by cancer (OR 0.20, 95% CI (0.09-0.46)) and heart failure patients (OR 0.16, 95% CI (0.05-0.46)) than ALS patients.

CONCLUSIONS ALS patients should timely be helped to cope with psychosocial symptoms, e.g. by informing them about the low risk of suffocation in the terminal phase and the possible means of preventing this.

3.1 INTRODUCTION

In the final stage of life, patients often suffer from physical, psychosocial or existential symptoms. When this suffering becomes unbearable, patients may request euthanasia or physician-assisted suicide (EAS), even if it is not legal for the physicians to perform it.[1-3] In the Netherlands, where EAS is allowed under certain circumstances, 1.8 percent of all deaths in 2005 were the result of EAS.[4] People mainly associated EAS with cancer, since patients who receive EAS frequently suffer from cancer. EAS proportions differ between diseases. Of all the cancer patients who died in the Netherlands, EAS had been performed in five percent[4], compared to 20 percent [5] in ALS patient deaths and 0.5 percent in heart failure patients deaths.[6]
One of the mandatory conditions in Dutch law for performing EAS is that the patient requesting EAS is suffering unbearably and the outlook is hopeless. More insight into the disease-specific aspects of suffering, which causes patients to prefer death to life, may help to improve palliative care.
In the present study, we wanted to gain insight into the physical and psychological symptoms of ALS patients who requested EAS and into the factors that made their suffering unbearable. To study disease-specific differences, we compared the results of ALS patients with those of cancer and heart failure patients, two groups with a lower EAS proportion than in ALS patients. Together, the three groups represent a disease with a high EAS proportion (ALS), a disease with a low EAS proportion (heart failure) and a disease most frequently associated with EAS (cancer).

3.2 METHODS

Design and population
The data used in this study were collected for the "Support and Consultation in Euthanasia in the Netherlands" (SCEN) evaluation study.[7] SCEN is an organization that provides physicians (SCEN physicians) who can be consulted for a second opinion by treating physicians of patients who are considering or requesting EAS. The SCEN physicians can also give expert advice to colleagues who have questions about EAS. The SCEN physicians are trained in palliative care and the requirements of due care for performing EAS according to the Dutch law. During a formal consultation, the SCEN physician talks with the treating physician, reads the patient

medical file, and visits the patient, in order to come to a judgment on whether all requirements for due care are met. The consultant records his reasoned judgment in a consultation report. Examples of summaries of such consultation reports are presented in box 1. In the SCEN evaluation study, all consultations of the SCEN physicians were registered. Shortly after each consultation, the SCEN physician filled out a questionnaire on the consultation and sent it together with a copy of the consultation report to the researchers. The SCEN physicians also handed a questionnaire to the treating physician, who could send the questionnaire back to the researchers. All questionnaires and consultation reports were anonymous, but by using a registration number, the treating physician's questionnaire could be linked to the consultant's questionnaire and report.

Study population

Consultation reports and treating physicians' questionnaires were collected between April 1st 2000 and January 1st 2003. Since 1999, SCEN has been gradually implemented in the Netherlands, being available to 60 percent of all primary care physicians since the first half of 2001, and to all primary care physicians and some specialists since the second half of 2002. A total of 3891 SCEN questionnaires were sent to the researchers and 3337 (86%) treating physicians' questionnaires were also returned. From these questionnaires we selected all questionnaires on patients with the diagnosis ALS (n=52) and heart failure (n=68). Of 51 ALS patients and 61 heart failure patients the corresponding SCEN consultation report was also available. In addition we randomly selected 80 patients from all those with the diagnosis cancer (n=2842); in 73 of them a SCEN consultant report was available as well. Both patients whose request for EAS was granted and those whose request did not result in EAS were subject of this study.

In the present study, euthanasia and physician-assisted suicide (EAS) was defined as follows: Physicians administer, supply or prescribe a drug with the explicit intention to end the patient's life (or to enable the patient to end his or her own life), at the explicit request of the patient.

Questionnaires

Beside questions on the consultation of the SCEN physician, which were relevant for the evaluation of SCEN, the questionnaire for the consulting treating physicians contained also questions on sex, age, diagnosis and

physical and depressive symptoms at the moment of consultation of the patients requesting EAS. The symptoms of depression were measured using a short version of a validated mood dimension scale, the NOSGER (Nurses' Observation Scale for Geriatric Patients).[8] Treating physicians also had to state whether EAS was performed.

The written consultation report of the SCEN physician consists of a text indicating the patient's medical situation, and a reasoned answer to the question whether or not the requirements for due care are met. The way of doing this was typically to discuss each of the substantive requirements for due care, including a well-considered voluntary request from the patient, the presence of unbearable and hopeless suffering and the absence of realistic alternatives for treatment. Two independent researchers assessed each consultation report. They determined which aspects of suffering were the reasons for the patient's suffering being unbearable. A comprehensive list of possible aspects of suffering was derived from the SOS-V, which is a device to categorizes unbearable nature of suffering at the end of life.[9] If the two researchers did not score the same codes of suffering, they discussed the SCEN report together to reach consensus.

Box 1: Examples of unbearable suffering in requests for euthanasia and physician-assisted suicide (source: SCEN reports)

ALS patient

The patient is a 64-year-old man. He spent his whole life working in his own bakery together with his two sons and his wife. About two years before his death, the patient developed difficulty talking and was diagnosed with bulbar ALS. The patient refused to take Rilutec prescribed by the neurologist, because it would only prolong his life and not alleviate his symptoms. After the diagnosis, the patient frequently visited a rehabilitation clinic. In addition to the help of the clinic, the patient and his sons invented specific tools that helped him to continue working. One year after the diagnosis, the patient was no longer able to speak. Initially, the patient used a computer with voice output, but because of muscle weakness in his arms and hands he could no longer use the computer. Communication was only possible by posing yes/no questions. A little over two years after the diagnosis, the patient dictated advanced directives on hastening his death and discussed euthanasia with his family and his primary care physician (PP).

Six months later, the patient became totally dependent on his wife for his personal hygiene. A month later, the patient made an explicit request for euthanasia to his PP. A SCEN physician visited the home of the patient at the request of the PP to consult on the patient's request for EAS.

When the SCEN physician visited the patient at his home, the patient was sitting in a specially adapted chair. He was practically unable to move. His head was resting on a platform, as he could not hold his head up by himself. He was resting his chin on a kitchen roll, because of his continuous drooling. During the SCEN consultation the sons showed the SCEN physician around in the bakery. They spoke highly of their father's working crafts and they still tried to consult him about difficult work problems. His sons and wife are very sad that the patient has requested EAS, but seeing his suffering every day, they respected his wish.

When the SCEN physician was alone with the patient, the SCEN physician wanted to know if the patient was requesting EAS because he felt he was a burden on his family. The patient denied this. The SCEN physician also checked with some questions whether the patient was incompetent or depressed and whether his request was persistent. The patient was mainly suffering from loss of dignity and not being able to do anything, which was in shear contrast to the active life that he lived two years earlier.

The SCEN physician concluded that all requirements of due care were met and reported to the PP that the EAS request of the patient could be fulfilled, if the PP wished to comply.

(The patient died following euthanasia.)*

Heart failure patient

The patient is a 63-year-old married woman with children. She suffered chronically from diabetes mellitus and amyloidoses. Following a vacation one-and-a-half years prior to her death, she developed an unstable angina pectoris, which did not improve after surgery. The patient suffered from dyspnea and exercise intolerance.

About six months later, the patient had a circulation collapse and was successfully resuscitated. After some time in the hospital the patient and the physician agreed that no acceptable curative treatment was available. The patient decided on a "do not resuscitate" order, received the last sacrament from here Roman-Catholic priest and went home. At home, the patient received oxygen, durogesic and primperan. She suffered from fatigue, dyspnea, nausea, constipation and was confined to bed. The patient hoped to die quickly as a result of a new circulation collapse. However, when she actually suffered a collapse, she survived. As the patient did not want to go through another collapse she requested her PP for euthanasia. A SCEN physician visited her and her husband at the request of the PP. The SCEN physician reported that fear of a new collapse and the inability to enjoy anything because of her extreme fatigue, were the most important reasons for requesting euthanasia. The life expectancy of the patient was a couple of weeks. There was no acceptable alternative treatment and the SCEN physician did not have the impression that the patient suffered from depression. The SCEN physician concluded that all requirements of due care were met.
(The patient died following euthanasia.)*

Cancer patient

The patient is a 73-year-old married man with two children. Three years prior to his death, he was diagnosed with rectal carcinoma, which was treated with radiotherapy. He received a colonic stoma; a new tumor was blocking the right kidney leading to pain. NSAID were prescribed for the pain, as the patient did not want morphine, because of the negative side-effects. A few months before the SCEN consultant's visit, the patient was referred to the hospital because of increasing pain. He underwent partial resection of the small intestine. He also had disturbed liver- and kidney functions. Morphine was administered through a pump, but he still suffered pain. The patient had already discussed euthanasia with his wife two years after the diagnosis, and now that it was clear that his pain could not be diminished further, he was sure that he wanted euthanasia. The PP, the treating physician at the hospital and his wife expected that the patient would die in a normal way very soon. Also, the patient stopped eating to hasten his own death. However, the patient did not die and made an explicit request to his PP for euthanasia. A SCEN physician visited the patient at the request of the PP and the treating physician in the hospital. The SCEN physician talked to the patient and his wife separately and reported that he thought that the patient was very sick, starving, dehydrated, sometimes unconscious due to the morphine, had jaundice, but most of all suffered from severe pain. The patient said that pain was the most important reason for requesting euthanasia. He reported that there were no alternatives for treating the pain and that all requirements of due care were met.
(The patient died following euthanasia.)*

* data is from questionnaire of treating physician

Data analysis
To analyze differences in sex and age, we used the chi-square test and the t-test. The physical and depressive symptoms were measured using a 5-point scale, in which lower points indicated fewer symptoms. When patients reported 1 or 2 on these 5 point-scales, symptoms were assumed to be absent. When patients reported 3, 4 or 5 on the 5 point scale, symptoms were assumed to be present (tables 1 and 2). Differences between ALS, cancer and heart failure patients regarding symptoms and reasons for unbearable suffering were calculated using multivariate logistic regression analysis, which was adjusted for sex and age at the time of the EAS request. Aspects of unbearable suffering that were based on the similar underlying condition were combined together into more general categories and are presented in table 4. The provided tables have a maximum of six missing or less.

3.3 RESULTS

Patients' characteristics
Forty-nine percent of the ALS patients, 37 percent of the cancer patients and 46 percent of the heart failure patients were women. The average age at the time of the EAS request was 65 years for ALS, 66 years for cancer and 80 years for heart failure patients. The distribution of sex did not differ significantly between the three patients groups ($p \geq 0.18$). The heart failure patients were significantly older than the ALS ($p \leq 0.001$) and the cancer patients ($p \leq 0.001$).
During the SCEN evaluation study, 28 of the 51 ALS patients died due to EAS, one patient had his or her request for EAS denied, two patients changed their mind and five patients died before EAS could be performed. Forty-five of the 73 cancer patients died due to EAS, two patients had their request for EAS denied, four patients changed their mind and seven patients died before EAS could be performed. Forty-one of the 61 heart failure patients died due to EAS, four patients had their request for EAS denied, three patients changed their mind, and seven patients died before EAS could be performed. All other patients died before the physician decided on the EAS or the study ended before the physician decided on the EAS request. Thirteen patients had missing data.

Symptoms
According to the treating physicians, ALS patients demonstrated the following symptoms less often than the cancer patients: fatigue (80% vs. 96%), pain (33% vs. 63%), nausea (16% vs. 62%) and vomiting (8% vs. 42%). Compared to heart failure patients, ALS patients were less often fatigued (80% vs. 97%), affected by poor appetite (76% vs. 87%), dyspneic (57% vs. 85%) and nauseous (16% vs. 44%) (Table 1).

Depressive symptoms
As shown in table 2, no statistically significant differences in the four NOSGER-items on depressive symptoms, which might indicate a possible depression, were observed in ALS patients compared to cancer patients or in ALS patients compared to heart failure patients.

Unbearable suffering
Table 3 lists the five most frequently reported reasons leading to the classification 'unbearable suffering' in ALS, cancer and heart failure patients. The reasons for unbearable suffering of the patient as recorded in the SCEN consultation reports combined in more general categories are presented in table 4.
Compared to cancer and heart failure patients, ALS patients reported to the SCEN physician somatic symptoms significantly less often as being unbearable. Physicians of cancer patients indicated pain and fatigue significantly more often as being unbearable than physicians of ALS patients. Dyspnea was more often a reason for the request for heart failure patients than for ALS patients. In contrast to physicians of cancer and heart failure patients, physicians of ALS patients did not report gastro-intestinal symptoms, incontinence, pressure sores or other somatic complaints as a reason for requesting euthanasia. In addition, physicians of ALS patients reported dependency, being limited in communication and anxiety as reasons for unbearable suffering more often than physicians of cancer patients.

Table 1: Symptoms of patients at the time of request for euthanasia or physician-assisted suicide according to the treating physician.

	ALS Patients %	Cancer patients %	Heart failure patients %	ALS-Cancer		ALS-Heart failure	
Symptoms	n=51	n=73	n=61	OR	(95% CI)	OR	(95% CI)
Not active	92	96	98	0.49	ns	0.18	ns
Feeling sick	92	97	98	0.30	ns	0.23	ns
Fatigue	80	96	97	0.17	(0.04-0.66)	0.12	(0.02-0.68)
Poor appetite	76	89	87	0.38	ns	0.18	(0.05-0.65)
Dyspnea	57	47	85	1.54	ns	0.24	(0.08-0.72)
Pain	33	63	43	0.27	(0.12-0.59)	0.70	ns
Frequently coughing	28	30	30	0.96	ns	0.78	ns

	ALS Patients %	Cancer patients %	Heart failure patients %	ALS-Cancer		ALS-Heart failure	
Symptoms	**n=51**	**n=73**	**n=61**	**OR**	**(95% CI)**	**OR**	**(95% CI)**
Anxious	28	34	28	0.62	ns	0.57	ns
Depressed	26	27	31	0.94	ns	0.73	ns
Nausea	16	62	44	0.11	(0.04-0.27)	0.34	(0.11-0.99)
Vomiting	8	42	18	0.09	(0.03-0.31)	0.27	ns
Pressure sores	8	13	12	0.64	ns	1.10	ns
Decreased consciousness	8	10	8	0.85	ns	0.67	ns
Confused	6	13	8	0.28	ns	0.29	ns

95% confidence interval (95% Cl) of the Odds Ratio (OR) for the various symptoms for amyotrophic lateral sclerosis (ALS) patients compared to cancer patients (reference group) and ALS patients compared to heart failure patients (reference group) adjusted for sex and age.
Ns= not significant
ALS= Amyotrophic lateral sclerosis

Table 2: Depressive symptoms of patients at the time of request for euthanasia or physician-assisted suicide according to the treating physician.

	ALS Patients %	Cancer patients %	Heart failure patients %	ALS-Cancer		ALS-Heart failure	
Symptoms	**n=51**	**n=73**	**n=61**	**OR**	**95% CI**	**OR**	**95% CI**
Feeling worthless	34	30	41	1.45	ns	1.01	ns
Feeling depressed	32	33	36	0.90	ns	0.87	ns
Was in a happy mood	54	49	41	1.32	ns	1.20	ns
Interested in up-coming events	53	43	35	1.45	ns	1.25	ns

95% confidence interval (95% Cl) of the Odds Ratio (OR) for depressive symptoms for amyotrophic lateral sclerosis (ALS) patients compared to cancer patients (reference group) and ALS patients compared to heart failure patients (reference group) adjusted for sex and age.
Ns= not significant
ALS= Amyotrophic lateral sclerosis

Table 3: Top five most reported uncombined reasons for unbearable suffering

	ALS patients n=51	Cancer patients n=73	Heart failure patients n=61
1	Fear of suffocation 45%	Pain 46%	Dyspnea 52%
2	Dependency 29%	Fatigue 28%	Dependency 37%
3	Loss of dignity 20%	Loss of dignity 24%	Knowing that the suffering will only get worse 30%
4	Dyspnea/Poor communication 16%	Dependency 18%	Being bedridden 25%
5	Fear of dependency 14%	Dyspnea 17%	Pain 23%

ALS= Amyotrophic lateral sclerosis

Table 4: Reasons for unbearable suffering of patients with a euthanasia or physician-assisted suicide request.

Reasons	ALS patients % n=51	Cancer patients % n=73	Heart failure patients % n=61	ALS-Cancer OR	ALS-Cancer (95% CI)	ALS-Heart failure OR	ALS-Heart failure (95% CI)
Psychosocial	*96*	*88*	*92*	*1.26*	*ns*	*1.76*	*ns*
Anxious [a]	65	39	25	2.73	(1.26-5.92)	3.95	(1.49-10.45)
Fear of increase in somatic complaints	12	15	10	0.63	ns	0.60	ns
Fear of coma or vegetating	10	1	2	7.07	ns	4.97	ns
Fear of dependence	14	7	2	1.99	ns	4.16	ns
Fear of not being able to communicate	10	3	0	3.82	ns	-	-
Fear of suffocation	45	11	3	6.61	(2.48-17.65)	14.66	(2.86-75.12)
Dependency [a]	39	21	42	2.41	(1.05-5.55)	2.66	ns
Hopelessness [a]	27	22	33	1.16	ns	0.76	ns
Loss of dignity [a]	20	24	8	0.70	ns	2.05	ns
Limited communication [a]	18	1	7	14.90	(1.80-123.1)	3.84	ns
Limited in leisure, work or personal care [a]	14	17	23	0.87	ns	0.61	ns
General depressive thoughts [a]	12	15	3	0.79	ns	6.06	ns
Other psychosocial reasons [a]	10	7	8	1.50	ns	3.56	ns

Reasons	ALS patients % n=51	Cancer patients % n=73	Heart failure patients % n=61	ALS-Cancer OR	ALS-Cancer (95% CI)	ALS-Heart failure OR	ALS-Heart failure (95% CI)
Cognitive decrease [a]	2	7	3	0.27	ns	1.08	ns
Feeling a burden on others [a]	2	3	0	0.76	ns	-	-
Symptoms of depression [a]	0	7	8	-	-	-	
Somatic	*51*	*83*	*85*	*0.20*	*(0.09-0.46)*	*0.16*	*(0.05-0.46)*
Immobility [a]	29	22	40	1.45	ns	0.84	ns
Dyspnea [a]	16	18	52	0.70	ns	0.12	(0.04-0.41)
Fatigue [a]	14	45	25	0.22	(0.08-0.59)	0.44	ns
Pain	12	46	23	0.16	(0.06-0.42)	0.30	ns
Difficulty swallowing	10	3	2	3.58	ns	6.34	ns
Gastro-Intestinal complaints [a]	0	18	12	-	-	-	-
Incontinence [a]	0	4	12	-	-	-	-
pressure sores	0	4	10	-	-	-	-
Other somatic reasons [a]	0	8	18	-	-	-	-

95% confidence interval (95% Cl) of the Odds Ratio (OR) for the various reasons for unbearable suffering for amyotrophic lateral sclerosis (ALS) patients compared to cancer patients (reference group) and ALS patients compared to heart failure patients (reference group) adjusted for sex and age. ALS= Amyotrophic lateral sclerosis

[a] Similar reasons for unbearable suffering are combined together in this more general category.

