



UNDERSTANDING THE CLINICAL COURSE OF DEMENTIA

A search to optimize palliative
care for nursing home residents

SIMONE A. HENDRIKS

Understanding the clinical course of dementia

A search to optimize palliative care for nursing home residents

Simone A. Hendriks

The study presented in this thesis was conducted within the EMGO institute for Health and Care Research (EMGO+), Department of General Practice & Elderly Care Medicine of the VU University Medical Center, Amsterdam, The Netherlands. The EMGO+ Institute participates in the Netherlands School of Primary Research (CaRe), which has been acknowledged by the Royal Dutch Academy (KNAW).

This study was funded by a career award to Dr. van der Steen from the Netherlands Organisation for Scientific Research (NWO; Veni grant number 916.66. 073); ZonMw The Netherlands Organisation for Health Research and Development, grant number 1151.0001; the VU University Medical Center, EMGO Institute for Health and Care Research, Department of General Practice and Elderly Care Medicine, and Department of Public and Occupational Health, Amsterdam, the Netherlands; and by a grant from the SBOH (the employer for GP trainees and elderly care medicine trainees), the Netherlands.

Financial support for the printing of this thesis was kindly provided by the SBOH (the employer for GP trainees and elderly care medicine trainees), the Netherlands, the VU University Amsterdam and Gerion.

Cover design: Bernard Smit

Lay-out: Nicole Nijhuis, Gildeprint

Printed by: Gildeprint

ISBN: 978-94-6233-573-8

Copyright © 2017, Simone A. Hendriks

All rights reserved. No part of this book may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, recording or otherwise, without prior written permission of the author.

VRIJE UNIVERSITEIT

Understanding the clinical course of dementia

A search to optimize palliative care for nursing home residents

ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad Doctor aan
de Vrije Universiteit Amsterdam,
op gezag van de rector magnificus
prof.dr. V. Subramaniam,
in het openbaar te verdedigen
ten overstaan van de promotiecommissie
van de Faculteit der Geneeskunde
op maandag 10 april 2017 om 11.45 uur
in de aula van de universiteit,
De Boelelaan 1105

door

Simone Arianne Hendriks
geboren te Haarlem

promotor: prof. dr. C.M.P.M. Hertogh

copromotoren: dr.ir. J.T. van der Steen-van Kampen
dr. M. Smalbrugge

Time is
Too slow for those who Wait,
Too swift for those who Fear,
Too long for those who Grieve,
Too short for those who Rejoice,
But for those who Love,
Time is not.

Henry Van Dyke, 1904

CONTENTS

CHAPTER 1	General introduction	9
CHAPTER 2	The Bedford Alzheimer Nursing-Severity Scale to assess dementia severity in advanced dementia: A nonparametric item response analysis and a study of its psychometric characteristics	19
CHAPTER 3	Pneumonia, intake problems, and survival among nursing home residents with variable stages of dementia in the Netherlands: Results from a prospective observational study	33
CHAPTER 4	From admission to death: Prevalence and course of pain, agitation, and shortness of breath and treatment of these symptoms in nursing home residents with dementia	53
CHAPTER 5	Dying with dementia: Symptoms, treatment and quality of life in the last week of life	71
CHAPTER 6	Changes in care goals and treatment orders around the occurrence of health problems and hospital transfers in dementia: A prospective study	89
CHAPTER 7	End-of-life treatment decisions in nursing home residents dying with dementia in the Netherlands	107
CHAPTER 8	General discussion	121
	Appendices	141
	Summary	191
	Nederlandse samenvatting	199
	Dankwoord	207
	Curriculum Vitae	213



Chapter 1

General introduction

INTRODUCTION

This thesis aims to contribute to the understanding of the clinical course of dementia and to optimize palliative care for people with dementia in nursing homes. Understanding the clinical course of dementia forms the foundation of physician prognostication and supports palliative care actions, decision-making, and advance care planning. This general introduction explains the context and the outline of this thesis.

Dementia, one of the biggest health challenges worldwide

Many people and their families will be confronted with dementia. In the Netherlands, 270,000 people have dementia, and as the population ages this number will double in the coming decades.¹ Dementia is one of the main causes of dependency and disability in older age, and it is associated with a reduced life expectancy.^{2,3} Eventually, the majority of people with dementia in western countries will be admitted to, and die in, a nursing home.^{4,5} Dementia is one of the biggest health challenges, considering the high prevalence, the ageing population, the serious impact on disability, and the burden for all involved.^{2,6-9}

In the last two decades, awareness that people with dementia need palliative care in the last phase of life has increased.¹⁰⁻¹⁴ There is a need for adequate palliative care for people with dementia, to improve quality of life. The World Health Organization defined palliative care as “an approach that improves the quality of life of patients and their families facing the problems associated with life threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial, and spiritual.”¹⁵ Based on evidence and consensus, the European Association for Palliative Care identified eleven domains for palliative care and defined optimal care for people with dementia.¹⁶ To date, many questions about providing adequate palliative care for people with dementia still need to be answered.

Palliative care across dementia stages

One of these questions concerns the optimal starting point of palliative care across dementia stages. Palliative care that focuses on maximization of comfort and relief of suffering is generally accepted as the primary goal of care for people with dementia in the end stage of the disease,^{16,17} but a palliative care goal may also be appropriate in earlier stages. The European Association for Palliative Care recommends taking the moment of the dementia diagnosis as the starting point for palliative care.¹⁶ Nonetheless, the identification of the palliative phase and of palliative care needs in dementia is a point of discussion, and opinions vary among health care professionals.¹⁶

The disease trajectory of dementia is variable and hard to predict. People survive an average of 4 to 8 years after the diagnosis of dementia, but individual survival can be up to 20 years and depends, among other things, on the age at onset.¹⁸ Dementia is caused by neurodegeneration, and the most common underlying pathologies of dementia are Alzheimer's disease (50-75%), vascular dementia (20-30%), frontotemporal dementia (5-10%), Lewy body (<5%), and mixed pathologies, mostly Alzheimer in combination with vascular dementia.² Dementia is a disease that involves progressive decline, severe enough to reduce a person's ability to perform everyday activities, in the cognitive and physical domain. Examples of cognitive performance are executive functioning, memory, and attention; examples of physical performance are endurance capacity, muscle strength, balance, and mobility.¹⁹⁻²¹

A variety of instruments and scales are used in research to define the stages of dementia.^{22;23} One of the most commonly used staging scales for people who have Alzheimer's disease is the Global Deterioration Scale for Assessment of Primary Degenerative Dementia (GDS), which divides the disease process into seven stages.²⁴ Another scale that differentiates more severe stages, is the continuous Bedford Alzheimer Nursing-Severity Scale (BANS-S).^{25;26} Yet in practice different terminology is used for the stages of dementia.

For people with dementia and their families, the most obvious, and perhaps most relevant differentiation is in type of care setting: people who live in the community and can function independently at home versus people who are admitted to long-term care (LTC) facilities because they can no longer live safely at home and require a higher level of care.^{4;27} Admission to a nursing home may be an important severity indicator for people with dementia themselves and their families.

The need for research of the clinical course of dementia in the nursing home setting
Although the majority of people with dementia are eventually admitted to and die in LTC facilities,^{4;5} our understanding of the clinical course of dementia, palliative care needs and decision-making in nursing home residents is inadequate. Knowledge about the clinical course of dementia in nursing home residents is mostly based on retrospectively collected data, limited to the dying phase, or limited to nursing home residents with advanced dementia.²⁸ For example, Mitchell et al. reported that advanced dementia has been linked to higher risk of developing health problems such as pneumonia and intake problems.¹⁷ Moreover, pneumonia and dehydration and cachexia have been reported as the three most common direct causes of death in nursing home residents with advanced dementia.²⁹ In addition, nursing home residents with advanced dementia develop burdensome symptoms such as pain, agitation, and shortness of breath shortly before death.²⁸ However, the majority of nursing home residents in the Netherlands die before reaching the advanced stages of dementia. Only few residents reach the stage of dementia with severe verbal

impairment, complete ADL impairment, incontinence, and bedridden status.^{5,23;29;30} It is therefore highly relevant to study a nursing home population in various stages of dementia, to investigate the clinical course of the disease, and to explore the palliative care needs during nursing home stay from admission to death.

Multiple domains play a role in palliative care in dementia in long-term care. Relevant clinical domains concern intercurrent health problems and survival. In addition, the course of symptoms and symptom management, and domains related to decision-making and advance care planning play a role in palliative care. Advance care planning especially concerns timely and ongoing discussions about end-of-life issues between residents, their families, and professional caregivers. The concept of advance care planning was introduced in 1994 by Joan Teno et al., and the definitions differ slightly over time, but all indicate that advance care planning can be defined as a dialogical process of supporting patients and their families to think ahead and formulate goals of care as they have the diagnosis of dementia and confront the challenge of this progressive illness trajectory.^{10;31;32} Informing residents and families can help initiate a discussion about care goals,^{16;17} and these care goals can help guide care decisions and help to prevent potentially burdensome and unwanted treatment. In the Netherlands, the Dutch association of elderly care physicians “Verenso” formulated four main types of care goals: Life prolongation; Maintaining or improving of functioning; Palliative goals; and Symptomatic care goals. A palliative care goal and a symptomatic care goal are both aimed primarily at safeguarding optimal wellbeing and an acceptable quality of life of the patient with dementia. These goals are achieved by: treatment of other complaints, co-morbidity, symptoms and complications resulting from the dementia. However, for a palliative care goal, extending life as a potential side effect of this treatment is not contraindicated – or is even part of the care goal. In contrast, for a symptomatic care goal, a life-extending side-effect as a result of medical treatment aimed at this goal is undesirable.³³ Before the Dutch End of Life in Dementia (DEOLD) study nationally representative data about care goals, treatment decisions and symptom management were not available for residents with dementia during nursing home stay.

Long-term care for people with dementia in the Netherlands

The way care for people with dementia in long-term care is organized depends on culture, and health care setting. Long-term care in the Netherlands distinguishes between people with predominantly somatic illnesses (who live in somatic units, 57% of the admitted people) and people with dementia and dementia-like disorders (who live in dementia special care units, 43% of the admitted people). In 2008 there were 400 psychogeriatric wards for people with dementia (or dementia special care units) in the Netherlands, and approximately 70,000 people with dementia resided in a nursing home or a residential home.^{34;35} Dutch long-term care is characterized by the presence of elderly care physicians. Elderly care physicians are employed by

the nursing home, which is their principal site of practice, and their expertise is readily available when needed. Moreover, elderly care physicians in the Netherlands follow a 3-year vocational training in elderly care medicine that includes training in palliative care, end-of-life decision-making, shared decision-making and advance care planning.³⁶

Objectives of this thesis

The overarching goal of this thesis is to achieve a better understanding of the clinical course of dementia in people in various stages of dementia in Dutch nursing homes, to help optimize palliative care for nursing home residents. To this end we formulated the following objectives:

- 1) To explore changes in dementia severity, and how pneumonia and intake problems affect survival during nursing home stay.
- 2) To investigate the course of burdensome symptoms and treatment provided for these symptoms during nursing home stay.
- 3) To explore changes in care goals during nursing home stay, and to investigate end-of-life treatment decisions.

Study methods

To address the objectives of this thesis we used data from the Dutch End of Life in Dementia (DEOLD) study. The DEOLD study³⁰ was conducted to investigate end-of-life care, including comfort, symptom burden and decision-making, and to assess associated factors. This longitudinal observational study employed both prospective (upon admission) and retrospective (after death) recruitment of residents. Data were collected between 2007 and 2011 in 34 long-term care facilities. Elderly care physicians were responsible for data collection in nursing homes and affiliated residential homes. The study population consisted of residents in variable stages of dementia who were newly admitted to a long-term care facility. The residents had a physician's diagnosis of dementia of any stage and any type. Individual assessments were performed for a maximum period of 3½ years (January 2007-July 2010; and survival was monitored for an additional year, until summer 2011).

For this thesis we performed quantitative analyses to investigate the full period from admission until death, using 2 temporal perspectives: the follow-up perspective starting from admission, and the follow-back perspective from the moment of death. For most residents we could perform analyses with both perspectives. Methods and statistical analyses are addressed in greater detail in the separate chapters.

Outline of this thesis

Chapters 2 and 3 focus on the first study objective. Chapter 2 includes a methodological study to explore changes in dementia severity by examining the hierarchical properties of the items of the Bedford Alzheimer Nursing-Severity Scale. Chapter 3 includes a longitudinal study of the incidence of pneumonia and intake problems, and includes an exploration of the disease dynamics in relation to the severity of dementia and mortality.

Chapters 4 and 5 concern objective 2. Chapter 4 describes the prevalence and course of pain, agitation, and shortness of breath, and the provided treatment for these symptoms during nursing home stay. Chapter 5 describes the last week of life of nursing home residents, focusing in detail on treatment provided for the most important burdensome symptoms, and on the use of opioids and palliative sedation.

Chapters 6 and 7 focus on objective 3. Chapter 6 describes changes in care goals and treatment orders around the occurrence of pneumonia and intake problems, and also whether hospitalization is in line with earlier agreed upon do-not-hospitalize orders. Chapter 7 describes end-of-life treatment decisions in the last weeks of life.

Finally, Chapter 8, the general discussion, reflects on the results of this thesis. The methodological strengths and limitations are discussed, and the implications of this study for both clinical practice and research are described.

REFERENCES

1. Ferri CP, Prince M, Brayne C et al. Global prevalence of dementia: a Delphi consensus study. *Lancet* 2005;366:2112-2117.
2. Alzheimer's Disease International. World Alzheimer report 2014. Dementia and Risk Reduction, an analysis of protective and modifiable factors. London, 2014.
3. Todd S, Barr S, Roberts M, Passmore AP. Survival in dementia and predictors of mortality: a review. *Int J Geriatr Psychiatry* 2013;28:1109-1124.
4. Reyniers T, Deliens L, Pasman HR et al. International variation in place of death of older people who died from dementia in 14 European and non-European countries. *J Am Med Dir Assoc* 2015;16:165-171.
5. Houttekier D, Cohen J, Bilsen J, ddington-Hall J, Onwuteaka-Philipsen BD, Deliens L. Place of death of older persons with dementia. A study in five European countries. *J Am Geriatr Soc* 2010;58:751-756.
6. Alzheimer Nederland. Jaarverslag 2015, Dementie in beeld. Available at: <http://jaarverslag2015.alzheimer-nederland.nl/media/pdf/jaarverslag-2015.pdf>. Accessed 2016.
7. Alzheimer's Disease International. World Alzheimer Report 2015. The Global Impact of Dementia An analysis of prevalence, incidence, cost and trends. Available at: <https://www.alz.co.uk/research/WorldAlzheimerReport2015.pdf>. Accessed 2016.
8. Alzheimer's Disease International. Alzheimer's disease facts and figures 2015. *Alzheimers Dement* 2015;11:332-384.
9. Prince M, Bryce R, Albanese E, Wimo A, Ribeiro W, Ferri CP. The global prevalence of dementia: a systematic review and metaanalysis. *Alzheimers Dement* 2013;9:63-75.
10. Hertogh CM. Advance care planning and the relevance of a palliative care approach in dementia. *Age Ageing* 2006;35:553-555.
11. van der Steen JT, Ribbe MW. Dying with dementia: what do we know about it?. *Tijdschr Gerontol Geriatr* 2007;38:288-297.
12. Sampson EL, Ritchie CW, Lai R, Raven PW, Blanchard MR. A systematic review of the scientific evidence for the efficacy of a palliative care approach in advanced dementia. *Int Psychogeriatr* 2005;17:31-40.
13. Mitchell SL, Kiely DK, Jones RN, Prigerson H, Volicer L, Teno JM. Advanced dementia research in the nursing home: the CASCADE study. *Alzheimer Dis Assoc Disord* 2006;20:166-175.
14. Alzheimer's Disease International. World Alzheimer report 2007. Available at: https://www.alz.org/national/documents/Report_2007FactsAndFigures.pdf. Accessed 2016.
15. WHO (2002). National cancer control programmes: policies and managerial guidelines. Geneva, World Health Organization, 2002.
16. van der Steen JT, Radbruch L, Hertogh CM et al. White paper defining optimal palliative care in older people with dementia: a Delphi study and recommendations from the European Association for Palliative Care. *Palliat Med* 2014;28:197-209.
17. Mitchell SL, Teno JM, Kiely DK et al. The clinical course of advanced dementia. *N Engl J Med* 2009;361:1529-1538.
18. Xie J, Brayne C, Matthews FE. Survival times in people with dementia: analysis from population based cohort study with 14 year follow-up. *BMJ* 2008;336:258-262.
19. Barberger-Gateau P, Fabrigoule C, Amieva H, Helmer C, Dartigues JF. The disablement process: a conceptual framework for dementia-associated disability. *Dement Geriatr Cogn Disord* 2002;13:60-66.
20. Bossers WJ, van der Woude LH, Boersma F, Scherder EJ, van Heuvelen MJ. Recommended measures for the assessment of cognitive and physical performance in older patients with dementia: a systematic review. *Dement Geriatr Cogn Dis Extra* 2012;2:589-609.

21. Gershon RC, Cella D, Fox NA, Havlik RJ, Hendrie HC, Wagster MV. Assessment of neurological and behavioural function: the NIH Toolbox. *Lancet Neurol* 2010;9:138-139.
22. Byrne EJ, Benoit M, Lopez Arrieta JM et al. For whom and for what the definition of severe dementia is useful: an EDCON consensus. *J Nutr Health Aging* 2008;12:714-719.
23. Koopmans RT, Ekkerink JL, van WC. Survival to late dementia in Dutch nursing home patients. *J Am Geriatr Soc* 2003;51:184-187.
24. Reisberg B, Ferris SH, de Leon MJ, Crook T. The Global Deterioration Scale for assessment of primary degenerative dementia. *Am J Psychiatry* 1982;139:1136-1139.
25. Volicer L, Hurley AC, Lathi DC, Kowall NW. Measurement of severity in advanced Alzheimer's disease. *J Gerontol* 1994;49:M223-M226.
26. Bellelli G, Frisoni GB, Bianchetti A, Trabucchi M. The Bedford Alzheimer Nursing Severity scale for the severely demented: validation study. *Alzheimer Dis Assoc Disord* 1997;11:71-77.
27. Alzheimers association. Stages of Alzheimer 2016. Available at: http://www.alz.org/alzheimers_disease_stages_of_alzheimers.asp. Accessed 2016.
28. van der Steen JT. Dying with dementia: what we know after more than a decade of research. *J Alzheimers Dis* 2010;22:37-55.
29. Koopmans RT, van der Sterren KJ, van der Steen JT. The 'natural' endpoint of dementia: death from cachexia or dehydration following palliative care? *Int J Geriatr Psychiatry* 2007;22:350-355.
30. van der Steen JT, Ribbe MW, Deliens L, Gutschow G, Onwuteaka-Philipsen BD. Retrospective and prospective data collection compared in the Dutch End Of Life in Dementia (DEOLD) study. *Alzheimer Dis Assoc Disord* 2014;28:88-94.
31. Teno, J. M. (2003). Advance care planning for frail, older persons. In *Geriatric Palliative Care* (pp. 307-313). Oxford: Oxford University Press, 2015.
32. Hertogh CPM. Advance care planning and palliative care in dementia. In *Supportive care for the person with dementia* (pp. 271-80). Oxford: Oxford University Press, 2010.
33. Verenso, the Dutch Association of Elderly Care Physicians and Social Geriatricians. [Guideline: Concepts and Requirements of Care in relation to end-of-life decisions in long-term care]. [in Dutch]. 2007. Available from: <http://www.verenso.nl/assets/Uploads/Downloads/Handreikingen/Levensinde-beleidsversie-070607.pdf>. Accessed 2016.
34. de Klerk M. Zorg in de laatste jaren. Gezondheid en hulpgebruik in verzorgings- en verpleeghuizen 2000-2008. Sociaal Cultureel Planbureau, 2011.
35. Alzheimer Nederland. Cijfers en feiten over dementie, factsheet 2016. Available at: http://www.alzheimer-nederland.nl/media/840711/factsheet_dementie_algemeen_-_publieksversie_26-01-2016.pdf. Accessed 2016.
36. Koopmans RT, Lavrijsen JC, Hoek JF, Went PB, Schols JM. Dutch elderly care physician: a new generation of nursing home physician specialists. *J Am Geriatr Soc* 2010;58:1807-1809.



Chapter 2

The Bedford Alzheimer Nursing-Severity Scale to assess dementia severity in advanced dementia: A nonparametric item response analysis and a study of its psychometric characteristics

Francisca Galindo-Garre
Simone A. Hendriks
Ladislav Volicer
Martin Smalbrugge
Cees M.P.M. Hertogh
Jenny T. van der Steen

ABSTRACT

The Bedford Alzheimer Nursing-Severity Scale (BANS-S) assesses disease severity in patients with advanced Alzheimer's disease. Since Alzheimer is a progressive disease, studying the hierarchy of the items in the scale can be useful to evaluate the progression of the disease. Data from 164 Alzheimer's patients and 186 patients with other dementia were analyzed using the Mokken Scaling Methodology to determine whether respondents can be ordered in the trait dementia severity, and to study whether an ordering between the items exist. The scalability of the scale was evaluated by the H coefficient. Results showed that the BANS-S is a reliable and medium scale ($0.4 \leq H < 0.5$) for the Alzheimer group. All items with the exception of the item about mobility could be ordered. When later item was eliminated from the scale, the H coefficient decreased indicating that the scalability of the scale in the original form is more accurate than in the shorter version. For the other dementia group, the BANS-S did not fit any of the Mokken Scaling models because the scale was not unidimensional. In this group, a shorter version of the scale without the sleeping cycle item and the mobility item has better reliability and scalability properties than the original scale.

INTRODUCTION

Several instruments to assess physical and mental functioning have been developed and validated in nursing research and practice. These instruments can support practitioners in making health care decisions. Two examples are the activities of daily living (ADLs) questionnaire developed by Katz et al¹ and the Mini-Mental State Examination developed by Folstein et al.² Two approaches are commonly used to study the reliability and validity of these instruments. Classical test theory is concerned with the estimation of measurement error and the estimation of the true score, and item response theory (IRT) evaluates the responses to individual items. Another alternative approach that is becoming popular in nursing research³ is the Mokken scaling.^{4,5} This scaling methodology follows the principles of IRT for assessing the relationship between items but it requires less rigid assumptions.

One interesting property of IRT models is that items and measured constructs or traits are measured in the same scale. Thanks to this property, items can be ordered along latent trait levels and a hierarchy of symptoms can be established. Hierarchical scales have been useful for measuring a range of constructs for instance, feeding behavior in dementia,⁶ distress,⁷ or happiness.⁸ All these articles used Mokken scaling to determine whether some symptoms are expected to be more frequently observed than other symptoms in the scale.

Further, for an Alzheimer's disease severity scale, assessing the ordering of the items within the scale may be useful. Alzheimer's disease is a progressive disease characterized by limitations in cognitive and physical performance.⁹ Although the progression is not uniform for patients, the first symptoms are usually cognitive deficits, followed by functional impairments, and finally pathological symptoms.¹⁰ For dementia severity, ordering scales' items implies that the ordering of the items is the same for all patients, irrespective of dementia severity. This means that people with low-dementia severity are expected to have difficulties only with complex items or it is expected that, in general, some problems will appear earlier than others in the dementia disease process.

The Bedford Alzheimer Nursing-Severity Scale (BANS-S) was developed to assess disease severity in patients with advanced Alzheimer's dementia. The scale is based on clinical information about the development of Alzheimer-type dementia. The BANS-S combines measurements of cognitive and functional deficits with the occurrence of other symptoms. It is composed of 7 polytomous items, 2 cognitive items (speech and eye contact), 3 functional items (dressing, eating, and ambulation), and 2 items referring to pathological symptoms (sleep-wake cycle disturbance and muscle rigidity/contractions). The BANS-S total score ranges from 7 to 28, summing the 7 items each ranging from 1 to 4.

The BANS-S has been used extensively in nursing practice and has been quoted in 39 publications (eg, in a large prospective study on advanced dementia in nursing homes by Mitchell et al¹⁰). The first validation of the current version of the scale¹¹ showed that the scale is psychometrically strong. Bellelli et al¹² performed a new validation study and they demonstrated that this instrument is valid and that it discriminates between groups of patients with different dementia severity. Volicer et al¹³ performed a study on the progression of Alzheimer's dementia with the BANS, which is a previous version of the BANS-S. They estimated dementia duration after which at least 50% of the patients had problems with each BANS item. The patients first had problems with dressing themselves (after 5 years), then sleep-wake cycle dysfunctions (after 6 years), then they lost the ability of feeding themselves and ambulating independently (after 8 years), and finally the ability to keep eye contact (after 12 years). Although this pattern did not apply to all patients because some patients retained some functions despite a long duration, these results indicate a possible hierarchy in the appearance of dementia symptoms.

Establishing the hierarchical properties of the BANS-S provides information additional to the total score obtained by summing patient responses. A scale with hierarchical properties has items that can be ordered according to their mean scores in the total group. Dementia severity is the latent trait assessed by the scale. Patients with a higher dementia severity score are expected to have higher scores in items that are high in the hierarchy than patients with a lower dementia severity score.

The Mokken scaling methods to study the hierarchical properties of a scale with polytomous items are more complex than for a scale with dichotomous items.¹⁴ A set of polytomous items with ordered categories forms a hierarchical scale when the ordering of the items according to their mean score is the same across different values of the latent trait or the measured construct. This property is also named invariant item ordering (IIO). Recently, Ligtoet et al¹⁵ have developed a method to assess IIO for polytomous items.

The present study assesses the hierarchical properties of the items of the BANS-S using Mokken scaling. First, we assess whether the probability of presenting difficulties with the BANS-S' item scores is higher for patients with higher scores in the trait dementia severity. Then, we use Ligtoet et al¹⁵ method to investigate whether the BANS-S items can reliably be invariantly ordered as severity indicators of dementia. Since the BANS-S was developed for patients with Alzheimer's disease, we first study the subgroup of patients with Alzheimer's disease and then we study whether the ordering of the items found for patients with Alzheimer's disease applies to the group of patients with other types of dementia, because this instrument is often used in research in nursing homes in the United States, Italy, and the Netherlands to assess patients with different types of dementia.¹⁶⁻²² Finally, we study the ordering of the BANS-S items for the complete scale to investigate whether the BANS-S measures different traits for the different groups.

METHODS

Description of the sample

The data were collected as part of the Dutch End of Life in Dementia study describing quality of dying and end-of-life care and assessing associated factors. We enrolled 372 residents in 28 long-term care facilities upon admission. A comprehensive description of the participants of this study can be found in van der Steen et al.²³ The diagnoses of dementias were based on international guidelines.²⁴⁻²⁶

Description of the instrument

The BANS-S is a nursing staff-administered questionnaire comprising 7 items with 4 ordered categories. Respondents are evaluated in their ability to perform 3 ADLs (“dressing,” “eating” [dependence], and “mobility” [ability to walk independently]), their ability to speak (“speech”), their capacity to maintain eye contact (“eye contact”), the regularity of their sleep–wake cycle (“sleeping”), and the state of their muscles (“muscles”). The item categories have different labels, and they range from 1 to 4. The total score is the sum of the item scores, and it ranges from 7 (no impairment) to 28 (complete impairment).

In our study, the BANS-S was administered by a nurse or a physician every 6 months. For this analysis, we used the first measurement approximately 8 weeks after admission to the long-term care facility.

Statistical methods

The R package *Mokken*^{27,28} was used to study the hierarchy of the BANS-S instrument. First, we fit the Monotone Homogeneity model (MHM). If the MHM fits, the mean of the latent trait increases as the total score increases,²⁹ and the sum score can be used to order patients stochastically on the trait in most practical situations.³⁰ To fit this model, 3 model assumptions are tested, (1) unidimensionality: all items in the instrument measure the same latent trait (the construct dementia severity); (2) monotonicity: the probability of choosing a higher category of the item increases with increasing dementia severity; and (3) conditional independence: The responses regarding the same patient to different items are only related to his dementia severity level. Assumptions 1, 2, and 3 can be tested by checking the following restrictions on the scalability coefficients H^{28} (Theorem 4.3): the total H coefficient value, the H coefficient for each item, and the H coefficient for each pair of items must be between 0 and 1. The procedures to check these restrictions are the automated-item selection procedure³¹ and the item rest score regression. The scalability coefficient H^4 was computed to determine the strength of the relationship of each item with the latent trait. A set of items form a scale if the H coefficient for each pair of items is higher than or equal to .3. Furthermore, scales are classified according to the following criteria for the H

value: (1) $.3 \leq H < .4$: weak scale, (2) $.4 \leq H < .5$: medium scale, and (3) $H \geq .5$: strong scale. The unidimensionality assumption was also assessed by exploratory factor analysis, but the results are not reported because they were equivalent to the results obtained with the MHM. The reliability of the scale was checked with the Cronbach's α and the Molenaar Sijtsma statistic (MS), which is a more accurate reliability coefficient. For a description of the properties of these coefficients see van der Ark.³²

Next, we fitted Double Monotonicity Model (DMM) for polytomous items. This model fits when the previously described assumptions hold, and when the items are ordered among patients. This means that people with a higher dementia severity have a higher probability to experience more difficulties to perform complex activities without help. This—IIO—is a necessary condition for a scale to be hierarchical, and it can be tested by the method of manifest IIO (MIIO).¹⁵ Items involved in violations of the IIO assumption are removed from the questionnaire by the backward method.³² After IIO was established, the H^T coefficient was calculated to assess the precision of the item ordering.¹⁵ The H^T coefficient was evaluated following the criteria described for the H coefficient.