- cannot be calculated due to empty cells.

Although significant difference could not be tested due to small numbers, the percentages show that immobility was an important reason for unbearable suffering to all patients. Two kinds of immobility will be distinguished here: for instance paralyzed extremities and being bedridden due to fatigue or dyspnea. ALS patients had more frequently paralyzed extremities as a reason for their unbearable suffering (12% ALS, 0% Cancer and heart failure patients) while heart failure patients had more frequently being bedridden as the reason for their unbearable suffering (25% heart failure patients, 4% cancer patients, 0% ALS patients). None of the SCEN physicians of ALS patients reported symptoms of depression as a reason for unbearable suffering. Seven percent of the cancer patients and eight percent of the heart failure patients scored at least one symptom of depression. These symptoms of depression consisted out of three subcategories based on the DSM IV classification of depression, feeling excessively guilty, depressed mood and a diminished interest or pleasure in all, or almost all, activities for most of the day, nearly every day for a minimum of two consecutive weeks.

3.4 DISCUSSION

This study showed that fear of suffocation is the most frequently mentioned reason for unbearable suffering in ALS patients presenting with an EAS request. In cancer and heart failure patients with an EAS request, somatic complaints are most important reasons for unbearable suffering.
Strengths of our study are the high response rate, anonymity of the respondents and a minimal chance of recall bias because the reports were completed shortly after the consultation. A limitation is the lack of patient perspective on symptoms and suffering as the respondents were consultants and treating physicians. When describing suffering, physicians may tend to focus more on physical suffering than patients do.[10] Another limitation is the fact that the treating physician reported symptoms of the patients using a standard list, which did not include all the typical disease-specific symptoms. Nevertheless, in the SCEN reports, in which the physicians were free to report every type of suffering, we found comparable physical symptoms. Furthermore, this study focuses mainly on primary care physicians who in fact do receive the majority of requests for EAS in the Netherlands.[11]

Previous research showed that ALS patients who died following EAS did not differ from ALS patients who did not request EAS regarding physical function (mobility and communication).[5] This indicates that there may be factors, other than physical symptoms, that explain the high proportion of EAS in ALS patients. In our study, treating physicians of ALS patients with an EAS request reported fewer physical symptoms compared to treating physicians of cancer and heart failure patients with an EAS request. These findings suggest that in ALS patients, psychosocial reasons and especially anxiety may play a larger role in unbearable suffering than in cancer and heart failure patients. The fewer physical symptoms in ALS patients reported by the treating physician corresponds to the lower reported frequency of somatic complaints by SCEN physicians as a reason for unbearable suffering of ALS patients than cancer and heart failure patients.

Dependence on others is a psychosocial reason for suffering being unbearable that is mentioned frequently by all patient groups. Dependency in ALS patients often is the consequence of paralysis, while for cancer and heart failure patients, dependency usually is caused by fatigue or dyspnea.

The median survival of ALS after onset of first symptoms is three to five years, however also survival of more than ten years has been reported.[12;13] The first symptoms of ALS are usually muscle weakness and increased dependency on others. Psychosocial suffering in ALS therefore may not, be restricted to the terminal phase. In general the muscle weakness in ALS may lead to a more severe dependence for a longer period of time than in cancer and heart failure.

A possible explanation for the higher proportion of EAS in ALS patients may be the lack of palliative alternatives. Suffering caused by pain in cancer patients, or dyspnea in heart failure patients can be relieved by opioids, and in the case of refractory symptoms by palliative sedation. In psychosocial suffering in ALS patients, these treatments are not an adequate option. In addition, for palliative sedation, guidelines from the Royal Dutch Medical Association stipulate that life expectancy in continuous deep sedation should be two weeks or less. Therefore it can not be a solution for medical or psychosocial problems in ALS that occur before the terminal fase.[14] As psychosocial symptoms cannot always be prevented, patients should be helped to cope with these symptoms at the earliest possible stage.[15]

Although, the percentage of ALS patients that actually dies following acute respiratory distress is small (0-3%), a large percentage of the ALS patients is

afraid of suffocating.[16-18] A retrospective study carried out in ALS caregivers, however, reported that 52 percent of the ALS patients had moderate to severe choking episodes during the last month of their life.[19] Adequately informing ALS patients about the limited chance of experiencing an unpleasant death due to suffocation and about ways of preventing this may diminish their fear, ease their suffering and might influence the high EAS rate among ALS patients. From our data it cannot be concluded that the high percentage of EAS in ALS is the causal result of fear, dependency and communication problems. Nevertheless, these specific psychosocial symptoms are important factors that need special attention when caring for ALS patients.

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CHAPTER 4
END-OF-LIFE PRACTICES; A RETROSPECTIVE STUDY

Picture: The men's ward of the general hospital at the Catharijnesingel 15 in Utrecht in ± 1900, the precursor of today's University Medical Center Utrecht. In the middle internist Prof. Talma and assistant director sister Ültermülhen.
Based on Maessen M, Veldink JH, Onwuteaka-Philipsen BD, de Vries JM, Wokke JHJ, van der Wal G, van den Berg LH. Trends and Determinants of End-of-Life Practices in ALS in the Netherlands, accepted for publication in Neurology.

4.0 ABSTRACT

BACKGROUND In the Netherlands the proportion of patients with ALS who choose the option of euthanasia or physician-assisted suicide (EAS) is relatively high (20%). The objective of this study was to determine which factors influence end-of-life practices in ALS and whether rates are changing over time.

METHODS In a cohort survey, 204 physicians and 198 informal caregivers of ALS patients who died between 2000 and 2005 filled out questionnaires on the end-of-life circumstances of the patient. Results were compared with those of a similar study performed during the period 1994-1998.

RESULTS In 2000-2005, 16.8% of the patients died due to EAS compared to 20.2% in 1994-1998. Thirty-one (14.8%) patients died during continuous deep sedation (CDS) in 2000-2005. EAS, but not CDS, was significantly associated with religion not being important to the patient, being more educated and dying at home. EAS was not associated with quality of care items or symptoms of depression. Loss of function was similar in both groups. Informal caregivers of patients who died due to EAS, more frequently reported fear of choking ($p=0.003$), no chance of improvement ($p=0.001$), loss of dignity ($p= 0.02$), being dependent on others ($p=0.002$) and fatigue ($p=0.018$) as reasons for shortening life. Hopelessness was associated with both EAS and CDS.

CONCLUSION The frequency of EAS in ALS appeared stable over time and one in seven patients died during CDS. CDS is relatively common in ALS, but appears to have other determinants than EAS. Subjective factors may be important in explaining EAS in ALS.

4.1 INTRODUCTION

It appears that ALS specialists in particular are confronted with requests for physician-assisted suicide.[1] In most countries it is currently illegal for physicians to grant such requests. In the Netherlands, physicians will not be prosecuted for actions to end the life of patients as long as the actions are consistent with the requirements of due care laid down in the euthanasia act in 2002. These requirements include a voluntary and well-considered request from the patient to die, unbearable and hopeless suffering, the physician informing the patient about his/her situation and prospects, the absence of realistic alternatives for treatment, consulting a second independent physician, performance of euthanasia or physician-assisted suicide (EAS) with due medical care and that the cause of death is reported as non-natural to the authorities.[2]

We previously reported on the relatively high rate of EAS (20%) in ALS in the Netherlands between 1994 and 1998.[3] From this study, it was unclear whether quality of palliative care or other factors were associated with the choice of EAS and whether the rate of EAS was increasing.[4] It has been suggested that the relatively high rate of EAS could be the result of inadequate palliative care, patients feeling they were a burden on others, hopelessness, a financial burden or devaluation of the dying.[4-6]

Identifying factors that are associated with EAS could improve care for ALS patients. The relatively high rate of EAS in ALS combined with the legal climate in the Netherlands, allowed a more detailed follow-up study on factors influencing the choice of EAS and on a possible increase in the rate of EAS and other end-of-life practices.

4.2 METHODS

Design and participants

We performed a cohort study in the University Medical Center Utrecht, a national referral center for patients with ALS. In 2005 we used a hospital study database containing ALS patients who had visited the hospital or out-patients clinic to select all known patients who had probable or definite ALS according to the El Escorial criteria and died between January 2000 and June 2005.[7] We sent a questionnaire to each patient's treating physician and informal caregiver, i.e. a closely related person involved in the care of

the patient, usually the spouse (76%) or a child (17%), with a request to complete and return the form on a voluntary basis. We identified 273 physicians and 248 informal caregivers. A total of 204 (75%) physicians reported on 209 individual patients and 198 (80%) informal caregivers completed the questionnaires and returned them. The procedure allowed for anonymity of physicians, deceased patients and their informal caregivers. In order to study a possible change in the rate of end-of-life practices over time, a comparison was made with our previous study in ALS patients who died between 1994 and 1998.[3] In this study, 203 physicians of deceased patients (response 84%) completed questionnaires on circumstances at the end of the life of these patients. In addition, we combined the data from the periods 1994-1998 and 2000-2005.

Questionnaires

The questionnaires were based on a format used in 1990 and 1995 for nationwide surveys concerning end-of-life practices in the Netherlands and in our previous study in ALS patients.[3;8] The questionnaire for the physician included additional questions related to continuous deep sedation (CDS), the need for interdisciplinary consultation on medical decisions, palliative care and the occurrence of symptoms of depression in the last phase of life. The questionnaire for the informal caregiver addressed patient's social structure, feelings, religion, and symptoms of depression. One way of measuring symptoms of depression included three questions from the DSM-IV i.e. feeling depressed, diminished interest or pleasure in all, or almost all, activities and feeling excessively guilty for most of the day, nearly every day for a minimum of two consecutive weeks. We targeted these symptoms of depression because they did not overlap with ALS symptoms, unlike the other 6 symptoms of depression of the DSM-IV which did overlap with symptoms of ALS.[9] In addition, we asked whether the patient had feelings of hopelessness for most of the day, nearly every day for a minimum of two consecutive weeks. The questionnaire for the informal caregiver also included a validated Dutch questionnaire used to evaluate palliative healthcare by a caregiver which addresses quality and availability of physical and mental care, the timing and usefulness of the aids, cooperation of different health care professionals, the emotional and spiritual support reported by the informal caregiver.[10]

Euthanasia was defined as the administration of drugs by a physician with the explicit intention of ending the patient's life, at the patient's explicit request. In physician-assisted suicide (PAS), patients swallow the drugs themselves, although they may need assistance due to ALS related muscle weakness, for instance, bringing a straw to the mouth. If a physician reported more than one end-of-life practice, only the practice considered to have the larges potential to influence the hastening of a patient's death was included in the analysis.[8] The practices in order of decreasing influence were: EAS, withholding or withdrawing medical treatment with the explicit intention of hastening death, intensified alleviation of pain or symptoms while taking into account the possible hastening of death, and withholding or withdrawing medical treatment while taking into account the possible hastening of death. CDS was not categorized under these options, but was treated as a separate end-of-life practice.[8] CDS was defined as the administration of drugs to keep the patient in deep sedation or coma until death. CDS is distinct from "the intensified alleviation of pain or symptoms while taking into account the possible hastening of death", because of the explicit goal of sedation and the absence of taking into account the hastening of death due to CDS per se. Nevertheless, CDS is often combined with an end-of-life practice, for instance the withdrawing of food/fluids.
Identical to the procedure used in the previous nation-wide studies, we asked the physician to estimate the amount of time that the end of life might have been hastened due to their actions.[11]

Data analysis
To analyze changes in rates of end-of-life practices over time, we compared data with our earlier study by calculating differences using the chi-square test. We determined the significant difference in distribution of factors between patients who had died as a result of EAS or CDS, and those who had not (excluding sudden deaths) using the chi-square test. Fisher's exact test was used when cells had an expected frequency of less than five. The Mann-Whitney U test was used to analyze continuous variables. Multivariate logistic regression was used to determine the significant difference in distribution of hopelessness between patients who had died as a result of EAS or CDS, and those who had not (excluding sudden deaths). Patients

with missing data were not included in the analyses. All tests were two-tailed ($p<0.05$).

4.3 RESULTS

Patients

Table 1 shows that the characteristics of the patients included in the 1994-1998 and 2000-2005 studies do not differ and are similar to the characteristics of a general ALS population.[12] Diagnosis, sex, site and age at onset of the disease also did not differ significantly from the non-responders (not shown).

Table 1: Characteristics of patients with amyotrophic lateral sclerosis

	1994-1998	2000-2005
	n = 203	n = 209
Diagnosis,%		
Sporadic ALS	94.6	93.3
Familial ALS	5.4	5.3
Sex,%		
Female	41.4	37.8
Male	58.6	62.2
Site of onset,%		
Spinal	69.5	61.7
Bulbar	30.5	35.4
Age at onset-yr		
Median (range)	58.9 (24.9-81.1)	62.3 (30.6-86.4)
Survival time-yr		
Median (range)	2.4 (0.5-10.1)	2.3 (0.4-9.1)
Tracheotomy,%	3.4	2.9

Trends in end-of-life practices

Between 2000 and 2005, thirty-five (16.8%) ALS patients decided on EAS compared to 41 (20.2%) ALS patients in 1994-1998. This decrease was not significant (Table 2). The frequency of other end-of-life practices also did not change significantly between these two time periods. Nor was the rate of EAS before and after the enactment of the new Dutch Law in 2002 different ($p= 0.86$; data not shown).

Thirty-one patients (14.8%) died during CDS between 2000 and 2005 (Table 2). In all patients who died during CDS, another end-of-life practice was performed. No data are available for 1994-1998, as that study did not include CDS.

Patient and disease characteristics

The caregivers of patients who died due to EAS more often reported that the patient had a higher level of education (p=0.03) and that the patient thought that religion was not important (p=0.04, Table 3). In contrast to EAS, no significant association was found between dying during CDS and any of the patient characteristics. None of the disease characteristics was significantly associated with EAS or CDS. Table 3 also shows that EAS appears to be performed in the end-stage of the disease.

Table 2: Trend in frequencies of euthanasia, physician-assisted suicide, and other end-of-life practices in amyotrophic lateral sclerosis (ALS) patients in the Netherlands [a]

Practices % (95% CI)	1994-1998 n = 203	2000-2005 n = 209	p
Unexpected sudden death	18.2 (12.9-23.5)	18.2 (13.0-23.4)	0.99
No end-of-life practices	26.6 (20.5-32.7)	25.8 (19.9-31.8)	0.86
Total end-of-life practices performed	55.2 (48.3-62.0)	56.0 (49.3-62.7)	0.87
Euthanasia	17.2 (12.0-22.4)	15.8 (10.8-20.7)	0.69
Physician-assisted suicide	3.0 (0.6-5.3)	1.0 (0.0-2.3)	0.17
Ending of life without explicit request by patient	1.0 (0.0-2.3)	0.0 (0.0-1.7)	0.24
Intensified alleviation of symptoms	23.6 (17.8-29.5)	26.8 (20.8-32.8)	0.50
Withholding or withdrawal of medical treatment	10.3 (6.2-14.5)	12.1(8.0-16.9)	0.46
Continuous deep sedation [b]	NA	14.8 (10.0-19.7)	NA

[a] Unexpected sudden death, no end-of-life practices and total end-of-life practices performed add up to 100%.

[b] The category continuous deep sedation has been provided in conjunction with 'intensified alleviation of symptoms' or 'withholding medical treatment' in all patients.

"Intensified alleviation of symptoms" represents the patients who received intensified alleviation of pain or symptoms while taking into account the possible hastening of death.

95% Cl = 95% confidence interval.

NA = not available.

Depression and hopelessness

Hopelessness was associated with dying due to EAS (p=0.04) or during CDS (p=0.007). Not surprisingly, all patients who died due to EAS had at some time expressed to their physician the wish to hasten death; this was also found for 51.6% of the patients who died during CDS and 39.6% of the patients who died without EAS or CDS.

We found no significant association between EAS and a history of depression, the use of anti-depressive medication, depression or symptoms of depression according to the physician, and the measured DSM-IV symptoms of depression (Table 4). Thirty-five percent of the caregivers reported that the patients who received EAS felt depressed and/or had diminished interest or pleasure in all, or almost all, activities for most of the day, nearly every day for a minimal two-week period. Only one patient's caregiver answered all three DSM-IV items positively. This patient died without any end-of-life practices. A history of depression was found more frequently in patients who died due to EAS (p=0.06). However, of the six patients who had a history of depression and died following EAS, the physician reported that they did not have a depression during the weeks before death.

Combined analysis of hopelessness and depression according to the physician showed no important change in the association between hopelessness and EAS (p=0.04) or CDS (p=0.01). Also after adjusting hopelessness for religion being important to the patient both associations with EAS remained (hopelessness, p=0.01, religion p=0.02).