RESULTS

Of the 372 patients assessed with the BANS-S questionnaire, 350 had completed all the items. Almost half (47%, $n = 164$) of these patients had Alzheimer's dementia, 22% ($n = 77$) had vascular dementia, 17% ($n = 60$) had Alzheimer's and vascular dementia, and 14% ($n = 49$) had another type of dementia. Since the BANS-S was built for patients with Alzheimer's disease, the psychometric characteristics of 2 groups of patients were studied separately: patients ($n = 164$) with Alzheimer's disease and the other type of dementia ($n = 186$) group which includes combinations of Alzheimer's dementia with other dementias.

The MHM

Table 1 shows the mean scores and the scalability coefficients (H) for the BANS-S items computed for the Alzheimer's, the other dementia, and the complete groups. For the Alzheimer's group, the BANS-S scale was a medium scale ($H = .47$) and had a high reliability according to both reliability coefficients used (MS = .82 and Cronbach's $\alpha = .81$). The scale was unidimensional and there were no violations in the assumption of monotonicity. Therefore, we can conclude that the MHM model fits for this scale.

Table 1. Mean item scores and scalability coefficients (H) with the standard errors (SEs) in parentheses for the BANS-S items^a

Item label	Alzheimer dementia (N= 164)		Other dementias (N = 186)		Complete group (N = 350)	
	Mean scores	H (SE)	Mean scores	H (SE)	Mean scores	H (SE)
1. Dressing	2.76	.58 (.04)	2.96	.58 (.03)	2.86	.58 (.03)
2. Sleeping	1.64	.31 (.06)	1.48	.22 (.08)	1.56	.25 (.05)
3. Speech	1.83	.37 (.06)	1.77	.40 (.05)	1.79	.38 (.04)
4. Eating	1.76	.49 (.05)	1.87	.50 (.04)	1.82	.50 (.03)
5. Mobility	1.76	.55 (.04)	2.11	.49 (.04)	1.94	.51 (.03)
6. Muscles	1.82	.50 (.05)	1.93	.42 (.05)	1.88	.45 (.03)
7. Eye contact	1.43	.47 (.05)	1.48	.39 (.07)	1.45	.42 (.04)

Abbreviations: BANS-S, Bedford Alzheimer Nursing-Severity Scale; SE, standard error; MS, Molenaar Sijtsma statistic.

^a Scale: Alzheimer dementia: H = .47 (.04); reliability MS = .82, Cronbach's α = .81. Other dementias: H = .44 (.04); reliability MS=.81, Cronbach's α = .80.

For the other dementia group, the scalability and the reliability coefficients were very similar (H = .44, MS = .81, and Cronbach's α = .80) to the coefficients reached by the Alzheimer's group. There was no violation in the monotonicity assumption for both the groups. However, the results from the Mokken's automated-item selection algorithm to check unidimensionality showed that the "sleeping" item did not belong to the same dimension as the other items in the scale. After eliminating this item, the remaining 6 items formed a strong scale with H = .51 (standard error [SE] = .04), and the reliability coefficients for the new scale were MS = .82 and Cronbach's α = .81. Therefore, we cannot conclude that the MHM fits for the complete BANS-S scale for the other dementia group, because the assumption of unidimensionality is violated. Finally, the results for the complete group were close to the results for the other dementia group (H = .45, MS = .82, and Cronbach's α = .80). Again, the "sleeping" belonged to another dimension. The scalability coefficient for the scale without the "sleeping" item was H = .52 (SE = .03), and the reliability coefficients were MS = .83 and Cronbach's α = .82. For both the other dementia and the complete groups, the MHM fits for a 6-item subscale without the "sleeping" item.

Table 2. Mokken scale of the BANS-S checked for violations of invariant item ordering for the Alzheimer dementia group (N = 164) and for the other dementias group (N = 186): Mean item scores and scalability coefficients (H) with the standard errors (SEs) in parentheses.^a

Item label	Alzheimer dementia (N = 164)		Other dementias (N = 186)	
	Mean scores (Ordering)	H (SE)	Mean scores (Ordering)	H (SE)
1. Dressing	2.76 (1)	.58 (.04)	2.96	.57 (.04)
2. Sleeping	1.64 (5)	.29 (.06)		
3. Speech	1.83 (2)	.37 (.06)	1.77	.45 (.06)
4. Eating	1.76 (4)	.45 (.05)	1.87	.54 (.04)
5. Muscles	1.82 (3)	.44 (.05)	1.93	.41 (.06)
6. Eye contact	1.43 (6)	.46 (.05)	1.48	.43 (.07)

Abbreviations: BANS-S, Bedford Alzheimer Nursing-Severity Scale; SE, standard error; MS, Molenaar Sijtsma statistic.

^a Scale: Alzheimer dementia: H = .42 (.04); reliability MS = .77, Cronbach's α = .76. Other dementias: H = .48 (.04); reliability MS = .79, Cronbach's α = .77.

The DMM

As with MHM, to fit the DMM, the ordering of the items was evaluated for the Alzheimer, the other dementia, and the complete groups. In the Alzheimer's group, 5 items ("mobility," "muscles," "eating," "speech," and "sleeping") were involved in several significant violations of MIIO. The items for which MIIO violations occur do not follow the same ordering by difficulty for all individuals in the population of interest. The backward selection procedure suggested that the item "mobility" should be eliminated from the scale. After removing the "mobility" item, no violations were left. The new scale has a H^T coefficient of .57 that suggests strong support for IIO ($H^T > .5$). This means that the item ordering found has a high accuracy. Table 2 shows the coefficients for the scale after excluding the "mobility" item. Lower mean scores indicate that these deficits appear with higher dementia severity. After adjusting for IIO, the scalability and reliability coefficients for the scale without the mobility item decreased (H = .42, MS = .77, and α = .76). The scalability coefficients for all the items decreased and for the "sleeping" item, it became lower than the cutoff for the H coefficient of .3. These results indicate that, although the "mobility" item cannot be ordered in the hierarchy, the scale should stay in its original form for the group of patients with Alzheimer's disease, because it achieves better values for reliability and scalability in this form.

For the other dementia group, the "sleeping" item was removed from the scale, and the DMM model was fitted for the remaining items. The "mobility," "muscles," "eating," and "speech" items were involved in several significant violations of MIIO. The backward selection procedure also indicated that the "mobility" item should be eliminated from the scale. After removing the "mobility" item, no violations were left, and the new scale had a H^T coefficient of .62. This

means that the item ordering found has a high accuracy. After adjusting for IIO, the reliability coefficients for the scale without the “mobility” decreased ($MS = .79$ and $\alpha = .77$), but the scalability coefficient increased from $H = .44$ to $H = .48$. The scalability coefficients for all the items increased or remained the same.

Finally, we fit the DMM model for the complete group to assess whether the BANS-S measured different traits for the different groups. Four items (“mobility,” “muscles,” “eating,” and “speech”) were involved in several significant violations of MIIO. The backward selection procedure indicated that the item mobility should be eliminated from the scale for this group too. After removing the mobility item, no violations were left ($H^T = .59$). The item ordering found for the complete group was very similar to the ordering obtained for the other dementia group.

DISCUSSION

In this article, we have fitted Mokken models to the BANS-S to study its psychometric properties. We found that the BANS-S meets the criteria for an ordinal scale for the patients with Alzheimer’s disease. The DMM did not fit well because the “mobility” item could not be accurately ordered in the scale. However, if we remove the “mobility” item from the scale the reliability and the scalability of the scale decrease indicating that the “mobility” item must be retained in the scale.

We found that the BANS-S also meets the criteria for an ordinal scale for other dementias, but the “sleeping” item could not be accurately ordered in the scale. The scale without the “sleeping” item did not fit well with DMM because the “mobility” item could not be accurately ordered in the scale for other dementias. Removing the “mobility” item from the scale increases the scalability of the scale and only slightly decreased the reliability. Our results pointed out that the ordering of the symptoms was different for the patients with Alzheimer’s disease compared with the other dementia group but the differences vanished when patients with Alzheimer’s disease and other dementia patients were combined.

The reliability of the instrument was already studied for the development population (see Voilcer et al¹¹) using classical test theory. They found that a Cronbach’s α ranged from .64 to .80, an excellent correlation between raters’ score and Spearman correlations higher than .5 with other related test measuring physical functioning, cognitive functioning, speech ability, and dementia progression. In our population, we also studied the reliability of the instrument. We found a Cronbach’s α of .81 for the Alzheimer’s group and .80 for the other dementia group.

The range of the mean scores suggests that the items can discriminate between patients with different degrees of dementia. These findings confirm the results reported in Bellelli et al.¹² We found that patients with Alzheimer's disease had the highest mean score for the dressing item and the lowest for the eye contact item. Volicer et al.¹³ also found that patients with a short dementia duration often have problems with dressing themselves and that a high proportion of patients could keep eye contact 12 years after diagnosis.

For both the Alzheimer's and the other dementia groups, the "mobility" item could not be ordered in the dementia intensity scale. This means that the scores for this item do not have the same ordering for all the values of the latent trait. The reason may be that not only dementia but also other diseases such as stroke, arthritis or the effects of a fall may affect a person's ability to walk independently.

The results differed between the group of patients with Alzheimer's disease and the group of other dementias. The last group comprised patients who had vascular dementia, a combination of vascular dementia and Alzheimer's dementia or other types of dementias and, therefore, this group was more heterogeneous. The scale was not unidimensional for the other dementia group, because the "sleeping" belonged to a different dimension. Problems with the "sleeping" item were already reported by van der Steen et al.²⁰ Furthermore, a lower mean score for the other dementia group in Table 1 suggest that people with other types of dementia had sleeping problems less often than patients with Alzheimer's disease. The proportion of patients who report an irregular sleep-wake cycle in the other dementia group was 44% versus 56% of the patients in the Alzheimer's group. Although an irregular sleep-wake rhythm is a symptom that may occur for all dementia types, differences in sleep symptoms and signs may vary according to the dementia (sub) type.³³ Sleep disturbances may occur more frequently and in an earlier stage of the Alzheimer's disease in comparison with other dementia types. In a population of patients with autopsy-confirmed Alzheimer's disease, a unique profile of disordered activity was found when compared to those with other neurodegenerative dementias. The hypothesized mechanism of circadian rhythm disturbance includes damage to the suprachiasmatic nucleus, circadian pacemaker damage, and alterations in pineal gland function and melatonin secretion.³³

Another difference in the results for the Alzheimer's and the other dementia groups was that the place of the item "speech" in the hierarchy was different. This result is difficult to interpret clinically because the moment in the course of the dementia in which this item is affected may vary between type of dementia.³⁴ For example, speech is often affected early in frontotemporal dementia^{35,36} while it may be a later symptom in Alzheimer's disease.³⁷⁻³⁹ However, whether this symptom is affected in vascular dementia or not depends on the location of the lesion.⁴⁰

The present study has some limitations that warrant comment. First, this study is based on cross-sectional analyses limited to the first measurement of a longitudinal study. Further work may replicate the analyses for measurements obtained later after admission to study, to investigate whether the relationships between the items change, and to study individual disease progression. Second, we had no external criterion against which to evaluate the responsiveness of the scale to clinical changes. Third, we could not explain associations between mobility and comorbidity, because we do not know if the mobility problems were caused by the dementia or by other diseases. Finally, the differentiation between dementia types was mostly based on clinical findings, which may not always correlate with neuropathological evaluation.⁴¹

Determining IIO gives a clear meaning to test scores because we learn about the ordering of the problems. The probability of having problems with an item with a higher mean score (higher in the hierarchy) was higher for patients with high-dementia severity than for people with low-dementia severity. This result is relevant because many scales do not discriminate between patients with more severe dementia. However, this scale may present a floor effect for patients with lower levels of dementia, because they did not have difficulties with most of the items. This was not the case because only 26% of the patients has a sum score of ≤ 9). Furthermore, it should be also taken into account that the data were from baseline measurements and that the patient population at this point was not always severely demented. Further research should be done to study whether the dementia patterns found for this population apply to the course of the dementia for an individual and to evaluate the responsiveness of the scale to individual changes.

REFERENCES

1. Katz S, Ford A, Moskowitz R, Jackson B, Jaffe M. Studies of illness in the aged. *JAMA*. 1963;185:914-919.
2. Folstein M, Folstein S, McHugh P. MiniMental State: a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975;12(3):189-198.
3. Watson R, van der Ark A, Lin L, Fieo R, Deary I, Meijer R. Item response theory: how Mokken scaling can be used in clinical practice. *J Clin Nurs*. 2011;21(19-20):2736-2749.
4. Mokken R. *A Theory and Procedure of Scale Analysis with Applications in Political Research*. New York: De Gruyter; 1971.
5. Molenaar I. Nonparametric Models for Polytomous Responses. In: van der Linden W, Hambleton R, eds. *Handbook of Modern Item Response Theory*. New York: Springer-Verlag; 1997; 367-380.
6. Watson R. Mokken scaling procedure (MSP) applied to feeding difficulty in elderly people with dementia. *Int J Nurs Stud*. 1996;33(4):385-393.
7. Watson R, Deary I, Shipley B. A hierarchy of distress: mokken scaling of the GHQ-30. *Psychol Med*. 2008;38(4):575-579.
8. Stewart M, Watson R, Clark A, Ebmeier K, Deary I. A hierarchy of happiness? Mokken scaling analysis of the oxford happiness inventory. *Pers Indiv Differ*. 2010;48(7):845-848.
9. Bossers W, van der Woude L, Boersma F, Scherder E, van Heuvelen M. Recommended measures for the assessment of cognitive and physical performance in older patients with dementia: a systematic review. *Dement Geriatr Cogn Dis Extra*. 2012;2(1):589-609.
10. Mitchell SL, Teno JM, Kiely DK, et al. The clinical course of advance dementia. *N Engl J Med*. 2009;361(16):1529-1538.
11. Volicer L, Hurley A, Lathi D, Kowall N. Measurement of severity in advanced Alzheimer's disease. *J Gerontol*. 1994;49(5):223-226.
12. Bellelli G, Frisoni G, Bianchetti A, Trabucchi M. The Bedford Alzheimer nursing severity scale for the severely demented: validation study. *Alzheimer Dis Assoc Disord*. 1997;11(2):71-77.
13. Volicer L, Seltzer B, Rheaume Y, et al. Progression of Alzheimer-type dementia in institutionalized patients: a cross-sectional study. *J Appl Gerontol*. 1987;6(1):83-94.
14. Sijtsma K, Meijer R, van der Ark LA. Mokken scale analysis as time goes by: an update for scaling practitioners. *Pers Indiv Differ*. 2011;50(1):31-37.
15. Ligtoet R, van der Ark LA, te Marvelde JM, Sijtsma K. Investigating an invariant item ordering for polytomously scored items. *Educ Psychol Meas*. 2010;70(4):578-595.
16. Brandeis GH, Berlowitz DR, Coughlin N. Mortality associated with an influenza outbreak on a dementia care unit. *Alzheimer Dis Assoc Disord*. 1998;12(3):140-145.
17. Frisoni GB, Gozzetti A, Bignamini V, et al. Special care units for dementia in nursing homes: a controlled study of effectiveness. *Arch Gerontol Geriatr*. 1998;26(suppl 1):215-224.
18. Camberg L, Woods P, Ooi WL, et al. Evaluation of simulated presence: a personalized approach to enhance well-being in persons with Alzheimer's disease. *J Am Geriatr Soc*. 1999;47(4):446-452.
19. Colombo M, Vitali S, Cairati M, et al. Wanderers: features, findings, issues. *Arch Gerontol Geriatr Suppl*. 2001;7:99-106.
20. van der Steen JT, Ooms ME, van der Wal G, Ribbe MW. Pneumonia: the demented patient's best friend? discomfort after starting or withholding antibiotic treatment. *J Am Geriatr Soc*. 2002; 50(10):1681-1688.
21. van der Steen JT, Ooms ME, David R, van der Wal G, RibbeMW. Severe dementia and adverse outcomes of nursing home-acquired pneumonia: evidence for mediation by functional and pathophysiological decline. *J AmGeriatr Soc*. 2002;50(3):439-448.

22. Pasma HR, Onwuteaka-Philipsen BD, Kriegsman DM, et al. Discomfort in nursing home patients with severe dementia in whom artificial nutrition and hydration is forgone. *Arch Intern Med.* 2005;165(15):1729-1735.
23. van der Steen JT, Ribbe MW, Deliens L, Gutschow G, Onwuteaka-Philipsen BD. Retrospective and prospective data collection compared in the Dutch End Of Life in Dementia (DEOLD) study. *Alzheimer Dis Assoc Disord* 2014;28:88-94.
24. McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the national institute on aging-Alzheimer's association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement.* 2011;7(3):263-269
25. Roman GC, Tatemichi TK, Erkinjuntti T, et al. Vascular dementia. diagnostic criteria for research studies: report of the NINDSAIREN international workshop. *Neurology.* 1993;43(2):250-260.
26. McKeith IG, Galasko D, Kosaka K, et al. Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): Report of the consortium on DLB international workshop. *Neurology.* 1996;47(5):1113-1124.
27. van der Ark LA. Mokken scale analysis in R. *J Stat Software.* 2007;20(11):1-19.
28. Sijtsma K, Molenaar I. Introduction to Nonparametric Item Response Theory. Thousand Oaks, CA: Sage; 2002.
29. Sijtsma K, Emons W, Bouwmeester, Nyklíček I, Roorda LD. Nonparametric IRT analysis of quality-of-life scales and its application to the World Health Organization quality-of-life scale (WHOQOL-Bref). *Qual Life Res.* 2008;17(2):275-290.
30. van der Ark LA. Stochastic ordering of the latent trait by the sum score under various polytomous IRT models. *Psychometrika.* 2005;70(2):283-304.
31. Molenaar I, Sijtsma K. MSP5 for Windows. A Program for Mokken Scale Analysis for Polytomous Items. Groningen: ProGamma; 2000.
32. van der Ark LA. New developments in Mokken scale analysis. *J Stat Software.* 2013;48(5):1-27.
33. Zhou QP, Jung L, Richards KC. The management of sleep and circadian disturbance in patients with dementia. *Curr Neurol Neurosci Rep.* 2012;12(2):193-204.
34. Duffy JR, Josephs KA. The diagnosis and understanding of apraxia of speech: why including neurodegenerative etiologies may be important. *J Speech Lang Hear Res.* 2012;55(5):S1518-S1522.
35. Amici S, Gorno-Tempini ML, Ogar JM, Dronkers NF, Miller BL. An overview on primary progressive aphasia and its variants. *Behav Neurol.* 2006;17(2):77-87.
36. Kirshner HS. Primary progressive aphasia and Alzheimer's disease: brief history, recent evidence. *Curr Neurol Neurosci Rep.* 2012;12(6):709-714.
37. Nelissen N, Dupont P, Vandenbulcke M, Tousseyn T, Peeters R, Vandenberghe R. Right hemisphere recruitment during language processing in frontotemporal lobar degeneration and Alzheimer's disease. *J Mol Neurosci.* 2011;45(3):637-674.
38. Cera ML, Ortiz KZ, Betolucci PH, Minett TS. Speech and orofacial apraxias in Alzheimer's disease. *Int Psychogeriatr.* 2013; 25(10):1679-1685.
39. Emery VO. Language impairment in dementia of the Alzheimer type: a hierarchical decline? *Int J Psychiatry Med.* 2000;30(2): 145-164.
40. Vuorinen E, Laine M, Rinne J. Common pattern of language impairment in vascular dementia and in Alzheimer disease. *Alzheimer Dis Assoc Disord.* 2000;14(2):81-86.
41. Harper DG, Stopa EG, Kuo-Leblanc V, et al. Dorsomedial SCN neuronal subpopulations subserve different functions in human dementia. *Brain.* 2008;131(pt 6):1609-1617.



Chapter 3

Pneumonia, intake problems, and survival among nursing home residents with variable stages of dementia in the Netherlands: Results from a prospective observational study

Simone A. Hendriks
Martin Smalbrugge
Arianne B. Gageldonk-Lafeber
Francisca Galindo-Garre
Maarten Schipper
Cees M.P.M. Hertogh
Jenny T. van der Steen

ABSTRACT

Objectives: We explore how pneumonia and intake problems affect survival in nursing home residents in variable stages of dementia.

Methods: In a longitudinal observational study (372 residents) with up to 3.5 years of follow-up, we examined relationships between dementia severity, the development of pneumonia, intake problems and mortality using joint modelling, Cox models and mediation analyses. Dementia severity was measured semi-annually with the Bedford Alzheimer Nursing Severity-Scale (BANS-S).

Results: The median BANS-S score at baseline was 13 (range 7 to 28). Pneumonia occurred in 103 (28%), and intake problems in 126 (34%) of 367 residents with complete registration of pneumonia and intake problems. Compared with dementia severity, incident pneumonia and, even more so, incident intake problems were more strongly associated with mortality risk. Pneumonia and intake problems both mediated the relationship between more severe dementia and mortality.

Discussion: Developing pneumonia and intake problems affects survival, and this is not limited to advanced dementia. The occurrence of pneumonia and intake problems are important signals to consider a palliative care approach in nursing home residents with dementia, and an active focus on advance care planning is needed. Future studies should investigate whether this is also relevant for patients in primary care.

INTRODUCTION

Dementia is an incurable disease and many people will die with or from this disease.¹ In many countries, more than half of people with dementia die in long-term care setting. The majority of these nursing home residents can no longer safely live on his or their own.² Few nursing home residents reach the end-stages of dementia with complete ADL impairment, severe verbal and physical impairment, and severe impairment in decision making.^{2,3}

During the course of dementia, pneumonia and intake problems frequently occur and may influence quality of life and survival.⁴⁻⁸ A focus on palliative care goals may be appropriate for nursing home residents with advanced dementia.^{1,5,9} However, a palliative goal of care may be also helpful in earlier stages of the disease trajectory,¹ because many nursing home residents die before reaching the stage of advanced dementia.^{3,10}

Understanding the clinical course of dementia forms the foundation of physician prognostication and supports advance care planning and palliative care actions.^{1,11} However, knowledge about the clinical course of dementia in nursing home residents is limited and based on findings from retrospective studies, cross-sectional studies, and studies of patients in the advanced stage of dementia.^{1,5,12,13} Mitchell et al.⁵ reported that infections and eating difficulties are hallmarks of advanced dementia, and residents with advanced dementia have a high mortality rate. This is consistent with three commonly reported causes of death in nursing home residents with dementia which are pneumonia, dehydration and cachexia.^{4,8}

Using longitudinal data is important to characterize the disease dynamics, survival, and the role of pneumonia and intake problems as potential mediating factors. This information may help physicians to inform patients and families about the clinical complications to be expected during the course of dementia and support them in establishing care goals, palliative care actions and advance care planning. To further these goals, we sought to determine the incidence of pneumonia and intake problems and how these health problems affect survival of nursing home residents with dementia. Further, we assessed whether the severity of dementia is associated with development of pneumonia, intake problems, and with mortality and whether pneumonia and intake problems mediated the relationship between dementia severity and death.

METHODS

Data collection

We used data from a longitudinal observational study, the Dutch End of Life in Dementia (DEOLD) study.³ Between 2007 and 2011, we collected prospective and retrospective data on 491 residents in 34 long-term care facilities residing on psychogeriatric wards (almost all dementia).³ In this article, we only use the data prospectively collected on 372 residents with dementia at any stage who were newly admitted to 28 long-term care facilities and who were enrolled upon admission between January 2007 and July 2009.³ Elderly care physicians were responsible for data collection by completing written questionnaires.

Individual assessments were performed for up to 3½ years (January 2007-July 2010) and survival was monitored for an additional year (until summer 2011). A baseline assessment was scheduled 8 weeks after admission, followed by up to a maximum of 5 semi-annual assessments. In case of death during the study period, a questionnaire about the last week of life was completed within 2 weeks after death. Physicians additionally registered any incident pneumonia and incident intake problems on a continuous basis. Since the median survival time after developing pneumonia and intake problems in our dataset was almost 2 months, we censored survival data in this article at 2 months after having concluded the monitoring of incident pneumonia and intake problems (at 31 August 2010). The study protocol was approved by the Medical Ethics Review Committee of the VU University Medical Center Amsterdam, and written informed consent was obtained from the families.

Measurements

At baseline we measured several resident characteristics. We assessed the place of residence before admission and the 2 most important reasons for admission with pre-structured items. Type of dementia was assessed with a pre-structured item comprising the categories Alzheimer disease, vascular dementia, Alzheimer disease and vascular dementia, Lewy body / Parkinson disease, and other. The diagnosis of dementia was based on international guidelines.¹⁴⁻¹⁶ We assessed activity of daily living with the Minimum Dataset Set-ADL-Long Form scale,^{17,18} ranging from 7 to 28, with higher scores indicating poorer function. We rated residents' illness severity on the Illness Severity Score,^{19,20} ranging from 1 to 9; higher scores indicating more severe illness. We assessed nutritional status and one hydration status item with pre-structured items²¹: (1) cachectic (combining very cachectic and cachectic), or not cachectic (combining normal, adipose, and very adipose), (2) weight loss of $\geq 5\%$ in last month, $\geq 10\%$ in the last 6 months, or no weight loss, and (3) hydration status [not dehydrated (normal), mildly dehydrated, dehydrated or severely dehydrated].

At baseline and at every semi-annual assessment, we assessed dementia stage in 2 ways. To define the severity of dementia on a continuous scale, we used the Bedford Alzheimer Nursing Severity-Scale (BANS-S), with a range of 7 to 28 and higher scores indicated more severe dementia.^{22;23} It is suggested that a cutoff score of 17 is appropriate for defining severe (or advanced) dementia, and a score of ≥ 17 is comparable with a mini mental-state examination (MMSE) score under 10.^{17;22;23} Physicians (20%, 181/917), or nurses under supervision by the physician (80%, 736/917), assigned the BANS-S scores. In addition, we used the Global Deterioration Scale (GDS)²⁴ and the Cognitive Performance Scale (CPS)²⁵ to compare our findings with those of other studies and defined advanced dementia as a GDS score of 7, and a CPS score of 5 or 6. CPS 5 and 6 are associated with mean MMSE scores of 5 and 1.²⁵

Physicians continuously registered any incident pneumonia or intake problem, with the date of diagnosis. We collected data about diagnostics, symptoms and health condition at the time of diagnosis. Pneumonia was judged by the attending physician. To investigate pneumonia severity, we assessed mortality risk with a score specific for patients with pneumonia and dementia, estimating the risk of death within 14 days when treated with antibiotics.²⁶⁻²⁸ We defined intake problems as an eating or drinking problem as judged by the attending physician. Physicians assessed the primary reason for the intake problem, with pre-structured categories including the option "other reason."

Statistical analyses

The analyses considered the first episode of pneumonia and the first occurrence of an intake problem. We calculated the length of time from admission until the development of pneumonia or an intake problem, and the survival time afterwards, or censored time. Further, we reported the hazard rate of developing pneumonia and of developing intake problems in the first year, and the hazard rate of mortality in the first year.

Table 1 summarizes the stepwise approach in examining the relationships along with the statistical models. First, we assessed the unadjusted direct relationship between dementia severity and mortality (1). The BANS-S that measures dementia severity also includes ADL items (3 out of 7).²⁹ Second, we separately assessed the relationship between dementia severity and first occurrence of pneumonia (2a), and between dementia severity and first occurrence of intake problems (2b). As the severity of dementia may change over time and therefore may influence the survival time, we used joint modelling. These models jointly analyze longitudinal data and time-to-event data and account for both non-random dropout in the longitudinal data and endogenous time-varying covariates.³⁰ In the first step of the joint model analysis, a linear mixed regression model was used for the longitudinal severity of dementia (BANS-S scores) data.