Quality of care

With regard to quality of care characteristics, no significant differences were detected between patients who died due to EAS or CDS and those who did not (Table 4). Almost all physicians (97%) who performed EAS indicated they had sufficient professional support for themselves when they considered or performed an end-of-life practice on a patient.

Table 3: Characteristics of amyotrophic lateral sclerosis (ALS) patients who died between 1994 and 2005 [a]

	2000-2005			1994-2005	
	No EAS and CDS	EAS	CDS	No EAS	EAS
Variable %	**n=105**	**n=35**	**n=31**	**n=266**	**n=76**
Patient characteristics					
Age onset					
≤ 55 yr.	23.1	27.3	29.0	32.2	34.8
55-70 yr.	62.5	63.6	54.8	54.8	58.0
≥ 71 yr.	14.4	9.1	16.1	13.0	7.2
Female sex	35.2	37.1	41.9	38.7	47.4
Married	80.6	82.8	78.3	85.7	82.9
Children	89.6	83.3	82.6	87.5	87.1
Religion important to the patient	54.4	31.0*	54.5	62.0	36.7**
Education patient					
0-6 yr.	20.9	3.4*	4.5	14.0	4.7*
>6 yr.	79.1	96.6	95.5	86.0	95.3
Disease characteristics					
Onset at bulbar region	39.8	31.3	33.3	33.6	31.5
Able to speak	44.0	45.7	56.7	49.2	48.0
Tube feeding	50.5	37.1	45.2	48.6	38.0
Arm function					
Able to raise arms to mouth	46.9	38.2	24.1	41.7	31.9
Unable to reach arms to mouth	32.1	32.4	44.8	35.5	37.5
Paralysis arms	21.0	29.4	31.0	22.8	30.6
Leg function					
Walk unsupported	8.7	5.7	6.7	5.7	6.6
Walk supported	21.4	8.6	3.3	17.2	7.9
Dependent on wheelchair	18.4	42.9	36.7	23.0	35.5
Confined to bed	51.5	42.9	53.3	54.0	50.0
Disease duration, median yr.	2.2	2.2	2.7	2.4	2.5

* = $p<0.05$, **= $p<0.01$ between patients who died by euthanasia or physician-assisted suicide and those who did not.

[a] All cases of unexpected sudden death were excluded, since no end-of-life practices could be performed.

EAS= euthanasia or physician-assisted suicide CDS= continuous deep sedation

Table 4: Depression, quality of care, and reasons for hastening death of amyotrophic lateral sclerosis (ALS) patients who died between 2000 and 2005 [a]

Variable %	No EAS or CDS n=105	EAS n=35	CDS n=31
Depression/hopelessness			
Feeling hopeless [b]	37.3	60.0*	69.6**
Had at some time expressed wish to hasten death [c]	39.6	100.0**	51.6
History of depression [b]	4.5	17.2	9.1
Use of anti-depressants in end-stage	10.7	11.8	9.7
Depression or symptoms of depression in end-stage	16.2	11.4	13.3
DSM-IV items [b]			
Diminished interest or pleasure in all, or almost all, activities according to informal caregiver	23.9	23.3	8.7
Feeling depressed according to informal caregiver	17.9	20.7	26.1
Feeling guilty according to informal caregiver	9.0	13.3	0.0
Quality of Care			
Sufficient information to ease future suffering [b]	90.2	92.9	100.0
General availability health care sufficient [b]	92.4	90.0	100.0
General quality health care sufficient [b]	93.8	86.7	95.7
Adequate financial reimbursement [b]	90.6	86.2	100.0
Sufficient aids and appliances [b]	78.5	81.5	69.6
Healthcare providers provided sufficient mental support [b]	81.1	80.0	94.1
Healthcare providers relieved physical symptoms sufficient [b]	73.0	75.9	81.8
Healthcare providers had sufficient experience and knowledge to help [b]	63.9	70.0	72.7
Patient had sufficient confidence in healthcare providers [b]	69.8	60.0	73.9
Healthcare providers should have taken a larger role in the care [b]	4.6	3.3	13.6
Sufficient professional support for physician in end-of-life practices	72.0	96.9*	65.2

Variable %	No EAS or CDS n=105	EAS n=35	CDS n=31
Reasons for hastening death [d]			
Fear of choking	34.2	70.0**	59.1
No chance of improvement	23.7	63.3**	31.8
Loss of dignity	26.3	53.3*	27.3
Dependency	7.9	36.7**	13.8
Fatigue/extreme weakness	7.9	30.0*	4.5
Feeling a burden on family or friends	13.2	20.0	18.2
Pain	0.0	0.0	4.5

* $p<0.05$, ** $p<0.01$ between patients who died due to euthanasia, physician-assisted suicide or continuous deep sedation and those who did not.

[A] All cases of unexpected sudden death were excluded, since no end-of-life practices could be performed.

[b] Question is from the informal caregivers questionnaire

[c] Patients with an unexpected sudden death were included.

[d] Question is from the informal caregivers questionnaire and only applicable for patients who had an end-of-life practice.

EAS= euthanasia or physician-assisted suicide

CDS= continuous deep sedation

Reasons for hastening death

The informal caregivers of patients who decided on EAS, compared to patients whose lives were shortened by an end-of-life practice other than EAS, reported the following reasons for hastening death significantly more frequently: fear of choking, no chance of improvement, loss of dignity, being dependent on others and fatigue (Table 4). Pain and the feeling they were a burden on family or friends were not reported more frequently as reasons for hastening death by the informal caregiver.

End-of-life characteristics

Patients who decided on EAS most often died at home ($p=0.007$), while patients who died during CDS were more likely to die in a nursing home/hospice compared to patients who died without EAS and CDS ($p=0.04$; Table 5). Patients who decided on EAS appeared to feel less anxiety during the last few hours before death ($p=0.002$). Almost all deaths were considered to be "peaceful" according to the physician (EAS 94.1%,

CDS 96.6%, no EAS or CDS 96.0%), which was confirmed by the results from the informal caregivers (EAS 89.7%, CDS 90.9%, no EAS or CDS 91.8%). The time by which the lives of patients was shortened by the end-of-life practices performed, was estimated by the treating physician. It appeared that the amount of time by which life was shortened was less in patients who died during CDS, than in patients who died due to EAS.

Table 5: End-of-life Characteristics of amyotrophic lateral sclerosis (ALS) patients who died between 1994 and 2005[a].

	2000-2005			1994-2005	
End-of life characteristics %	**No EAS or CDS n=105**	**EAS n=35**	**CDS n=31**	**No EAS n=266**	**EAS n=76**
Place of death		**	*		**
Death at home	61.0	88.6	61.3	62.8	90.8
Death at hospital	22.9	2.9	6.5	19.9	1.3
Death at nursing home /hospice	16.2	8.6	32.3	17.3	7.9
Peaceful death according to the physician	96.0	94.1	96.6	94.8	94.6
Anxiety hours before death according to physician	24.7	13.3	32.1	30.9	11.8**
Physicians estimated life shortening effect [b]		**	*		**
More than four weeks	13.3	34.3	0.0	11.6	28.4
Between seven days and four weeks	15.6	28.6	6.7	9.4	47.3
Less than seven days	71.1	37.1	93.3	79.0	24.3

*= p<0.05; ** p<0.01; between patients who died due to euthanasia or physician-assisted suicide or continuous deep sedation and those who did not.

[a] All cases of unexpected sudden death were excluded, since no end-of-life practices could be performed.

[b] Only applicable for patients who had an end-of-life practice i.e. "Intensified alleviation of symptoms" and "Withholding or withdrawal of medical treatment".

EAS= euthanasia or physician-assisted suicide

CDS= continuous deep sedation

4.4 DISCUSSION

Our study shows that the use of EAS in ALS remained stable during 1994-2005 in the Netherlands. From our study there is no evidence of a "slippery slope" in terms of increasing numbers of assisted deaths in the face of open acceptance and, since 2002, official legalization of EAS. This is in accordance with a recent nationwide study on EAS in the Netherlands showing a decrease in the number of cases of euthanasia from 2.6% (95% CI 2.3-2.8) in 2001 to 1.7% (95% CI 1.5-1.8) in 2005. Concomitantly, the rate of CDS in this study increased from 5.6% (95% CI 5.0-6.2) to 7.1% (95% CI 6.6-7.6) which may suggest that the choice for EAS had been replaced by CDS.[11] We show that almost 15% of ALS patients in the Netherlands died during CDS. It is unlikely, however, that CDS is being used to replace EAS in ALS as the relatively high rate of EAS remained stable over a period of ten years and the determinants of CDS appeared to be different from those of EAS. The choice for EAS, but not for CDS, was associated with religion not being important to the patient and with being more educated, which confirms previous studies on EAS.[13] In addition, when compared to patients who died without EAS or CDS, patients died more often at home in the EAS group, while CDS was performed more often in a nursing home or hospice. A possible explanation for EAS being performed less in nursing homes or hospices is that hospices frequently do not allow EAS. We also showed that 93% of the patients who died during CDS had a life expectancy of less than seven days compared to 37% of the patients who died due to EAS and 71% of patients who died after other end-of life practices. The reasons for hastening death in EAS were more frequently 'no chance of improvement', 'loss of dignity', 'fear of choking', 'being dependent' and 'fatigue', but not feeling a burden on family or friends. In contrast, patients who died during CDS appeared more similar to patients who died without CDS or EAS as far as their reasons for hastening death were concerned. This is most probably related to the fact that CDS, like intensified alleviation of pain or symptoms while taking into account the possible hastening of death", is a more medical response to physical suffering, while the emphasis in the choice for EAS lies more on existential suffering, for example, the loss of dignity.[14]

The frequency of depressive symptoms was similar to frequencies previously reported in ALS studies, and in a general cohort of older (>54

years), Dutch individuals.[9;13;15] No association was found between symptoms of depression and the choice for EAS or CDS (p=0.49, p=1.00). Hopelessness can occur in the absence of depression: dysphoria and inability to experience pleasure in the present are cardinal features of depression, while hopelessness projects these feelings into the future.[4] Apparently, a common determinant of EAS and CDS is feeling hopeless during the last two weeks of life. These results are in agreement with two previous studies which showed that ALS patients who were inclined to choose physician-assisted suicide or who had a wish to die, more often had a feeling of hopelessness, but not depression.[13;16] The progressive nature of the disease robs many patients of the hope that the most dreaded symptoms can be avoided which may be an important factor in ALS.[4] Since it has been show that quality of life in ALS is correlated more strongly with social support and hopelessness than with the physical state of the patient, these results emphasize the importance of psychological and social support in the care of patients with ALS.[17]

No association was found between EAS or CDS and detailed items addressing quality of care for the patient. In our study about 20% of caregivers indicated that aids and appliances were inadequate and about 25% indicated that physical symptoms were not sufficiently treated. These numbers are similar to previous studies on quality of care characteristics performed in Europe and the United States, and indicate that further improvements may be needed in the care of patients with ALS.[18;19] However, our data on quality of care characteristics in patients who died due to EAS do not provide evidence that the high rate of EAS in ALS in the Netherlands reflects lack of palliative care, as we could not find any significant associations between items addressing quality of care and EAS.

Among the reasons for requesting hastening of death, fear of choking was present in 70% of patients who decided on EAS. This is in sharp contrast to the reported low frequency of choking in the end stage of ALS and to our finding that deaths are considered peaceful in more than 94% of ALS patients.[18;20;21] This emphasizes the need for adequate and timely information regarding choking in the final stage of the disease to reduce fears concerning choking situations.

The median disease duration of the patients included in the present study was shorter (2.3 years) than the median disease duration (3 years) in patient cohorts previously reported by us and others.[12;22] This is most probably

because we selected deceased patients from a new database of patients seen in our outpatient clinic. There is, therefore, a bias towards patients with a relatively short disease, as patients with a long disease duration are still alive and do not contribute to the median survival in the current study. A limitation of our study is the fact that patients' proxies and physicians answered the questions regarding the ALS patients retrospectively. Therefore, our results should be interpreted with caution. For example, physicians tend to under-diagnose depression.[23;24] On the other hand, a study in terminal cancer patients showed that patients and their family caregivers agreed well on the patients' quality of life, although family caregivers tend to be more negative than patients.[25] To overcome these limitations, a prospective study on end-of-life practices and quality of care in patients with ALS is clearly desirable.

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CHAPTER 5
END-OF-LIFE PRACTICES; A PROSPECTIVE STUDY

Picture: Transporting a patient into a car of Municipal Health Service at St. Johannes de Deo hospital at Mariaplaats 28 in Utrecht in ± 1923.
Based on Maessen M, Veldink JH, Onwuteaka-Philipsen BD, Hendricks HT, Schelhaas HJ, Grupstra HF, ten Klooster L, van der Wal G, van den Berg LH. A prospective study of characteristics of care, depression and quality of life in relation to physician-assisted death, submitted.

5.0 ABSTRACT

BACKGROUND The desire for euthanasia or physician-assisted suicide (EAS) might be caused by unmet palliative care needs. The relatively high proportion (20%) of EAS in amyotrophic lateral sclerosis (ALS) and the legal climate in the Netherlands provide the unique opportunity to study this association prospectively.

METHODS We performed a prospective observational cohort study on end-of-life circumstances of 102 patients with end-stage ALS. Structured questionnaires on characteristics of care, quality of life and symptoms of depression were filled out every three months until death and the results were correlated with a request for EAS.

RESULTS Thirty-one percent of the patients requested EAS, of whom 69% eventually died due to EAS. In the last measurement before the patients' death 84% of all patients thought that the health care in general was good or excellent. Of the patients who requested EAS, 16% felt depressed, 39% were in pain, 45% experienced loss of dignity, 65% felt a burden on their family and 74% thought there was no chance of improvement. The physical quality of life significantly decreased at the end of their lives ($p<0.001$), but the mental quality of life did not changed statistically significantly ($p\geq0.09$). Nevertheless, none of these items differed significantly between the patients who requested EAS and those who did not.

CONCLUSION Our data show that the vast majority of all patients thought that the health care in general was good. We observed no statistical significant difference in received care, quality of life or symptoms of depression in ALS patients who request or received EAS and those who do not.

5.1 INTRODUCTION

Since April 1st 2002 euthanasia and physician-assisted suicide (EAS) are no longer prosecuted in the Netherlands, provided that the requirements of due care have been fulfilled and that the cause of death is reported as non-natural to the authorities.[1] The requirements to be met are "a voluntary and well-considered request of the patient to die", "unbearable and hopeless suffering", "the physician informing the patient about his or her situation and prospects", "the absence of realistic alternatives for treatment", "consulting a second independent physician" and "termination of life with due medical care".

In 2005, 1.8% of all deaths in the Netherlands was the result of EAS.[2] The majority of the patients who request EAS have cancer[2]. However, patients with amyotrophic lateral sclerosis (ALS) are a well-known and frequently used example in case studies and television broadcasts on euthanasia, due to the poor prognosis of the disease and the visible burden of suffering at the end of life. ALS is characterized by progressive degeneration of motor neurons and the clinical hallmarks are progressive limb weakness, respiratory failure and bulbar palsy. Cognition in patients with ALS is rarely severely affected.[3] Approximately 50% of the patients die within three years after onset of the disease mostly due to respiratory insufficiency. Therefore patients with ALS and their physicians are often confronted with several end-of-life practices, including forgoing treatment with antibiotics in case of a pneumonia and treatment with opioids with a possibility of hastening death, or EAS.

Since there is no cure for ALS, specialized palliative care is the best treatment available.[4] As 73% of patients die at home, palliative care for ALS patients in the Netherlands is mainly provided by primary care physician, rehabilitation physicians and home care nurses.[5] In the remainder of patients, the terminal phase takes place in a hospice, nursing home (13%) or hospital (14%). In 1998, the Minister of Health, Welfare and Sport in the Netherlands decided to establish a program to promote palliative care, especially in the terminal phase. As a result six Centers for the Development of Palliative Care (COPZ) were founded to enhance coordination, develop education, increase expertise and performed research on palliative care. Since 2004, the COPZ are partly integrated in the nine Comprehensive Cancer Centers and provide multidisciplinary consultations teams for

healthcare professionals on palliative care of all diseases. Through regional networks, they foster expertise and multidisciplinary cohesion in the delivery of palliative care.
In 2002 we examined the actual end-of-life practices performed in patients with ALS retrospectively and found that 20% died due to EAS.[5] Experts considered this EAS proportion as unacceptably high.[6] The quality and availability of palliative care in the Netherlands was questioned, and concerns were raised about the possibility of these ALS patients feeling a burden on their families and the devaluation of the dying. It is suggested that the identification of patients with a wish for EAS early enough in the course of their illness enables an intervention and that intensive palliative treatment will decrease the interest in euthanasia.[6]
In view of these grave concerns and the relative high proportion of EAS in ALS in the Netherlands, we performed a prospective study on factors that may influence a positive attitude towards EAS and a final decision of EAS in ALS patients. Due to the high proportion of EAS in ALS in the Netherlands, it was possible to conduct a prospective follow-up study, which has methodological advantages over retrospective and cross-sectional studies. This study approach enables determination of the proportion EAS in a large cohort of terminally ill patients with ALS. More importantly, it allows for a detailed insight in the patient characteristics, the care- and quality of life related factors, and longitudinal functional and mental assessments that are associated with a request for EAS and receiving EAS.

5.2 METHODS

Study population
One hundred and ninety-two patients with ALS were selected through three national referral centers for motor neuron disease in the Netherlands. All patients were diagnosed with probable or definite ALS.[7] Patients were invited to participate in the study when a neurologist specialized in ALS estimated their life expectancy six months or less. Life expectancy estimates were based on clinical knowledge and a forced vital capacity of less than 60%.[8] Furthermore, eligibility was restricted to patients who understood the Dutch language, could communicate at least "yes" and "no", were not dependent on tracheotomy with mechanical ventilation, did not have a

severe cognitive impairment and died during the study. One hundred and thirty-six (71%) of the 192 selected patients agreed to participate in the study. However, 17 of these patients left the study early, because they felt too tired or decided to reserve all their energy for their loved ones.
Three patients developed severe cognitive impairment and were excluded from the study. Another 14 patients did not die during the study and were therefore excluded from the analyses of this study. All included patients (n=102) died between October 2003 and March 2008. The 56 non-responders and the 34 patients that dropped out or were excluded from the study did not differ with regard to sex, age and site of onset of the disease from the 102 participants.

Study design
Participating patients completed questionnaires every three months until the patient died. The follow-up consisted of a selection of the questionnaires that were used at baseline (see below). When the patient died, the treating physician filled out a questionnaire in which end-of-life practices and received requests were documented.
The questionnaires of the patients and the physicians were all but three (ALSFRS-r, CIDI, MMSE, see below) self administered. However, a trained interviewer helped the patient to complete all the questionnaires in their home, when they were no longer able to write or type. The institutional ethics committee of the University Medical Center in Utrecht approved the study protocol, and all patients and informal caregivers gave their informed consent.

Characteristics of patients
Demographic and disease characteristics such as the site and age of onset of muscle weakness were collected from the patients medical files. Stage of the disease was assessed with the revised ALS functional rating scale (ALSFRS-r).[9] This measure includes 12 questions on a five-point scale, which measures disease severity in the areas of gross motor tasks, fine motor tasks, bulbar functions and respiratory function. The maximum score is 48, with a higher score meaning less severe impairments.
The patient's symptoms were measured with a structured questionnaire based on a questionnaire of a Dutch nationwide survey.[10]

We examined how the patient coped with problems and unpleasant events using the Utrecht Coping List (UCL).[11] The 47 items of the UCL describe possible reactions to problematic or unpleasant events and are to be answered as a 4-point rating scale. Patients can indicate whether they would generally use this response when confronted with these events (1 =rarely or never, 4 =very often). The 47 items are grouped into seven subscales: active coping (i.e., sort out the situation and working to solve the problem); palliative coping (i.e., seeking distraction to avoid thinking about the problem); avoidance coping (i.e., leaving the problem as it is and not trying to solve it); social coping (i.e., seeking comfort and understanding from others); passive coping (i.e., being totally overwhelmed by the problem, feeling unable to solve the problem); emotional coping (i.e., showing irritation and anger or vent one's irritation on someone/something); and comforting coping (i.e., using comforting thoughts, like 'after rain comes sunshine').
The Mini Mental State Examination (MMSE) was performed to test for severe cognitive impairment which was an exclusion criteria.[12]

End-of-life practices
The questions for the physicians on end-of-life practices were based on the questionnaire of the Dutch nationwide survey containing medical end-of-life practices.[10] In these questions we avoided the terms "euthanasia", "physician-assisted suicide" and "sedation", because their connotations are too varied. Instead, we used wording which describes more closely actual medical practice, permitting us to classify the answers in the categories defined here. Euthanasia was defined as the administration of drugs by a physician with the explicit intention of ending the patient's life, on the patient's explicit request. Physician-assisted suicide was defined as the prescription or supplying of drugs by a physician with the explicit intention of enabling the patient to end his or her own life. Continuous deep sedation (CDS) was defined as the administration of drugs to keep the patient in deep sedation or coma until death.
If a physician reported more than one end-of-life practice, only the practice considered to have the larges potential to influence the hastening of a patient's death was included in the analysis.[10] The practices in order of decreasing influence were: EAS, withholding or withdrawing medical treatment with the explicit intention of hastening death, intensified

alleviation of pain or symptoms while taking into account the possible hastening of death, and withholding or withdrawing medical treatment while taking into account the possible hastening of death. CDS was not categorized under these options, but was treated as a separate practice.[10]

Symptoms of depression

Symptoms of depression were assessed with three different questionnaires. Firstly we used the Hospital Anxiety and Depression Scale (HADS) that can screen for anxiety disorders and symptoms of depression among patients in non-psychiatric hospital clinics.[13] It does not include questions on somatic symptoms that can be caused by both a depression and physical diseases. It contains two 7-items subcategories: one for anxiety and one for symptoms of depression. The maximum score for both categories is 21, with a higher score meaning more (severe) symptoms of depression and anxiety. A symptoms of depression score of 11 or higher is considered an indication of a possible depression and an anxiety score of 10 or higher as an indication of anxiety.[14] Secondly, depression was assessed by asking the patients: Did you feel depressed in the last three months?[15] Answers were categorized in: Depression present or absent. Thirdly, we used a selection of questions from the Composite International Diagnostic Interview (CIDI). The CIDI is designed to be used by trained lay interviewers and based on the definitions and criteria of DSM-IV. The CIDI can only be positive for depression if the patient was depressed and/or had diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day for a minimum of two consecutive weeks.[16] In this study we used these two key questions as they did not overlap with symptoms of ALS.

Quality of life

Quality of life was measured with the 40 item ALS assessment questionnaire (ALSAQ-40) on a five-point scale. This questionnaire measures five areas of health status: Eating and Drinking, Communication, independence, Physical mobility, Emotional Functioning.[17] We combined the first four subscales into the physical subscale and emotional functioning is the mental subscale. Each subscale is assessed using a summary score ranging from 0 to 100, with 0 representing the best possible lower quality of life and 100 representing the worst possible quality of life.

Characteristics of care
We used the patient version of the Palliative Outcome Scale (POS) to assess quality of care characteristics.[18] The POS has 10 closed questions on the quality of the palliative care. The outcome of POS questions ranges from one to four, with a higher score meaning a poorer situation. All the received care questions as shown in table 4 were assessed with a structured questionnaire which was based on a previous Dutch ALS study.[19]

Data analysis
Chi-square test was used to analyze differences between the patients who explicitly requested EAS and the patients who did not explicitly requested EAS. Fisher's exact test was used when cells had an expected frequency of less than five. For differences in continuous variables the Mann-Whitney U test was used to calculate significant differences. The above analyses were also performed for patients who actually died due to EAS and the patients who did not die due to EAS. The 11 patients with an unexpected sudden death were excluded from these analyses as these patients were not able to choose EAS.[10]
Change over time in quality of life, symptoms of depression, anxiety and stage of disease for the participants who had more than one measurement (n=61) was examined with a linear mixed effect model using maximum likelihood fitting. All tests were two-sided, and a p-value of less than 0.05 was considered to indicate statistical significance.

5.3 RESULTS

Characteristics of patients
The characteristics of the 102 participants are presented in Table 1. The median time between the last measurement and death of the patient was 67 days. There were no significant differences in the stage of disease, the experienced symptoms and the coping styles between patients who explicitly requested for EAS and those who did not explicitly requested EAS.
The most frequently reported symptoms in the last measurement before the patient's death of the patients who actually died due to EAS were dependency (86%), fatigue (76%) and no chance of improvement (76%). Patients also reported most frequently that being dependent was their most

important problem. These same result account for patient with an explicit request for EAS.

End-of-life practices

Table 2 shows the end-of-life practices that were actually performed and shows that 22 percent of the patients died due to EAS. The table also presents the outcome of the 32 patients that explicitly requested their physician for EAS. Ten patients' requests were not carried out. These ten patients eventually all died due to respiratory insufficiency, pneumonia or a myocardial infarct.

In addition, ten patients died during continuous deep sedation, of which one received artificial fluids and nutrition during sedation. In nine patients, continuous deep sedation was provided in conjunction with 'intensified alleviation of symptoms' or 'withholding medical treatment'. Only one of these ten patients requested EAS and eventually died during continuous deep sedation.

The patients explicitly requested their physician for EAS between one and 72 weeks before their death (median 9 weeks).

Symptoms of depression and quality of life

The results show that there were no significant differences in the quality of life and depressive symptoms between patients who explicitly requested for EAS and those who did not explicitly request EAS (Table 3). Almost all patients who scored 11 or higher on the HADS depression subscale reported that they felt less eager when looking forward to joyous events than they had prior to becoming ill (100%) and that they felt (much) less joy about things they used to enjoy (96%). The majority reported that they could rarely appreciate a good book, TV- or radio show (70%). Almost all patients who scored 10 or higher on the HADS anxiety subscale reported they felt (very) frequently anxious (94%) and they panicked suddenly (94%). In total, 17 patients thought of themselves as being depressed.

Table 1: Characteristics of patients with amyotrophic lateral sclerosis (ALS).

	Explicit request for EAS		
Variable median (range)	**No n=70**	**Yes n=32**	**p**
Demographic characteristics			
Sex-%			0.79
Female	37	34	
Male	63	66	
Place of death-%			0.79
Nursing home or hospice	21	16	
Hospital	17	10	
Home	62	74	
Disease characteristics			
Site of onset-%			0.45
Bulbar	36	28	
Spinal	64	72	
Age at onset (years)	61 (33-82)	62 (40-80)	0.66
Survival time (years)	2.8 (0.8-7.4)	2.8 (0.4-6.4)	0.82
Diagnosis -%			
Sporadic ALS	96	100	0.55
Familial ALS	4	0	
Stage of disease			
ALSFRS-r	21 (4-45)	20 (7-36)	0.60
Coping Styles			
Active coping	18 (9-27)	20 (13-27)	0.25
Palliative coping	17 (8-29	17 (11-25)	0.25
Avoiding coping	15 (9-29)	15 (10-23)	0.21
Social coping	13 (6-20)	13 (8-24)	0.31
Passive coping	10 (7-19)	11 (7-16)	0.35
Emotional coping	5 (3-11)	5 (3-9)	0.63
Comforting coping	11 (6-20)	12 (7-19)	0.56

	Explicit request for EAS		
Variable median (range)	**No n=70**	**Yes n=32**	**P**
Symptoms in last 3 months of study-%			
Fatigue	85	77	0.35
Pain	38	39	0.93
Vomiting	7	7	1.0
Immobility	72	71	0.91
Dependency	85	90	0.75
No chance of improvement	64	74	0.32
Fear of choking	41	42	0.93
Feeling a burden on family	51	65	0.21
Suffering without improvement	36	42	0.58
Futile suffering	16	16	0.97
Loss of dignity	52	45	0.61

A higher ALSFRS-r score reflects a healthier stage of disease
EAS= euthanasia or physician-assisted suicide

Table 2: End-of-life practices in 102 patients with amyotrophic lateral sclerosis in the Netherlands [a]

End-of-life practices	n
Unexpected sudden death	11 (11%)
No end-of-life practices	21 (20%)
Total end-of-life practices performed	70 (69%)
Euthanasia	21
Physician-assisted suicide	1
Ending of life without explicit request by patient	0
Intensified alleviation of symptoms	32
Withholding or withdrawing of life-prolonging treatment	16
Patient made explicit request for euthanasia or physician-assisted suicide	32 (31%)
Actual end-of-life practice:	
Euthanasia	21
Physician-assisted suicide	1
No euthanasia or physician-assisted suicide because:	10
-Patient withdrew request and received withholding or withdrawing of life-prolonging treatment	2
-Patient died before euthanasia or physician-assisted suicide could be performed and received intensified alleviation of symptoms	4
-Patient died during decision making process and received	4
Intensified alleviation of symptoms	1
Withholding or withdrawing of life-prolonging treatment	1
No end-of-life practices	2

[a] Unexpected sudden death, no end-of-life practices and total end-of-life practices performed add up to 100%.

Ten of these 17 patients were treated with antidepressants. Seven patients did not receive antidepressants, however two patients had not yet discussed their symptoms with a physician, and two patients were offered treatment, but refused it. Two of the remaining three patients with depressive symptoms who were not treated with antidepressants, consulted a social worker and did not wish to visit a psychologist. One patient did not receive any treatment, but wished to consult a psychologist or social worker. This patient did not explicitly request EAS.

Table 3: Symptoms of depression and quality of life of 102 patients with amyotrophic lateral sclerosis (ALS).

	Explicit request for EAS		p
Variable median (range)	No n=70	Yes n=32	
Symptoms of depression			
HADS; Total score	14 (1-42)	13 (1-28)	0.83
Anxiety score	5 (1-21)	6 (0-14)	0.90
Depression score	8 (1-21)	7 (1-20)	0.65
Anxiety score ≥ 10 %	19	13	0.45
Depression score ≥ 11 %	26	28	0.80
Depressed according to patient %	18	16	0.78
CIDI; Depression %	16	13	0.77
Quality of Life			
ALSAQ-40; Total score	65 (8-98)	65 (29-98)	0.67
Mental score	35 (0-90)	44 (0-93)	0.30
Physical score	76 (10-100)	74 (39-120)	0.79

A higher HADS score reflects more symptoms of depression.
CIDI is positive for depression if the patient was depressed and/or had diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day for a minimum of two consecutive weeks.
A higher ALSAQ-40 score reflects a lower quality of life.
EAS= euthanasia or physician-assisted suicide

Characteristics of care

The care received from the professional caregivers and the available aids and appliances were mostly reported as adequate (Table 4). In the last measurement before the patients' death 84% of all patients thought that the health care in general was good or excellent. Only one patient thought the care of professional caregivers was very bad. This 75 years old married women lived in a nursing home, was not able to walk or speak, had difficulties swallowing and was short of breath, and explicitly requested EAS. She was dissatisfied with the care of the rehabilitation physician, dietician, occupational therapist and social worker. While the physician was still in the decision making process, she died of a myocardial infarction. The patient scored 18 on the HADS depression subscale and nine on the HADS anxiety subscale, she did not receive antidepressants nor did she visit a psychologist, but she indicated that she did not want to do so. She also did

not want artificial fluids and nutrients to compensate for her swallowing difficulties.
Three other patients thought that the aids and appliances were very bad. They were mainly dissatisfied about the appliances for their mobility problem e.g. their wheelchairs. They reported that they received their wheelchairs too late and that the wheelchairs were not adequate. Two of these three patients scored 11 or higher on the HADS depression subscale and one patient scored ten or higher on the HADS anxiety subscale but none of these patients requested EAS.
As can be seen in the received care professional caregivers section in table 4 over 71% of the patients was satisfied with the frequency of the consultations of all professional caregivers. In the last three months of the study, patients desired relatively most frequently more consultations from the primary care physician (10%), the rehabilitation physician (10%) and assistance at home with personal care (11%). Patients who explicitly requested their physician for EAS more frequently consulted an occupational therapist.

Table 4: Characteristics of care of 102 patients with amyotrophic lateral sclerosis during last 3 months of study.

	Explicit request for EAS		p
Care during last 3 months of study median (range)	**No n=70**	**Yes n=32**	
Was care in general adequate?			
Professional caregivers	2 (1-4)	2 (1-5)	0.52
Aids and appliances	2 (1-5)	2 (1-4)	0.63
Palliative outcome scale			
Pain	0 (0-4)	1 (0-3)	0.16
Other symptoms, like coughing or constipation	0 (0-4)	1 (0-3)	0.67
Anxiety of patient	1 (0-4)	2 (0-4)	0.13
Anxiety of family or friends	2 (2-4)	2 (2-4)	0.51
Received information	0 (0-4)	0 (0-4)	0.71
Able to share feelings	0 (0-4)	0 (0-4)	0.35
Life considered as worthwhile	1 (0-4)	1 (0-4)	0.69
Positive feeling about oneself	1 (0-4)	1 (0-4)	0.94
Wasted time due to care appointments	0 (0-2)	0 (0-2)	0.70
Personal affairs taken care of	2 (0-4)	0 (0-4)	0.16
Received aids and appliances %			
Artificial nutrition and/or hydration (PEG/RIG)	36	44	0.44
Non-invasive respiration	43	53	0.33
Aids and appliances for communication were[a]:			
Provided on time	72	94	0.14
Adequate	78	100	0.04
Aids and appliances for eating and drinking were[a]:			
Provided on time	88	94	0.66
Adequate	79	84	0.74
Aids and appliances for mobility were[a]:			
Provided on time	80	94	0.13
Adequate	66	68	0.83
Received care professional caregivers %			
Frequency of all consultations by professional caregivers was adequate	71	78	0.48
Primary care physician			
Consulted a primary care physician	97	97	1.00
Consultation more frequently desired	10	9	0.92
Rehabilitation physician			
Consulted a rehabilitation physician	81	84	0.74
Consultation more frequently desired	10	3	0.43

Care during last 3 months of study median (range)	Explicit request for EAS		p
	No n=70	Yes n=32	
Neurologist			
Consulted a neurologist	60	63	0.81
Consultation more frequently desired	6	6	1.00
Physiotherapist			
Consulted a physiotherapist	79	86	0.33
Consultation more frequently desired	4	0	0.55
Occupational therapist			
Consulted a occupational therapist	66	88	0.03
Consultation more frequently desired	3	0	1.00
Dietician			
Consulted a dietician	54	55	0.96
Consultation more frequently desired	3	3	1.00
Speech therapist			
Consulted a speech therapist	54	58	0.60
Consultation more frequently desired	3	0	1.00
Physician of the centre of artificial respiration at home (CARH)			
Consulted a physician of the CARH	52	58	0.60
Consultation more frequently desired	1	0	1.00
Assistance at home with personal care			
Received assistance at home	59	61	0.84
Consultation more frequently desired	11	6	0.50
Assistance at home with housekeeping			
Received assistance at home	36	36	0.93
Consultation more frequently desired	7	0	3.22
Social worker			
Consulted a social worker	46	66	0.06
Consultation more frequently desired	1	0	1.00
Psychologist			
Consulted a psychologist	11	3	0.43
Consultation more frequently desired	7	3	0.66

"Was care in general adequate" ranges from 1= very good to 5= very bad.
POS ranges 0=best situation to 4=worst situation.
[a] Only when used aids or appliances
EAS= euthanasia or physician-assisted suicide

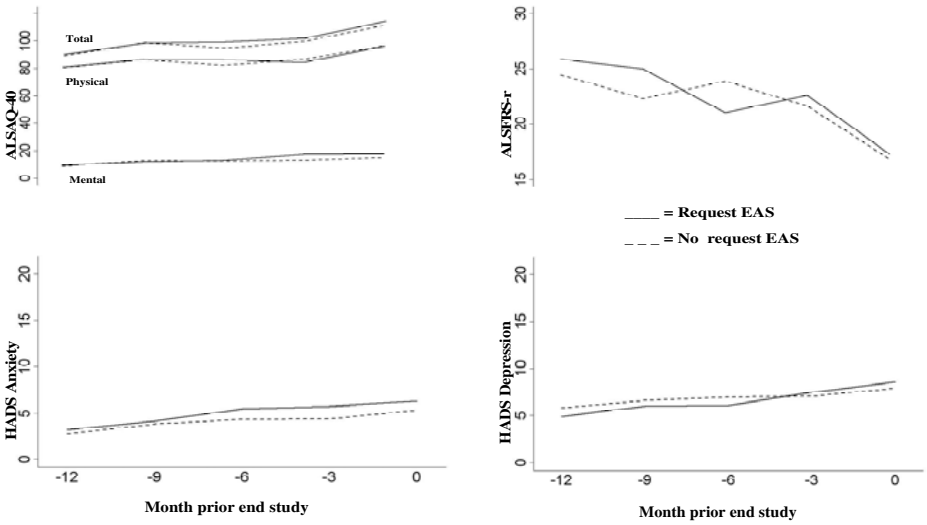
Changes over time

The graphs in figure 1 show the quality of life (ALSAQ-40), stage of disease (ALSFRS-r), symptoms of depression and anxiety (HADS) of the patients during the last year before the end of the study. The overall decrease in the stage of the disease scores was -0.81 ALSFRS-r points per month, which was a statistically significant change ($p<0.001$). The increase in the physical quality of life scores was 1.86 ALSAQ-40 points per month and was also a statistically significantly change ($p<0.001$). This illustrate that the physical abilities of all patients decreased towards the end of life. The mental ALSAQ-40 quality of life scores increased 0.20 ALSAQ-40 points per month and showed no statistically significantly change ($p=0.12$). The HADS depression scores increased 0.11 points per month, and showed no statistically significantly change ($p=0.12$). The HADS anxiety scores increased 0.75 points per month, and showed no statistically significantly change ($p=0.05$). Also, if we concentrate on the last measurement before death, the physical scores were statistically significant ($p\leq0.001$) as the mental scores were not statistically significant ($p\geq0.09$). None of the scores above were significantly different between the patients who explicitly requested EAS and those who did not (all $p\leq 0.14$).