Table 1. Statistical analyses used for the explored relationships

Association	Method	Time-dependent covariates	Dependent variables	HR (95% CI), P-value; Coefficient, standard error
(1) Direct relationship between dementia severity and mortality	Joint model	Dementia severity (BANS-S* at every assessment) - time between assessments of BANS-S* - survival time/censored time	Mortality	1.19 (1.14-1.23; per point increment), <0.001; 0.172, 0.020
(1+) Advanced dementia, versus less advanced dementia and mortality	Cox proportional hazard models with time dependent covariates	Advanced dementia versus less advanced dementia [†] - time until advanced dementia - survival time/censored time	Mortality	1.7 (1.2-2.4), 0.005; 0.51, 0.18
(2a) Direct relationship between dementia severity and first occurrence of a pneumonia	Joint model	Dementia severity (BANS-S* at every assessment) - time between assessments of BANS-S* - time until pneumonia - survival time/censored time	Pneumonia [†]	1.07 (1.01- 1.14; per point increment), 0.0220; 0.071, 0.031
(2a+) Advanced dementia, versus less advanced dementia and first occurrence of a pneumonia	Cox proportional hazard models with time dependent covariates	Advanced dementia versus less advanced dementia [†] - time until advanced dementia - time until pneumonia - survival time/censored time	Pneumonia [†]	1.2 (0.7-2.2), 0.57; 0.18, 0.31
(2b) Direct relationship between dementia severity and first occurrence of an intake problem	Joint model	Dementia severity (BANS-S* at every assessment) - time between assessments of BANS-S* - time until intake problem - survival time/censored time	Intake problem [†]	1.16 (1.10-1.23; per point increment), <0.001; 0.152, 0.029
(2b+) Advanced dementia, versus less advanced dementia and first occurrence of an intake problem	Cox proportional hazard models with time dependent covariates	Advanced dementia versus less advanced dementia [†] - time until advanced dementia - time until intake problem - survival time/censored time	Intake problem [†]	1.6 (0.94-2.6), 0.087; 0.44, 0.25
(3a) Direct relationship between pneumonia and mortality	Cox proportional hazard models with time dependent covariates	Pneumonia [†] (Unadjusted) - time until pneumonia - time from pneumonia until survival/censored time	Mortality	4.1 (3.1-5.4), <0.001; 1.4, 0.148
(3a+) Whether the dementia severity changed the strength of this associations	Cox proportional hazard models with time dependent covariates	Pneumonia [†] (Adjusted) - dementia severity (BANS-S* at every assessment) - time between assessments of BANS-S* - time until pneumonia - time from pneumonia until survival/censored time	Mortality	4.6 (1.2-6.2), <0.001; 1.5, 0.155

Association	Method	Time-dependent covariates	Dependent variables	HR (95% CI), P-value; Coefficient, standard error
(3b) Direct relationship between intake problems and mortality	Cox proportional hazard models with time dependent covariates	Intake problem* (Unadjusted) - time until intake problem - time from intake problem until survival/censored time	Mortality	10.2 (7.7-13.5), <0.001; 2.32, 0.144
(3b+) Whether the dementia severity changed the strength of this associations	Cox proportional hazard models with time dependent covariates	Intake problem* (Adjusted) - dementia severity (BANS-S* at every assessment) - time between assessments of BANS-S* - time until intake problem - time from intake problem until survival/censored time	Mortality	6.2 (6.1-11.3, <0.001); 2.12, 0.155
(4a) Relation between pneumonia and intake problems	Cox proportional hazard models with time dependent covariates	Pneumonia - time until pneumonia - time until intake problem - survival time/censored time	Intake problem	1.7 (1.0-2.8), 0.036; 0.54, 0.252
(4b) Relation between intake problems and pneumonia	Cox proportional hazard models with time dependent covariates	Intake problems - time until intake problem - time until pneumonia - survival time/censored time	Pneumonia	3.1 (1.9-5.1), <0.001; 1.13, 0.253
(5a) Whether pneumonia mediated the relationship between the severity of dementia and mortality	Product method of Sobel	Pneumonia* Coefficients of 2a/3a		0.025
(5b) Whether intake problems mediated the relationship between the severity of dementia and mortality	Product method of Sobel	Intake problems* Coefficients of 2b/3b		<0.001

Clustering of residents within long-term care facilities is taken into account in all models. The HR are bolded.

*BANS-S = Bedford Alzheimer Nursing Severity-Scale (range 7-28, with higher scores indicating more severe dementia).

†Advanced dementia = a Global Deterioration Scale score of 7 and a Cognitive Performance Scale of 5 or 6.

*38 patients developed both a pneumonia and an intake problem. These patients were included in both variables which concerned pneumonia and variables which concerned intake problems.

In the second step, we fitted a Cox proportional hazard model to analyze the time to event. In the final step, these 2 models were linked (joined) through their shared random effects. In addition to the joint models, and for reasons of comparability with other studies, we used Cox proportional hazard models with time-dependent covariates to assess the relationships between advanced dementia (yes/no) and respectively mortality, pneumonia and intake problems (1 +, 2a + and 2b +). Third, to estimate the association between pneumonia and mortality (3a), and between intake problems and mortality (3b), we used two Cox proportional hazard models with time-dependent covariates. To assess whether and how dementia severity changed the strength of these two associations, we added the longitudinal BANS-S scores to the Cox models (3a +, 3b +). Fourth, we explored the relation between the development of pneumonia and intake problems (4a), and vice versa (4b) with Cox proportional hazard models with time-dependent covariates. To assess whether pneumonia and intake problems mediated the relationship between the severity of dementia and mortality (5a, 5b), we used the product method to compute indirect effects and the Sobel test to assess significance.³¹⁻³³ The strength of relationships was expressed in terms of Hazard Ratios (HR) and statistical significance level was set to 0.05. To account for clustering of residents within 34 long-term care facilities, we adjusted for clustering all the analyses, and reported these results. The analyses were performed using R software version 3.0.2,³⁴ and IBM SPSS 20.0 (SPSS, 2011).

RESULTS

Resident characteristics

Of all residents (N = 372), 10 (3%) were lost to follow-up, due to moving to another long-term care facility, or due to the physician withdrawing from collecting data. In 34 cases (9%), residents died shortly after admission, and therefore the physicians had no chance to complete the baseline assessment. Of all newly admitted residents, 58% was admitted from their own home or from a residential home. The most important reasons for admission were neuropsychiatric symptoms, physical health problems and distress of the caregiver. The most common type of dementia was Alzheimer's disease (46%). The median BANS-S score at baseline was 13.0, with a range from 7 to 28 covering the theoretical range (7 to 28) of the BANS-S scores. Of the residents, 25% had a BANS-S score of 7 to 9, which implies that those residents were not completely dependent for any of the ADL items (bed mobility, transfer, locomotion on unit, dressing, eating, toilet, personal hygiene). The median CPS score was 3.0, 88% had a GDS score of < 7, and only 9% of the residents had advanced dementia upon admission. The median score of ADL-functioning was 10 (range, 0 to 28) (Table 2).

Table 2. Resident characteristics

Characteristics at baseline = assessment 8 weeks after admission	Total population (N = 372)	
	n/N*	%
Female	260/372	70
Age, median (range)	372/372	84.5 (79.9, 88.2)
Residence before admission		
Private home	117/364	32
Residential home	96/364	26
Other nursing home	56/364	15
General/ psychiatric hospital	70/364	19
Other	25/364	7
2 most important reasons for admission		
Neuropsychiatric symptoms	227/355	64
Physical health problems	203/355	57
Distress of caregiver	144/355	41
Other reasons	5/355	1
Type of dementia		
Alzheimer disease	167/363	46
Vascular	82/363	23
Alzheimer and vascular	67/363	18
Lewy body/ Parkinson disease	19/363	5
Other types or combinations	28/363	8
Advanced dementia, [†]	28/329	9
CPS [‡] , median (25 th percentile, 75 th percentile)	323/372	3.0 (3.0, 5.0)
Score 0, 1 or 2	70/323	22
Score 3 or 4	143/323	44
Score 5 or 6	110/323	34
GDS [§] score of 7	39/328	12
BANS-S [¶] , median (25 th percentile, 75 th percentile)	362/372	13.0 (9.0, 17.0)
ADL functioning [¶] , median (25 th percentile, 75 th percentile)	359/372	10 (5, 19)
Illness Severity Score ^{**} , median (25 th percentile, 75 th percentile)	326/372	2 (1, 5)
Nutritional status ^{††} , cachectic	46/326	14
Hydration status ^{††} , dehydrated	23/327	7
Weight loss ^{§§}	33/310	11
Characteristics shortly before dying = a maximum of 6 months before death	Total residents who died during follow-up (N = 227)	
	n/N	%
Advanced dementia [†] in the last month of life	80/210	38
CPS [‡] , median (25 th percentile, 75 th percentile)	209/227	5 (3, 5)
Score 0, 1 or 2	16/209	8
Score 3 or 4	63/209	30
Score 5 or 6	130/209	62
GDS [§] score of 7	78/210	41
BANS-S [¶] , median (25 th percentile, 75 th percentile)	200/227	16.0 (13.0, 19.0)
Median time until death in weeks (25 th percentile, 75 th percentile)	199/227	12 (3, 19)

*In some cases, the total number refers not to 372 residents, because of 34 residents died before or shortly after the baseline assessment and therefore the physicians had no chance to complete the baseline assessment prospectively, or because of missing values. We used a shortened baseline assessment, to complete only the data of resident characteristics that we deemed not particularly vulnerable to recall bias.

[†]Advanced dementia = a Global Deterioration Scale score of 7 and a Cognitive Performance Scale of 5 of 6.

[‡]CPS = Cognitive Performance Scale.

[§]GDS = a Global Deterioration Scale.

[¶]BANS-S = Bedford Alzheimer Nursing Severity-Scale (theoretical range 7-28, with higher scores indicating more severe dementia); the range of BANS-S scores at baseline was 7 to 28.

[¶]ADL-functioning = Activities of Daily Living Scale-Long Form (range 0-28, with higher scores indicating more dependency).

^{**}Illness Severity Score = scores range from 1 to 9, with higher scores indicating more severe illness.

^{††}Nutritional status, cachectic = cachectic (very cachectic/cachectic), or not cachectic (normal/adipeus/very adipeus).

^{††}Hydration status, dehydrated = dehydrated (mildly dehydrated/dehydrated/severely dehydrated) or not.

^{§§}Weight loss = weight loss of 5% or more in last month, or 10% or more in the last 6 months.

Table 3. The median length of time until the first pneumonia, symptoms and health condition (n = 103)

Items*	n/N [†]	%
Median length of time from admission to pneumonia, in months (25 th percentile, 75 th percentile)	103/103	6.5 (2.2, 15.7)
Advanced dementia [‡] at baseline	5/93	5
Advanced dementia [‡] before pneumonia [§]	12/74	16
BANS-S [¶] score at baseline, median (25 th percentile, 75 th percentile)	101/103	13.0 (9.0, 16.7)
BANS-S [¶] score before pneumonia [§] , median (25 th percentile, 75 th percentile)	75/103	14.0 (10.0, 18.0)
X-ray performed (and positive) [#]	4/90	4
Sputum examination performed	1/90	1
Blood examination performed	17/91	19
(Suspected) cause aspiration	25/88	28
Systolic blood pressure assessed	51/89	57
Mean (sd)**	49/51	123 (23)
Pulse rate per minute, assessed	70/98	71
Mean, per minute (sd)**	77/79	90 (17)
Temperature, assessed ^{††}	86/99	87
mean (sd)**	85/86	38.2° Celsius (0.8)
Respiratory rate per minute, assessed	38/94	40
Mean rate, per minute (sd)**	37/38	31 (10)
Dyspnea	72/98	73
Decreased alertness	40/97	41
Decubitus	4/97	4
Min 1.5 l/day drunk in last week	43/92	47
Eating dependency		
Independent	20/94	21
Requires assistance	45/94	48
Fully dependent	29/94	31
Risk score ^{††} , mean (sd)**	60/89	13.8 (4.6)
Estimated risk of death within 14 days ^{††}	60/89	16

*Because of the observational nature, the physicians were not requested to perform additional assessments for purpose of the study.

[†]Total number does not refer to total number of 103, because of missings, and because 22 residents developed the first pneumonia before the baseline assessment. The number refers to the cases who developed the first pneumonia. This includes 38 residents who also developed an intake problem.

[‡]Advanced dementia = a Global Deterioration Scale score of 7 and a Cognitive Performance Scale of 5 of 6.

[§]Assessment was maximal 6 months before developing pneumonia.

[¶]BANS-S = Bedford Alzheimer Nursing Severity-Scale (theoretical range 7-28, with higher scores indicating more severe dementia); the range of BANS-S scores at baseline was 7 to 24; 20% of the residents had a BANS-S score of 7 to 9, which implies that those residents were not completely dependent for any of the ADL items).

[#]X-ray was obtained for 4 residents, which were all positive for pneumonia.

**sd = standard deviation.

^{††}Temperature was assessed rectally in 73%, auricularly 22%, axillary 5%.

^{††}Risk score to estimate risk of death within 14 days in patients with pneumonia, and dementia when treated *with* antibiotics (89 residents received antibiotics of whom 60 had completed data for estimating the risk score).

The relationship between pneumonia, intake problems and severity of dementia During follow-up, 103 (28%) residents developed pneumonia, 126 (34%) residents developed intake problems, and 38 (10%) developed both pneumonia and an intake problem. The most important symptoms and health conditions of the residents with pneumonia and/or intake problems are shown in Table 3 and Table 4. The hazard rate of developing pneumonia in the first year was 0.27 (95% CI, 0.20-0.33), and the hazard rate of developing intake problems in the first year was 0.29 (95% CI, 0.23-0.35).

Table 4. The median length of time until the first intake problem, health condition, and primary reason for the intake problem (N = 126)

Items	n/N*	%
Median length of time from admission to intake problem, in months (25 th percentile, 75 th percentile)	125/126	7.6 (2.3, 17.0)
Advanced dementia [†] at baseline	11/109	10
Advanced dementia [†] before intake problem [†]	17/94	18
BANS-S [§] score at baseline (median, range)	126/126	14.0 (10.0, 18.0)
BANS-S [§] score before intake problem [†] , median (25 th percentile, 75 th percentile)	96/126	15.5 (12.0, 19.0)
New acute medical illness	32/119	27 [¶]
Became too weak or large decline	25/119	21
Refusal to eat or drink but unknown cause	20/119	17
Swallowing problem	13/119	11
No appetite	12/119	10
Unexplained decrease oral intake or weight loss	11/119	9
Unable to eat independently	10/119	8
Chewing problem	9/119	8
Refusals to eat or drink because of suspected depression	7/119	6
Eating apraxia	6/119	5
Other reasons (eg, teeth problems, nausea)	18/119	15

*Total number does not refer to total number of 126, because of missings, and because 23 residents developed the first intake problem before the baseline assessment. The number refers to the cases when residents developed a first intake problem. This includes the 38 residents who also developed a pneumonia.

[†]Advanced dementia = a Global Deterioration Scale score of 7 and a Cognitive Performance Scale of 5 of 6.

[‡]Assessment was maximum of 6 months before developing an intake problem.

[§]BANS-S = Bedford Alzheimer Nursing Severity-Scale (theoretical range 7-28, with higher scores indicating more severe dementia); the range of BANS-S scores at baseline was 7 to 23; 13% of the residents had a BANS-S score of 7 to 9, which implies that those residents were not completely dependent for any of the ADL items). The BANS-S includes an eating-item (degree of dependency); however, "unable to eat independently" was the underlying cause of intake problems in only 8% of cases.

[¶]Total percentages do not refer to total number of 119, because more reasons per resident were possible.

At baseline there were no significant differences in BANS-S scores and proportion of advanced dementia between the residents who did or did not develop pneumonia. The median BANS-S score before developing a pneumonia was 14.0 (range, 7 to 24; 20% of the residents had a BANS-S score of 7-9). More severe dementia, in terms of BANS-S scores, was significantly associated with a higher risk of developing pneumonia, the Hazard ratio (HR) per point increment BANS-S score was 1.07 [95% CI, 1.01-1.14; Table 1 (2a) and Fig. 1].

Residents who developed an intake problem had more severe dementia at baseline (a higher BANS-S score, mean difference 1.5, 95% CI, 0.6-2.4), than residents who did not, but there was no significant difference in the proportions of advanced dementia. The median BANS-S score before developing an intake problem was 15.5 (range, 7 to 23; 13% of the residents had a BANS-S score of 7 to 9). More severe dementia was associated with a higher risk of developing intake problems, with a HR of 1.16 per point increment BANS-S score [95% CI, 1.10-1.23; Table 1 (2b) and Fig. 1].

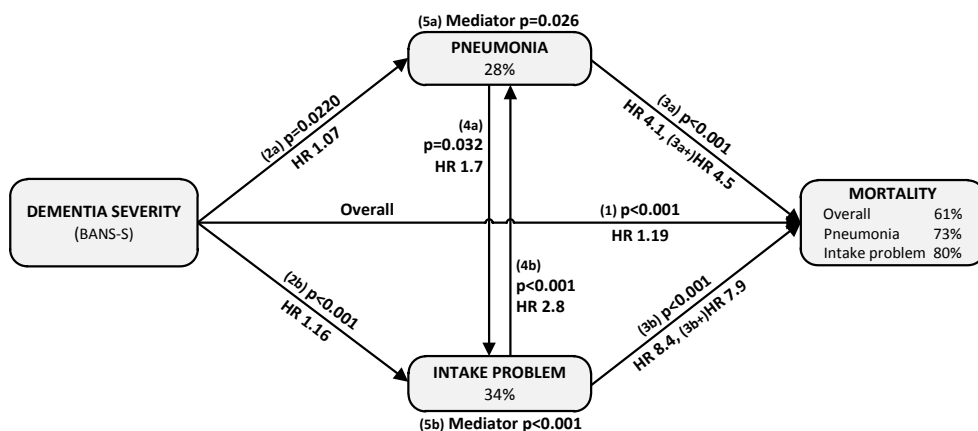


Figure 1. Model of the relationships between dementia severity, pneumonia, intake problems and mortality. Note that Table 1 presents detail about the modelling of the relationships. HR indicates hazard ratio.

Mortality and the mediation of pneumonia and intake problems

During follow-up, 227 (61%) residents died with a median survival time of 8.4 months (25th percentile = 3.9, 75th percentile = 17.3). For the first year after admission, the hazard rate of mortality was 0.45 (95% CI, 0.37-0.53). Residents who died had more severe dementia at baseline than the residents who survived during follow-up (a higher BANS-S score, mean difference 2.9, 95% CI, 2.1-3.8, and a corresponding larger proportion had advanced dementia: 12% versus 4%, $X^2 = 5.3$, $P = 0.022$). Overall, the median increment in BANS-S score in one year was 1.3 (25th percentile = 0.0, 75th percentile = 3.0). Over the follow-up period, more severe dementia was significantly associated with a higher mortality risk, the HR per point increment BANS-S score was 1.19 [95% CI, 1.14-1.23; Table 1 (1) and Fig. 1].

Of the 103 residents with pneumonia, 75 (73%) died during follow-up with a median survival time of 5 weeks since the development of pneumonia, and of the 126 residents with an intake problem, 101 (80%) residents died, with a median survival time of 4 weeks since the development of intake problems. Pneumonia and intake problems were significantly associated with mortality. When the association between pneumonia and mortality was adjusted for the BANS-S score, the HR remained similar with a change from 4.1 (95% CI, 3.1-5.4), to 4.6 [95% CI, 1.2-6.2; Table 1 (3a, 3a +) and Fig. 1]; similarly, when the association between intake problems and mortality was adjusted for the BANS-S score, the HR changed from 10.2 (95% CI 7.7-13.5) to 6.2 [95% CI, 6.1-11.3; Table 1 (3b, 3b +) and Fig. 1]. Moreover, using the product method of Sobel, we found that the relationship between the severity of dementia and death was significantly mediated by both the development of pneumonia ($P = 0.025$) and intake problems [$P < 0.001$; Table 1 (5a, 5b) and Fig. 1].

DISCUSSION

To our best knowledge, this is the first prospective study exploring how pneumonia and intake problems affect survival in patients with dementia admitted to a long-term care facility. It is also the first study that explores whether and how dementia severity is related to pneumonia, intake problems, and mortality in nursing home residents. We show that after admission, residents frequently developed pneumonia and intake problems, which in turn were important risk factors for mortality, regardless the stage of dementia. Intake problems and pneumonia were more strongly associated with mortality than severity of dementia. Further, compared to pneumonia, intake problems were a more important risk factor for mortality, and were also more strongly related to more severe dementia in nursing home residents.

Mitchell et al.⁵ reported eating or drinking problems in 85.8%, and pneumonia in 41.4% of residents with advanced dementia (CPS score of 5 or 6 and GDS score of 7) during a study period of 18 months. Pneumonia and intake problems are regarded as hallmarks of the advanced stage of dementia, and it is generally accepted that in case of advanced dementia palliation is a reasonable primary goal of care.^{1,5,35} Our study shows that residents with less advanced dementia (range BANS-S scores 7 to 24; CPS < 5 and GDS < 7) also frequently developed pneumonia and intake problems, in line with recently reported findings from an after-death study.³⁶

Dementia severity is a risk factor for mortality in nursing home residents with dementia, but pneumonia and intake problems were found to be even more important risk factors and were both partly dependent on dementia severity. Our study found that almost 3 per 10 residents developed at least one pneumonia in the first year, and of the residents who died (after

developing a pneumonia) during follow-up the median survival time was just 5 weeks. Even so, 3 per 10 residents developed an intake problem in the first year and of the residents who died, the median survival time was just 4 weeks. Other studies also concluded that pneumonia and intake problems often occur in patients with dementia, and are associated with poorer survival; however, these studies are limited to advanced dementia, or limited to patients who developed a pneumonia.^{35;37;38} We found that compared to pneumonia, intake problems are more strongly associated with both the progression of dementia and mortality.

Strengths and limitations

Our study is unique in that we performed longitudinal survival analyses and studied jointly the severity of the dementia, pneumonia and intake problems. Pneumonia diagnoses were based on clinical judgment and in most cases not confirmed by X-ray. However, since this is consistent with usual diagnostic procedures in Dutch primary care and long-term care²⁶ and elsewhere,³⁹ it increases the relevance for the clinical practice. Some limitations should be acknowledged. First, this study is limited to residents who were newly admitted to a long-term care facility. Therefore, our findings may not be generalizable to patients who live in the community; however, our study population consists of nursing home residents with variable stages of dementia (the range of BANS-S scores covers the theoretical range of the BANS-S scores) and who were just newly admitted to a long-term care facility. In addition, the majority of people with dementia in the United States and Western Europe are admitted to or die in long-term care facilities.⁴⁰ Second, our definition of intake problems includes different underlying causes of intake problems (eg, new acute medical illness, became too weak or strong decline, swallowing problem). The associations we found for intake problems may differ in strength for different underlying causes of intake problems, but subgroup analyses were not feasible because of small numbers in each category. In addition, the BANS-S includes an eating-item (degree of dependency), which may have influenced the association with intake problems. However, "unable to eat independently" was the underlying cause of intake problems in only 8% of cases. Third, joint models could not be used to model all the longitudinal covariates because the JM R package cannot handle dichotomous time-dependent covariates.³⁰ Fourth, because not all the relationships were estimated by joint models, it was not possible to test the strength of the mediation of pneumonia and intake problems by comparing C-coefficients of models with and without the mediator. Therefore, we used the product method to compute indirect effects, which is also an accepted method of mediation. Finally, proposed mechanisms for increased mortality due to pneumonia in dementia include swallowing problems, poor dentition, decreased mobility and impaired immune function, which presumably are also related to intake problems.^{38;41} However, the statistical power was limited for the analyses of inter-relation between pneumonia and intake problems, because only 38 residents had both pneumonia and intake problems.

Recommendations

Dementia is a disease without cure and following nursing home admission, residents of dementia special care units have a high risk of developing pneumonia and intake problems with poor survival. Moreover, developing pneumonia and intake problems involved elevated levels of suffering and might be the most common end-of-life complications.^{4,8,42,43} Therefore, developing pneumonia and intake problems are import signals to consider palliative care actions.

Our findings may also have implications for the timing and initiation of advance care planning. Preferably, advance care planning should start directly after nursing home admission, or perhaps even earlier, provided that people are open and willing to look ahead and plan for the future.⁹ In any case: our study suggests that we should not wait until the stage of advanced dementia. Providing accurate information about the course of dementia and expected health problems may facilitate adequate palliative care for nursing home residents with dementia, and may help patients and families prepare for the future.

Future studies may explore whether patients and their families are receptive to start advance care planning in an early phase of the disease, and how advance care planning could be facilitated in an early phase. Further, there is a strong policy tendency to postpone nursing home admission as long as possible. As a consequence, there will be more and more patients living at home and treated in primary care with more severe stages of dementia. Therefore, future studies may investigate whether a palliative care approach is also relevant in patients with dementia in primary care.

Conclusion

Pneumonia and intake problems are not limited to, or typical of, advanced dementia. Moreover, these health-problems are important risk factors for mortality in nursing home residents in all stages of dementia. The high risk of developing pneumonia and intake problems, and the poor survival of residents with dementia in a long-term care facility even shortly after admission, call for a palliative care approach and an active focus on advance care planning upon nursing home admission, or preferably earlier. Informing patients and families about the course of dementia and expected health problems may help to formulate realistic care goals and to translate these goals into appropriate palliative care. Addressing palliative care needs may benefit residents in all stages of dementia and should not be a privilege for patients with advanced dementia only.

ACKNOWLEDGMENTS

We would like to thank Prof. David Mehr and Dr. Liz Sampson for their suggestions to an earlier version of the manuscript.

REFERENCES

1. van der Steen JT, Radbruch L, Hertogh CM et al. White paper defining optimal palliative care in older people with dementia: a Delphi study and recommendations from the European Association for Palliative Care. *Palliat Med* 2014;28:197-209.
2. Houttekier D, Cohen J, Bilsen J, ddington-Hall J, Onwuteaka-Philipsen BD, Deliens L. Place of death of older persons with dementia. A study in five European countries. *J Am Geriatr Soc* 2010;58:751-756.
3. van der Steen JT, Ribbe MW, Deliens L, Gutschow G, Onwuteaka-Philipsen BD. Retrospective and prospective data collection compared in the Dutch End Of Life in Dementia (DEOLD) study. *Alzheimer Dis Assoc Disord* 2014;28:88-94.
4. Vandervoort A, Van den Block L, van der Steen JT et al. Nursing home residents dying with dementia in Flanders, Belgium: a nationwide postmortem study on clinical characteristics and quality of dying. *J Am Med Dir Assoc* 2013;14:485-492.
5. Mitchell SL, Teno JM, Kiely DK et al. The clinical course of advanced dementia. *N Engl J Med* 2009;361:1529-1538.
6. Volicer L, Seltzer B, Rheaume Y et al. Eating difficulties in patients with probable dementia of the Alzheimer type. *J Geriatr Psychiatry Neurol* 1989;2:188-195.
7. Teno JM, Coppola KM. For every numerator, you need a denominator: a simple statement but key to measuring the quality of care of the "dying". *J Pain Symptom Manage* 1999;17:109-113.
8. Hendriks SA, Smalbrugge M, Hertogh CM, van der Steen JT. Dying with dementia: symptoms, treatment, and quality of life in the last week of life. *J Pain Symptom Manage* 2014;47:710-720.
9. Hertogh CM. Advance care planning and the relevance of a palliative care approach in dementia. *Age Ageing* 2006;35:553-555.
10. Koopmans RT, van der Sterren KJ, van der Steen JT. The 'natural' endpoint of dementia: death from cachexia or dehydration following palliative care? *Int J Geriatr Psychiatry* 2007;22:350-355.
11. Vandervoort A, Houttekier D, Van den Block L, van der Steen JT, Vander SR, Deliens L. Advance care planning and physician orders in nursing home residents with dementia: a nationwide retrospective study among professional caregivers and relatives. *J Pain Symptom Manage* 2014;47:245-256.
12. van der Steen JT. Dying with dementia: what we know after more than a decade of research. *J Alzheimers Dis* 2010;22:37-55.
13. Todd S, Barr S, Roberts M, Passmore AP. Survival in dementia and predictors of mortality: a review. *Int J Geriatr Psychiatry* 2013;28:1109-1124.
14. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology* 1984;34:939-944.
15. Roman GC, Tatemichi TK, Erkinjuntti T et al. Vascular dementia: diagnostic criteria for research studies. Report of the NINDS-AIREN International Workshop. *Neurology* 1993;43:250-260.
16. McKeith IG, Galasko D, Kosaka K et al. Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): report of the consortium on DLB international workshop. *Neurology* 1996;47:1113-1124.
17. van der Steen JT, Volicer L, Gerritsen DL, Kruse RL, Ribbe MW, Mehr DR. Defining severe dementia with the Minimum Data Set. *Int J Geriatr Psychiatry* 2006;21:1099-1106.
18. Morris JN, Fries BE, Morris SA. Scaling ADLs within the MDS. *J Gerontol A Biol Sci Med Sci* 1999;54:M546-M553.
19. Oye RK. A simple method for rating illness severity at admission and expected functional status at discharge: how should we use the information? *Am J Med* 2000;109:250-251.
20. Charlson ME, Hollenberg JP, Hou J, Cooper M, Pochapin M, Pecker M. Realizing the potential of clinical judgment: a real-time strategy for predicting outcomes and cost for medical inpatients. *Am J Med* 2000;109:189-195.