Performing EAS

The reported associations in table 3 and 4 were also calculated between the 21 patients who actually died due to EAS and those who died without EAS (not shown). We could not find a statistically significant difference between these two groups in any of the symptoms of depression, quality of life and care items.

Figure 1: Mean mental, physical and total quality of life, anxiety, symptoms of depression and stage of disease of patients with amyotrophic lateral sclerosis in last 12 month prior end study.



Higher HADS score stands for more symptoms of depression.
Higher ALSAQ-40 score stands for lower quality of life.
Higher ALSFRS-r score stands for healthier stage of disease.

5.4 DISCUSSION

In this prospective cohort study in 102 patients with ALS, we could not find differences in the patients characteristics, characteristics of care, symptoms of depression and quality of life between ALS patients who explicitly requested EAS and those who did not, which indicates that the relative high proportion of EAS in ALS in the Netherlands is probably not related to these characteristics.

Approximately one of every three patients with ALS explicitly requested their physician for EAS and one of every five patients actually died due to EAS. These results are consistent with a previous retrospective study on EAS in ALS in the Netherlands performed between 1994 and 1999[5] and therefore suggest a stable proportion of EAS in this population even though ALS care in general has been improved in this period.[20;21]

Patients who explicitly requested their physician for EAS were mostly consistent in their wish to hasten death. Only two patients withdrew their request. Patients may have discussed EAS with their physician and then changed their mind about EAS before explicitly requesting it. However, it is important for physicians to know that when patients explicitly request EAS, they mostly stick with this decision.

The findings of this study do not support that continuous deep sedation is used as a substitute for EAS in ALS. Only one of ten patients who died during continuous deep sedation had explicitly requested her physician for EAS. According to this physician the sedation was performed without appreciating the possible hastening of death. The last national study on end-of-life practices in the Netherlands showed that the general EAS proportion decreased and that continuous deep sedation increased suggesting that continuous deep sedation may be used as a substitution for EAS.[2] Some physicians may prefer continuous deep sedation over EAS, as in sedation it is not necessary to fulfill all the requirements of due care and it may be more acceptable according to their own ethics or religion. Nevertheless, our study could not confirm this change in practice.

The findings in this study do not support the idea that patients who request EAS received less care.[6] Patients who explicitly requested EAS received the same care and were just as satisfied with the care as patients who did not explicitly requested EAS. Nevertheless, our study shows that shortcomings exist in the care for patients with ALS. In this study, 84% of all patients thought that the health care in general was good, and over 71% of the patients was satisfied with the frequency of the consultations of all professional caregivers. Literature on the satisfaction with the quality of the received palliative care in patients with ALS with a wish to die is rare. A study in Oregon showed that 20% of the caregivers of patients with ALS were dissatisfied with the patient's dyspnoea management, 16% with the information on symptom management and 18% with the pain relief efforts of the medical team.[22] The North American ALS CARE project reported that 89% of the patients with ALS were satisfied with their medical care.[23] Except for psychological/psychiatric counseling, the reported received nonpharmacological care in the ALS CARE database is lower compared to the received care in our study. This difference may be the result of more severe stages of disease in our study or differences in study design. As data collection in the ALS CARE study is based on voluntary surveys, 63% was

lost to follow-up after 24-months. Patients who were lost in follow-up, may have had more need for nonpharmacological care. Apparently, shortcomings exist in the care for patients with ALS both in the Netherlands and abroad, but according to this study these shortcomings are unrelated to a request for, EAS or performing EAS.

At the end of life, patients who request EAS did not differ in occurrence of depressive symptoms with patients who did not request EAS. This is in agreement with two other studies, one in Oregon (USA) showing that 17% of the ALS and cancer patients who received a lethal prescription for physician-assisted suicide had a depression. However they did not find a statistically significant differences on the HADS depression score for patients who received and did not receive a prescription for lethal drug.[14] The second study showed that patients with ALS who expressed the wish to die were more likely to meet criteria for depressive disorders but only because of their more frequent reports that they "would be better off dead". The authors conclude that these findings suggest caution in concluding that the desire to hasten dying is simply a feature of depression, but instead is part of a broader syndrome of end-of-life despair.[24] This includes an existential suffering with loss of autonomy and control as crucial elements.[25]

We expected that personal traits could be related to the wish to hasten death. To test this hypothesis, we determined the patients' coping styles, as this is a trait that can be specific for patients but may be possible to influence. However, the coping style was not different between patients who explicitly requested EAS and patients who did not. Patients demonstrated similar coping mechanisms as healthy Dutch persons of the same age group.[11]

A limitation of our study is that we did not use a psychiatrist or psychologist or a complete official standardized clinical measure to determine a possible clinical depression. However, in end-stage patients with ALS, symptoms of a depression according to the DSM-IV may overlap with symptoms of ALS (i.e. weight loss, sleeping problems, fatigue, thoughts of death), which may result in an over estimation of depression. Therefore, we chose to use a short version of the CIDI and the HADS which does not include questions on somatic symptoms and was also used in previous studies.[24;26] Another limitation is that, although we follow-up a relative large number of ALS patients during the terminal phase of the disease, the 32 patients who explicitly requested EAS and the 22 patients who died due to EAS, still limit

the statistical power of the study. However, the results on received care, symptoms of depression and quality of life of patient who explicitly requested EAS and those who did not, do not show any suggestion of association. Strengths of this study are the longitudinal design, the high response rates, the decreased chance of social desirable answers due to the open culture towards EAS in the Netherlands, and the availability of information on actual performed EAS and not only a wish to hasten death.
In conclusion, we could not find that patients who request EAS are likely to do so as a result of the characteristics of their care or symptoms of a depression. Possible, more personal, psychosocial or existential traits should be studied prospectively for more insight in the reasons for patients requesting EAS. Although statistical analyses do not show a relation between the received care as provided in the Netherlands and the wish for EAS, lack of care still might influence the patients' wish to hasten death. Professional caregivers of patients with ALS should be aware that their patients may suffer from depressive symptoms or a depression, even thought they do not request or even turned down mental support or treatment.

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CHAPTER 6
BURDEN OF CARE ON INFORMAL CAREGIVERS

Picture: Hospital ward of the Roman Catholic orphan and elderly institution at the Maliesingel 67 (later change into 77) in ± 1900.
Based on Maessen M, Veldink JH, Onwuteaka-Philipsen BD, Hendricks HT, Schelhaas HJ, Grupstra HF, ten Klooster L, van der Wal G, van den Berg LH. Quality of life and burden of care on caregivers of ALS patients, submitted.

6.0 ABSTRACT

BACKGROUND Caring for loved-ones with the disabling disease amyotrophic lateral sclerosis (ALS) can be demanding and time consuming. More insight into the determinants of the burden of care on informal caregivers, may improve the quality of life of caregivers and patients.

METHODS We performed a prospective observational study on the physical and emotional circumstances of 75 patients with advanced ALS and their informal caregivers. Structured questionnaires were filled out six months before (patients and caregivers) and after the death of the patient (caregivers).

RESULTS Fifty-nine percent of informal caregivers felt completely overwhelmed by the care they gave. Informal caregivers who experienced a higher burden of care had a lower mental quality of life and coped more frequently with palliative and emotional coping styles. Burden of care was also related to the coping style after the death of the patient. Patients whose informal caregivers experienced a higher burden of care more frequently felt they were a burden on their family, were more frequently anxious, had a lower mental quality of life, and used more emotional and comforting coping styles.

CONCLUSION The majority of informal caregivers of patients with advanced ALS have a high burden of care. The burden is especially related to the mental situation and coping styles of the patient and the informal caregiver. It is unclear, whether coping styles of informal caregivers lead to a lower mental quality of life of patients, or *vice versa*, but more professional attention for coping style in the care for ALS patients may help caregivers and patients to optimize their coping style.

6.1 INTRODUCTION

Caring for loved-ones with the disabling disease amyotrophic lateral sclerosis (ALS) can be demanding and time consuming.[1] ALS patients have a median age of disease onset around sixty years.[2] When this incurable neuromuscular disease gets worse and the patient experiences progressive weakness, assistance with daily activities of the patient is necessary. If possible, patients prefer to stay at home and in the Netherlands actually 73% die at home.[3] Both, professional and informal caregivers are involved in the care for the patient.

An informal caregiver is a person who is not paid and provides physical, emotional, financial, or other support to a patient. When an informal caregiver perceives difficulty performing roles or feels overwhelmed by his or her task, the burden of the care may be too high. Caregivers' burden in ALS and other diseases was found to be associated with the physical and mental health of the caregiver and the patient.[4-7] Terminally ill patients have reported that they find it important that they are not a burden on their family and friends.[8] In general, the time needed to take care of ALS patients is related to their overall disability. Mean time of care giving can range from five hours a day for ALS patients with mild disability (revised ALS Functional Rating Scale (ALSFRS-r) >30) to 15 hours for those with severe disability (ALSFRS-r score ≤10).[9] However, the objective care giving burden may differ from the burden of care as experienced by informal caregivers (subjective burden). Several factors can influence the way an informal caregiver experiences the burden of care giving. Another study with ALS patient-caregiver couples showed that the perceived caregiver burden was positively associated with finding positive meaning in care giving, suggesting that the latter is an adaptive coping strategy.[10] An other study reported that informal caregivers of ALS patients were mostly affected by time restrictions due to their caring duty, compared to other categories of the caregivers burden i.e. physical, social and emotional burden.[11]

More information on the burden of care on informal caregivers and the factors influencing this may improve the quality of life of informal caregivers and patients. Therefore we performed a study to answer the following research questions: 1) how high is the experienced burden of care and the quality of life of informal caregivers of patients with advanced ALS,

2) is the experienced burden of care on informal caregivers related to physical or mental characteristics of the ALS patient and the informal caregiver, 3) what is the quality of life, complicated grief symptoms and symptoms of depression of the informal caregivers after the death of the patient and 4) are these item after the death of the patients related to burden of care before the death of the patient?

6.2 METHODS

Study design and population

We included couples of patients and informal caregivers. Patients had probable or definite ALS according to the El Escorial criteria and no severe cognitive disorder measured on the Mini Mental State Examination (MMSE)[12]: they understood the Dutch language, could communicate at least "yes" and "no", were not dependent on tracheotomy with mechanical ventilation and had a estimated life expectancy of less than 6 months.[13] An neurologist specialized in ALS estimated the life expectancy which was based on clinical knowledge and a forced vital capacity of less than 60%.[14] The majority of the patients lived at home. The informal caregiver is a closely related person who was most involved in the care of the patient on a voluntarily basis. The informal caregiver was mutually selected by the patient and the researcher.

Patients and informal caregivers filled out questionnaires at enrollment in the study. This was in the hospital or later at home. The questionnaires for the patient and the informal caregiver were self administered in all cases but two (ALSFRS-r, MMSE). Patients who were not able to fill out the questionnaires were helped by a trained interviewer. All patients died between October 2003 and March 2008. Approximately six months after the death of the patients the informal caregiver filled out a follow-up questionnaire.

One hundred and ninety-two patients were selected through three national referral centers for motor neuron disease in the Netherlands. One hundred and thirty-six (71%) patients agreed to participate in the study. However, the informal caregiver of 27 patients did not want to participate, resulting in 109 (80%) patient-informal caregiver couples. Another 14 patients did not die during the study period and 20 patient-informal caregiver couples stopped participation in the study and therefore could not be part of the

analyses of this study. Eventually, 75 patient-informal caregivers couples were available for the analyses before the death of the patient. After the death of the patient another 14 informal caregiver stopped participation in the study. As a result, 61 informal caregivers filled out the questionnaire six months after the death of the patient.

Measures

The informal caregiver filled out the MOS Short-Form 36 (SF-36), the Utrecht Coping List (UCL), the Caregiver Strain Index (CSI), Hospital Anxiety and Depression Scale (HADS) and demographical questions. After the death of the patient the caregiver filled out the SF-36, the UCL, the Inventory of traumatic grief (ITG) and the HADS. The patient completed the UCL, the HADS, a Likert scales on feeling a burden on others, revised ALS Functional Rating Scale (ALSFRS-r), ALS assessment questionnaire (ALSAQ-40), MMSE and demographical questions.

The UCL examines how the patient copes with problems and unpleasant events.[15] The UCL describes possible reactions to problematic or unpleasant events. Patients can indicate whether they would generally demonstrate this reaction when confronted with these events (scale 1 to 4; 1 = rarely or never, 4 = very often). The 47 items of the UCL are grouped into seven subscales: active coping (i.e., sort out the situation and working to solve the problem); palliative coping (i.e., seeking distraction to avoid thinking about the problem); avoidance coping (i.e., leaving the problem as it is and not trying to solve it); social coping (i.e., seeking comfort and understanding from others); passive coping (i.e., being totally overwhelmed by the problem, feeling unable to solve the problem); emotional coping (i.e., expressing anger about the problem or vent one's irritation on someone/something); and comforting coping (i.e., using comforting thoughts, like 'after rain comes sunshine').[15]

The SF-36 examines quality of life and is divided into nine domains. Domain scores are calculated from a selection of the 36 item responses. Two total summary scores can be calculated representing physical (PCS) and mental (MCS) quality of life. A higher domain score or summary score reflects a better quality of life and the score ranges from 0 to 100.[16]

The experienced burden on the informal caregiver for caring for the patient was measured with the CSI. The CSI is comprised of 13 questions which can be responded to with yes (1 point) or no (0 point).[17] Previous

researchers have used the cut-off of 7 points or more to indicate a considerable or high burden of care or strain on the informal caregiver.[18-21]
The HADS is a 14 item questionnaire that can screen for anxiety disorders and symptoms of depression among patients in non-psychiatric hospital clinics.[22] It consists of two domains i.e. symptoms of depression and anxiety. The maximum score for both domains is 21, with a higher score meaning more (severe) symptoms of depression and anxiety. We considered a symptom of depression score of 11 or higher as an indication of possible depression and an anxiety score of 10 or higher as an indication of anxiety. [23]

The ALSFRS-r is a 12 item scale on physical functioning of ALS patient. Items address speech, eating, dressing, walking, breathing, etc. Different physical functions can be rated from 0 (unable to attempt task) to 4 (normal function). Higher summary scores reflect a better health related state.
Quality of life was measured with the 40 item ALSAQ-40 on a five-point scale. This questionnaire measures five areas of health status: Eating and Drinking, Communication, independence, Physical mobility, Emotional Functioning.[24] We combined the first four subscales into the physical subscale and emotional functioning is the mental subscale. Each subscale is assessed using a summary score ranging from 0 to 100, with 0 representing the best possible lower quality of life and 100 representing the worst possible quality of life.
The ITG is a self-administered 29 item questionnaire measuring maladaptive symptoms of grief. It provides a summery score, with a higher score indicating a greater risk for traumatic or complicated grief and with a cut-off score of >90. [25]

Data analysis
Chi-square test determined the significant difference in distribution between informal caregivers who had a CSI score equal to or higher than seven and lower than seven. Fisher's exact test was used when cells had an expected frequency of less than five. The Mann-Whitney U test was used to analyze unpaired continuous factors. All tests were two-tailed ($p < 0.05$) and couples with missing data were not included in the analyses.

6.3 RESULTS

Study population
The median time between the baseline questionnaires and the death of patient was 0.7 years. The median time between the death of the patient and the follow-up questionnaires of the informal caregiver was 0.6 years. Sixty percent of the patients were male and the median age at onset of the disease was 60 years (range 40-82). Sex, site and age at onset of the disease were similar to the average Dutch ALS population.[26] Patients who could not be included in the analysis did not significantly differ from the patients enrolled in the study with respect to these baseline characteristics.
Of the informal caregivers 31% were male and the median age was 60 years (range 31-80). The majority were married to the patient (77%) and lived in the same house as the patient (81%). Thirty percent of the informal caregivers had a paid job.