21. Health Care Financing Administration. Long-Term Care Facility Resident Assessment Instrument (RAI) User's Manual. Washington,DC: Health Care Financing Administration; 1995.
22. Volicer L, Hurley AC, Lathi DC, Kowall NW. Measurement of severity in advanced Alzheimer's disease. *J Gerontol* 1994;49:M223-M226.
23. Bellelli G, Frisoni GB, Bianchetti A, Trabucchi M. The Bedford Alzheimer Nursing Severity scale for the severely demented: validation study. *Alzheimer Dis Assoc Disord* 1997;11:71-77.
24. Reisberg B, Ferris SH, de Leon MJ, Crook T. The Global Deterioration Scale for assessment of primary degenerative dementia. *Am J Psychiatry* 1982;139:1136-1139.
25. Morris JN, Fries BE, Mehr DR et al. MDS Cognitive Performance Scale. *J Gerontol* 1994;49:M174-M182.
26. van der Steen JT, Mehr DR, Kruse RL et al. Predictors of mortality for lower respiratory infections in nursing home residents with dementia were validated transnationally. *J Clin Epidemiol* 2006;59:970-979.
27. EMGO Institute. The Risk Score for Patients With Pneumonia and Dementia Explanation and Background. Amsterdam: VU University Medical Center; 2010. Available at: <http://www.emgo.nl/files/119.2010>. Accessed January 19, 2016.
28. EMGO Institute. Risk Score in Pneumonia and Dementia. Amsterdam: VU University Medical Center; 2008. Available at: <http://www.emgo.nl/files/105>. Accessed January 19, 2016.
29. Byrne EJ, Benoit M, Lopez Arrieta JM et al. For whom and for what the definition of severe dementia is useful: an EDCON consensus. *J Nutr Health Aging* 2008;12:714-719.
30. Rizopoulos D. Joint Models for Longitudinal and Time-to-Event Data With Applications in R Joint Models for Longitudinal and Time-to-Event Data. Boca Raton: Chapman and Hall/CRC Biostatistics Series; 2012.
31. Preacher KJ, Hayes AF. Asymptotic and resampling strategies for assessing and comparing indirect effects in multiple mediator models. *Behav Res Methods* 2008;40:879-891.
32. Sobel ME. Asymptotic intervals for indirect effects in structural equations models. *Social Methodol.* 1982;13:290-312.
33. Preacher KJ, Leonardelli GJ. Calculation for the Sobel test. An interactive calculation tool for mediation tests; 2014. Available at: <http://www.quantpsy.org/sobel/sobel.htm>. Accessed January 19, 2016.
34. R Core Team. R: A Language and Environment for Statistical Computing. Vienna, Austria: R Foundation for Statistical Computing; 2013. Available at: <http://www.R-project.org/> Accessed. Accessed January 19, 2016.
35. Mitchell SL, Kiely DK, Hamel MB, Park PS, Morris JN, Fries BE. Estimating prognosis for nursing home residents with advanced dementia. *JAMA* 2004;291:2734-2740.
36. Vandervoort A, Houttekier D, Vander SR, van der Steen JT, Van den Block L. Quality of dying in nursing home residents dying with dementia: does advanced care planning matter? A nationwide postmortem study. *PLoS One* 2014;9:e91130.
37. Hanson LC, Ersek M, Lin FC, Carey TS. Outcomes of feeding problems in advanced dementia in a nursing home population. *J Am Geriatr Soc* 2013;61:1692-1697.
38. van der Steen JT, Ooms ME, Mehr DR, van der Wal G, Ribbe MW. Severe dementia and adverse outcomes of nursing home-acquired pneumonia: evidence for mediation by functional and pathophysiological decline. *J Am Geriatr Soc* 2002;50:439-448.
39. Helton MR, Cohen LW, Zimmerman S, van der Steen JT. The importance of physician presence in nursing homes for residents with dementia and pneumonia. *J Am Med Dir Assoc* 2011;12:68-73.
40. Reyniers T, Deliëns L, Pasman HR et al. International variation in place of death of older people who died from dementia in 14 European and non-European countries. *J Am Med Dir Assoc* 2015;16:165-171.
41. Kelaiditi E, Demougeot L, Lilamand M, Guyonnet S, Vellas B, Cesari M. Nutritional status and the incidence of pneumonia in nursing home residents: results from the INCUR study. *J Am Med Dir Assoc* 2014;15:588-592.

42. van der Steen JT, Ooms ME, Van der WG, Ribbe MW. Pneumonia: the demented patient's best friend? Discomfort after starting or withholding antibiotic treatment. *J Am Geriatr Soc* 2002;50:1681-1688.
43. van der Maaden T, van der Steen JT, de Vet HC, Hertogh CM, Koopmans RT. Prospective Observations of Discomfort, Pain, and Dyspnea in Nursing Home Residents With Dementia and Pneumonia. *J Am Med Dir Assoc* 2016; 17: 128-135.



Chapter 4

From admission to death: Prevalence and course of pain, agitation, and shortness of breath, and treatment of these symptoms in nursing home residents with dementia

Simone A. Hendriks
Martin Smalbrugge
Francisca Galindo-Garre
Cees M.P.M. Hertogh
Jenny T. van der Steen

Published in Journal of the American Medical Directors Association 2015; 16:475-81

Awarded the "Jaarprijs palliatieve zorg 2015".

ABSTRACT

Objectives: Burdensome symptoms frequently develop as part of the dementia trajectory and influence quality of life. We explore the course of symptoms and their treatment during nursing home stay to help target adequate symptom management.

Design: Data were collected as part of the Dutch End of Life in Dementia study, a longitudinal observational study with up to 3.5 years of follow-up. Physicians performed assessments at baseline, semiannually, and shortly after death of pain, agitation, shortness of breath, and treatment provided for these symptoms.

Setting: Long-term care facilities (28) in the Netherlands.

Participants: Newly admitted nursing home residents (372) in variable stages of dementia.

Measurements: We described prevalence and course of symptoms, and treatment provided for these symptoms. We used generalized estimating equations to evaluate the longitudinal change in symptoms and their treatment, and the associations between the symptoms of pain and agitation, as well as between stage of dementia and symptoms.

Results: Pain was common (varying from 47% to 68% across the semiannual assessments) and frequently persistent (36%-41% of all residents); it increased to 78% in the last week of life. Agitation was the most common symptom (57%-71%), and also frequently persistent (39%-53%), yet it decreased to 35% in the last week of life. Shortness of breath was less common (16%-26%), but it increased to 52% at the end of life. Pain was not significantly associated with agitation. Advanced dementia was associated with more pain only. Treatment changed in particular at the end of life. Pain was treated mostly with acetaminophen (34%-52%), and at the end of life with parenteral opioids (44%). Agitation was mostly treated nonpharmacologically (78%-92%), and at the end of life anxiolytics were the most frequently prescribed treatment (62%). Overall, aerosolized bronchodilators were the most frequently prescribed treatment for shortness of breath (29%-67%), but at the end of life, this was morphine (69%).

Conclusion: Pain and agitation were common and frequently persisted in residents with dementia during nursing home stay, but symptom management intensified only at the end of life. Symptom control may be suboptimal from admission, and a stronger focus on symptom control is needed at an earlier stage than the end of life.

INTRODUCTION

Burdensome symptoms frequently occur in patients with dementia, while adequate symptom control is important to maintain or improve quality of life.¹ In the United States and Western Europe, most people with dementia are eventually admitted to, and die in long-term care facilities.^{2,3} Pain, agitation, and shortness of breath are the most prevalent and important symptoms at the end of life.⁴ At any given time, 12% to 76% of nursing home residents are in pain and prevalence may increase when death approaches,^{4,5} and up to 80% present with challenging behavior.^{6,7} More severe dementia may be associated with more pain^{8,9} and with more agitation.^{10,11} The rates of shortness of breath vary widely, from 8% to 80%.⁴ Optimal symptom control needs a holistic approach because symptoms may be interrelated; for example, pain may be associated with agitation.¹²⁻¹⁵

These findings are from work that has several specific limitations. First, study populations are often limited to advanced dementia,⁵ whereas in the Netherlands, half of all patients with dementia may die before having reached this stage.¹⁶ Second, most studies are limited to the period shortly before dying,⁴ whereas symptoms present earlier.¹ Last, data collection is frequently limited to retrospective collection or fixed periods per individual.^{12,17} In addition, there are few studies on how specific symptoms are managed with pharmacological and nonpharmacological treatment.⁹

To achieve adequate symptom control in dementia, a better understanding is needed of the longitudinal course of symptoms and the treatment provided.¹⁸ Therefore, the objectives of this study were to explore changes in symptoms and provided treatment in Dutch nursing home residents in variable stages of dementia during their nursing home stay. We report on the prevalence and course of pain, agitation, and shortness of breath. We explore the longitudinal association between pain and agitation, and between stage of dementia and symptoms. Furthermore, we report on specific pharmacological and nonpharmacological treatment provided for pain, agitation, and shortness of breath during nursing home stay.

METHODS

Data Collection

Data were collected as part of a longitudinal observational study, the Dutch End of Life in Dementia study. Between 2007 and 2011, data were prospectively and retrospectively collected on 491 residents in 34 long-term care facilities, nursing homes, and affiliated residential homes. In this article, we used only prospectively collected data from 28 facilities (23 nursing homes and 5 residential care facilities that the physicians visit from their nursing home practice) on 372 newly

admitted residents. Elderly care physicians, who are certified after 3 years of training, employed by the nursing homes were responsible for data collection. The residents had a physician's diagnosis of dementia in all possible stages. A total of 372 residents were enrolled on admission between January 2007 and July 2009; during the study period, 218 residents died before summer 2010.¹⁶

Individual assessments were performed for a maximum period of 3.5 years (January 2007-July 2010; and survival was monitored for an additional year, until summer 2011). The baseline measurement was carried out 8 weeks after admission, and it was followed by a maximum of 5 semiannual assessments. We refer to the baseline measurement and the semiannual assessments as regular assessments. In case of death during the study period, a questionnaire about the last week of life was completed within 2 weeks after death, and we refer to this questionnaire as the after-death assessment. The study protocol was approved by the Medical Ethics Review Committee of the (VU University Medical Center in Amsterdam), and written consent was obtained from all participants or their families.

Measurements

The diagnosis of dementia was based on international guidelines.¹⁹⁻²² Type of dementia was assessed with a prestructured item comprising the categories Alzheimer disease, vascular dementia, Alzheimer disease and vascular dementia, Lewy body/Parkinson disease, and other. Advanced dementia (versus less advanced dementia) was defined as a maximum score of 7 on the Global Deterioration Scale (GDS)²³ and a score of 5 or 6 on the Cognitive Performance Scale (CPS, range 0-6).²⁴

The physicians assessed frequency of pain and shortness of breath as "never," "rarely" (< 5 days a month), "sometimes" (5-10 days per month), "often" (11-20 days/month), and "almost daily" (> 20 days per month). The frame of reference was the previous month for the baseline assessments, and the 3 months before the semiannual assessments (frequency on average per month over last 3 months). During the last week of life, the physicians assessed frequency of pain and shortness of breath as "never," "rarely" (≤ 1 day), "sometimes" (2-3 days), "often" (4-5 days), and "almost daily" (6-7 days). We dichotomized into "never" versus "other" for all assessments. Prevalence of agitation, such as restlessness, calling out, resistance to care, verbal aggression, or physical aggression was assessed as present or not, during the month before baseline, the 3 months before the semiannual assessments, and during the last week of life.

Treatment provided for pain, agitation, and shortness of breath was assessed using prestructured items. The categories for pain treatment were nonpharmacological (eg, physiotherapy, occupational therapy, transcutaneous electrical neurostimulation, massage); acetaminophen (paracetamol); nonsteroidal anti-inflammatory drugs (NSAIDs); oral narcotic; parenteral narcotic (including transdermal patch), each separately assessed as PRN ("as needed") only or scheduled

dose; other; and no therapy. Treatment provided for agitation comprised nonpharmacological treatments (eg, 1:1 sitter, separate, involve family to participate in care), trunk or limb restraints, antipsychotic medication, anxiolytic or hypnotic medication, other, and no therapy. Finally, treatment of shortness of breath was prestructured as oxygen, morphine, aerosolized bronchodilators, diuretics, other, and no therapy.

Analyses

We analyzed the results by taking 2 perspectives, one prospective, reporting on consecutive regular follow-up assessments, and the other retrospective, anchoring the after-death assessment and following back to the last regular assessment. For the follow-back analyses, we selected the last regular assessment before death from the assessments 1 through 6. For each assessment, we described symptom prevalence. To investigate the individual course of symptoms in more detail, we calculated the following frequency parameters for each consecutive assessment: persistence of a symptom and persistence of no symptom, incidence, and resolution of a symptom relative to the total number of residents at the assessments concerned. A symptom persisted if it occurred on 2 consecutive assessments, or a symptom was persistently absent if it did not. Incidence was defined as a symptom present at one assessment but not present at the previous assessment. We defined resolution as presence of a symptom at one assessment but not at the next assessment. For each assessment, we described the targeted treatment and for the most frequently provided treatments we calculated the proportion of continued treatment in case of a persistent symptom.

To evaluate the longitudinal associations (change in symptoms, and change in treatment), we used the generalized estimating equation (GEE) model, with an exchangeable correlation structure. We evaluated 5 models of longitudinal associations. Three models used assessment as the independent predictor with repeated contrast levels: (1) change in symptoms; (2) course of symptoms, with persistency and persistency of no symptoms; (3) change in provided treatment. Further, we evaluated the longitudinal association between (4) pain and agitation, with agitation as the dependent variable and pain as the independent variable. The final model (5) represented the association between the stage of dementia (less advanced dementia versus advanced dementia was the independent variable) and the presence of symptoms. For models 1, 3, 4, and 5, we separately analyzed the follow-up perspective (the regular assessments 1 through 6), and the follow-back perspective (last regular assessment and the after-death assessment). For model 2, we analyzed the follow-up perspective only, because at least 3 assessments are needed for the analysis of the course of symptoms (change in persistency). For the follow-up perspective analyses, we adjusted for the last regular assessment before death. For all follow-back perspective analyses, we adjusted for the exact number of days between the 2 assessments. We defined a significant difference as a *P* value less than .05. A significant change between 2 consecutive assessments indicates a change at the population level (ie, change in the total proportion of residents with a symptom) or at an individual level (ie, the individual change in symptoms). Detail

on the statistical analyses is available on request. Analyses were performed with PASW 20.0 (SPSS, Inc., Chicago, IL 2013).

RESULTS

Residents

Most residents were women, 9% had advanced dementia at admission and 38% at death. The most common type of dementia was Alzheimer disease (46%; Table 1). Through follow-up, the number of residents decreased across consecutive assessments because residents died or reached the conclusion of data collection (possible from assessment [A] 3 onward). In total, 218 residents died during follow-up, with a median survival time of 8 months from admission. In case of death, the median length of time between the last regular assessment and the after-death assessment was 13 weeks (25th percentile = 8, 75th percentile = 21). The median length of time between the day of death and the day the physician completed the after-death questionnaires was 16 days (first quartile = 1 day, second quartile = 8 days, third quartile = 32 days, fourth quartile = 214 days). Ten residents were lost to follow-up because they moved to another long-term care facility, or the physician withdrew from data collection. Detail on number of residents through data collection is available from online resource Figure 1.

Table 1. Resident characteristics

Characteristics	n = 372	
Female, %	70	
Age at admission, mean (SD)	84	(7)
Age at death, mean (SD)*	85	(7)
Median length of stay until death (months), (25 th perc, 75 th perc)*	8	(4, 17)
Type of dementia, %		
Alzheimer disease	46	
Vascular	23	
Alzheimer and vascular	18	
Lewy body/ Parkinson disease	5	
Other types	8	
Advanced dementia at admission, % [‡]	9	
Advanced dementia at death, % [‡]	38	
Residence before admission, %		
Private home	32	
Residential home / other nursing home	42	
General / psychiatric hospital	19	
Other	7	

*Percentage refers to 213 residents who died during the follow-up period with completed after-death assessments.

[‡]Percentage refers to 329 residents. This is because for the residents who died before or shortly after the baseline assessment, we used a shortened baseline assessment, to complete only the data of resident characteristics which we deemed not particularly vulnerable to recall bias.

General patterns of change in symptoms over time

Overall, the prevalence of pain, agitation, and shortness of breath changed marginally across the regular assessments (Table 2, online resource Figures 2-4). Moreover, we found only 2 significant changes: the prevalence of pain at A2 was significantly higher than at A1, and the prevalence of shortness of breath was significantly higher at A3 compared with at A2. In the last week of life, however, the (overall) prevalence of pain and shortness of breath increased, while the prevalence of agitation decreased significantly (Table 2, online resource Figures 2-4), as detailed in the following sections.

Pain

Table 2 (and online resource Figure 2) provides details on the prevalence of and change in pain, and shows the course over the consecutive assessments. Across the regular assessments, the prevalence of pain varied from 47% to 68%, and the prevalence at A2 was significantly higher than at A1 ($P = .004$; Table 2). Pain persisted in many residents (ie, in 36%-41%) across the consecutive regular assessments. Further, the proportion of persistent pain at A3 was significantly ($P = .006$) higher than at A2. At 20% to 35%, the proportion of residents without pain on 2 consecutive regular assessments was much lower. Only at A3 versus A2 did we find a significantly ($P = .017$) lower proportion of residents with persistent absence of pain.

An intermittent course of pain in some residents is illustrated by incidence proportions of 6% to 24%, and resolution of pain proportions of 10% to 13% across the consecutive regular assessments.

Further, over the last weeks of life the (overall) prevalence of pain increased significantly (from 67% to 78% ($P = .011$; Table 2). We also found a significantly ($P = .009$) smaller proportion of residents with persistent absence of pain at the after-death assessment (versus the last regular assessment before death).

Agitation

Table 2 (and online resource Figure 3) shows the prevalence of and change in agitation, and shows the course over the consecutive assessments. Across the regular assessments, agitation was the most prevalent symptom, varying from 57% to 71%, and it did not differ significantly between the assessments. Agitation persisted in 39% to 53% of all residents. There were no significant changes in the proportion of persistency between the consecutive regular assessments. At 9% to 25%, the proportion of residents with absence of agitation on 2 consecutive regular assessments was much smaller and it did not change significantly. An intermittent pattern of agitation occurred in some residents, with 6% to 17% incident agitation, and 11% to 18% resolution of agitation.

Yet, in the last week of life, the prevalence of agitation decreased significantly (from 58%) to 35%. We also found a significantly ($P < .001$) larger proportion of residents with persistent agitation at the after-death assessment (versus the last regular assessment before death).

Table 2. The prevalence and change in symptoms over 2 consecutive assessments

Symptom	Assessment		Prevalence		Change
		(n; m)*	%	n	P^{\ddagger}
Pain	A1	(327; 7)	52	171	
	A2	(221; 30)	61	134	0.004
	A3	(170; 36)	68	115	0.093
	A4	(120; 18)	58	70	0.135
	A5	(77; 9)	56	43	0.693
	A6	(34; 3)	47	16	0.350
	A<† [§]	(162; 33)	67	108	
	A†	(211; 6)	78	165	0.011
Agitation	A1	(328; 6)	57	188	
	A2	(221; 30)	58	128	0.941
	A3	(170; 36)	62	105	0.263
	A4	(120; 18)	57	68	0.208
	A5	(77; 9)	66	51	0.258
	A6	(34; 3)	71	24	0.894
	A<† [§]	(163; 30)	58	94	
	A†	(213; 4)	35	75	<0.001
Shortness of breath	A1	(327; 7)	19	62	
	A2	(219; 32)	18	39	0.891
	A3	(170; 36)	24	41	0.018
	A4	(120; 18)	16	19	0.059
	A5	(77; 9)	25	19	0.144
	A6	(34; 3)	26	9	0.813
	A<† [§]	(163; 30)	28	46	
	A†	(213; 4)	52	111	<0.001

As also described in the methods, for the follow-up perspective analyses (A1 through A6) we adjusted for the last regular assessment before death. For the follow-back perspective analyses (A<† through A†), we adjusted for the length of time between these two consecutive assessments.

The complete output of the GEE analyses is available upon request.

* (n; m) = Number of residents per assessment; number of missing values.

† GEE with repeated contrast between two consecutive assessments. The p-value is an indication for change over time over two consecutive assessments at a population level and at an individual level.

Therefore, even when the total proportion of a symptom is unchanged, significance change is possible due to change of individual patterns. We defined a $P < 0.05$ as significant, and prevalence and p-values of significant changes are bolded.

Online resource Figures 2, 3, and 4 present detail about the course of symptoms.

§ A<† = The last regular assessment before death is one of A1 through A6.

|| A† = The after-death assessment.

Shortness of breath

Table 2 (and online resource Figure 4) shows the prevalence of and change in shortness of breath, and shows the course over the consecutive assessments. The prevalence of residents with shortness of breath varied from 16% to 26%, and was significantly higher at A3 than at A2 (in line with Table 2).

The proportion of residents with persistent shortness of breath was small with 8% to 18% over the consecutive regular assessments. There were no significant changes in the proportion of persistency. The proportion of residents with persistently absent shortness of breath was 62% to 75%. Only at A3 versus A2 did we find a significantly ($P = .003$) lower proportion of residents with persistently absent shortness of breath. The proportions residents with incident shortness of breath ranged 6% to 13%, and 3% to 13% for resolution of shortness of breath.

In the last week of life, the prevalence of shortness of breath increased substantially and significantly (from 28%) to 52%, and we also found a significantly ($P < .001$) smaller proportion of residents with persistently absent shortness of breath at the after-death assessment (versus the last regular assessment before death).

Table 3. Longitudinal associations

Association	Assessment	Unadjusted		Adjusted [§]		95% Wald CI	
		OR	Lower	Upper	OR	Lower	Upper
Pain and agitation	A1 - A6	1.2	0.95	1.6	1.2	0.95	1.6
	A<†*- A† [‡]	1.3	0.81	1.2	1.4	0.86	2.3
Advanced dementia and pain	A1 - A6	1.9	1.3	2.7	1.8	1.2	2.6
	A<†*- A† [‡]	1.7	1.0	3.1	1.7	0.94	3.2
Advanced dementia and agitation	A1 - A6	1.3	0.87	2.0	1.3	0.88	2.0
	A<†*- A† [‡]	0.84	0.53	1.3	0.87	0.54	1.4
Advanced dementia and Shortness of breath	A1 - A6	1.3	0.90	2.0	1.3	0.85	2.0
	A<†*- A† [‡]	0.89	0.56	1.4	1.03	0.63	1.7

In case of A<†-A†: we adjusted for the length of time between these two consecutive assessments. We defined a $P < 0.05$ as significant and ORs of significant associations are bolded.

GEE for longitudinal associations.

*A<† = The last regular assessment before death is one of A1 through A6.

†A† = The after-death assessment.

§In case of A1 through A6, we adjusted for the last regular assessment before death.

Association between pain and agitation

Across the regular assessments, the prevalence of simultaneously reported pain and agitation in residents varied from 29% to 42%, and in the last week of life it was 27%. We found a

positive but insignificant longitudinal association between presence of pain and agitation across the regular assessments (adjusted odds ratio [OR] 1.2; confidence interval [CI] 0.95-1.6) and across the last regular assessment and the after-death assessment (adjusted OR 1.4; CI 0.86-2.3; Table 3).

Association between the stage of dementia and the presence of symptoms

We found a significant longitudinal association between advanced dementia (versus less advanced dementia) and pain across the regular assessments (adjusted OR 1.8; CI 1.2-2.6), but insignificant across the last regular assessment and the after-death assessment (adjusted OR 1.7; CI 0.94-3.2; Table 3). We did not find a significant association between advanced dementia and agitation (A1 through A6: adjusted OR 1.3; CI 0.88-2.0; A<†-A†: adjusted OR 0.87; CI 0.54-1.4; Table 3). We also did not find an association between advanced dementia and shortness of breath (A1 through A6: adjusted OR 1.3; CI 0.85-2.0; A<†-A†: adjusted OR 1.03; CI 0.63-1.7; Table 3).

Treatment of pain

Table 4 shows the treatment provided for the symptoms. Over the regular assessments, pain was most frequently treated with nonpharmacological treatments (24%-34%) and acetaminophen (paracetamol, 34%-52%). We found a significantly higher percentage of acetaminophen only at assessment 3 versus 2, and a significantly higher percentage of oral narcotics at A3 versus A2. Continued nonpharmacological treatment across the regular assessments ranged from 35% to 67%, and for acetaminophen from 48% to 80%.

Compared with the last regular assessment, at the after-death assessment, a significantly larger proportion of residents received parenteral narcotics PRN (increase from 2% to 17%) or parenteral narcotics (from 5% to 44%). A significantly smaller proportion of residents received nonpharmacological treatment (decrease from 26% to 11%), acetaminophen PRN (from 26% to 11%), and a significantly smaller proportion received no therapy (from 11% to 4%).

Treatment of agitation

Over the regular assessments, treatment provided for agitation was mostly nonpharmacological (78%-92%), or with antipsychotics (27%-46%) or anxiolytics (29%-33%; Table 4). We found only a few significant changes between the regular assessments. Across the regular assessments, continued nonpharmacological treatment ranged from 88% to 100%, continued use of antipsychotics from 58% to 74%, and continued use of anxiolytics from 50% to 75%.

Compared with the last regular assessment, at the afterdeath assessment, a significantly smaller proportion received nonpharmacological treatment (from 85% to 50%), and antipsychotics (from 59% to 44%), and a significantly larger proportion of residents received anxiolytics (from 41% to 62%; Table 4).

Table 4. Treatment provided for symptoms per assessment and change over 2 consecutive assessments

Symptom	Treatment* %	Assessment								Change P value
		A1	A2	A3	A4	A5	A6	A<† [‡]	A† [§]	
Pain (n)		(171)	(133)	(114)	(70)	(42)	(16)	(108)	(157)	
	Non-pharmacological	27	26	24	34	31	25	26	11	[‡] 0.005
	Acetaminophen PRN	26	34	29	21	29	44	26	11	[‡] 0.002
	Acetaminophen	40	34	49 ^{1†}	52	52	38	49	43	0.252
	NSAID PRN	1	4	3	3	2	6	2	1	0.423
	NSAID	13	15	11	15	12	13	14	9	0.269
	Oral narcotic PRN [¶]	1	1	2	0	0	0	1	4	0.307
	Oral narcotic [¶]	5	2	8 ^{2†}	6	2	0	6	10	0.203
	Parental narcotic PRN [¶]	0	1	0	3	0	6	2	17	[‡] 0.002
	Parental narcotic [¶]	4	2	2	0	7	0	5	44	[†] <0.001
	Other	4	4	7	4	2	6	6	1	0.091
	No therapy	16	11	11	4	10	6	11	4	[‡] 0.018
Agitation (n)		(188)	(128)	(103)	(69)	(51)	(24)	(94)	(68)	
	Non-pharmacological	86	86	88	78 ^{3‡}	92 ^{4†}	88	85	50	[‡] <0.001
	Trunk and limb restraints**	11	5 ^{5‡}	2	4	4	4	13	3	0.104
	Antipsychotics	46	45	37	33	27	38	59	44	[‡] 0.007
	Anxiolytics	29	30	31	29	33	29	41	62	[‡] 0.032
	Antidepressant drug ^{††}	3	2	11 ^{6†}	6	8	8	5	3	0.305
	Other	7	9	12	17	12	8	4	9	0.171
	No therapy [¶]	0	0	1	0	0	4	0	4	[¶]
Shortness of breath (n)		(62)	(39)	(41)	(19)	(17)	(9)	(46)	(106)	
	Limiting physical exertion ^{††}	8	10	15	5	18	11	11	1	[‡] 0.019
	Aerosolized bronchodilators	38	36	32	53	29	67	30	16	[‡] 0.041
	Diuretics	27	26	12	32	29	11	37	12	[‡] 0.008
	Antibiotic ^{†††}	21	18	12	11	18	0	11	2	[‡] 0.040
	Oxygen [¶]	5	8	0	11	0	0	4	32	[‡] 0.002
	Morphine [¶]	2	0	0	0	0	0	2	69	[†] <0.001
	Other therapy	15	10	12	16	12	0	15	14	0.965
	No therapy	19	23	29	21	18	11	13	10	0.386

[‡] = Lower percentage / [†] = higher percentage: Significant change in GEE analyses with repeated contrasts between 2 consecutive regular assessments and change between the last regular assessment before death and the after-death assessment. We defined a $P < 0.05$ as significant. Only significant changes are reported, in case of the semi-annual assessments, and prevalence of significant changes are bolded.

In case of two consecutive regular assessments we adjusted for the last regular assessment before death. In case of the last regular assessment before death and the after-death assessment, we adjusted for the length of time between these two consecutive assessments.

^{1†} $P = .003$, ^{2†} $P = .041$, ^{3‡} $P = .023$, ^{4†} $P = .006$, ^{5‡} $P = .036$, ^{6†} $P = .013$. Coefficients of the GEE analyses are available upon request.

*Receiving more than one treatment is possible.

[‡]A<† = The last regular assessment before death is one of A1 to A6.

[§]A† = The after-death assessment.

^{||}GEE analyses with repeated contrast between A<† and A†.

[¶]GEE analyses with repeated contrast is not possible between assessments with a proportion of 0%, thus only assessments with a proportion > 0% were included in the GEE analyses.

** Strictly regulated within legal framework.

^{††}Not separately assessed but derived from the category "other."

Treatment of shortness of breath

The most frequently provided treatments for shortness of breath across the regular assessments were aerosolized bronchodilators (29%-67%) and diuretics (11%-32%; Table 4). We did not find significant changes between the regular assessments. Across the regular assessments, continued aerosolized bronchodilators ranged from 33% to 100%, and continued diuretics from 0% to 50% (only 1-7 residents).

Compared with the last regular assessment, the after-death assessment showed a significantly larger proportion of residents receiving morphine (increase from 2% to 69%) and oxygen (from 4% to 32%). Limiting physical exertion (from 11% to 1%), aerosolized bronchodilators (decrease from 30% to 16%), diuretics (from 37% to 12%), and antibiotics (from 11% to 2%) were prescribed significantly less often (Table 4).

DISCUSSION

Dementia is a disease without a cure, and many people diagnosed with dementia will die with or of this disease. Burdensome symptoms frequently develop during the disease trajectory. Therefore, adequate symptom control to maintain or improve quality of life should be one of the most important care goals.¹ To our knowledge, (Dutch End of Life in Dementia) is the first study that describes the longitudinal course, from admission to a nursing home until death, of burdensome symptoms and provided treatment for patients in variable stages of dementia. Agitation was persistent and the most common symptom, yet it decreased at the end of life. Pain was also common and persistent and increased in the last week of life. Shortness of breath was less common, but it often persisted and increased at the end of life. We found no significant longitudinal association between pain and agitation. We found a positive significant longitudinal association between advanced dementia and pain, but not at the end of life and there was no association with other symptoms. Pharmacological management of symptoms was more intensive at the end of life. Parenteral opioids, morphine, and anxiolytics were prescribed substantially more frequently at the end of life.

Many residents were in pain, consistent with the pain prevalence observed in previous studies.^{25;26} Of note, in our earlier analyses of symptoms at the end of life,¹⁷ we also reported pain prevalence over the last week of life, but we reported lower percentages because we dichotomized differently, combining "never" with "rarely." It should be noted that residents already suffered from pain shortly after admission. Acetaminophen was frequently provided, which is in line with guideline recommendations,²⁷ but in view of frequently persisting pain, it is remarkable that the treatment was intensified only at the end of life. Perhaps this is because physicians are more inclined to

accept side effects, such as sedation, in case of a nearing death, or due to increasing pain or a new origin of pain at the end of life, requiring a different treatment strategy. Reports in the literature support the value of stepped approaches of analgesia administration, both for the treatment of pain and as an important component of the management of agitation,^{8,27} because pain may be the underlying cause of behavioral symptoms.^{8,9} However, we found no significant association between pain and agitation. Absence of an association has been reported in more studies.¹²⁻¹⁵ Ahn and Horgas¹⁴ reported that the relationship between pain and disruptive behaviors depends on the type of behaviors examined, and found that pain is positively correlated with disruptive behaviors that do not involve locomotion (eg, aggression and agitation).

Agitation was highly prevalent shortly after admission and often persisted. Agitation did not tend to increase over time. This is in line with a study of Selbaek et al,¹⁰ which also had a long follow-up period, but reported on aggression only. Nonpharmacological approaches based on person-centered care combined with medication review should be the first-line approach for treatment of agitation in people with dementia.^{1,28,29} Nonpharmacological treatments were frequently provided in our study, as well as antipsychotics and anxiolytics. These psychotropic drugs were continued in more than half of the residents with persistent agitation, despite the recommendation that these psychotropic drugs be reduced or discontinued within 3 months, because of possible limited benefits in longer-term therapy.²⁹⁻³¹ An explanation for less agitation reported at the end of life may be the worsening condition at the end of life, or the sedative effect of opioids at the end of life. Shortness of breath was less common and persisted in only a small proportion of residents; however, at the end of life, shortness of breath is increasingly present and may be attributed to different causes, such as pneumonia and heart failure.

Diagnosing symptoms and symptom management is challenging in residents with dementia. It is remarkable that overall, despite almost all residents dying with a palliative goal of care,³² nonpharmacological types of treatment decreased at the end of life, although we do not know if some were also replaced by other types of nonpharmacological treatment. This suggests that the available nonpharmacological treatment is not suitable at the end of life, and that tailored treatment is not available or not offered. Further intervention research is needed to improve symptom management and to develop more evidence-based guidelines for pharmacological and nonpharmacological treatment. A strong focus on palliative care needs is recommended from admission. Research should focus on the how of providing comfort, with optimal treatment of symptoms to improve the quality of life of patients with dementia.¹

Strengths and limitations

The strength of our study is the inclusion of residents in all stages of dementia, making the results representative of a wide population of nursing home residents with dementia. Our findings apply

to institutional long-term care rather than to community settings. International differences in health care systems potentially reduce generalizability. Elderly care medicine is a separate specialty in the Netherlands, and elderly care physicians are employed by the nursing homes, and have patient contact frequently.^{33,34} They work with low-educated nursing staff. However, this system does not necessarily result in a better recognition of symptoms and treatment. Further, through the long follow-up period and the adoption of 2 temporal perspectives, we investigated the full period from admission until death, and for most residents, from both perspectives. In addition, our study was unique in that it provided detailed information on symptom management, such as type of medication.

Some limitations should be acknowledged. First, to allow for longitudinal analyses, we collapsed the response options for frequencies of pain and shortness of breath. However, the full response options showed similar patterns and stable distributions across assessments. Of all residents, 18% to 25% "rarely" had pain, 12% to 25% "sometimes," 3% to 10% "often," and 7% to 17% had pain "almost daily." Across the assessments, 6% to 18% had shortness of breath "rarely," 8% to 20% "sometimes," 1% to 9% "often," and 3% to 9% had shortness of breath "almost daily." Second, we used the physician's evaluation of symptoms. In approximately half of the cases (52%) the same physician completed all assessments, in 35% the resident was assessed by 2 physicians, in 11% by 3 physicians, and in 2% by 4 physicians. The median length of time between the day of death and the day the physician completed the after-death questionnaire was 16 days. However, recall bias may be limited, because physicians could rely on both the chart and their own memory. Accordingly, we found no significant correlation between length of time and symptom levels (pain: $r = -0.058$, $P = .405$; agitation: $r = 0.048$, $P = .482$; shortness of breath: $r = 0.030$, $P = .666$). Third, the statistical power was adequate for analyzing, but the analyses of change in treatment were less powerful, because of the reduced sample sizes of those receiving specific treatments. Further, unfortunately, we cannot draw conclusions about the most effective treatment for symptom relief, because of the observational study design, and we did not assess treatment that effectively resolved symptoms. We did not assess the intensity of symptoms or change in dosage of medication, and we did not specify nonpharmacological treatment. Finally, we did not consider changes in (co)morbidity and underlying change in causation and nature of symptoms.

Conclusion

Pain and agitation are common and frequently persist. Symptom control may be suboptimal in patients in variable stages of dementia during nursing home stay in the Netherlands. We recommend a strong focus on palliative care and palliative care needs with meticulous assessment and subsequent treatment of burdensome symptoms, from admission until the end of life. Our observations call for further research into interventions targeted at pain and agitation and the

relation between both symptoms. This will contribute to the development of evidence-based guidelines for treatment of burdensome symptoms in patients with dementia.

Supplementary Data

Online resource Figures 1-4 can be found in the appendix of this thesis.

REFERENCES

1. van der Steen JT, Radbruch L, Hertogh CM, et al. White paper defining optimal palliative care in older people with dementia: A Delphi study and recommendations from the European Association for Palliative Care. *Palliat Med* 2014;28:197-209.
2. Houttekier D, Cohen J, Bilsen J, et al. Place of death of older persons with dementia. A study in five European countries. *J Am Geriatr Soc* 2010;58:751-756.
3. Mitchell SL, Teno JM, Miller SC, Mor V. A national study of the location of death for older persons with dementia. *J Am Geriatr Soc* 2005;53:299-305.
4. van der Steen JT. Dying with dementia: What we know after more than a decade of research. *J Alzheimers Dis* 2010;22:37-55.
5. Mitchell SL, Teno JM, Kiely DK, et al. The clinical course of advanced dementia. *N Engl J Med* 2009;361:1529-1538.
6. Zuidema SU, Derksen E, Verhey FR, Koopmans RT. Prevalence of neuropsychiatric symptoms in a large sample of Dutch nursing home patients with dementia. *Int J Geriatr Psychiatry* 2007;22:632-638.
7. Selbaek G, Kirkevold O, Engedal K. The prevalence of psychiatric symptoms and behavioural disturbances and the use of psychotropic drugs in Norwegian nursing homes. *Int J Geriatr Psychiatry* 2007;22:843-849.
8. Corbett A, Husebo B, Malcangio M, et al. Assessment and treatment of pain in people with dementia. *Nat Rev Neurol* 2012;8:264-274.
9. Achterberg WP, Pieper MJ, van Dalen-Kok AH, et al. Pain management in patients with dementia. *Clin Interv Aging* 2013;8:1471-1482.
10. Selbaek G, Engedal K, Benth JS, Bergh S. The course of neuropsychiatric symptoms in nursing-home patients with dementia over a 53-month followup period. *Int Psychogeriatr* 2014;26:81-91.
11. Zuidema SU, de Jonghe JF, Verhey FR, Koopmans RT. Predictors of neuropsychiatric symptoms in nursing home patients: Influence of gender and dementia severity. *Int J Geriatr Psychiatry* 2009;24:1079-1086.
12. Pieper MJ, van Dalen-Kok AH, Francke AL, et al. Interventions targeting pain or behaviour in dementia: A systematic review. *Ageing Res Rev* 2013;12: 1042-1055.
13. Husebo BS, Ballard C, Cohen-Mansfield J, et al. The response of agitated behavior to pain management in persons with dementia. *Am J Geriatr Psychiatry* 2014;22:708-717.
14. Ahn H, Horgas A. The relationship between pain and disruptive behaviors in nursing home residents with dementia. *BMC Geriatr* 2013;13:14.
15. Husebo BS, Ballard C, Aarsland D. Pain treatment of agitation in patients with dementia: A systematic review. *Int J Geriatr Psychiatry* 2011;26:1012-1018.
16. van der Steen JT, Ribbe MW, Deliens L, et al. Retrospective and prospective data collection compared in the Dutch End of Life in Dementia (DEOLD) study. *Alzheimer Dis Assoc Disord* 2014;28:88-94.
17. Hendriks SA, Smalbrugge M, Hertogh CM, van der Steen JT. Dying with dementia: Symptoms, treatment, and quality of life in the last week of life. *J Pain Symptom Manage* 2014;47:710-720.
18. Wetzels R, Zuidema S, Jansen I, et al. Course of neuropsychiatric symptoms in residents with dementia in long-term care institutions: A systematic review. *Int Psychogeriatr* 2010;22:1040-1053.
19. McKhann G, Drachman D, Folstein M, et al. Clinical diagnosis of Alzheimer's disease: Report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology* 1984;34:939-944.
20. Roman GC, Tatemichi TK, Erkinjuntti T, et al. Vascular dementia: Diagnostic criteria for research studies. Report of the NINDS-AIREN International Workshop. *Neurology* 1993;43:250-260.

21. McKeith IG, Galasko D, Kosaka K, et al. Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): Report of the consortium on DLB international workshop. *Neurology* 1996;47:1113-1124.
22. Dutch Geriatrics Society. CBO: [in Dutch] Guideline diagnostics and pharmacological treatment of dementia. 2012. Available at: <http://www.platformouderenzorg.nl/uploads/files/guidelines/dementie1.pdf>. Accessed January 29, 2015.
23. Reisberg B, Ferris SH, de Leon MJ, Crook T. The Global Deterioration Scale for assessment of primary degenerative dementia. *Am J Psychiatry* 1982;139: 1136-1139.
24. Morris JN, Fries BE, Mehr DR, et al. MDS cognitive performance scale. *J Gerontol* 1994;49:M174-M182.
25. Scherder EJ, Sergeant JA, Swaab DF. Pain processing in dementia and its relation to neuropathology. *Lancet Neurol* 2003;2:677-686.
26. Husebo BS, Strand LI, Moe-Nilssen R, et al. Who suffers most? dementia and pain in nursing home patients: A cross-sectional study. *J Am Med Dir Assoc* 2008;9:427-433.
27. Verenso, the Dutch Association of Elderly Care Physicians and Social Geriatricians. Guideline: pain [in Dutch]. 2008. Available at: <http://www.verenso.nl/assets/Uploads/Downloads/Richtlijnen/VERrichtlijnPijnDeel1web.pdf>. Accessed October 20, 2014.
28. Ballard C, Corbett A. Agitation and aggression in people with Alzheimer's disease. *Curr Opin Psychiatry* 2013;26:252-259.
29. Verenso, the Dutch Association of Elderly Care Physicians and Social Geriatricians. Guideline: behaviour problems [in Dutch]. 2008. Available at: <http://www.verenso.nl/wat-doen-wij/vakinhoudelijke-producten/richtlijnen/probleemgedrag>. Accessed October 20, 2014.
30. Ballard CG, Gauthier S, Cummings JL, et al. Management of agitation and aggression associated with Alzheimer disease. *Nat Rev Neurol* 2009;5: 245-255.
31. Schneider LS, Tariot PN, Dagerman KS, et al. Effectiveness of atypical antipsychotic drugs in patients with Alzheimer's disease. *N Engl J Med* 2006;355: 1525-1538.
32. van Soest-Poortvliet MC, van der Steen JT, de Vet HCW, et al. Comfort goal of care and end-of-life outcomes in dementia: a prospective study. *Palliat Med* 2015; Jun;29(6):538-46.
33. Koopmans RT, Lavrijsen JC, Hoek JF, et al. Dutch elderly care physician: a new generation of nursing home physician specialists. *J Am Geriatr Soc* 2010;58: 1807-1809.
34. Helton MR, van der Steen JT, Daaleman TP, et al. A cross-cultural study of physician treatment decisions for demented nursing home patients who develop pneumonia. *Ann Fam Med* 2006;4:221-227



Chapter 5

Dying with dementia: Symptoms, treatment, and quality of life in the last week of life

Simone A. Hendriks
Martin Smalbrugge
Cees M.P.M. Hertogh
Jenny T. van der Steen

Published in Journal of Pain and Symptom Management 2014; 47:710-720

Awarded the "Jan Stooprijis" for the best article 2013 young talented researchers.
Nominated for the "Jaarprijis palliatieve zorg 2014."

ABSTRACT

Context: Burdensome symptoms present frequently in dementia at the end of life, but we know little about the symptom control provided, such as type and dosage of medication.

Objectives: To investigate symptom prevalence and prescribed treatment, explore associations with quality of life (QOL) in the last week of life, and examine symptom prevalence by cause of death of nursing home residents with dementia.

Methods: Within two weeks after death, physicians completed questionnaires about symptoms and treatment in the last week for 330 nursing home residents with dementia in the Dutch End of Life in Dementia study (2007-2011). We used linear regression to assess associations with QOL, measured by the Quality of Life in Late-Stage Dementia scale. Causes of death were abstracted from death certificates.

Results: Pain was the most common symptom (52%), followed by agitation (35%) and shortness of breath (35%). Pain and shortness of breath were mostly treated with opioids and agitation mainly with anxiolytics. At the day of death, 77% received opioids, with a median of 90 mg/24 hours (oral equivalents), and 21% received palliative sedation. Pain and agitation were associated with a lower QOL. Death from respiratory infection was associated with the largest symptom burden.

Conclusion: Symptoms are common in dementia at the end of life, despite the large majority of residents receiving opioids. Dosages may be suboptimal with regard to weighing of effects and side effects. Future research may employ observation on a day-to-day basis to better assess effectiveness of symptom control and possible side effects.

INTRODUCTION

Worldwide mortality rates of death with dementia have increased and so has awareness that patients with dementia need palliative care in the last phase of life. This has generated a considerable research interest in end-of-life care for patients with dementia.¹ A high symptom burden and inappropriate treatment at the end of life have been reported.^{1,2} However, these reports lack detail on how specific symptoms are being treated, for example, which pharmacological treatment is being provided to relieve pain and shortness of breath at the end of life. Moreover, many reports are limited to nursing home residents with advanced dementia, whereas about half of patients may die before having reached this stage.³

Burdensome symptoms present frequently in the last phase of life, as Mitchell et al.² reported. Pain and shortness of breath are the most prevalent symptoms at some point in the process of dementia, with a peak when death approaches. The rates of these symptoms vary widely, from 12% to 76% for pain, and from 8% to 80% for shortness of breath.¹ Agitation is less frequently studied but was reported in 20%-54% of nursing home residents with advanced dementia at the end of life.^{2,4,5}

We know little about types of medication administered to treat burdensome symptoms, and more specifically, the use and dosages of opioids and palliative sedation in residents with dementia at the end of life. Symptom control is an important factor in maintaining or improving quality of life (QOL) in end-of-life care.⁶⁻⁸ So far, treatment has been mostly empirical or based on general palliative care guidelines, which are not tailored to dementia.^{1,2,9,10}

In this study, we report on burdensome symptoms and on specific pharmacological and nonpharmacological treatments provided for the most important symptoms in the last week of life of nursing home residents in variable stages of dementia. We report on the use of opioids as important drugs to treat pain and shortness of breath and explore associations with QOL in the last week of life and symptom prevalence related to direct causes of death.

METHODS

Data collection

Data were collected as part of the Dutch End of Life in Dementia (DEOLD) study.³ The primary aims of the study were to describe quality of dying and end-of-life care and assess associated factors. This observational study employed both prospective (on admission) and retrospective (after death) recruitment of residents. Data were collected between 2007 and 2011 in 34 long-term care facilities.

The mean number of beds per facility was 82, ranging from 11 to 210 beds. Dutch nursing homes employ elderly care physicians, certified after three years of training,¹¹ who were responsible for data collection in nursing homes and affiliated residential homes. The residents had a physician's diagnosis of dementia of any stage and a family representative able to understand and write Dutch or English.

Prospectively, 372 residents were enrolled on admission; 218 (59%) died within the data collection period, resulting in 213 cases with complete physician after-death assessments. Retrospectively, 119 of 121 eligible residents were enrolled, resulting in 117 physician assessments. For analyses, we selected the 330 residents with complete physician after death reports, involving 103 physicians. No longer than two weeks after death, written questionnaires were completed by physicians or, in part, by nurses under supervision of the physician. The study protocol was approved by the Medical Ethics Committee of the VU University Medical Center in Amsterdam.

Measurements

The diagnosis of dementia was based on international guidelines.¹²⁻¹⁵ Type of dementia was assessed with a prestructured item comprising the categories Alzheimer's disease, vascular dementia, Lewy body/Parkinson's disease, and other. Advanced dementia (vs. less advanced dementia) was defined as a Global Deterioration Scale score of 7¹⁶ and a Cognitive Performance Scale score of 5 or 6.¹⁷

The level of consciousness that most frequently occurred during the last week was scored as: awake and alert, awake, awake but drowsy looking, falling asleep, light sleep, or deep looking sleep. The physicians scored this item in 53% of cases and nurses in 47%. They assessed frequency of pain and shortness of breath during the last week of life as: never, rarely (≤ 1 day), sometimes (2-3 days), often (4-5 days), and almost daily (6-7 days). We dichotomized these assessments as never or rarely vs. sometimes, often, and almost daily.² Prevalence of agitation was described with the examples restlessness, resistance to care, calling out, or verbal and physical aggression and was assessed as present or not in the last week of life.

Treatment provided for pain, shortness of breath and agitation was assessed using prestructured items. The categories for pain treatment were nonpharmacological (eg, physiotherapy, occupational therapy, transcutaneous electrical neurostimulation, massage), paracetamol (acetaminophen), nonsteroidal anti-inflammatory drugs, oral opioid or parenteral opioid (each separately assessed as "as needed" only or scheduled dose), other, and no therapy. Treatment provided for shortness of breath was prestructured as: oxygen, opioids, aerosolized bronchodilators, diuretics, scopolamine, suctioning, intubation, other, and no therapy. Similarly, treatment of agitation comprised nonpharmacological treatments (eg, 1:1 sitter, separate, involve family to participate

in care), trunk or limb restraints, antipsychotic medication, anxiolytic or hypnotic medication, other, and no therapy.

Physicians reported the type and dosage of opioids that were given during the last 24 hours of life. They further reported the dosage pattern in the last three days, visualized graphically as no increase, gradual increase, or large increase on the last day. We converted all opioid dosages into oral morphine equivalents (OMEs) to allow for comparison of dosages between opioid types.¹⁸ Physicians reported how many hours before death opioid administration started. Palliative sedation was defined as continuous deep sedation or sleep until death.¹⁹ Physicians reported the type and dosage of drugs they provided for palliative sedation and how many hours before death palliative sedation was started.

QOL of residents in the last week of life was measured with the 11-item Quality of Life in Late-Stage Dementia (QUALID)²⁰ scale, which was translated and tested in an independent Dutch population.²¹ The minimum and best summed score is 11 points; the maximum and worst score is 55 points. The physicians completed QUALID in 51% of cases and nurses in 49%. Analogous to the Dutch death certificate, physicians registered the causes of death. For analyses, we used the three most common immediate causes of death (Part 1a of the Dutch death certificate). Cardiovascular disorders were defined as diseases of the circulatory system, and respiratory infection was defined as pneumonia, other lower respiratory tract infections, or upper respiratory infections.

Statistical analyses

We used t-tests for independent samples, Chi-square tests, and Gamma correlations to compare subgroups where appropriate, as well as Spearman's correlation coefficients. We report the results for the total sample, and when different, separately for the prospectively and retrospectively recruited samples. To assess variability in prescribing at the physicians' level, we estimated the intraclass correlation coefficient (ICC), using the formula: $ICC = \text{variance in intercept} / (\text{variance in intercepts} + 3.29)$.²² Random intercepts were used at the physicians' level for use of opioids and palliative sedation. Linear regression models were developed to evaluate associations with QOL, with the QUALID score as the dependent variable and symptoms of pain, shortness of breath, and agitation as the independent variables. We adjusted for simultaneously occurring symptoms, use of morphine during the last 24 hours, level of consciousness, and advanced vs. less advanced dementia.

In all analyses, fewer than 5% of values were missing, except for 6.0% missing values in treatment for agitation and 5.5% of QUALID scores, after having imputed with item means if a maximum four of 11 items were missing (3%). An additional 3.5% of cases was missing in the regression

analyses because of missing independent variables. Analyses were performed with PASW 20.0 (SPSS, Inc., Chicago, IL).

RESULTS

Characteristics

Most residents were female, and almost half (43%) had Alzheimer's disease (Table 1). Almost all residents (99%) died in the facility, except for four residents (1%), who died in a hospital. The populations recruited prospectively and retrospectively differed in two ways: advanced dementia, which was present in 38% and 53% of cases, respectively, and mean length of stay, 10.5 months (range 0.2-37.7) and 30.2 months (range 0.2-178.4), respectively.

Table 1. Resident characteristics

Characteristics	(N = 330)	
Female, %	67	
Age at death, mean (SD)	85.2	(7.4)
Advanced dementia, %	43	
Type of dementia, %		
Alzheimer disease	43	
Vascular	24	
Alzheimer and vascular	19	
Lewy body/ Parkinson disease	6	
Other types	9	
Residence before admission, %		
Private home	36	
Residential home/ other nursing home	40	
General/ psychiatric hospital	18	
Other	6	
Physicians' expectation of residents' death, %		
Expected	64	
Expected, yet sooner than anticipated	22	
Neither expected nor unexpected	3	
Unexpected	11	

Symptoms

Fig. 1 shows the proportions of residents with symptoms of pain, shortness of breath and agitation in the last week of life. Pain was reported in 52% of the residents. Agitation and shortness of breath were both reported in 35% of the residents. Symptom prevalence did not differ between residents with advanced and less advanced dementia (pain: 55% vs. 50%, $P = 0.34$; shortness of breath: 31% vs. 38%, $P = 0.16$; agitation: 33% vs. 38%, $P = 0.37$, respectively). Presence of one of the symptoms was reported in 39% of residents, two symptoms in 32%, all three symptoms

in 6%, and 23% were free from these symptoms. Pain and agitation without shortness of breath was present in 15% of residents.

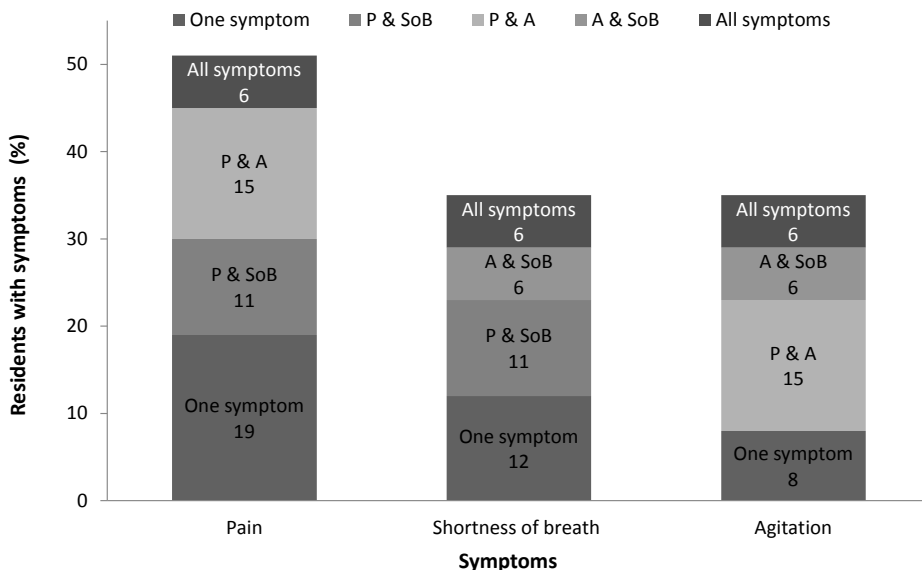


Figure 1. Nursing home residents with symptoms of pain, shortness of breath and agitation in the last week of life. P = pain; SOB = shortness of breath; A = agitation.

Treatment of symptoms

Table 2 shows the treatments prescribed to address the specific symptoms in the last week of life. At least one type of opioid (oral or parenteral) was provided to 73% of residents in pain (not shown in table). Opioids were administered as monotherapy in 43% of cases, and 57% of residents received combination therapy, mostly with paracetamol (acetaminophen) (87%). Nonpharmacological treatment was combined with analgesics in all but one resident who received nonpharmacological treatment exclusively.

Shortness of breath was treated with opioids in 71% of cases and in 58% with combination therapy, mostly (74%) with oxygen. Aerosolized bronchodilators and/or diuretics were prescribed to 31% (not shown in table).

For agitation, nonpharmacological therapy was provided to 62% of residents. A combination with pharmacological treatment was prescribed in 71% of these cases (48/68). Overall, at least one type of medication was provided to 79% of residents. Anxiolytic or hypnotic medications were the most frequently prescribed types (57%). The combination of anxiolytic or hypnotic medications with antipsychotic medication was prescribed to 30% of residents (not shown in table).

Table 2. Treatment provided for symptoms in the last week of life

Symptom (N)	Treatment ^a	n	% ^b	PRN only, %
Pain (169)	Parenteral opioids	109	67	15
	Paracetamol	97	60	7
	NSAID	28	17	1
	Oral opioids	22	13	2
	Non- pharmacological	17	10	
	Other	2	1	
	No therapy	2	1	
Shortness of breath (115)	Opioids	79	71	
	Oxygen	48	43	
	Aerosolized bronchodilators	22	20	
	Diuretic	17	15	
	Scopolamine	14	13	
	Other	6	5	
	Non-pharmacological ^c	5	4	
	No therapy	5	4	
Agitation (116)	Suctioning	4	4	
	Non-pharmacological	68	62	
	Anxiolytic or hypnotic medication	62	57	
	Antipsychotic medication	54	50	
	Other	6	6	
	Trunk or limb restraints	5	5	
	Antidepressant drug ^c	5	5	
No therapy	3	3		

PRN = as needed; NSAID = nonsteroidal anti-inflammatory drug.