Burden of care
The median CSI score was 8.0, the mean 7.4 and the score ranged from 1 to 13. Fifty-five percent of the informal caregivers answered seven or more of the 13 CSI items on burden positively.
Table 1 shows the individual CSI questions. It demonstrates that the large majority of the caregivers had to make adjustments in the family because of disrupted routines (90%) and had to change personal plans (86%). Fifty-nine percent of the informal caregivers felt completely overwhelmed by the care they had to give and 43% had to make work adjustments. One third of the caregivers experienced the care giving as a physical strain.

Table 1: Burden of care on informal caregivers of amyotrophic lateral sclerosis (ALS) patients.

Burden of care Caregiver strain index %	n=75[a]
I have made adjustments in the family because of disrupted routines.	90.4
I have made changes in personal plans.	86.3
I have had other demands on my time.	76.7
It is upsetting to find the person I cared for has changed so much from his/her former self.	72.6
Caregiving is confining.	68.3
Caregiving takes much time and efforts	60.3
I feel completely overwhelmed.	58.9
Some of the patient's behavior is upsetting to me.	56.2
My sleep is disturbed.	43.8
I have hade to make emotional adjustments.	42.5
I have had to make work adjustments	42.5
Caregiving is a physical strain	32.9
Caregiving is a financial strain	9.6

[a] Two missing observations

Patient and caregiver characteristics in relation to burden of care

Characteristics of the patient Table 2 shows that the age and sex of the patient were not related to the burden of care. Patients of informal caregivers who reported a high burden (CSI≥7), more frequently reported that they felt a burden on their family (p=0.03) and that their medical condition caused stress for their family (p=0.003). Of the 40 informal caregivers who reported a high burden of care, 11 patients also often felt they were a burden on their family. The survival time (time between onset of the first ALS symptoms and the questionnaire of the patient) was similar for patients who had informal caregivers with a CSI≥7 (1.7 yr) and a CSI<7 (1.9 yr) (p=0.91). We could not find a significant difference in stage of disease, since the total and individual items of the ALSFRS-r, the survival time, the site of onset and the age at onset were similar between informal caregivers with a CSI≥7 and a CSI<7 (Table 2). Patients of informal caregivers with a CSI≥7 reported significantly more frequently emotional and comforting copings styles, anxiety, but not symptoms of depression. They also had a statistically significant lower mental quality of life (Table 2). Seventy percent of all patients thought that the aids and appliances were good and 82% thought that the care of the professional caregivers was good. Only one patient desired more professional assistance with personal

care and one patient desired more assistance with housekeeping. These factors were not related to burden of care. Also financial problems were not related to the burden of care (p=0.55).

Characteristics of the informal caregiver The age and sex of the informal caregiver were not related to the burden of care. Informal caregivers with a CSI≥7 significantly more frequently reported palliative and emotional coping styles and a lower quality of life on the SF-36. The mental summary scale (MCS) before the death of the patient was lower (mean 45.8) than the physical summary scale (PCS) (mean 49.6). Seventy percent of the informal caregivers with a CSI ≥7 and 68% of the informal caregivers with a CSI<7 thought that the professional care was sufficient (not shown).

Table 2: The burden of care on informal caregivers and characteristic of the amyotrophic lateral sclerosis (ALS) patient and informal caregiver

Variables n (%)	CSI < 7 n=33	CSI ≥7 n=40	p
Characteristics patient			
Education			0.39
< 6 yr	6 (18.2)	3 (7.5)	
6-12 yr	17 (51.5)	22 (55.0)	
>12 yr	10 (30.3)	15 (37.5)	
Sex			
Female	14 (42.4)	15 (37.5)	0.67
Male	19 (57.6)	25 (62.5)	
Site of onset			0.38
Spinal	19 (57.6)	27 (67.5)	
Bulbar	14 (42.4)	13 (32.5)	
Age at onset (years)			
Median (range)	63.7 (45.6-80.6)	59.5 (40.0-82.9)	0.18
Stage of disease			
ALSFRS-r median (range)	29 (12-41)	26 (12-37)	0.18
Dressing and personal hygiene			0.26
Normal	9 (27.3)	5 (13.2)	
Need some assistance	4 (12.1)	7 (18.4)	
Needs a lot of assistance	7 (21.2)	14 (36.8)	
Totally dependent on others	13 (39.4)	12 (31.6)	

Variables n (%)	CSI < 7 n=33	CSI ≥7 n=40	p
Leg function			0.78
Walk unsupported	13 (39.4)	11 (28.9)	
Walk supported	9 (27.3)	12 (31.6)	
Unable to walk	5 (15.2)	5 (13.2)	
Can not move legs	6 (18.2)	10 (26.3)	
Able to speak	20(60.6)	24 (63.2)	0.83
Patient feels a burden on family?			0.03
Never	19 (57.6)	14 (35.0)	
Sometimes	12 (36.4)	15 (37.5)	
Often	2 (6.1)	11 (27.5)	
Coping Styles			
Active coping	18 (9-27)	18 (10-27)	0.66
Palliative coping	17 (9-26)	18 (10-29)	0.05
Avoiding coping	15 (9-21)	15 (10-23)	0.41
Social coping	13 (8-20)	13 (6-22)	0.14
Passive coping	10 (7-16)	12 (7-19)	0.08
Emotional coping	4 (3-11)	6 (3-10)	<0.01
Comforting coping	10 (7-20)	12.5 (7-19)	<0.01
Symptoms of depression			
HADS			
Total score median (range)	11 (2-27)	14 (2-29)	0.15
Anxiety score ≥ 10	2 (6.1)	12 (30.0)	0.01
Depression score ≥ 11	5 (15.2)	8 (20.5)	0.56
Quality of Life median (range)			
ALSAQ-40; Total score	49 (19-87)	61(21-93)	0.04
Mental score	30 (0-63)	43 (5-95)	0.03
Physical score	53 (28-100)	65 (27-98)	0.25
Was care in general adequate?			
Professional caregivers			0.68
Bad	2 (6.5)	1 (2.5)	
Neutral	3 (9.7)	5 (12.5)	
Good	26 (83.9)	34 (85.0)	

Variables n (%)	CSI < 7 n=33	CSI ≥7 n=40	p
Aids and appliances			0.57
Bad	1(3.4)	4 (10.0)	
Neutral	6(20.7)	7(17.5)	
Good	22(75.9)	29(72.5)	
Received care professional caregivers			
Frequency of all consultations by professional caregivers was adequate			0.61
Yes	23 (69.7)	30 (75.0)	
No	10 (30.3)	10 (25.0)	
Received assistance at home with personal care			0.26
Yes	11 (63.3)	20 (50.0)	
No	19 (36.7)	20 (50.0)	
Assistance with personal care more frequently desired	1 (3.0)	1 (2.5)	0.89
Received assistance at home with housekeeping			0.21
Yes	9 (30.0)	17 (44.7)	
No	21 (70.0)	21 (55.3)	
Assistance with housekeeping more frequently desired	0 (0.0)	1 (2.5)	0.36
Characteristic informal caregiver			
Education			0.89
< 6 yr	5 (15.2)	7 (17.5)	
6-12 yr	20 (60.6)	22 (55.0)	
>12 yr	8 (24.)	11 (27.5)	
Sex			0.59
Female	22 (66.7)	29 (72.5)	
Male	11 (33.3)	11 (27.5)	

Variables n (%)	CSI < 7 n=33	CSI ≥7 n=40	p
Age median (range)	61 (34-80)	59 (31-76)	0.50
Relation with patient			0.23
Married or partners	22 (66.7)	34 (85.0)	
Father	0 (0.0)	1 (2.5)	
Mother	0 (0.0)	0 (0.0)	
Daughter	4 (12.1)	3 (7.5)	
Son	1 (3.0)	1 (2.5)	
Friend	2 (6.1)	0 (0.0)	
Other	4 (12.1)	1(2.5)	
Relation with patient			0.07
Married or partners	22 (66.7)	34 (85.0)	
Other	11 (33.3)	6 (15.0)	
Lived together with patient			0.32
Yes	25 (75.8)	34 (85.0)	
No	8 (24.2)	6 (15.0)	
Employed			0.97
Yes	10 (30.3)	12 (30.0)	
No	23 (69.7)	28 (70.0)	
Quality of life median (range)			
SF-36			
General health (GH)	72.0 (45-100)	67.0 (20-97)	0.61
Health change (change)	50.0 (0-100)	50.0 (25-100)	0.14
Physical functioning (PF)	90.0 (5-100)	85.0 (30-100)	0.37
Role-physical (RP)	100.0 (0-100)	75.0 (0-100)	0.03
Role- emotional (RE)	100.0 (0-100)	66.7 (0-100)	0.01
Social functioning (SF)	93.7 (50-100)	62.5 (13-100)	<0.001
Bodily pain (BP)	100.0 (31-100)	74.0 (12-100)	0.03
Vitality (VT)	65.0 (30-100)	55.0 (5-95)	0.04
Mental health (MH)	68.0 (32-100)	64.0 (4-100)	0.28
Physical Summary Scale (PCS)	55.1 (18-63)	49.2 (23-61)	0.05
Mental Summary Scale (MCS)	51.3 (28-63)	43.9 (18-65)	<0.01

Variables n (%)	CSI < 7 n=33	CSI ≥7 n=40	p
Coping median (range)			
Active coping	18 (11-26)	20 (11-28)	0.09
Palliative coping	15 (9-21)	17 (10-25)	0.02
Avoiding coping	13 (8-21)	14 (9-23)	0.73
Social coping	13 (6-20)	14 (7-24)	0.72
Passive coping	10 (7-15)	11 (7-16)	0.08
Emotional coping	4 (3-7)	5 (3-8)	0.02
Comforting coping	11 (5-17)	11 (6-16)	0.37
Symptoms of depression			
HADS			
Total score median (range)	16.5 (0-26)	18.0 (4-37)	0.36
Depression score ≥ 11	7 (21.9)	16 (41)	0.09
Anxiety score ≥ 10	11 (34.4)	20 (51.3)	0.15

A CSI ≥7 score represents a high burden of care on the informal caregiver
Higher SF-36 score represents a higher quality of life
Higher HADS score represents more symptoms of depression
Higher ALSFRS-r score represents a better physical functioning
Higher ALSAQ-40 score represents a lower quality of life

Complicated grief, symptoms of depression and quality of life

Approximately six months after the death of the patient the total median mental summary (47.0) score and the physical summary score (54.4) of the SF-36 were similar to the scores before the death of the patient (46.5 and 51.7, Table 3). The proportion of caregivers with anxiety and symptoms of depression was significantly lower after the death of the patient. Nevertheless 20% of the informal caregivers had a high score on symptoms of depression (HADS depression ≥11) and 18% had a high anxiety score (HADS anxiety ≥10) after the death of the patient (Table 3). The median score on complicated grief was low (66).

Table 3: Quality of life and symptoms of depression of informal caregiver before and after the death of the patient

Variables n (%)	Before death of patient n=75	After death of patient n=61	p
Quality of life median (range)			
SF-36			
General health (GH)	67.0 (20-100)	69.5 (10-97)	0.77
Health change (change)	50.0 (0-100)	50.0 (0-100)	0.08
Physical functioning (PF)	88.9 (5-100)	90.0 (5-100)	0.31
Role-physical (RP)	75.0 (0-100)	100.0 (0-100)	0.72
Role- emotional (RE)	100.0 (0-100)	100.0 (0-100)	0.66
Social functioning (SF)	75.0 (13-100)	75.0 (12-100)	0.71
Bodily pain (BP)	84.0 (12-100)	84.0 (41-100)	0.99
Vitality (VT)	60.0 (5-100)	60.0 (0-100)	0.54
Mental health (MH)	68.0 (4-100)	72.0 (12 -100)	0.60
Physical Summary Scale (PCS)	51.7 (18 -63)	54.4 (29-63)	0.64
Mental Summary Scale (MCS)	46.5 (18-65)	47.0 (15-62)	0.56
Symptoms of depression			
HADS			
Total score median (range)	18.0 (0-37)	12.0 (0-42)	<0.001
Depression score ≥ 11	23 (30.2)	12 (19.7)	0.03
Anxiety score ≥ 10	33 (44.0)	11 (18.0)	<0.01
Grief (ITG) median (range)	N.A.	66 (30-110)	NA

Higher SF-36 score represents a higher quality of life
Higher ITG score represents a higher risk on traumatic grief
NA = Not available; Grief is not measured before the death of the patient

Burden of care in relation to grief, depression and quality of life after the patients' death
Table 4 shows that the informal caregiver who experienced a high burden of care (CSI ≥7) reported significantly more active and emotional coping styles after the patient's death. There were no significant differences in complicated grief, symptoms of depression and anxiety and quality of life between informal caregivers with CSI<7 and with CSI≥7.

Table 4: Quality of life, complicated grief, depression of informal caregivers after the death of the patient in relation to burden of care

Variables n (%)	**CSI < 7 n=27**	**CSI ≥7 n=33**	**p**
Grief (ITG) median (range)	65.0 (33-108)	68.0 (30-110)	0.73
ITG >90	2 (8.3)	4 (12.9)	0.69
Symptoms of depression			
HADS			
Total score median (range)	12.0 (0-42)	13 (0-34)	0.79
Depression score ≥ 11-%	6 (22.2)	6 (18.2)	0.70
Anxiety score ≥ 10-%	4 (14.8)	7 (21.2)	0.52
Quality of life			
SF-36 median (range)			
General health (GH)	67.0 (10-97)	72.0 (20-97)	0.65
Health change (change)	50.0 (0-100)	50.0(0-75)	0.06
Physical functioning (PF)	90.0 (5-100)	95.0 (45-100)	0.19
Role-physical (RP)	87.5 (0-100)	100.0 (0-100)	0.99
Role- emotional (RE)	100.0 (0-100)	100.0 (0-100)	0.36
Social functioning (SF)	87.5 (37.5-100)	75.0 (13-100)	0.14
Bodily pain (BP)	77.0 (41-100)	84.0 (41-100)	0.67
Vitality (VT)	60.0 (0-100)	60.0 (20-100)	0.69
Mental health (MH)	72.0 (12-100)	72.0 (28-100)	0.78
Physical Summary Scale (PCS)	52.7 (29-61)	52.5 (35-63)	0.60
Mental Summary Scale (MCS)	48.6 (15-62)	43.6 (30-62)	0.33
Coping median (range)			
Active coping	18 (11-24)	19 (13-27)	0.02
Palliative coping	15 (9-21)	17 (10-25)	0.76
Avoiding coping	16 (9-24)	15 (8-22)	0.70
Social coping	13 (8-19)	13 (7-23)	0.74
Passive coping	11 (7-21)	11 (7-18)	0.64
Emotional coping	4 (3-7)	6 (3-11)	0.01
Comforting coping	12 (6-18)	12 (7-18)	0.37

Higher SF-36 score represents a higher quality of life
Higher CSI score represents a higher burden of care
Higher HADS score represents a more symptoms of depression
Higher ITG score represents a higher risk on traumatic grief

6.4 DISCUSSION

Fifty-nine percent of informal caregivers felt completely overwhelmed by the care they gave. The data show that patients whose informal caregivers reported a higher burden of care more frequent experienced anxiety, a lower mental quality of life, and used more emotional (i.e., expressing anger about the problem or vent one's irritation on someone/something) and comforting (i.e., using comforting thoughts, like 'after rain comes sunshine') coping styles. In addition, informal caregivers who experienced a higher burden of care had a lower quality of life and coped more frequently with palliative (i.e., seeking distraction to avoid thinking about the problem) and emotional (i.e., expressing anger about the problem or vent one's irritation on someone/something) coping styles before the death of the patient. However, after the death of the patient the relation between burden of care and quality of life disappeared and coping styles were more often active (i.e., sort out the situation and working to solve the problem) and emotional (i.e., expressing anger about the problem or vent one's irritation on someone/something) for caregivers who had experienced a higher burden of care.

In our study, 40 out of 73 caregivers had a CSI≥7 (total mean 7.4), which indicates that they felt a considerable caregivers burden and merit attention from health- and social-care professionals. To put this in perspective, a study on informal caregivers of patients recovering from a stroke that happened six months ago reported a mean CSI score of 4.5. These caregivers spent an average of 16 hours a day with the patient of which they used six hours to help the patient.[27] A study on informal caregivers of patients with chronic obstructive pulmonary disease, who were waiting approximately one year for a long transplantation, reported a mean CSI of 7.[28]

The patients who felt they were a burden on their family and the informal caregivers who experienced a high burden of care were not always the same. This difference may be the result of patients who may think that their care was a strain for family, but did not see themselves as a burden on their family. On the other hand some patients might have felt more as a burden on their family, than they really were. These results are in agreement with a previous study with end-stage ALS patients showing that patients rated the

informal caregiver's burden significantly higher than the caregivers themselves. In the same study, it was reported that patients' perception of caregiver burden was related to patients' understanding of how demanding their care is, and also to what they see in the caregivers' reaction to these demands.[29]

Previous research showed that the burden for caregivers of ALS patients according to the Caregiver Strain Index (CSI) was significantly associated with the mental and physical summary scores of the caregivers and the patient.[4] In our study, informal caregivers who experienced a high burden of care also had a lower quality of life before the death of the patient in all but one scale (health change) of the SF-36. These differences were significant for the mental summary scale (MCS). Of the two SF-36 summary scales of the informal caregiver, only the mean MCS (45.8) before and after the death of the patient was lower compared to Dutch normative SF-36 means of adults (MCS=52.1, PCS=49.7).[30] In addition, patients of informal caregivers with a high burden of care also showed a significantly lower quality of life as measured by the mental subsection of the ALSAQ-40. This indicates that the mental situation of both the patient and the informal caregiver are especially strained when the burden of care is high.