^aReceiving more than one treatment for a specific symptom is possible.

^bTotal percentages do not refer to total numbers with symptoms because of missing treatment (6 cases for treatment of pain, 2 for type of opioids, 3 for shortness of breath, and 7 for agitation, so refer to 163 cases in pain, 112 with shortness of breath, and 109 with agitation).

^cNot separately assessed, but derived from the category "other".

Opioids

Overall (for any symptom), in the last 24 hours before death, 77% of residents received opioids; this differed between the prospectively (74%) and retrospectively (84%; $P = 0.03$) recruited samples. The variance at the physicians' level of the proportion of prescribed opioids was 0.05 (SE 0.3), with an ICC of 0.02. Fig. 2 shows that the proportion of residents receiving opioids increased every day in the week before death, with a larger increase in the last two days before death.

The median duration of receiving opioids until death was 48 hours (25th percentile, 96 hours; 75th percentile, 19 hours before death). The median total opioid dosage was 90 mg (OME) in the

last 24 hours (25th percentile, 52; 75th percentile, 150 OME). The most frequently used method of administration was by injection (88%) (Table 3).

The dosage pattern of opioids of the last three days was described as no increase in 51% of the residents, a gradual increase in 24%, and a large increase in the last day in 25% of cases. A pattern of larger increase (none, gradual, large) of opioid dosages correlated significantly with the dosage in the last 24 hours ($r = +0.30, P < 0.001$) and with the duration of using opioids until death ($r = +0.20, P = 0.002$).

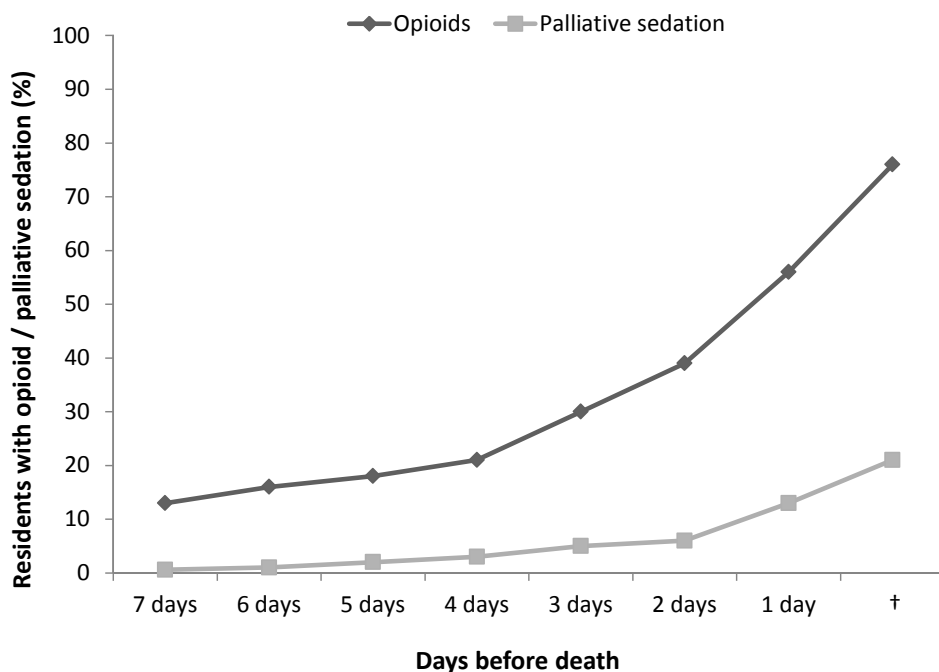


Figure 2. Proportions of residents receiving opioids and palliative sedation over the days before death.

Palliative sedation

Of all residents, 21% received palliative sedation: 17% of the prospectively and 28% of the retrospectively recruited sample ($P = 0.015$). The variance at the physicians' level of use of palliative sedation was 0.39 (SE 0.38), with an ICC of 0.11. The proportion of all residents who received palliative sedation increased strongly two days before death (Fig. 2). The median duration of receiving sedative medication until death was 24 hours (25th percentile, 48; 75th percentile, 12 hours before death). Midazolam was the most commonly prescribed drug (86%), with a median dosage of 30 mg/24 hours (Table 4). In 61% of residents, midazolam was prescribed as monotherapy, and in 33%, it was combined with morphine. Oxazepam, haloperidol, and levomepromazine were only provided as additional to midazolam (5%).

Table 3. Opioid dosage in the last 24 hours before death (N = 125)

Type of Opioids	% ^a	OME, mg over last 24 h		
		Median	25 th perc	75 th perc
Patch fentanyl	12	60	30	60
Pump	10	90	60	180
Subcutaneous bolus injection	88	90	30	120
Tramadol drops	2	20	7	28
Controlled-release tablet	1	10	10	10
Oxycodon tablet	0.4	40	40	40
Drink	0.4	5	5	5
Summed dosage (≥1 type of opioid)		90	52	150

OME = oral morphine equivalents.

^aTotal percentages do not refer to total numbers with opioids because receiving more than one type of opioid was possible and there were seven missing cases of type of opioids.

Table 4. Palliative sedation: type of medication and dosages (N = 67)

Sedation medication	% ^a	mg / 24h		
		Median	25 th perc	75 th perc
Midazolam	86	30	15	30
Morphine ^b	39	90	90	180
Diazepam	3	15	10	10
Haloperidol	3	3	1	1
Oxazepam	2	10	10	10
Levomepromazine	2	50	50	50

^aTotal percentages do not refer to total numbers with palliative sedation because of two missing cases of type of medication).

^bmg/24h in oral morphine equivalents.

Table 5. Associations of symptoms with quality of life (QUALID^a score)

Symptom		Coefficient ^b	95% CI
Pain	Unadjusted	5.5	3.5 to 7.5
	Adjusted ^c	4.0	2.1 to 6.0
Shortness of breath	Unadjusted	0.1	-2.1 to 2.3
	Adjusted ^c	0.7	-1.2 to 2.6
Agitation	Unadjusted	6.6	4.6 to 8.6
	Adjusted ^c	6.1	4.2 to 8.1

^aQUALID = Quality of Life in Late-Stage Dementia. (The minimum and best score is 11 points; the maximum and worst score is 55 points.)

^bUnstandardized regression coefficients from linear regression models.

^cAdjusted for advanced dementia, use of morphine during the last 24 hours, level of consciousness and pain, shortness of breath or agitation. The adjustment for specific symptoms differs according to which symptom is analyzed (e.g., analysis of pain was adjusted for shortness of breath and agitation).

Relationship of symptoms with QOL

The mean QUALID score was 28.8 (SD 9.0). The mean QUALID score of residents did not differ significantly whether scored by a physician or a nurse (28.6 vs. 29.2; $P = 0.61$). The median level of consciousness was “falling asleep” and did not differ whether assessed by a physician or a nurse ($P = 0.86$).

QUALID correlated significantly with pain and with agitation but not with shortness of breath (Table 5). Residents with agitation had a 6.1 points higher (worse) mean QUALID score than residents without agitation. Furthermore, the mean QUALID score for residents with pain was 4.0 points higher than residents with otherwise similar symptom levels but without pain.

Causes of death related to symptoms

The three most common direct causes of death were dehydration/cachexia (38%), cardiovascular disorders (19%), and respiratory infection (18%). Most respiratory infections (82%) concerned pneumonia, and 18% were other lower and upper respiratory infections. Fig. 3 shows the association of causes of death with symptoms. In residents who died from dehydration/cachexia, pain was the most frequently reported symptom. Residents who died with cardiovascular disorders frequently presented with pain and shortness of breath, and in residents who died with respiratory infection, shortness of breath was the most frequently occurring symptom. Respiratory infection related to the largest symptom burden.

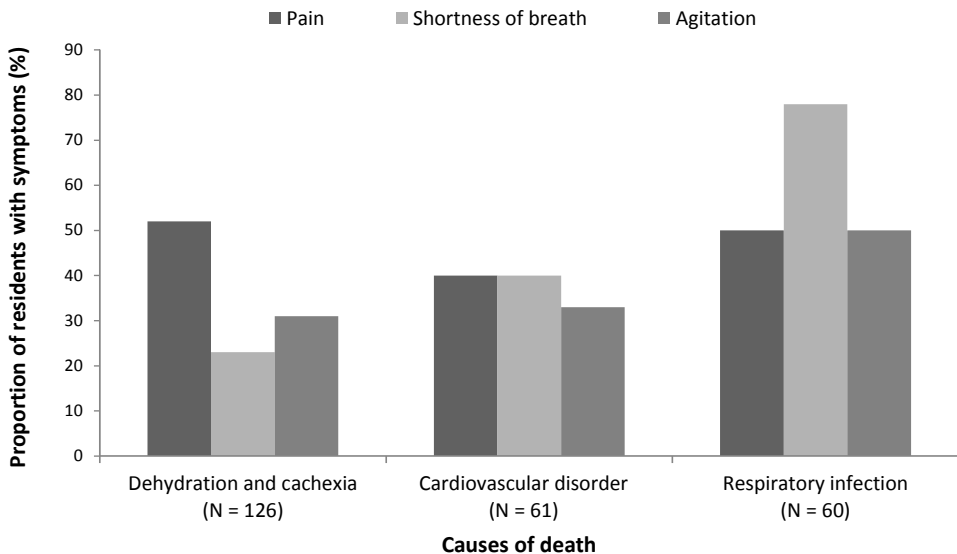


Figure 3. Proportion of symptoms in the last week of life related to the three main immediate causes of death.

DISCUSSION

To our knowledge, DEOLD is the first study that describes the last week of life of nursing home residents with variable stages of the dementia, focusing in detail on treatment provided for the most important burdensome symptoms, and on use of opioids and palliative sedation. The distressing symptoms pain (52%), shortness of breath (35%), and agitation (35%) were common. Pain and shortness of breath may even be underestimated in our study because we combined the frequencies “never” and “rarely” into “no presence of symptoms” for reasons of clinical relevance. The prevalence of pain rises to 80% if pain “rarely” is included, and similarly, the prevalence of shortness of breath rises to 57%. Death from respiratory infections was associated with more burdensome symptoms than death from cardiovascular disorders or dehydration/cachexia. Distressing symptoms were mostly treated pharmacologically. Furthermore, QOL in the last week was worse in residents with pain or agitation, despite the large majority of all residents (77%) receiving opioids and one-fifth (21%) receiving palliative sedation until death.

We found substantially more pain (52% vs. 25%) but only slightly more shortness of breath (35% vs. 32%) and agitation (35% vs. 33%) in comparison with the Choices, Attitudes, and Strategies for Care of Advanced Dementia at the End-of-Life (CASCADE) study.² These differences cannot be explained by dichotomizing the presence of symptoms but may be affected by a difference in time frame (symptoms on, at most, 1 day in the last week vs. maximum 4 days per month over the last 3 months, respectively).^{2,23} Furthermore, symptom prevalence did not differ between those with advanced dementia (in which CASCADE was limited) and less advanced dementia.² The observed differences may be interpreted in three ways. First, the physicians in DEOLD may have reported more symptoms, as they were asked directly and could rely on both the chart and their own memory, whereas in the CASCADE study, the data were mostly obtained from chart reviews by research assistants (for agitation, the nurse was interviewed as well).² In contrast to the U.S., the Dutch physicians are employed by the nursing homes, resulting in physicians having a firsthand understanding and intimate knowledge of the patient.²⁴ Second, generalizability for the nation differed: DEOLD facilities performed “average” on general quality indicators,³ whereas CASCADE facilities performed better than average.^{2,23} Third, symptom control may be suboptimal in Dutch long-term care facilities and of lower standards than in the U.S. This is supported by research findings that indicated more favorable U.S. family reports compared with Dutch family reports on comfort in the last week of life.²⁵

The finding that death from respiratory infections was associated with more burdensome symptoms is in line with earlier research observations, where death with pneumonia compared with death after intake problems was associated with higher levels of discomfort.^{26,27} In another Dutch study, dehydration/cachexia was a common cause of death as well.²⁸ Dutch elderly care

physicians rarely provide tube feeding in case of intake problems,²⁹ and this implies that death from dehydration/cachexia is an acceptable scenario.

We found a significant association between pain and agitation, and lower QOL measured by the QUALID scale. Santangelo,³⁰ in dementia patients more generally, also found lower QOL in patients with pain. These findings are in contrast with the findings from Cordner et al.⁶ who used the Alzheimer Disease-Related Quality of Life scale and found that residents with pain identified at the end of life had a better QOL. This might be explained by more adequate treatment, although the percentage of residents treated with medication was similar.

Opioids were the most frequently provided medication for pain and were prescribed as monotherapy in almost half of the cases. This is inconsistent with pain guideline recommendations¹⁸ of prescribing opioids supplementary to nonsteroidal anti-inflammatory drugs and paracetamol (acetaminophen). Yet in the terminal phase, reducing and avoiding burdening interventions (i.e., oral and rectal medication) is important, and monotherapy with parenteral opioids may be preferred.

Almost one-sixth (15%) of residents experienced both pain and agitation. There may be underuse of effective pain medication in cases of agitation because unrecognized pain may cause agitation³¹⁻³³ and, therefore, possibly also overuse of anxiolytics, which were used mostly for agitation in line with Dutch guidelines for behavior problems.³⁴ However, physicians also should be aware of the risk of delirium (with agitation as an important symptom) because of the accumulation of opioids in the last phase of life (caused by renal dysfunction). In these cases, the dosage of opioids should be decreased in the dying phase, as side effects may involve an increased symptom burden.

We found no association between shortness of breath and QOL measured by the QUALID scale. Caprio et al.⁷ found a positive association between dyspnea and quality of dying as evaluated by families with a scale that also included psychosocial aspects. They explained this by shortness of breath attracting more caregiver attention in these patients than other symptoms.⁷ It may be viewed as a more alarming symptom and, therefore, followed by more prompt treatment, such as parenteral opioids, which is in line with general palliative care guidelines.¹⁸ This might result in faster relief of shortness of breath and limited negative effects on QOL measured over the full last week, as was done in this study.

We observed a gradual increase in use of opioids, with a median duration of 48 hours until death and a median dosage of 90 OME in the last 24 hours. The course of dementia and the nearing of death are less predictable than, for example, in patients with cancer.³⁵ This may result in this

specific pattern of increase in use of opioids in the last few days of life. Alternatively, an increased symptom burden may present later, that is, closer to death, than in cancer.

Our results showed a substantially higher frequency of palliative sedation (21%) in comparison with European studies concerning all deaths nationwide (2.5%-8.5%)³⁶ but lower compared with palliative care settings (15% to >60%).³⁷⁻⁴² In 2005, a national guideline on palliative sedation was released in The Netherlands, which recommended that to warrant sedation at the end of life, the patient's condition should be irreversible, with death expected within at most one to two weeks.^{10;19;43} ICC we found in this study (0.11) reflects substantial clustering of using palliative sedation within physician practices. This may raise questions as to whether the physicians applied the definitions and guidance consistently.

Different percentages for using opioids and palliative sedation between prospectively and retrospectively recruited samples were found, which were not explained by differences in proportions of advanced dementia. The retrospective data were collected in only six nursing homes with two physician teams, and prescribing practices may have differed between physician teams.

Limitations

The present study has some limitations that warrant comment. First, this study is based on cross-sectional analyses; consequently, we cannot interpret relationships between symptoms, their treatment, QOL, and direct causes of death as causal. Accordingly, we cannot draw conclusions about the most effective treatment for symptom relief. Second, our findings are limited to long-term care settings. In The Netherlands, up to 92% of patients with dementia may die in these settings,⁴⁴ so our findings are, to a large degree, representative of dying with dementia in The Netherlands.

Conclusion and recommendations

Current symptom control may be improved in Dutch long-term care facilities. Our observations call for further research into interventions targeted at pain and agitation in this population. Concerning pain and shortness of breath, which are common despite frequent treatment with opioids, the dosages of opioids may be suboptimal with regard to weighing of effects and side effects. Future research may employ observation on a day-to-day basis to better address effectiveness of symptom control and possible side effects at the end of life, employing observational or ethically acceptable experimental designs. This will contribute to the development of practice guidelines for this specific patient population in palliative care.

Acknowledgments

The authors thank Dr. Francisca Galindo-Garre for statistical advice.

REFERENCES

1. van der Steen JT. Dying with dementia: what we know after more than a decade of research. *J Alzheimers Dis* 2010;22:37-55.
2. Mitchell SL, Teno JM, Kiely DK, et al. The clinical course of advanced dementia. *N Engl J Med* 2009;361:1529-1538.
3. van der Steen JT, Ribbe MW, Deliëns L, Gutschow G, Onwuteaka-Philipsen BD. Retrospective and prospective data collection compared in the Dutch End Of Life in Dementia (DEOLD) study. *Alzheimer Dis Assoc Disord* 2014;28:88-94.
4. Di Giulio P, Toscani F, Villani D, et al. Dying with advanced dementia in long-term care geriatric institutions: a retrospective study. *J Palliat Med* 2008;11:1023-1028.
5. Black BS, Finucane T, Baker A, et al. Health problems and correlates of pain in nursing home residents with advanced dementia. *Alzheimer Dis Assoc Disord* 2006;20:283-290.
6. Corder Z, Blass DM, Rabins PV, Black BS. Quality of life in nursing home residents with advanced dementia. *J Am Geriatr Soc* 2010;58: 2394-2400.
7. Caprio AJ, Hanson LC, Munn JC, et al. Pain, dyspnea, and the quality of dying in long-term care. *J Am Geriatr Soc* 2008;56:683-688.
8. Stewart AL, Teno J, Patrick DL, Lynn J. The concept of quality of life of dying persons in the context of health care. *J Pain Symptom Manage* 1999;17: 93-108.
9. Borgsteede SD, Deliëns L, Zuurmond WW, et al. Prescribing of pain medication in palliative care. A survey in general practice. *Pharmacoepidemiol Drug Saf* 2009;18:16-23.
10. Van Deijck RH, Krijnsen PJ, Hasselaar JG, et al. The practice of continuous palliative sedation in elderly patients: a nationwide explorative study among Dutch nursing home physicians. *J Am Geriatr Soc* 2010;58:1671-1678.
11. Koopmans RT, Lavrijsen JC, Hoek JF, Went PB, Schols JM. Dutch elderly care physician: a new generation of nursing home physician specialists. *J Am Geriatr Soc* 2010;58:1807-1809.
12. Dutch Geriatrics Society. [Directive: diagnostics and pharmacological treatment of dementia]. [in Dutch]. Available from http://www.cbo.nl/Downloads/387/rl_dement_2005.pdf. Accessed July 6, 2013.
13. McKhann G, Drachman D, Folstein M, et al. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology* 1984;34:939-944.
14. Roman GC, Tatemichi TK, Erkinjuntti T, et al. Vascular dementia: diagnostic criteria for research studies. Report of the NINDS-AIREN International Workshop. *Neurology* 1993;43:250-260.
15. McKeith IG, Galasko D, Kosaka K, et al. Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): report of the consortium on DLB international workshop. *Neurology* 1996;47:1113-1124.
16. Reisberg B, Ferris SH, de Leon MJ, Crook T. The Global Deterioration Scale for assessment of primary degenerative dementia. *Am J Psychiatry* 1982;139:1136-1139.
17. Morris JN, Fries BE, Mehr DR, et al. MDS Cognitive Performance Scale. *J Gerontol* 1994;49: M174-M182.
18. De Graeff A, Bommel J, van Deijk R, Krol R, Oldenmenger WH. Palliative care: Guidelines for practice. Utrecht: Association of Comprehensive Cancer Centres, 2010. [in Dutch].
19. Committee on National Guideline for Palliative Sedation, Royal Dutch Medical Association. Guideline for palliative sedation. [in English]. Available from http://knmg.artsennet.nl/Publicaties/KNMG_publicatielevenseinde/Guideline-for-palliative-sedation-2009.htm. Accessed July 6, 2013.
20. Weiner MF, Martin-Cook K, Svetlik DA, et al. The quality of life in late-stage dementia (QUALID) scale. *J Am Med Dir Assoc* 2000;1:114-116.

21. Schalkwijk D, Verlaere LR, Muller MT, Knol DL, van der Steen JT. Measuring quality of life in nursing home residents with severe dementia: psychometric properties of the QUALID scale. *Tijdschr Gerontol Geriatr* 2009;40:184-192.
22. O'Connell A. An illustration of multilevel models for ordinal response data. Data and context in statistics education: towards an evidence-based society. Proceedings of the Eighth International Conference on Teaching Statistics, July 8, 2010. Available from www.stat.auckland.ac.nz/wiase/publications/icots8/ICOTS8_4C3_OCONNELL.pdf. Accessed July 6, 2013.
23. Mitchell SL, Kiely DK, Jones RN, et al. Advanced dementia research in the nursing home: the CASCADE study. *Alzheimer Dis Assoc Disord* 2006;20: 166-175.
24. Helton MR, van der Steen JT, Daaleman TP, Gamble GR, Ribbe MW. A cross-cultural study of physician treatment decisions for demented nursing home patients who develop pneumonia. *Ann Fam Med* 2006;4:221-227.
25. Cohen LW, van der Steen JT, Reed D, et al. Family perceptions of end-of-life care for long-term care residents with dementia: differences between the United States and the Netherlands. *J Am Geriatr Soc* 2012;60:316-322.
26. van der Steen JT, Pasman HR, Ribbe MW, Van der Wal G, Onwuteaka-Philipsen BD. Discomfort in dementia patients dying from pneumonia and its relief by antibiotics. *Scand J Infect Dis* 2009;41: 143-151.
27. van der Steen JT, Ooms ME, Van der Wal G, Ribbe MW. Pneumonia: the demented patient's best friend? Discomfort after starting or withholding antibiotic treatment. *J Am Geriatr Soc* 2002;50: 1681-1688.
28. Koopmans RT, van der Sterren KJ, van der Steen JT. The 'natural' endpoint of dementia: death from cachexia or dehydration following palliative care? *Int J Geriatr Psychiatry* 2007;22:350-355.
29. Pasman HR, Onwuteaka-Philipsen BD, Ooms ME, et al. Forgoing artificial nutrition and hydration in nursing home patients with dementia: patients, decision making, and participants. *Alzheimer Dis Assoc Disord* 2004;18:154-162.
30. Santangelo G. Relationship to subjective pain reports by patients and their caregivers. Abstract from the Gerontological Society of America 2012 annual conference. Available from www.geron.org/meeting/2012/ProgramBookFinal_web.pdf. Accessed July 6, 2013.
31. Rosenberg PB, Lyketsos CG. Treating agitation in dementia. *BMJ* 2011;343:d3913.
32. Manfredi PL, Breuer B, allenstein S, et al. Opioid treatment for agitation in patients with advanced dementia. *Int J Geriatr Psychiatry* 2003;18: 700-705.
33. Pieper MJ, Achterberg WP, Francke AL, et al. The implementation of the serial trial intervention for pain and challenging behaviour in advanced dementia patients (STA OPI!): a clustered randomized controlled trial. *BMC Geriatr* 2011;11:12.
34. Verenso, the Dutch Association of Elderly Care Physicians and Social Geriatricians. [Guideline: behaviour problems]. [in Dutch]. 2008. Available from <http://www.verenso.nl/wat-doen-wij/vakinhoudelijke-producten/richtlijnen/probleemgedrag>. Accessed July 6, 2013.
35. Swart SJ, Rietjens JA, van Zuyleen L, et al. Continuous palliative sedation for cancer and noncancer patients. *J Pain Symptom Manage* 2012;43:172-181.
36. Miccinesi G, Rietjens JA, Deliëns L, et al. Continuous deep sedation: physicians' experiences in six European countries. *J Pain Symptom Manage* 2006;31:122-129.
37. Fainsinger RL, Waller A, Bercovici M, et al. A multicentre international study of sedation for uncontrolled symptoms in terminally ill patients. *Palliat Med* 2000;14:257-265.
38. Muller-Busch HC, Andres I, Jehser T. Sedation in palliative care: a critical analysis of 7 years experience. *BMC Palliat Care* 2003;2:2.
39. Stone P, Phillips C, Spruyt O, Waight C. A comparison of the use of sedatives in a hospital support team and in a hospice. *Palliat Med* 1997; 11:140-144.

40. Chiu TY, Hu WY, Lue BH, Cheng SY, Chen CY. Sedation for refractory symptoms of terminal cancer patients in Taiwan. *J Pain Symptom Manage* 2001; 21:467-472.
41. Sykes N, Thorns A. The use of opioids and sedatives at the end of life. *Lancet Oncol* 2003;4: 312-318.
42. Rietjens JA, van Zuylen L, van Veluw H, et al. Palliative sedation in a specialized unit for acute palliative care in a cancer hospital: comparing patients dying with and without palliative sedation. *J Pain Symptom Manage* 2008;36:228-234.
43. Rietjens J, van Delden J, Onwuteaka-Philipsen B, et al. Continuous deep sedation for patients nearing death in the Netherlands: descriptive study. *BMJ* 2008;336:810-813.
44. Houttekier D, Cohen J, Bilsen J, et al. Place of death of older persons with dementia. A study in five European countries. *J Am Geriatr Soc* 2010;58:751-756.



Chapter 6

Changes in care goals and treatment orders around the occurrence of health problems and hospital transfers in dementia: A prospective study

Simone A. Hendriks
Martin Smalbrugge
Cees M.P.M. Hertogh
Jenny T. van der Steen

ABSTRACT

Objectives: To explore changes in care goals and treatment orders around the occurrence of pneumonia and intake problems, and whether hospitalization is in line with earlier agreed upon do-not-hospitalize orders.

Design: Data were collected as part of the Dutch End of Life in Dementia study (2007-2011), a longitudinal observational study with up to 3.5 years of follow-up.

Setting: Long-term care facilities (N = 28) in the Netherlands.

Participants: Newly admitted nursing home patients (N = 372) in various stages of dementia.

Measurements: Semi-annually, physicians completed questionnaires about care goals and treatment orders, and they continuously registered episodes of pneumonia, intake problems and hospitalization. We report on changes in care goals and treatment orders during follow-up in relation to the developing of pneumonia and intake problems and on hospitalization and reasons for hospitalization.

Results: The proportion of patients with palliative care goals and do-not-treat orders rose during follow-up, especially before death. Treatment orders most frequently referred to resuscitation and hospitalization (do-not order increased from 73% to 92%, and from 28% to 76% respectively). The proportions of patients with a palliative care goal and do-not-treat orders were similar after developing pneumonia, but increased after intake problems. During follow-up, 46 patients were hospitalized one or more times. Hospitalization occurred despite a do-not-hospitalize order in 21% of decisions. The most frequently reported reason for hospitalization was a fracture, especially in patients with a do-not-hospitalize order.

Conclusion: Care plans, including global care goals (predominantly palliative care goals), are made soon after admission, and specific treatment orders are agreed upon in more detail when the condition of the patient worsens. Establishing care plans shortly after nursing home admission may help to prevent burdensome treatment.

INTRODUCTION

Dementia is a disease without a cure, and one of the key components of the quality of palliative care for patients with dementia is advance care planning.¹⁻³ Advance care planning is especially important for people with dementia because the gradual loss of cognitive abilities complicates decision making at the end of life.^{1;4-6} In the last phase of life, the majority of people with dementia in the United States and Western Europe are admitted to and eventually die in long-term care facilities.⁷ Advance care planning in long-term care in dementia concerns timely and ongoing discussions about care goals, and part of this is communication about end-of-life issues. Most of the patients in long-term care are unable to make decisions at the end of life and discussions therefore often take place with proxy decision-makers^{1;4;8-11}

Informing patients and families about expected health problems that influence quality of life and survival, such as pneumonia and intake problems, can help initiate a discussion about care goals.^{1;3;12-18} In addition, physicians may discuss treatment orders such as resuscitation and hospitalization anticipating future scenarios with proxy decision-makers. A do-treat order or a do-not-treat order anticipating future scenarios can be recorded in the patients' medical file, and can be tailored to each specific scenario.^{6;19;20}

Establishing care plans may be influenced by culture, organizational models and health care settings.^{2;21-23} An environment with physicians specialized in dementia and advance care planning who are frequently present in the long-term care facilities may promote the development of care plans.^{2;23-25} In this type of setting, we found that more than half of patients with dementia had a palliative care goal shortly after admission to long-term care,²⁶ and 85% had documented treatment orders during nursing home stay.²⁰ However, no longitudinal data, and no data about care goals and treatment orders around the occurrence of expected health problems have been published so far. Therefore, the aim of our study was to explore the changes in care goals and treatment orders over time and around the occurrence of two common health problems during the course of dementia, i.e. pneumonia and intake problems. Further, we explored whether hospitalization of patients with dementia in long-term care in the Netherlands was in line with earlier agreed upon do-not-hospitalize orders.

METHODS

Data collection

Data were collected as part of a longitudinal observational study, the Dutch End of Life in Dementia study.²⁷ Between 2007 and 2011, data were prospectively and retrospectively collected on 491

patients in 34 long-term care facilities. In this study we only used prospectively collected data on 372 patients with dementia at any stage admitted to 28 facilities. They were enrolled upon admission between January 2007 and July 2009. We only used the prospectively collected data because only these longitudinal data can answer our research question. Elderly care physicians were responsible for data collection by completing written questionnaires.

Individual assessments were performed for a maximum period up to 3½ years (January 2007-July 2010; survival was monitored for an additional year, until summer 2011). A baseline assessment was scheduled eight weeks after admission, followed by a maximum of five semi-annual assessments. In case of death during the study period, a questionnaire about the last six months of life was completed within 2 weeks after death, and we refer to this questionnaire as the after-death assessment. Physicians additionally registered any incident pneumonia and intake problems on a continuous basis.

Characteristics of the patients have been published elsewhere; most patients were women (70%), at admission mean age was 84 years (SD = 7), 9% of the patients had advanced dementia (Cognitive performance Scale²⁸ score 5 or 6, and a Global Deterioration Scale²⁹ score 7), and the most common type of dementia was Alzheimer's disease (46%).³⁰ During follow-up, the number of patients decreased across consecutive assessments as patients died. In total, 218 patients died during follow-up; 34 died before or shortly after the baseline assessment, and 4 patients were lost to follow-up before the baseline assessment.³⁰ The median length of stay until death was 8 months (25th percentile = 4, 75th percentile = 17 months).³⁰ The study protocol was approved by the Medical Ethics Review Committee of the VU University Medical Center in Amsterdam, and written informed consent was obtained from the families.

Measurements

The attending physicians recorded their specialty, age, number of years of experience in long-term care, and the full-time equivalents they worked in the long-term care facilities. Further, physicians recorded whether there was a general discussion with proxy decision-makers about the care goals (at baseline) and the treatment orders (at all assessments). At baseline, at every semi-annual assessment, and after death, physicians recorded the main care goal. The main care goal categories were life prolongation, palliative care goal (palliative and symptomatic care goal), preserve functioning, other and no care goals. Palliative and symptomatic goals both refer to comfort, quality of life and well-being, but differ as to whether prolongation of life is desirable.³¹ In addition, physicians recorded treatment orders anticipating future scenarios. Treatment orders were assessed as a do-treat order, a do-not-treat order, or no order, and a pre-structured list of treatment orders was included in the questionnaires. First, for each treatment order separately, the physicians reported whether a discussion took place with a proxy-decision maker, and second, what decision the physician and the proxy-decision maker made in advance. They did this at the

baseline assessment (referring to the previous 8 weeks), at the semi-annual assessments (for the previous 6-month period), and at the after-death assessment (maximum 6 months prior to assessment). Further, physicians could report the reason for not discussing treatment orders in an open-ended question. Unfortunately, at the semi-annual and at the after-death assessment some physicians reported “no new order in the last six months” as “no order”, when an interim discussion did not take place. So in these cases, we recoded these answers into the last available “do-treat” or “do-not-treat order”. Further, physicians recorded at all assessment whether a patient was hospitalized in the previous period, including date of hospitalization and the reason for hospitalization.

Physicians registered any incident pneumonia and intake problems and the date of diagnosis on a continuous basis. Pneumonia was diagnosed by the attending physician. We defined intake problems as an eating or drinking problem as judged by the attending physician. After developing a pneumonia or an intake problem, the physician reported whether this patient had a do-not-treat order.

Statistical analyses

We describe the physician characteristics and timing of discussions as reported by the treating physician. We calculated the proportion of patients with care goals and treatment orders. In addition, we separately reported the main care goals and the treatment orders at the assessments before the patient developed pneumonia or intake problems (a minimum period of 6 months before), and after these health problems. Theoretically, the period between these health problems and the last assessment is at most 6 months. We only used the data of the first episode of pneumonia, and the first time an intake problem occurred.

We reported any possible differences in the prevalence of palliative care goals (versus all other goals) between patients who developed pneumonia and patients who did not develop a pneumonia, and between patients who developed intake problems and who did not.

To evaluate the longitudinal changes in palliative care goals (versus all other goals), we used the generalized estimating equation (GEE) model, with an exchangeable correlation structure. The models used assessment as the independent predictor with repeated contrast levels. We separately analyzed the assessments 1 through 6, and the last assessment before death through the after-death assessment. A significant change between two consecutive assessments indicates a change at the population level (i.e., change in the total proportion of patients with a palliative goal) or at an individual level (i.e., the individual change in palliative goal). To test changes in palliative care goals around the developing of pneumonia and intake problems, we separately analyzed the last assessment before the occurrence of the health problem and the first assessment after the occurrence of the health problem.

Further, we calculated the hazard ratio of hospitalization in the first year after admission, and the proportions of patients who were admitted to a hospital during follow-up. To explore whether hospitalization was in line with treatment orders discussed earlier, we compared these with the most recent treatment orders before hospitalization. Analyses were performed with SPSS 20.0.0 (IBM, 2011).

RESULTS

Physician characteristics

Of all physicians, 81% was an elderly care physician, 15% an elderly care physician in training, and 4% had other specialties; thus, 96% of the physicians received training in palliative care.³² Physicians' mean age was 41.2 years (SD = 9.2), and they had an average of 10.5 (SD = 8.1) years of experience in long-term care. The mean full-time equivalent that physicians worked in the long-term care facilities was 0.8 (SD = 0.2).

Discussions about care goals and treatment orders anticipating future scenarios

Physicians discussed care goals with proxy decision-makers of 80% (262/327) of the patients within the first eight weeks after admission. The proportion of patients with a palliative care goal increased significantly from 57% on admission to 65% in the six months afterwards, and increased significantly from the last semi-annual assessment before death to 90% at the day of death (Table 1). Although 19% of the patients did not have a care goal on admission, most of these patients (94%) did have a care goal in the six months afterwards (Table 1).

Physicians had discussions about treatment orders with proxy decision-makers for 80% of the patients at baseline, for 27%-51% across the semi-annual assessments, and for 79% in the last six months of life. The most frequently reported reasons for not discussing treatment orders semi-annually were (in total, 377 reasons were reported by physicians): there was no need to reassess the treatment orders (n = 136), treatment orders were already clear (n = 75), there were no changes (n = 55), and the condition of the patients was stable (n = 32).

The most frequently discussed treatment orders anticipating future scenarios were resuscitation and hospitalization. The proportion of patients with a do-not-resuscitate order rose from 73% shortly after admission to 84%-91% across the semi-annual assessments, and rose further to 92% in the last six months of life (Figure 1). The proportion of patients with a do-not-hospitalize order increased from 28% to 42%-59% and further to 76% in the last six months of life (Figure 1).

Changes in decisions around developing pneumonia and intake problems

At baseline, care goals for patients who subsequently developed pneumonia or an intake problem were very similar to care goals for patients who did not develop these problems (Table 1). The proportion with a palliative care goal was 72% at the semi-annual assessment prior to episodes of pneumonia and intake problems (Table 1). We found an upward trend of prevalence of palliative care goals related to the development of pneumonia. Related to intake problems, we found an significant upward trend in the proportion of patients with a palliative care goal, and the proportion at the day of death was significantly larger than patients who did not develop an intake problem (95% versus 84%) (Table 1).

At baseline, there was also no difference in distribution of treatment-orders between patients who developed pneumonia or intake problems, and those who did not. We found an upward trend of prevalence of do-no-treat orders related to the development of pneumonia similar to the whole sample, and for intake problems we found a stronger increase of the proportion patients with do-not-treat orders over time (Table 2 and Figure 1). For example, of the patients who developed pneumonia, the proportion with a do-not-hospitalize order was 25% at baseline, which rose to 35% before the occurrence of pneumonia and to 46% after developing pneumonia; of the patients who developed an intake problem, the proportion with a do-not-hospitalize order was 33% at baseline, which rose to 49% before occurrence of intake problems and to 62% after developing intake problems.

Table 1. Most important care goals and changes in palliative care goals over time

Care goal	Assessment	N	Life prolongation	Palliative	Preserve functioning	Other	No care goals	Change in palliative care goal P-value
			%	%	%	%	%	
All patients	1	(326) ^a	1	57	21	3	19	0.003 0.936 0.253 0.813 0.809 0.000
	2	(221)	5	65	23	4	2	
	3	(172)	5	65	27	2	2	
	4	(122)	5	69	23	2	1	
	5	(76)	4	70	25	0	1	
	6	(34)	6	65	24	3	3	
	At the day of death	(211)	1	90	4	1	4	
Neither problem	1	(158) ^a	0	53 ^f	22	3	22	0.004 0.660 0.392 0.680 0.482 0.005
	2	(115)	4	65	23	5	2	
	3	(92)	5	61	30	1	2	
	4	(67)	7	66	25	1	0	
	5	(42)	2	69	26	0	2	
	6	(18)	6	56	28	6	6	
	At the day of death	(74)	1	84 ^g	8	1	5	
Pneumonia	1	(86) ^b	3	63 ^f	14	3	16	0.880 ^h
	before	(78)	4	72	13	4	8	
	after	(73) ^c	3	73	18	3	4	
	At the day of death	(57)	4	86 ^g	5	0	5	
Intake problems	1	(102) ^d	0	60 ^f	18	5	18	0.000 ^h
	before	(100)	2	72	15	4	7	
	after	(94) ^e	1	93	5	0	1	
	At the day of death	(81)	1	95 ^g	2	0	1	

Changes in palliative care goals (versus all other care goals) over time was measured with GEE with repeated contrasts between 2 consecutive assessments. The *P*-value provides an indication for change over time over 2 consecutive assessments at a population level and at an individual level.

Van Soest et al.²⁶ reported only care goals at assessment 1 and at the day of death.

^a34 patients died before or shortly after the baseline assessment. We used a shortened baseline assessment, to complete only the data of patient characteristics that we deemed not particularly vulnerable to recall bias. 4 patients were lost to follow-up before the baseline assessment.

^b15 patients developed pneumonia before the baseline assessment; these cases were therefore removed from the selection for analyses. In 44 patients, the baseline assessment was also the assessment before developing pneumonia.

^c50 patients died within 6 months after developing pneumonia, so the assessment was also the after-death assessment and refers to the care goal at the time of death.

^d17 patients developed an intake problem before the baseline assessment and were therefore removed from the selection for analyses. In 48 patients, the baseline assessment was also the assessment before developing an intake problem.

^e79 patients died within 6 months after developing intake problems, so the assessment was also the after-death assessment and refers to the care goal at the time of death.

^fNo significant differences at baseline in proportions of patients with palliative care goals (versus all other goals) between the subgroups.

^gNo significant differences at the day of death in proportions of patients with palliative care goals (versus all other goals) between patient who developed a pneumonia and patients who did not develop a pneumonia ($X^2 = 1.026$, $P = 0.331$).

We found a significant larger proportion palliative care goal (versus all other goals) at the day of death in patients who developed an intake problem than patients who did not develop an intake problem ($X^2 = 4.902$, $P = 0.027$).

^hThe *P*-value provides an indication for changes in palliative care goals (versus all other care goals) over 2 consecutive assessments: the last assessment before the occurrence of the health problem and the first assessment after the occurrence of the health problem).

Table 2. Treatment orders around the developing of pneumonia and intake problems

		Baseline	Decided before health problem	Decided after health problem	Shortly before death ^b
	Do-not-treat order	%	%	%	%
Neither problem (n)		(158)			
	Resuscitation	69			94
	Intubate	28			55
	Hospitalization	28			72
	Tube-feeding	35			76
	Intravenous therapy	28			72
	Hypodermoclysis	19			51
	Antibiotics	7			33
Pneumonia (n)		(86) ^a	(86)	(86)	(58)
	Resuscitation	80	87	89	91
	Intubate	33	40	51	58
	Hospitalization	25	35	46	67
	Tube-feeding	39	50	59	66
	Intravenous therapy	25	36	48	57
	Hypodermoclysis	19	23	30	55
	Antibiotics	4	2	10	36
Intake problem (n)		(103) ^b	(105)	(105)	(81)
	Resuscitation	73	87	91	96
	Intubate	33	48	54	62
	Hospitalization	33	49	62	85
	Tube-feeding	41	53	65	80
	Intravenous therapy	34	47	55	61
	Hypodermoclysis	20	33	46	69 ^c
	Antibiotics	5	8	18	40

^aFifteen patients developed pneumonia before the baseline assessment; these cases were therefore removed from the selection for analyses. In 44 patients, the baseline assessment was also the assessment before developing pneumonia.

^bSeventeen patients developed an intake problem before the baseline assessment and were therefore removed from the selection for analyses. In 48 patients, the baseline assessment was also the assessment before developing an intake problem.

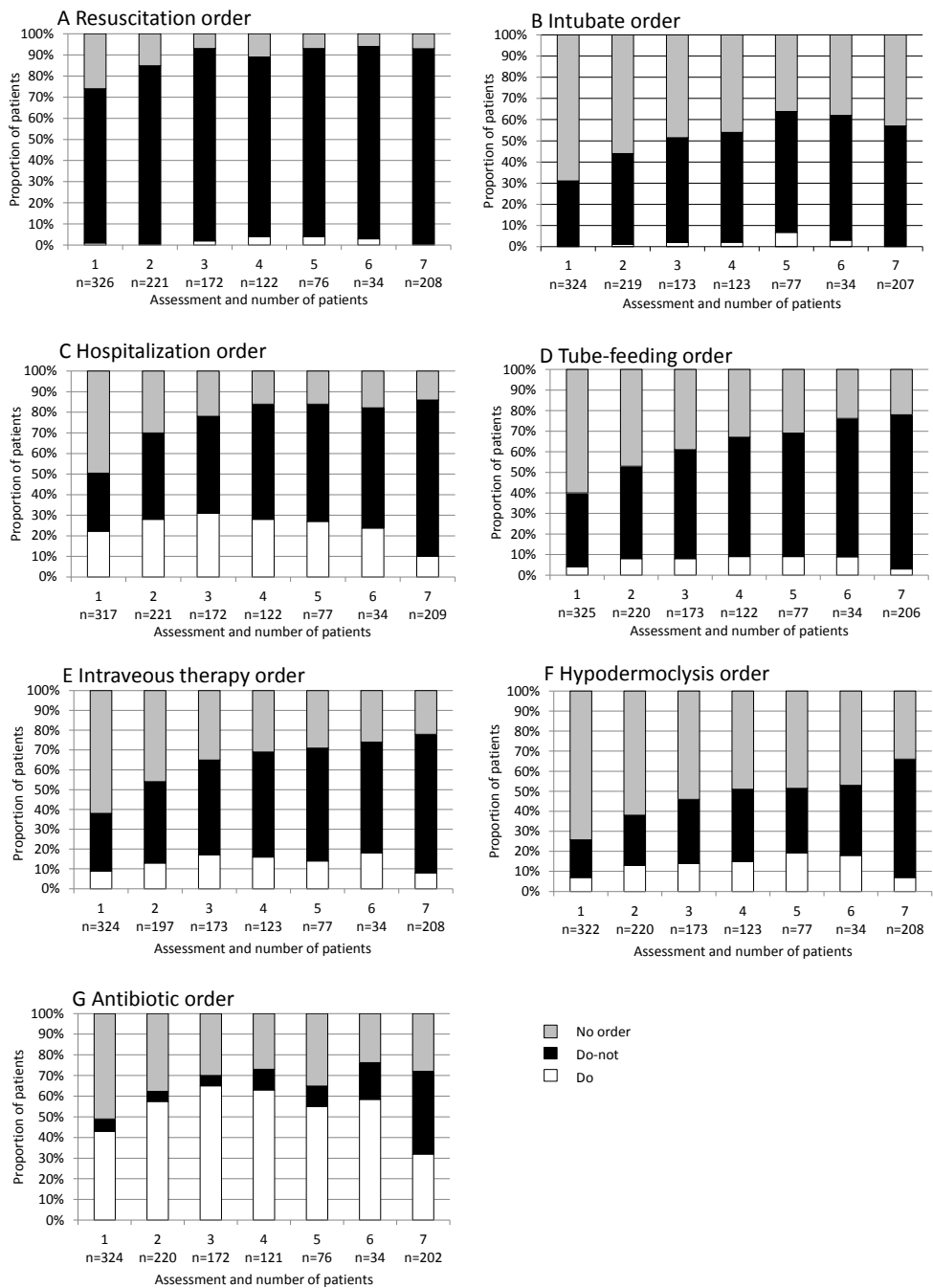


Figure 1. Trajectories of treatment orders over time of all patients. The numbers 1 through 7 on the x-axis refer to the assessments. 1 = baseline assessment, 2-6 = semi-annual assessments, 7 = after-death assessment.

Hospitalization

Overall, the hazard rate for hospitalization in the first year was 0.12 (95% CI 0.08 to 0.17). During follow-up, 46 patients were hospitalized (eight patients two times, one patient three times and one patient five times). One of these patients was admitted to an intensive care unit in the last 14 days of life. Of the 60 hospitalization decisions, 15 were referred to hospital in the first 8 weeks of admission; 16 in the last 6 months of life; and 29 hospitalizations occurred in between. Of the patients who were hospitalized during follow-up, 6% had life prolongation as care goal, 49% had a palliative care goal, 39% had preserve functioning as care goal, 2% had another care goal, and 12% had no care goal. Further, 57% (27/47; missing n = 13) had a do-hospitalize order, 21% (10/47) had a do-not-hospitalize order, and 21% (10/47) had no order (Supplementary Table S1). The most frequently reported reasons for hospitalization were bone fractures (43%; 25/58 (23 hip fractures, 1 jaw fracture, 1 rib/humerus fracture); missing n = 2), cardiovascular problems (12%; 7/58), and urogenital problems (10%; 6/58; Supplementary Table S1). A fracture was the reason for hospitalization for 6 of the 10 patients with a do-not-hospitalize order.

DISCUSSION

To the best of our knowledge, this is the first longitudinal study that describes the changes in care goals and treatment orders around the occurrence of health problems in patients with dementia during nursing home stay. We found that care plans including global care goals were made shortly after admission. The proportion of people with palliative care goals was unchanged after pneumonia, and increased substantially after intake problems and in the period shortly before death (last 6 months of life). Treatment orders most frequently referred to resuscitation and hospitalization. Although hospitalization was rare, one fifth of those with a do-not-hospitalize order were hospitalized. The most frequently reported reason for hospitalization was a fracture, especially in the group of patients with a do-not-hospitalize order.

We found that care plans were often established shortly after admission. Care plans were generally not reassessed as long as the condition of the patient was stable. Resuscitations and hospitalization were the most acute decisions and the most frequently discussed treatment orders in our study. We found an upward trend in the prevalence of non-treatment orders and a strong increase before death. We found a similar upward trend in the prevalence of non-treatment orders for patients who developed pneumonia or an intake problem. Moreover, our study, like other studies, suggests that intake problems are a relevant trigger for discussions and an important signal of a worsening condition.^{17,21,33,34} Although infection of the respiratory system may lead to critical decisions about treatment,²³ pneumonia may have been perceived as an intercurrent and reversible disease, unlike intake problems in patients with dementia.

Hospitalization was rare in our study; only 1 in 10 patients was hospitalized in the first year after admission. A do-not-hospitalize order did not always prevent hospitalization, as demonstrated by the 10 patients we found with a do-not-hospitalize order who were subsequently admitted to the hospital. However, these patients mainly had (hip) fractures, which generally require surgery to improve the quality of life.^{35;36}

Our findings may reflect Dutch medical practice in long-term care. In the Netherlands, quality of life is an important aspect in end-of-life decisions and often outweighs life prolongation. Forgoing medical interventions is accepted practice.³⁷ This may result in the fact that the majority of patients having a palliative care goal and this may lead to do-not-treat orders. Comparing our findings with other studies, we found some differences that may reflect different policies, organizational models and health care settings.^{2;38;39} First, we found a higher prevalence of do-not-hospitalize orders than Houttekier et al. in a retrospective Belgian study (76% in the last 6 month of life in the Netherlands versus 57% in the last month of life in Belgium).⁴⁰ We also found a higher prevalence of do-not-hospitalize orders than Lamberg et al. in a study from the United States (42-59% at least 6 months before death versus 34% at six months before death).²⁵ Patients in the United States with do-not-hospitalize orders were less likely to be hospitalized than patients without a do-not-hospitalize order.⁴¹ Second, we found a notably smaller proportion of patients who were hospitalized than Houttekier et al. in the Belgian study (8% was hospitalized in the Netherlands in the last sixth months of life versus 20% in Belgium)⁴⁰ and smaller proportions than in studies from the United States (12% was hospitalized in the Netherlands during nursing home stay versus 16%-25% in the United States during nursing home stay).^{25;42;43} Finally, reasons for hospital admission in our study were mostly (hip) fractures, and in a few cases cardiovascular problems, urogenital problems and gastrointestinal bleedings, while in the United States infection and pneumonia were found to be the most common reasons for hospitalization.⁴¹

Strengths and limitations

Our study was unique in that we investigated the changes in care goals and treatment orders from nursing home admission until death, and the longitudinal design allowed for studying changes related to pneumonia, intake problems and hospitalization. Some limitations should be acknowledged. First, we reported our results mainly from the perspective of physicians. Although physicians have an important role in initiating advance care planning, other disciplines can also play a role in observing needs and initiating advance care planning.¹ Second, any pneumonia and intake problems were recorded continuously, but we assessed changes in care goals and treatment orders semi-annually. Third, physicians reported for each treatment order separately whether a discussion took place, and which decision was made in advance. In case an interim discussion did not take place and the physician reported “no order” instead of “no new order in the last 6 months”, we recoded these answers into the last available “do-treat” or “do-not-

treat order". Recoding this data may underestimate the proportion of "no order", and may overestimate the proportion of "do-treat/do-not-treat orders". However, in practice it is very likely that an order only changed from "a do order"/"no-order" into a "do-not-treat order", and moreover it is very likely that an order only changed when this is discussed with family. For example, for resuscitation orders, we checked the recoded answers with the reported reason for not discussing treatment orders. In 91%, physicians explained that no discussion was needed because the condition of patient was stable and/or the treatment orders were already clear.

Recommendations

Dementia is a disease without a cure, and while many people diagnosed with dementia will die with or from this disease, intercurrent diseases and burdensome symptoms frequently develop during the disease trajectory.¹ Therefore, a strong focus on palliative care needs is recommended. This call for an active focus on advance care planning. Our findings suggest that establishing care plans shortly after nursing home admission helps to prevent burdensome and unnecessary treatment such as hospitalization. Although not all scenarios can be discussed beforehand,^{2;3;9;31;44} discussion of the most common health problems and the most acute decisions is recommended when establishing a care plan.^{1;17;21;40} Communication with proxy-decision makers about the circumstances and conditions surrounding future scenarios such as pneumonia, intake problems and hospital transfer is important to reduce burdensome, unnecessary treatment and to help patients and families prepare for the future.^{40;45}

In the Netherlands this is supported by an organization model with ample availability of physicians specially trained in elderly care medicine, who see their patients and relatives frequently. Elderly care physicians are employed by the nursing homes, and follow a 3-year training, which includes training in advance care planning and palliative care.³² Elderly care physicians have a strong and often decisive influence on decision making,^{32;46;47} and facilitate discussions on advance care planning and establishment of care plans.⁹ Characteristics of this type of organization model may have positive influence on advance care planning in dementia care. Further, there is a strong policy tendency from the government to postpone nursing home admission as long as possible. As a consequence, there will be more and more patients living at home and treated in primary care with more severe stages of dementia. Therefore, it is very important to establish care goals in an earlier phase of dementia to provide adequate care in primary care also.

There is an emerging need to understand how professionals deal with decision making in dementia and how establishing care goals and anticipation to the most common and acute health problems may influence care outcomes and quality of care. Therefore, future cross-national and qualitative research, in particular participant observation research, may explore the rationale of care actions that do not correspond with the care plan that was established in advance. Future studies should

examine what level of detail is most effective for care planning at different times, for example proximate to transitions, such as hospitalization, acute problems and gradual decline.

Conclusion

Care plans, including global care goals (predominantly palliative care goals), for patients with dementia in Dutch long-term care facilities, are drawn up soon after admission and are reassessed and discussed in more detail when the condition of the patient worsens. Care plans that anticipate expected health problems in the trajectory of dementia and that anticipate the most acute decisions may help prevent burdensome, unnecessary treatment such as transfers to the hospital.

Supplementary Data

Online supplementary table S1 can be found in the appendix of this thesis.

REFERENCES

1. van der Steen JT, Radbruch L, Hertogh CM et al. White paper defining optimal palliative care in older people with dementia: a Delphi study and recommendations from the European Association for Palliative Care. *Palliat Med* 2014;28:197-209.
2. van der Steen JT, van Soest-Poortvliet MC, Hallie-Heierman M et al. Factors associated with initiation of advance care planning in dementia: a systematic review. *J Alzheimers Dis* 2014;40:743-757.
3. Mitchell SL, Teno JM, Kiely DK et al. The clinical course of advanced dementia. *N Engl J Med* 2009;361:1529-1538.
4. Robinson L, Dickinson C, Rousseau N et al. A systematic review of the effectiveness of advance care planning interventions for people with cognitive impairment and dementia. *Age Ageing* 2012;41:263-269.
5. Chambaere K, Cohen J, Robijn L, Bailey SK, Deliens L. End-of-life decisions in individuals dying with dementia in Belgium. *J Am Geriatr Soc* 2015;63:290-296.
6. Vandervoort A, Houttekier D, Van den Block L, van der Steen JT, Vander SR, Deliens L. Advance care planning and physician orders in nursing home residents with dementia: a nationwide retrospective study among professional caregivers and relatives. *J Pain Symptom Manage* 2014;47:245-256.
7. Reyniers T, Deliens L, Pasman HR et al. International variation in place of death of older people who died from dementia in 14 European and non-European countries. *J Am Med Dir Assoc* 2015;16:165-171.
8. Gillick MR. Adapting advance medical planning for the nursing home. *J Palliat Med* 2004;7:357-361.
9. Hertogh CM. Advance care planning and the relevance of a palliative care approach in dementia. *Age Ageing* 2006;35:553-555.
10. Teno, J. M.: Advance care planning for frail, older persons. In Morrison RS, Meier DE, Eds. *Geriatric Palliative Care*. Oxford: Oxford University Press, 2003. pp. 307-313.
11. Sampson EL. Palliative care for people with dementia. *Br Med Bull* 2010;96:159-174.
12. Vandervoort A, Van den Block L, van der Steen JT et al. Nursing home residents dying with dementia in Flanders, Belgium: a nationwide postmortem study on clinical characteristics and quality of dying. *J Am Med Dir Assoc* 2013;14:485-492.
13. Hanson LC, Eckert JK, Dobbs D et al. Symptom experience of dying long-term care residents. *J Am Geriatr Soc* 2008;56:91-98.
14. Teno JM, Coppola KM. For every numerator, you need a denominator: a simple statement but key to measuring the quality of care of the "dying". *J Pain Symptom Manage* 1999;17:109-113.
15. Magaki S, Yong WH, Khanlou N, Tung S, Vinters HV. Comorbidity in dementia: update of an ongoing autopsy study. *J Am Geriatr Soc* 2014;62:1722-1728.
16. Brunnstrom HR, Englund EM. Cause of death in patients with dementia disorders. *Eur J Neurol* 2009;16:488-492.
17. Hendriks SA, Smalbrugge M, van Gageldonk-Lafeber AB, Galindo-Garre F, Schipper M, Hertogh CM, van der Steen JT. Pneumonia, intake problems, and survival among nursing home residents with variable stages of dementia in the Netherlands: Results from a prospective observational study. *Alzheimer Dis Assoc Disord*, 2016; Nov 15 [Epub ahead of print].
18. Volicer L, Seltzer B, Rheaume Y et al. Eating difficulties in patients with probable dementia of the Alzheimer type. *J Geriatr Psychiatry Neurol* 1989;2:188-195.
19. Verenso, the Dutch Association of Elderly Care Physicians and Social Geriatricians. [Guideline: Concepts and Requirements of Care in relation to end-of-life decisions in long-term care]. [in Dutch]. 2007. Available from: <http://www.verenso.nl/assets/Uploads/Downloads/Handreikingen/Levensindebeleidsversie-070607.pdf>. Accessed December 16, 2015.