A previous study with Dutch ALS patients and their informal caregivers showed that a passive coping style was related to a lower mental quality of life (MCS of the SF-36) and a higher burden of care on caregivers.[31] Our data also demonstrates more passive coping styles among caregivers who experience a higher burden of care compared to a lower burden of care, however this was not significant. We found a significantly higher use of emotional coping (i.e., expressing anger about the problem or vent one's irritation on someone/something) of caregivers who experienced a higher burden. Emotional coping of caregivers may cause a higher experienced burden of care, as these caregivers are more likely to make their negative emotions noticed in general and probably also in the CSI questionnaire. Informal caregivers who experienced a high burden of care also reported significantly more palliative coping (i.e., seeking distraction to avoid thinking about the problem). It may, therefore, be an undesirable coping style for caregivers, but it may also be the result of the high burden. Taking care of end-stage ALS patients can be very time consuming and overwhelming. These caregivers may in this particular period of their life actively take their mind off their care giving problems by doing something

that relaxes them (palliative coping). After the death of the patient the high burden of care is gone and that may be the reason that after the death of the patient caregivers who had a high burden of care do not use significantly more often palliative coping styles, anymore.

Coping is regarded as a personal trait in the UCL.[15] However, in our study informal caregivers changed their coping styles. As studies have shown that test-retest results of the UCL are sufficient in stable situations, the change may be the result of the extreme situation the informal caregivers are put in to (burden of care, loss of a significant others). A change in the UCL has also been shown in recent graduates, since the time around graduation can be considered a stressful period in a persons life.[15] However, all coping styles of patients and caregivers were similar (20-80 percentile) to age-matched Dutch norms.[15] Interestingly, this potential changeability of coping styles might be an anchor for palliative intervention in order to reduce burden of care and improve the quality of life in patients with ALS and their caregivers.

A high burden of care was not related to a declined physical functioning of the patient as was found in other studies.[7;32] A possible explanation for this might be that patients in this study all had an estimated life expectancy of approximately 6 months and therefore were all in an more severe stage of the disease. When ALS progresses it is likely that patients receive more informal and paid care. Caregivers of more disabled patient may receive more assistance and therefore may not have more care duties than caregivers of less disabled patients.[27] The result that almost no caregivers and patients desired more assistance with personal care and housekeeping supports this explanation.

A limitation of this study is that we excluded ALS patient with a severe cognitive disorder. Although, a severe cognitive disorder is not a typical symptom of ALS, it can be expected that caregivers of these patient experience an even higher burden of care. Another limitation is that we cannot determine the causality of the relation of the characteristic of the patient i.e. anxiety and the burden of care. Only a more qualitative study can determine if the caregiver's burden was high because the patient was anxious or that the patient had anxiety because the caregiver suffered from a high burden.

We can conclude that the majority of informal caregivers of patients with late-stage ALS have a high burden of care. This high burden of care is

especially related to the mental situation of the patient and the informal caregiver. Although burden of care is not related to complicated grief or symptoms of depression and quality of life of the informal caregiver after the death of the patient, it is related to the coping style after death. Patients and informal caregivers in the high burden category more frequently used emotional coping. Although, most patients and informal caregivers thought that their professional care was adequate, more professional attention for their coping style may help them to optimize their coping style or to express their discontent with their situation in the most constructive way.

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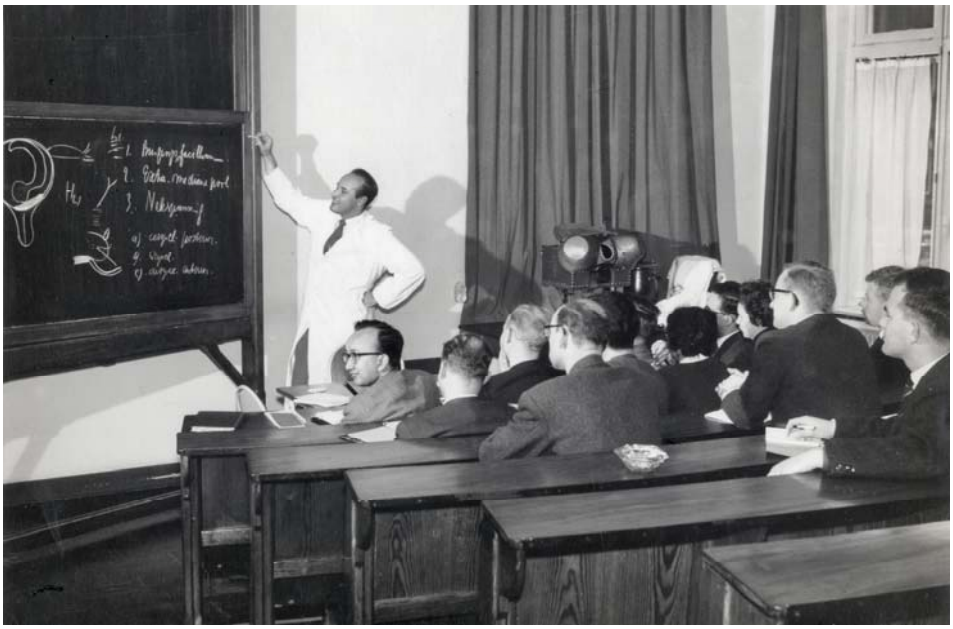
CHAPTER 7
GENERAL DISCUSSION



Picture: Small lecture room of the general hospital at the Catharijnesingel 101 in Utrecht in ±1965, the precursor of today's University Medical Center Utrecht.

7.1 INTRODUCTION

As outlined in the introduction, this thesis examines the rate of euthanasia and physician-assisted suicide (EAS) in amyotrophic lateral sclerosis (ALS) and explores the characteristics of the circumstances in the end-stage of ALS patients. Furthermore, it studies the determinants of requests for EAS among terminally ill ALS patients, focusing on symptoms of depression, palliative care characteristics and personal traits.
The structure of the general discussion is according to the main themes of this thesis: measuring quality of life in ALS patients (7.2), incidence and characteristics of EAS in ALS patients (7.3), influence of care characteristics (7.4), symptoms of depression (7.5), patient characteristics (7.6) and care burden on informal caregivers (7.7). In the discussion of these themes, the limitations of the study methods, and suggestions for practice and research are incorporated. Finally, section 7.8 presents the overall conclusion of this thesis.

7.2 MEASURING QUALITY OF LIFE IN ALS PATIENTS

There is no curative treatment for ALS, but numerous studies are performed today to discover ways to improve the lives of patients with ALS. Measurement of health-related quality of life, also called health status, is important when evaluating the effect of new treatments or therapies. The 40-item Amyotrophic Lateral Sclerosis Assessment Questionnaire (ALSAQ-40), introduced in the UK, seemed better suited for ALS patients than a generic health status measure like the MOS Short-Form 36 (SF-36) that was already available in Dutch.[1;2] Therefore we translated and validated the ALSAQ-40 and its shorter version, the ALSAQ-5. Chapter 2 shows that the psychometric properties of the Dutch ALSAQ-40 and ALSAQ-5 are comparable to those of the original UK version and therefore we used the ALSAQ-40 in this thesis. A disadvantage of the ALSAQ-40 and ALSAQ-5 is that there is no separate category in the questionnaires for 'patient always found it difficult to walk' and 'patient not able to walk at all'. This makes the questionnaire more vulnerable to a floor effect and less patient friendly. Nevertheless, we do think that the ALSAQ-40 is a valid and useful measurement of health status, but validation of the Dutch ALSAQ-40 and ALSAQ-5 might be further improved by a study on test-retest reliability.

7.3 EUTHANASIA AND PHYSICIAN-ASSISTED SUICIDE

Approximately 20% of the ALS patients dies due to EAS. This rate was similar in three studies performed in the UMC Utrecht between 1994-1998, between 2000-2005 (chapter 4) and between 2003-2008 (chapter 5). The stability of the EAS rate is interesting, as literature provides arguments that hypothesize a gradual increase in the EAS rate after its legalization: a "slippery slope".[3] This stability of EAS in ALS is not in agreement with the decrease found in the overall rate of EAS 2001 and 2005.[4] A possible explanation for the stability of the EAS rate in ALS patients is that, although the care options for ALS have improved [5;6], a lot of the ALS symptoms that are unbearable to patients are still untreatable, i.e. dependency and loss of communication. In chapter 3 it was shown that, in ALS patients, some psychosocial symptoms were more often the reason to request EAS than in cancer or heart failure patients. This combined with the fact that treatment options for psychosocial symptoms are limited, especially when life expectancy is low, may also be a reason why the EAS rate in ALS did not change significant. As psychosocial symptoms cannot always be prevented, patients should be helped to cope with them at the earliest possible stage.[7]

A national Dutch study shows that continuous deep sedation (CDS) may be used as a substitution for EAS.[4] In ALS patients approximately 10 to 15% dies during CDS. Chapter 4 shows that only half of these patients had at some time expressed a wish to hasten their death. And only 3% of the patients who explicitly requested for EAS eventually died during CDS (Chapter 5). Further, CDS appears to have other determinants than EAS (Chapter 4). These results indicate that in ALS patients it is unlikely that EAS is used as a substitute for CDS. Nevertheless, these results do not exclude this possibility completely as patients and physicians may have agreed on CDS as a final palliative option even before the patient explicitly requested EAS in our study. A prospective study is needed on patients' and physicians' motivations for choosing end-of-life practices and the exact timing of these.

The estimate of the rates of EAS may be biased due to the selection of participants through the three national referral centers for motor neuron disease in the Netherlands (Utrecht, Amsterdam and Nijmegen). Patients

who live further away from these centers may have been underrepresented in the studies, especially in the study described in chapter 5 in which participants had to have end-stage ALS. Regions further away from these national referral centers i.e Limburg and Zeeland, are known to be areas where more people are religious and therefore religious patients could be underrepresented.[8] Fortunately, the retrospective study in chapter 4 included only 1% more ALS patients who find religion important to them compared to the prospective study in chapter 5. However this is a non-specific measure and religion may still have influenced their attitude to EAS. Another limitation of the thesis is that the retrospective study in chapter 4 and the prospective study in chapter 5 partly overlapped in time, which makes it more likely to find similar results, but eventually, the data of only 7 patients were used in both studies, of whom only one died due to EAS. Chapter 3 shows that, in ALS patients, somatic symptoms are less often the reason to request EAS than in cancer or heart failure patients. This result should be used with caution as confidence intervals were broad and we had to categorize the numerous reasons for requesting EAS. Nevertheless, the frequencies of reasons for requesting EAS show that ALS patients distinguish themselves by suffering of fears.

7.4 SYMPTOMS OF DEPRESSION

Thinking about or desiring one's death is a symptom of depression according to the DSM-IV and therefore, depressed patients may be at risk for requesting EAS. These patients may feel that their disease symptoms are less bearable compared to patients without a depression. In the general practice depression is often underdiagnosed.[9] Diagnosing a depression in an ALS patient can be even more challenging due to overlapping depression and ALS symptoms and diminished communication and facial expression. We showed that in our studies EAS in ALS patients is relatively high, but does not seem to be the result of underdiagnosed depression in these patients. The data in this thesis showed no significant association between symptoms of a depression and (the request for) EAS according to the ALS patients (chapter 5), the informal caregivers, and the physicians of ALS patients (chapter 4). The reasons for ALS patients to request EAS were also rarely symptoms of depression (chapter 3). Thirteen percent of the patients who requested EAS reported that they felt depressed or had diminished

interest or pleasure in all, or almost all, activities for at least two weeks for most of the day (chapter 5); the physicians reported that 11% of the patients who received EAS had a depression or symptoms of a depression; and of the informal caregivers 35% reported that the patient who received EAS felt depressed or lost interest for two weeks for most of the day (Chapter 4). Considering the fact that ALS is a devastating disease, of all end stage ALS patients relatively few suffered from symptoms of depression (Chapter 4 and 5).[10] Even when death approached, a significant increase in symptoms of depression was not observed (Chapter 5).[10]

The above findings should be interpreted with caution as depressed patients are less likely to participate in scientific studies and therefore could have been underrepresented in our studies. However, the proportions of depression in the retrospective (chapter 4) and prospective (chapter 5) study were similar, which reduces the likelihood of under representation. Studying a rare event in a rare disease obviously limits the statistical power, but considering the circumstances our studies are relatively large. Larger study populations are generally realized by international multi-centre studies. However when EAS is the measure of outcome, the international differences in EAS law makes large international studies very difficult. By studying patients' death wishes in stead of euthanasia requests, international studies might be more feasible. Finally, depression rates may be overestimated as we did not use a complete structured clinical interview which is the gold standard for diagnosing depression, and it is known that screening instruments generally overestimate the depressionrate.[11] Although our data do not show an association between symptoms of a depression and EAS in ALS patients, in individual ALS patients depression can still be the most important reason for requesting EAS.

Although a significant relation between EAS and symptoms of depression does not seem to exist, in practice it remains important for physicians to consider depression when a patient requests euthanasia. Having a depression may in some patients interfere with the due care obligations of Dutch law that require a well-considered request for EAS of the patients. In the Netherlands it is not mandatory to consult a psychologist before performing EAS. Although in general it is desirable to treat a depression before deciding on EAS, in individual patients there may be exceptions. For example, patients may have a mild depression which does not interfere with their ability to make a well-considered request. Patients may have treatment

resistant depression or have such a short life expectancy that effective treatment of the depression is unlikely, and thus cannot be considered as a realistic treatment alternative that might make the patient withdraw his or her request.
It has been put forward that systematic examination for depression among ALS patients who want aid in dying is needed to adequately protect patients incompetent to make well-considered decisions on life and death.[12] However, as the proportion of symptoms of depression is similar between patients who request EAS and those who do not, screening should be for all ALS patients and not only for those with a higher risk or positive attitude towards hastening death. Because the main purpose should be to improve all patients' quality of life and not to prevent some patients to request EAS.[13]

7.5 CARE CHARACTERISTICS

In the Netherlands, ALS patients can be expected to have access to basic health care as health care insurance is mandatory and travel distances to health care providers are relatively short. Though basic care is provided, inadequate health care can still result in unnecessary suffering. This suffering could make some ALS patients more at risk for requesting EAS.[14;15] However, our data did not show that patients who requested EAS reported significantly more often dissatisfaction with their health care or financial situation than patients who did not requested EAS. Although only significant for communication appliances, the proportion of ALS patients who thought that the appliances were adequate was even higher in the EAS group. Approximately 2 months before the patients' death, 84% of all patients thought that the health care in general was good or excellent (Chapter 5).
Albeit most patients were satisfied with the care, there is still room for improvement. For instance, the most reported reason for unbearable suffering when requesting EAS was fear for suffocation. Although it is already in the ALS treatment guidelines to address palliative options for dyspnea[16;17], new initiatives or optimization of adequately informing patients and their (informal) caregiver on the palliative treatment options for dyspnea should be encouraged and evaluated, to reduce these fears. Another example of care that might be improved is that appliances were not

always found to be sufficient (Chapter 4, 5).[18] ALS is a very progressive disease and therefore appliances may not be provided on time or may be inadequate. If the occupational therapist requests an appliance from the health insurance company after recognition of symptoms that indicate that the patient may need the appliances in the near future, it is possible that by the time an appliance is delivered, adjusted to the patients' personal situation, and the patients become acquainted with it, the disease may already have progressed to such a degree that the patient cannot use the appliance anymore. To solve this problem, some, but unfortunately not yet all, municipalities or districts have special arrangements to reduce the delivery time for ALS patients. This is a good initiative to improve the quality of ALS care. It is also a good example to show that not only new treatment options, but also structured care planning may benefit the patients. More than 70% of the new ALS patients are treated in specialized ALS Rehabilitation Care Centres.[19] A study showed that ALS patients treated in the ALS Rehabilitation Care Centers had a better mental quality of life.[20] Palliative care for ALS patient is mainly provided by the rehabilitation physician, the primary care physician, and the home care nurse. Initiatives to bring ALS specialized care not only to the rehabilitation centers, but also into the home care setting of the primary care physician and the home care nurse is therefore the next challenge in optimizing ALS care.

The fact that most ALS patients die at home with their primary care physician as their treating physician was also postulated as a possible explanation for the high percentage of EAS in ALS, as primary care physicians are not always specialized in palliative care. We did not study if primary care physicians provided optimal palliative care, but we did find that the majority of the ALS patients were satisfied with the consultation frequency of the primary care physician, as only 10% desired more frequent consultations. Furthermore, the majority of the primary care physicians were satisfied with the professional support they received when they considered end-of-life practices in ALS patients. In the Netherlands, there is also an organization (Comprehensive Cancer Centers) that primary care physicians can consult if they have palliative care questions. When primary care physicians consider EAS in a patient, they have to consult an independent second physician, as part of the requirements for prudent

practice. This physician will mostly check for possible palliative alternatives.[21]
A limitation of our studies is that satisfaction with the provided care is a subjective measure of quality of care, and patients and informal caregivers may not be aware of alternative care options when judging their satisfaction with care. Informal caregivers tend to classify the suffering of ALS patients as worse than the patients do themselves[22;23] and therefore they may also be more dissatisfied with the health care than the patient. Finally, these results are only specific for the health care provided in the Netherlands in this specific period. Health care for ALS patients changes in time, even within the same study. Patients that participated at the beginning of the study may have received different care than patients at the end of the study, due to improvements in care or changes in government policy.

7.6 PATIENT CHARACTERISTICS

Our data could identify an association between EAS and the measured characteristics of the patient for religion not being important to the patient, more years of education, dying at home and feeling hopeless. Hopelessness is not only associated with EAS, but may also influence the quality of life.[24] Therefore, it may be useful to study how to reduce hopelessness in ALS patients. Although studies on this subject in ALS patients are rare, we did find a study that reported that externally orientated health locus of control and a poor sense of meaning and purpose in life are predictors of high levels of hopelessness in ALS patients. A externally orientated health locus of control means in generally that patients believe that their environment, some higher power, or other people control their decisions and their life[25]
Informal caregivers of patients who died due to EAS reported loss of dignity, fear of choking, feeling that there is no chance of improvement and dependency more frequently as a reason for EAS than informal caregivers of patients who did not die due to EAS (Chapter 4). Fear of choking, dependency and loss of dignity were also the most reported reasons for unbearable suffering in ALS patients when they requested a SCEN physician for EAS (Chapter 3). However, when we prospectively asked the ALS patients what their symptoms were we could not find an association between any of these symptoms and dying of EAS (Chapter 5). This may be the result of a difference in the moment that the questionnaires were

completed. In the prospective study the patients completed the questionnaires 2.2 months before their deaths when they were likely to be less ill. Another reason may be that we asked in the prospective study (chapter 5) which symptoms the patients had and not for explicit reasons for hastening death as was done in the retrospective study (chapter 4). Also, recall bias of the informal caregivers may have influenced the results in the retrospective study.

7.7 CARE BURDEN ON INFORMAL CAREGIVERS

Terminally ill patients do not want to be a burden on family.[26] Our study showed that the majority of informal caregivers of patients with advanced ALS have a high burden of care. This high burden is especially related to the mental situation and coping styles of the patient and the informal caregiver. Informal caregivers play a crucial role in the daily care for ALS patient, but 59% percent of informal caregivers felt completely overwhelmed by the care they give. Approximately 8 months (median) before their deaths, 40% percent of the ALS patients felt sometimes or often that they were a burden on their family (Chapter 6). Approximately 2 months (median) before their death 65% percent of the ALS patients who requested EAS felt a burden on their family (Chapter 5). Twenty percent of the informal caregivers thought that the patients feeling a burden on their family was a reason that the patients died due to EAS (Chapter 4). However, when we read the consultation reports of SCEN physician, only 2 of the 51 ALS patients that requested EAS reported feeling a burden on their family as a reason for unbearable suffering and therefore wanting EAS (Chapter 6). This suggests that many ALS patients feel a burden, but we could not find an association between burden and EAS.
Though many ALS patients feel a burden on their family, only a very small percentage reported that they wished more professional assistance at home with personal care or housekeeping. This difference may be caused by several reasons; patients preferred their privacy over professional assistance; they had low expectations of the professional assistance or feeling a burden is not a practical problem, but a psychosocial.

7.8 CONCLUSION

This thesis provides an insight in the care and decision-making at the end of life of ALS patients. Psychosocial, disease and care characteristics were measured to examine a broad spectrum of aspects of end-stage ALS patients. Research in a palliative care setting has its distinctive difficulties, and perhaps therefore prospective studies are relatively rare. Despite some limitations, our (prospective) study provides information on the end-of-life of ALS patients and can be used as a starting point for care interventions.

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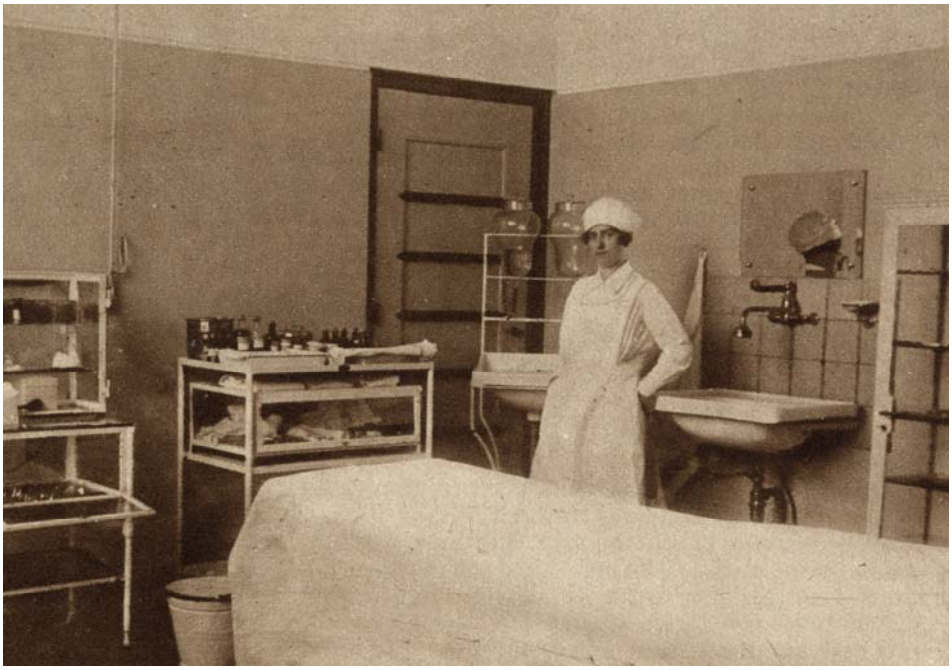
CHAPTER 8
SUMMARY
SAMENVATTING
DANKWOORD
CURRICULUM VITAE



Picture: Operating room of the general hospital at the Catharijnesingel 101 in Utrecht in 1928, the precursor of today's University Medical Center Utrecht.

8.1 SUMMARY

It is shown that one in five amyotrophic lateral sclerosis (ALS) patients die due to euthanasia and physician-assisted suicide (EAS) between 1994 and 1998 in the Netherlands. This relative high proportion of EAS in ALS might be the result of inadequate supportive or palliative care, unrecognized depressions, patients feeling they were a burden on others or hopelessness. This thesis examines the rate of EAS in ALS between 2000 and 2008 in the Netherlands and explores the characteristics of end-stage ALS patients. Furthermore, it studies the determinants of requesting for EAS among terminally ill ALS patients, focusing on symptoms of depression, palliative care characteristics, and personal traits.

In **chapter 2** we translated and validated the 40-item and 5-item Amyotrophic Lateral Sclerosis Assessment Questionnaire (ALSAQ-40, ALSAQ-5) to measure the health-related quality of life of ALS patients. Eighty-one ALS patients filled out the Dutch translation of the ALSAQ-40 and the MOS Short-Form 36 (SF-36) which is a frequently used quality of life questionnaire. The data showed that the ALSAQ-40 was sensitive to differences in disease severity, showed good construct validity and internal consistency. The good results of this study allowed us to use the ALAQ-40 in the studies described in chapter 5 and 6.

In **chapter 3** we compared the reasons of EAS request of patients suffering unbearable from ALS (n=51), heart failure (n=61), or cancer (n=73). Treating physicians of patients who are considering or requesting EAS can consult a SCEN physicians for a second opinion. In this study the SCEN physicians visited the patient and reported in the consultation report amongst others what kind of unbearable suffering the patient experienced. We studied questionnaires filled out by the treating physician of the patient and questionnaires and consultation reports filled out by the SCEN physicians. The most frequently reported reasons for unbearable suffering in ALS patients are fear of suffocation (45%) and dependency (29%), in cancer patients pain (46%) and fatigue (28%) and in heart failure patients dyspnea (52%) and dependency (37%). Cancer and heart failure patients reported somatic complaints as a reason for EAS more frequently than ALS patients ($P \leq 0.001$).

Chapter 4 describes a retrospective study in which 204 physicians and 198 informal caregivers of deceased ALS patients filled out questionnaires of the

end-of-life circumstances of the patient. Seventeen percent of the patients died due to EAS and 15% died during continuous deep sedation (CDS). These and other end-of-life practices appeared stable in time, compared to data on end-of-life practices in ALS reported between 1994-1998. The proxies of the patients who died due to EAS more often reported that the patient had a higher level of education ($p=0.03$), thought that religion was not important ($p=0.04$), felt hopeless ($p=0.04$), died at home ($p=0.007$) and appeared to feel less anxiety during the last few hours before their death ($p=0.002$) compared to patients who died without EAS. We found no significant association between EAS and a history of depression, the use of anti-depressive medication, symptoms of depression, or the satisfaction with the quality of care. Fear of choking, no chance of improvement, loss of dignity, being dependent on others, and fatigue, but not pain and feeling a burden on family or friends were reported more frequently as reasons for hastening death. Patients who died during CDS felt more often hopeless and were more likely to die in a nursing home/hospice compared to patients who died without EAS. It appeared that the amount of time by which life was shortened was less in patients who died during CDS, than in patients who decided on EAS.

Chapter 5 describes a prospective observational study on end-of-life circumstances of 102 patients with end-stage ALS. Structured questionnaires on characteristics of care, quality of life and symptoms of depression were filled out by the patients every three months until death. The results were correlated with patients who did or did not request their physician explicitly for EAS. When the patient died, the treating physician filled out a questionnaire on the performed end-of-life practices. Thirty-one percent of the patients requested their physician for EAS and 22% of the patients died due to EAS. One patient whose request for EAS was denied died during CDS. We could not find differences in the characteristics of care, symptoms of depression and burden between ALS patient who explicitly requested EAS and those who did not. The most frequently reported symptoms in the last measurement before the patient's death of the patients who actually died due to EAS were dependency (86%), fatigue (76%), and no chance of improvement (76%).

In **chapter 6** we describe a study on the burden of care on the informal caregiver of ALS patients. ALS patients and informal caregivers filled out structured questionnaires on the burden of care, quality of life,

characteristics of care, symptoms of depression and coping styles. Six months after the patient had deceased, the informal caregiver filled out questionnaires on quality of life, complicated grief, symptoms of depression and coping styles. Fifty-five percent of the informal caregivers answered 7 or more of the 14 Caregiver Strain Index (CSI) items positive, indicating a high burden. The data shows that patients whose informal caregivers experienced a higher burden of care were more frequently anxious, had a lower mental quality of life, and used more emotional and comforting coping styles. Informal caregivers who experienced a high burden of care had a lower quality of life and coped more frequently palliative and emotional before the death of the patient. However, after the death of the patient the association between burden of care and quality of life disappeared. The coping styles were more often active and emotional for caregivers who had experienced a high burden of care.

Chapter 7 contains the general discussion on the studies addressed in this thesis. The main results and methodological aspects of the various studies described in this thesis are reported here.

8.2 SAMENVATTING

In Nederland overleed tussen 1994 en 1998 één op de vijf mensen met amyotrofische laterale sclerose (ALS) door euthanasie of hulp bij zelfdoding (EHZ). Dit relatief hoge percentage EHZ bij ALS zou het gevolg kunnen zijn van inadequate palliatieve zorg, onderdiagnosticeren van depressie, zich een last voelen voor de omgeving of hopeloosheid. Dit proefschrift onderzoekt het percentage EHZ bij ALS patiënten in de periode 2000 en 2008 en de kenmerken van terminale ALS patiënten. Verder worden de determinanten van een EHZ verzoek bij deze patiënten onderzocht, waarbij is geconcentreerd op symptomen van een depressie en palliative zorg- en persoonskenmerken.

In **hoofdstuk 2** hebben we een Engelse kwaliteit van leven vragenlijst vertaald naar het Nederlands en gevalideerd, om zo de gezondheid gerelateerde kwaliteit van leven van ALS patiënten te kunnen meten. Deze Amyotrophic Lateral Sclerosis Assessment Questionnaire heeft een versie met 40 vragen (ALSAQ-40) en een versie met 5 vragen (ALSAQ-5). Eenentachtig ALS patiënten hebben de naar het Nederlands vertaalde ALSAQ-40 en een andere kwaliteit van leven vragenlijst (SF-36) ingevuld. De resultaten toonde aan dat de ALSAQ-40 sensitief was voor verandering in ernst van de ziekte, een goede construct validiteit heeft en een goede interne consistentie. Deze positieve resultaten lijden er toe dat we de Nederlandse ALSAQ-40 hebben gebruikt in de studies die beschreven staan in hoofdstuk 5 en 6.

In **hoofdstuk 3** vergelijken we de beweegredenen voor EHZ verzoeken van patiënten met ALS (n=51), hart falen (n=61), en kanker (n=73). Daarvoor bestudeerde wij de vragenlijsten van de behandelend artsen en de vragenlijsten en consultatieverslagen van de SCEN artsen. SCEN is een organisatie van artsen (SCEN artsen) die geraadpleegd kunnen worden door behandelend artsen van patiënten die EHZ overwegen of willen ontvangen. De SCEN artsen in deze studie bezochten de patiënt en rapporteerde onder andere in het consultatierapport welk ondragelijk lijden de patiënten ervoeren. De meest gerapporteerde redenen voor ondragelijk lijden van ALS patiënten waren angst om te stikken (45%) en afhankelijkheid (29%). In kanker patiënten waren dat pijn (46%) en moeheid (28%) en in patiënten met hartfalen waren dat benauwdheid (52%) en afhankelijkheid (37%).

Patiënten met kanker en hartfalen hadden vaker somatische klachten als reden voor hun EHZ verzoek dan ALS patiënten (P≤0.001).

Hoofdstuk 4 beschrijft een retrospectieve studie met 204 artsen en 198 informele zorgverleners van overleden ALS patiënten. Beide groepen vulden vragenlijsten in over de omstandigheden rond het levenseinde van de patiënt. Hieruit bleek dat 17% van de patiënten was overleden door EHZ en 15% tijdens continue diepe sedatie (CDS). Deze en andere percentages van medische beslissingen rond het levenseinde leken stabiel in de tijd wanneer zij vergeleken werden met de medische beslissingen rond het levenseinde van ALS patiënten uit een eerdere studie (1995-1998). De informele verzorgers van door EHZ overleden patiënten rapporteerde vaker dat de patiënten hoger waren opgeleid (p=0.03), religie belangrijk voor henzelf vonden (p=0.04), thuis overleden (p=0.007) en zich minder angstig of onrustig voelden gedurende de laatste uren van hun leven (p=0.002) vergeleken met patiënten die overleden zonder EHZ. Wij vonden geen significante associatie tussen EHZ en een voorgeschiedenis met depressie, gebruik van antidepressiva, symptomen van depressie of tevredenheid met de kwaliteit van zorg. Angst om te stikken, geen kans op verbetering, ontluistering, afhankelijkheid en moeheid, maar niet pijn en zich tot last voelen werden meer gerapporteerd als een reden om de dood te bespoedigen. Patiënten die overleden tijdens CDS voelde zich vaker hopeloos en overleden vaker in een verpleeghuis of hospice vergeleken met patiënten die zonder CDS of EHZ overleden. De levensbekorting was kleiner bij patiënten die overleden tijdens CDS dan bij patiënten die overleden door EHZ.

Hoofdstuk 5 beschrijft een prospectieve observationele studie over de omstandigheden rond het levenseinde van 102 ALS patiënten. Gestructureerde vragenlijsten over onder andere gezondheidszorg kenmerken, kwaliteit van leven en symptomen van depressie werden elke drie maanden ingevuld door de patiënt tot aan het overlijden. Deze resultaten werden geassocieerd met de patiënten die wel of niet hun arts nadrukkelijk verzochten om EHZ. Nadat de patiënten overleden, vulden de behandelend artsen een vragenlijst in over de genomen medische beslissingen rond het levenseinde. Eenendertig procent van de deelnemende patiënten had hun arts nadrukkelijk verzocht om EHZ en 22% van deze patiënten overleed door EHZ. Eén patiënt met een afgewezen verzoek voor EHZ was uiteindelijk overleden tijdens CDS. In deze studie konden wij

geen verschil vinden in de kenmerken van de gezondheidszorg, symptomen van depressie en zich tot last voelen tussen ALS patiënten met en zonder een nadrukkelijk verzoek voor EHZ. De meest gerapporteerde symptomen bij de laatste meting voor het overlijden door EHZ waren afhankelijkheid (86%), moeheid (76%) en geen kans op verbetering (76%).
In **hoofdstuk 6** beschrijven we een studie over de zorglast van informele zorgverleners van ALS patiënten. ALS patiënten en informele zorgverleners vulden gestructureerde vragenlijsten in over de zorglast, kwaliteit van leven, gezondheidszorg kenmerken, symptomen van depressie en coping stijlen. Zes maanden na het overlijden van de patiënt, vulden de informele zorgverleners nog een vragenlijst in over de kwaliteit van leven, gecompliceerde rouw, symptomen van depressie en coping stijlen. Vijfenvijftig procent van de informele zorgverleners antwoordden 7 van de 14 vragen van de Caregiver Strain Index (CSI) positief, wat duidt op een hoge zorglast. De data toont aan dat patiënten wiens informele zorgverleners een hoge zorglast ervaren, vaker angstig zijn, een lagere mentale kwaliteit van leven hebben en meer emotionele en geruststellende coping stijlen gebruiken. Informele zorgverleners die een hoge zorglast ervoeren hadden een lagere kwaliteit van leven en vertoonden vaker palliatieve en emotionele copingstijlen voor het overlijden van de patiënt. Echter na het overlijden van de patiënt verdween de relatie tussen zorglast en kwaliteit van leven en hun coping stijlen waren vaker actief en emotioneel.
Hoofdstuk 7 beschrijft de algemene discussie van alle studies in dit proefschrift. De hoofdresultaten en methodologische aspecten van de verschillende studies worden hier besproken.

8.3 DANKWOORD

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8.4 CURRICULUM VITAE

Maud Maessen was born on May 28th 1977, in Susteren, the Netherlands. She graduated in 1996 at the 'College Sittard' in Sittard.
In that same year she commenced her training in Nutrition and Public Health at Wageningen University. As part of her master course, she conducted three research projects and an internship, which she finished in 2002. For her specialization in Lifestyle and Public Health she conducted research at the Municipal Health Service in Rotterdam on interviewer bias. For her specialization in Nutrition she studied malnutrition among patients in the University Medical Center Utrecht. She performed an additional project at the department of Communication and Innovation Studies to evaluate national prevention campaigns of the government (the Netherlands Nutrition Centre, the Hague). During an additional internship at UNICEF, she worked on a research trial that studied different possibilities to prevent anemia in schoolgirls in Hyderabad (India).
In 2003 she started working on the PhD research described in this thesis at the University Medical Center Utrecht and the VU University Medical Center under supervision of Prof. dr. L.H. van den Berg and Prof. dr. G. van der Wal, Dr. J.H. Veldink and Dr. B.D. Onwuteaka-Philipsen. During her thesis she followed training to obtain her SMBWO registration for Epidemiologist A.