20. Bouwstra H, Smalbrugge M, Hertogh CM. Physician Treatment Orders in Dutch Nursing Homes. *J Am Med Dir Assoc* 2015;16:715.
21. Levy C. Expectation Conversations About the Very Predictable Events in Advanced Dementia. *J Am Med Dir Assoc* 2015;16:724-727.
22. Beck ER, McIlfatrick S, Hasson F, Leavey G. Health care professionals' perspectives of advance care planning for people with dementia living in long-term care settings: A narrative review of the literature. *Dementia (London)* 2015, Sep 16.
23. Toscani F, van der Steen JT, Finetti S et al. Critical decisions for older people with advanced dementia: a prospective study in long-term institutions and district home care. *J Am Med Dir Assoc* 2015;16:535-20.
24. Detering KM, Hancock AD, Reade MC, Silvester W. The impact of advance care planning on end of life care in elderly patients: randomised controlled trial. *BMJ* 2010;340:c1345.
25. Lamberg JL, Person CJ, Kiely DK, Mitchell SL. Decisions to hospitalize nursing home residents dying with advanced dementia. *J Am Geriatr Soc* 2005;53:1396-1401.
26. van Soest-Poortvliet MC, van der Steen JT, de Vet HC, Hertogh CM, Onwuteaka-Philipsen BD, Deliëns LH. Factors related to establishing a comfort care goal in nursing home patients with dementia: a cohort study among family and professional caregivers. *J Palliat Med* 2014;17:1317-1327.
27. van der Steen JT, Ribbe MW, Deliëns L, Gutschow G, Onwuteaka-Philipsen BD. Retrospective and prospective data collection compared in the Dutch End Of Life in Dementia (DEOLD) study. *Alzheimer Dis Assoc* 2014;28:88-94.
28. Morris JN, Fries BE, Mehr DR et al. MDS Cognitive Performance Scale. *J Gerontol* 1994;49:M174-M182.
29. Reisberg B, Ferris SH, de Leon MJ, Crook T. The Global Deterioration Scale for assessment of primary degenerative dementia. *Am J Psychiatry* 1982;139:1136-1139.
30. Hendriks SA, Smalbrugge M, Galindo-Garre F, Hertogh CM, van der Steen JT. From admission to death: prevalence and course of pain, agitation, and shortness of breath, and treatment of these symptoms in nursing home residents with dementia. *J Am Med Dir Assoc* 2015;16:475-481.
31. van der Steen JT, Onwuteaka-Philipsen BD, Knol DL, Ribbe MW, Deliëns L. Caregivers' understanding of dementia predicts patients' comfort at death: a prospective observational study. *BMC Med* 2013;11:105.
32. Koopmans RT, Lavrijsen JC, Hoek JF, Went PB, Schols JM. Dutch elderly care physician: a new generation of nursing home physician specialists. *J Am Geriatr Soc* 2010;58:1807-1809.
33. Hanson LC, Ersek M, Lin FC, Carey TS. Outcomes of feeding problems in advanced dementia in a nursing home population. *J Am Geriatr Soc* 2013;61:1692-1697.
34. Pasman HR, Onwuteaka-Philipsen BD, Ooms ME, van Wigcheren PT, van der Wal G, Ribbe MW. Forgoing artificial nutrition and hydration in nursing home patients with dementia: patients, decision making, and participants. *Alzheimer Dis Assoc Disord* 2004;18:154-162.
35. Handoll HH, Parker MJ. Conservative versus operative treatment for hip fractures in adults. *Cochrane Database Syst Rev* 2008;CD000337.
36. Jain R, Basinski A, Kreder HJ. Nonoperative treatment of hip fractures. *Int Orthop* 2003;27:11-17.
37. van der Steen JT, Kruse RL, Ooms ME et al. Treatment of nursing home residents with dementia and lower respiratory tract infection in the United States and The Netherlands: an ocean apart. *J Am Geriatr Soc* 2004;52:691-699.
38. Mehr DR, van der Steen JT, Kruse RL, Ooms ME, Rantz M, Ribbe MW. Lower respiratory infections in nursing home residents with dementia: a tale of two countries. *Gerontologist* 2003;43 Spec No 2:85-93.
39. van der Maaden T, Hendriks SA, de Vet HC et al. Antibiotic use and associated factors in patients with dementia: a systematic review. *Drugs Aging* 2015;32:43-56.

40. Houttekier D, Vandervoort A, Van den Block L, van der Steen JT, Vander SR, Deliens L. Hospitalizations of nursing home residents with dementia in the last month of life: Results from a nationwide survey. *Palliat Med* 2014; Oct;28(9):1110-7.
41. Givens JL, Selby K, Goldfeld KS, Mitchell SL. Hospital transfers of nursing home residents with advanced dementia. *J Am Geriatr Soc* 2012;60:905-909.
42. Gruneir A, Miller SC, Intrator O, Mor V. Hospitalization of nursing home residents with cognitive impairments: the influence of organizational features and state policies. *Gerontologist* 2007;47:447-456.
43. Gozalo P, Teno JM, Mitchell SL et al. End-of-life transitions among nursing home residents with cognitive issues. *N Engl J Med* 2011;365:1212-1221.
44. van Soest-Poortvliet MC, van der Steen JT, Gutschow G et al. Advance Care Planning in Nursing Home Patients With Dementia: A Qualitative Interview Study Among Family and Professional Caregivers. *J Am Med Dir Assoc* 2015; Nov 1;16(11):979-89.
45. Houben CH, Spruit MA, Groenen MT, Wouters EF, Janssen DJ. Efficacy of advance care planning: a systematic review and meta-analysis. *J Am Med Dir Assoc* 2014;15:477-489.
46. Helton MR, van der Steen JT, Daaleman TP, Gamble GR, Ribbe MW. A cross-cultural study of physician treatment decisions for demented nursing home patients who develop pneumonia. *Ann Fam Med* 2006;4:221-227.
47. Helton MR, Cohen LW, Zimmerman S, van der Steen JT. The importance of physician presence in nursing homes for residents with dementia and pneumonia. *J Am Med Dir Assoc* 2011;12:68-73.



Chapter 7

End-of-life treatment decisions in nursing home residents dying with dementia in the Netherlands

Simone A. Hendriks
Martin Smalbrugge
Luc Deliens
Raymond T.C.M. Koopmans
Bregje D. Onwuteaka-Philipsen
Cees M.P.M. Hertogh
Jenny T. van der Steen

ABSTRACT

Objective: The objective was to describe end-of-life treatment decisions for patients dying with dementia in various stages of dementia in long-term care facilities in the Netherlands with elderly care physicians responsible for treatment and care.

Methods: We present data collected in the nationally representative Dutch End of Life in Dementia study (2007-2011). Within two weeks after death, 103 physicians completed questionnaires about the last phase of life in 330 residents with dementia who resided in one of 34 participating long-term care facilities. We used descriptive statistics.

Results: Advance directives were rare (4.9%). A minority was hospitalized (8.0%) in the last month (mainly for fractures), or received antibiotics (24.2%) in the last week (mainly for pneumonia). Four residents received tube-feeding or rehydration therapy in the last week. In almost half of the residents (42.3%) decisions were made not to start potentially life-prolonging treatment such as hospital transfer and artificial nutrition and hydration. In more than half of the residents (53.7%), decisions were made to withdraw potentially life-prolonging treatment such as artificial nutrition and hydration and medication. Antibiotics were more frequently prescribed for residents with less advanced dementia, but otherwise there were no differences in treatment decisions between residents with advanced and less advanced dementia.

Conclusions: Physicians often withhold potentially burdensome life-prolonging treatment in nursing home residents in all stages of dementia in the Netherlands. This suggests that the physicians feel that a palliative care approach is appropriate at the end of life in dementia in long-term care.

Key points:

- 1) Residents of Dutch long-term care facilities with advanced as well as less advanced dementia rarely undergo potentially burdensome life-prolonging treatment.
- 2) Treatment decisions do not differ between residents with advanced and less advanced dementia, except that residents with less advanced dementia receive more antibiotics (than residents with advanced dementia).
- 3) Decisions not to start or to withdraw treatment shortly before death mainly relate to artificial nutrition and hydration and medication.

INTRODUCTION

In our greying societies many older people, up to one in three, will die with or from dementia.¹ Because of the loss of cognitive abilities, most are unable to make treatment decisions at the end of life. In many countries, more than half of people with dementia die in long-term care settings.²

Mitchell et al.³ reported in 2009 that nursing home residents with advanced dementia frequently underwent burdensome interventions in nursing homes in the USA, and recommended that residents with advanced dementia need a palliative care approach. Although a palliative care approach is more generally accepted in later stages of dementia, a palliative care approach may also be justified earlier.⁴

In the 90s, a palliative approach was introduced to the Dutch nursing home setting,^{5,6} and nowadays this approach is generally accepted in the Netherlands for residents admitted because of dementia.^{5,7,8} In Dutch nursing homes, certified elderly care physicians are on the staff, usually know the patient and family well, and have a strong and often decisive influence on decision making.⁹⁻¹¹ Besides providing symptom management, elderly care physicians may facilitate discussions on advance care planning and develop care plans.^{6,7}

The majority of residents with dementia in Dutch nursing homes has a palliative care goal.^{7,8,12} Such a goal may frame decisions to withhold potentially burdensome life-prolonging treatment such as resuscitation, hospitalization, drugs and artificial nutrition and hydration. However, no nationally representative data about treatment decisions at the end of life of nursing home residents with various stages of dementia have been available so far. In this article, we describe end-of-life treatment decisions in nursing home residents dying in various stages of dementia in Dutch long-term care facilities and cared for by elderly care physicians.

METHODS

We analysed data collected in the Dutch End of Life in Dementia study (DEOLD: assessments 2007-2010; monitoring of survival up to 2011).¹³ The primary aims of DEOLD-study were to describe quality of dying and end-of-life care and overall quality of care provided as evaluated by families and assess associated factors. In the DEOLD study, 34 long-term care facilities participated, and the facilities belonged to a total of 19 care organizations (sharing physician teams). The study was representative for the Netherlands in terms of geographic distribution.¹³ One of two observational designs was used per care organization: a prospective recruitment of residents (upon admission, with follow up until death or until the end of data collection) or a retrospective (after death) recruitment.

Residents with a dementia diagnosis admitted to a psychogeriatric ward (almost all dementia) were enrolled. Characteristics of the residents have been published elsewhere; most residents (66.7%) were female, mean age at death was 85.2 year,¹⁴ and most residents (91.1%) had a palliative care goal at the day of death.¹² The study protocol was approved by the Medical Ethics Review Committee of the VU University Medical Center Amsterdam, and written informed consent was obtained from the families.

Data collection

Within two weeks after death, 103 elderly care physicians completed questionnaires about 330 of 339 residents with dementia who died within the period of data collection (resident assessments up to summer 2010).^{13;15} In the prospective design, 218 residents died during the assessment period, and a physician after-death assessment was completed for 213 residents; in the retrospective design, 117 residents were enrolled retrospectively after death.

Measurements

Advanced dementia (vs. less advanced dementia) was defined as a Cognitive Performance Scale score¹⁶ of 5 or 6 and a Global Deterioration Scale¹⁷ score of 7 for comparability with other studies such as CASCADE.³ The physicians reported resident decisional capacity regarding preferred medical treatment as competent, partly competent, or incompetent.

Physicians reported on decision-making and context from the viewpoint of the treating physician. We report whether residents had an advance directive upon admission. Physicians recorded the main care goal using the pre-structured items life prolongation, preserve functioning, palliative care goal (palliative and symptomatic care goal: aimed at wellbeing and quality of life¹⁸), other and no care goal. These main care goals are defined by the Dutch association of elderly care physicians and social geriatricians "Verenso".¹⁹ Palliative and symptomatic goals both refer to comfort, quality of life and well-being, but differ as to whether prolongation of life is desirable. Because this distinction is not well integrated in practice²⁰ and unknown in other countries than the Netherlands, we combined the palliative and the symptomatic care goals and used for the combined goals the term 'palliative care goal'. We report on treatment decisions and the reason for treatment. We distinguished the following six treatments or actions: at the time of death, resuscitation; during the last month of life, hospitalization; and during the last week, any antibiotics, intravenous fluids, subcutaneous fluid infusion, and tube feeding. Further, physicians reported about decisions not to start treatment or to withdraw treatment shortly before death, including open-ended items to specify the treatment.

Statistical analyses

We report descriptive statistics, and explored and reported any possible differences between

residents with advanced and less advanced dementia. In all analyses, fewer than 5% of values were missing. Analyses were performed with SPSS 20.0.0 (IBM, 2011).

RESULTS

Characteristics

Less than half of the residents (43.2%) had advanced dementia upon death. A substantial minority of residents (36.5%) had been partly competent for decision making about medical treatment upon admission, and this decreased to 13.8% in the last week of life (Table 1). For residents with less advanced dementia the proportion that had been (partly) competent for decision making was significantly larger than for residents with advanced dementia ($P < 0.001$ upon admission, and $P < 0.001$ in the last week of life).

Treatment decision-making and context

Of all residents, 4.9% (16/325) had an advance directive: e.g. refusal of treatment such as no resuscitation, no artificial nutrition and hydration and no hospitalization. Of the 16 residents, four residents also had a wish for euthanasia. One of these resident had a wish for physician assisted death at baseline supported by an advance directive (formalized by a notary), and the physician commented that his/her death was due to physician-assisted suicide. Further, the attending physician found the resident competent for decision making in the last week. For the other three residents, a natural cause of death was reported.

Almost all residents had a palliative care goal on the day of death, and this referred to both residents with advanced dementia (94.2%) and residents with less advanced dementia (88.9%; no significant difference; Table 2). Resuscitation at the moment of death was rare (two residents; both had less advanced dementia), as was hospitalization in the last month (8.0%), and in the last week of life (1.5%). The most frequently reported reason for hospitalization was a fracture (33%; 7/21, 5 missings). Of the treatments, antibiotics were most commonly provided (24.2% in the last week). The treatment decisions did not differ between residents with advanced and less advanced dementia, except that residents with less advanced dementia received antibiotics significantly more often than residents with advanced dementia (Table 2). The most frequently reported reasons for antibiotic use were pneumonia (50.6%; 39/77 who received antibiotics) and urinary tract infection (33.8%; 26/77). Antibiotics were also provided for skin infections (3.9%; 3/77), and for other reasons (12%; 9/77). Four residents received tube feeding and the reasons were: vomiting due to an incident cerebrovascular accident, general malaise due to sepsis, one resident received tube-feeding for a year because of a minimally conscious state, and unknown. Fourteen residents received rehydration therapy and the reasons for therapy were: dehydration ($n = 8$), pneumonia ($n = 3$), diarrhoea ($n = 1$), and one missing.

Table 1. Residents' characteristics

	Total N = 330		Residents with advanced dementia n = 139		Residents with less advanced dementia n = 183		Differences (t-test or Fisher's exact test) P-value
	n	%	n	%	n	%	
Age at death, mean (SD)	330	85.2 (7.4) ^a	139	84.1 (7.8)	183	85.8 (7.1)	Mean diff 1.7, p=0.038
Ethnic origin other than Dutch	7	2.2	2	1.5	3	1.7	P = 1.000
Advanced dementia one month before death	139	43.2 ^a					
Competent for decisions on preferred medical treatment							
Upon admission							
- Yes	6	1.9	0	0	5	2.8	P < 0.001
- In part	118	36.5	41	30.4	77	42.5	
- No	199	61.6	94	69.6	99	54.7	
In the last week of life							
- Yes	4	1.2	2	1.4	2	1.4	P < 0.001
- In part	45	13.8	3	2.2	42	23.2	
- No	276	84.9	134	96.4	137	75.7	

Data about the severity of the dementia was missing for 8 residents.

^aAge at death and advanced dementia 1 month before death has also been reported elsewhere.¹⁴

Table 2. Decision-making and context in the last phase of life

	Total N = 330		Residents with advanced dementia n = 139		Residents with less advanced dementia n = 183		Differences (Fisher's exact test) P-value
	n	%	n	%	n	%	
Advance directives	16	4.9	12	6.6	4	2.9	P = 0.195
Resident had an advance directive according to physician, upon admission							
Care goals at the day of death	3	0.9	0	0	2	1.1	P = 0.424
Life prolongation	10	3.1	2	1.4	8	4.4	
Maintaining or improving of functioning	296	91.1	131	94.2	160	88.9	
Palliative(aimed at wellbeing and quality of life)	13	4.0	1	0.7	2	1.1	
Global goals of treatment had not been assessed	3	0.9	5	3.6	8	4.4	
Other							
Resuscitation attempt	2	0.6	0	0.0	2	1.1	P = 0.508
Hospitalization	26	8.0	7	5.1	18	9.8	P = 0.142
Admission last month of life	5	1.5	0	0.0	5	2.7	P = 0.073
Admission last week of life							
Specific treatment decisions in the last week of life	78	24.2	24	17.6	52	28.9	P = 0.024
Any antibiotics	4	1.2	1	0.7	2	1.2	P = 1.000
Tube feeding	14	4.3	4	2.9	8	4.4	P = 0.564
Rehydration (subcutaneous fluid infusion or intravenous fluids)							
Decisions	135	42.3	51	37.2	82	46.6	P = 0.107
Any decision to not start treatment shortly before death	174	53.7	67	48.6	103	57.2	P = 0.141
Any decision to withdraw treatment shortly before death							

Data about the severity of the dementia was missing for eight residents.

In 42.3% of the residents, decisions were made not to start treatment shortly before death, and in 53.7% of the residents, decisions were made to withdraw treatment shortly before death (Table 2). The type of decisions not to start treatment that were reported most frequently (in 135 residents), were decisions not to start with artificial nutrition and hydration (n = 96) or antibiotics (n = 34), and decisions not to hospitalize (n = 17). In case of withdrawing treatment, the type of treatments that were most frequently withdrawn were (in 172 residents): withdrawing all oral drugs (e.g. in case of no longer able to swallow; n = 134), withdraw antibiotics (n = 31), other drugs (n = 38), and withdraw rehydration or tube-feeding (n = 7).

DISCUSSION

In this article we describe end-of-life treatment decisions of nursing home residents dying with dementia in advanced and less advanced stages in long-term care settings in the Netherlands. We found, in this study in which 91.1% of the residents had a palliative care goal at the day of death,¹² low rates of interventions for residents with advanced dementia as well as for residents with less advanced dementia. Most residents did not have written advance directives when they were admitted to the long-term care facility. Also in Flanders, Belgium, only 8.4% of nursing home residents with dementia had an advance directive.²¹ In contrast with Europe, in the United States written advance directives are common, with 71-72% directives reported in older people at the day of death.^{22;23} The percentages of advance directives may be influenced by culture and type of organizational models.

Even though advance directives are rare in the Netherlands, earlier research found that the Netherlands, compared with the US, has a culture in which forgoing life-prolonging medical interventions is accepted practice, and in which quality of life is an important aspect in end-of-life decisions and often outweighs life prolongation.¹⁰ Consistently, we found low rates of life prolonging interventions for residents with advanced dementia as well as for residents with less advanced dementia. Because most residents were not competent for decision making anymore, most discussions about end-of-life treatment decisions take place with proxy decision-makers. There were multiple contact moments during nursing home stay between physicians, nurses and families in which care goals and treatment decisions were discussed.⁷ Resident's condition, wishes expressed by resident or family, family's willingness, family involvement, and general nursing home policy guides physicians in initiating discussions.²⁰

We found a smaller proportion of residents with advanced dementia who were hospitalized in the last week of life than in the US CASCADE study of Mitchell et al.³ (0% were hospitalized in the Netherlands versus 9% in the USA in the last week of life). Further, we found a smaller proportion

of residents who received tube feeding or parenteral therapy. In the Netherlands, it is common practice not to start artificial nutrition and hydration in residents with dementia in a nursing home setting,^{24,25} because physicians may accept the reduction of food and fluids intake, they may consider this problem inherent to dementia, and that interventions such as artificial food or fluids may not prolong survival or improve quality of life.²⁵⁻²⁷

In our study, we found that antibiotics were the most frequently provided treatment. About a quarter (24.2%) of the residents received antibiotics in the last week of life and the most frequently reported reasons for antibiotic use were pneumonia and a urinary tract infection. The severity of dementia has been associated with forgoing antibiotic treatment in other studies,²⁸ and we also found that residents with advanced dementia received antibiotics less frequently than residents with less advanced dementia. Clinical decisions about prescribing or withholding antibiotics are surrounded by uncertainties and therefore difficult to make. Because effects of antibiotics on survival are probably limited to only few patients,²⁹ especially in advanced dementia, and it remains unclear whether antibiotics actually enhance comfort.³⁰ Probable benefits of antibiotics must be weighed against potential adverse effects such as burdensome side effects, prolonging of the dying process, and antibiotic resistancy.^{28,31-33}

Health professionals often face dilemmas around whether the time has come not to start or to withdraw curative treatment because it does not add to quality of life.^{34,35} We found that decisions not to start treatment related mainly to artificial nutrition and hydration fluids, treatment with antibiotics, and hospital transfers. We found that decisions to withdraw treatment related particularly to withdrawal of oral drugs shortly before death, possibly at the moment that residents were in very poor condition and were no longer able to swallow. A study from Norway in a general nursing home population also found that changes in drug treatment were made just at the day of death.³⁶

Limitations

The present study has some limitations that warrant comment. First, the time frame “shortly before death” for decision-making was not defined. Second, we used data from both prospective and retrospective data collection. The reason for combining prospective data with retrospective data was because we could not follow-up all cases until death (right censoring) with prospective data collection. This combination of perspectives avoids the risk of recall bias involved in fully retrospective studies and provides the benefit of understanding how the truncated longitudinal sample differs from a representative sample of residents who died with dementia in Dutch nursing homes.¹³ Furthermore, we investigated the differences between the two cohorts, and the only significant difference found was a higher proportion of withdrawing treatment in the prospective design (59.2%) than in the retrospective design (43.4%; $P = 0.006$). Further, the

proportion of residents with advanced dementia was lower in the prospective design (38.1%) than in the retrospective design (52.7%; $P = 0.012$);¹⁴ however, we separately reported the results for residents with advanced and less advanced dementia.

Recommendation

End-of-life treatment decisions may affect the way that patients with dementia live their last months of life. Therefore, professional care givers should respond early to palliative care needs which may help to enhance comfort. Discussions with patients and families about palliative care needs and how to deal with multimorbidity and drug therapy at the end of life in nursing home residents with dementia are of great importance. Future qualitative research, in particular participant observation research, may explore how elderly care physicians communicate with patients and families about treatment decisions in the context of advance care planning and may explore the rationale of care actions at the end of life and how the severity of the dementia plays a role.

Conclusion

Advance directives are rare in nursing home residents with dementia in the Netherlands. Only few residents are hospitalized or undergo potentially burdensome interventions such as tube feeding or artificial nutrition and hydration. In addition, residents with advanced dementia as well as residents with less advanced dementia rarely undergo burdensome interventions. Physicians and families often agree upon a palliative care goal, and are inclined to withhold and to forgo potentially burdensome life-prolonging treatment. This suggests that they feel that a palliative care approach is appropriate when death is expected in all stages of dementia in long-term care.

REFERENCES

1. Weuve J, Hebert LE, Scherr PA, Evans DA. Deaths in the United States among persons with Alzheimer's disease (2010-2050). *Alzheimers Dement* 2014;10(2):e40-e46.
2. Houttekier D, Cohen J, Bilsen J, ddington-Hall J, Onwuteaka-Philipsen BD, Deliëns L. Place of death of older persons with dementia. A study in five European countries. *J Am Geriatr Soc* 2010;58(4):751-756.
3. Mitchell SL, Teno JM, Kiely DK et al. The clinical course of advanced dementia. *N Engl J Med* 2009;361(16):1529-1538.
4. van der Steen JT, Radbruch L, Hertogh CM et al. White paper defining optimal palliative care in older people with dementia: a Delphi study and recommendations from the European Association for Palliative Care. *Palliat Med* 2014;28(3):197-209.
5. Hertogh CM, Ribbe MW. Ethical aspects of medical decision-making in demented patients: a report from the Netherlands. *Alzheimer Dis Assoc Disord* 1996;10(1):11-19.
6. Hertogh CM. Advance care planning and the relevance of a palliative care approach in dementia. *Age Ageing* 2006;35(6):553-555.
7. Hendriks SA, Smalbrugge M, Hertogh CM, Van der Steen JT. Changes in care goals and treatment orders around the occurrence of health problems and hospital transfers in dementia: a prospective study. *JAGS*, 2016; Nov 21 [Epub ahead of print].
8. Bouwstra H, Smalbrugge M, Hertogh CM. Physician Treatment Orders in Dutch Nursing Homes. *J Am Med Dir Assoc* 2015;16(8):715.
9. Koopmans RT, Lavrijsen JC, Hoek JF, Went PB, Schols JM. Dutch elderly care physician: a new generation of nursing home physician specialists. *J Am Geriatr Soc* 2010;58(9):1807-1809.
10. Helton MR, van der Steen JT, Daaleman TP, Gamble GR, Ribbe MW. A cross-cultural study of physician treatment decisions for demented nursing home patients who develop pneumonia. *Ann Fam Med* 2006;4(3):221-227.
11. Helton MR, Cohen LW, Zimmerman S, van der Steen JT. The importance of physician presence in nursing homes for residents with dementia and pneumonia. *J Am Med Dir Assoc* 2011;12(1):68-73.
12. van Soest-Poortvliet MC, van der Steen JT, de Vet HC, Hertogh CM, Onwuteaka-Philipsen BD, Deliëns LH. Factors related to establishing a comfort care goal in nursing home patients with dementia: a cohort study among family and professional caregivers. *J Palliat Med* 2014;17(12):1317-1327.
13. van der Steen JT, Ribbe MW, Deliëns L, Gutschow G, Onwuteaka-Philipsen BD. Retrospective and prospective data collection compared in the Dutch End Of Life in Dementia (DEOLD) study. *Alzheimer Dis Assoc Disord* 2014;28(1):88-94.
14. Hendriks SA, Smalbrugge M, Hertogh CM, van der Steen JT. Dying with dementia: symptoms, treatment, and quality of life in the last week of life. *J Pain Symptom Manage* 2014;47(4):710-720.
15. Hendriks SA, Smalbrugge M, Galindo-Garre F, Hertogh CM, van der Steen JT. From admission to death: prevalence and course of pain, agitation, and shortness of breath, and treatment of these symptoms in nursing home residents with dementia. *J Am Med Dir Assoc* 2015;16(6):475-481.
16. Morris JN, Fries BE, Mehr DR et al. MDS Cognitive Performance Scale. *J Gerontol* 1994;49(4):M174-M182.
17. Reisberg B, Ferris SH, de Leon MJ, Crook T. The Global Deterioration Scale for assessment of primary degenerative dementia. *Am J Psychiatry* 1982;139(9):1136-1139.
18. van der Steen JT, Onwuteaka-Philipsen BD, Knol DL, Ribbe MW, Deliëns L. Caregivers' understanding of dementia predicts patients' comfort at death: a prospective observational study. *BMC Med* 2013;11:105.
19. Verenso, the Dutch Association of Elderly Care Physicians and Social Geriatricians. [Guideline: Concepts and Requirements of Care in relation to end-of-life decisions in long-term care]. [in Dutch]. 2007. Available from: <http://www.verenso.nl/assets/Uploads/Downloads/Handreikingen/Levensindebeleidsversie-070607.pdf>. Accessed 2016.

20. van Soest-Poortvliet MC, van der Steen JT, Gutschow G et al. Advance Care Planning in Nursing Home Patients With Dementia: A Qualitative Interview Study Among Family and Professional Caregivers. *J Am Med Dir Assoc* 2015;16(11):979-989.
21. De GC, Bilsen J, Stichele RV, Deliëns L. Advance care planning and dying in nursing homes in Flanders, Belgium: a nationwide survey. *J Pain Symptom Manage* 2013;45(2):223-234.
22. Teno JM, Gruneir A, Schwartz Z, Nanda A, Wetle T. Association between advance directives and quality of end-of-life care: a national study. *J Am Geriatr Soc* 2007;55(2):189-194.
23. Silveira MJ, Witala W, Piette J. Advance directive completion by elderly Americans: a decade of change. *J Am Geriatr Soc* 2014;62(4):706-710.
24. Mehr DR, van der Steen JT, Kruse RL, Ooms ME, Rantz M, Ribbe MW. Lower respiratory infections in nursing home residents with dementia: a tale of two countries. *Gerontologist* 2003;43 Spec No 2:85-93.
25. Pasman HR, Onwuteaka-Philipsen BD, Ooms ME, van Wigcheren PT, van der Wal G, Ribbe MW. Forgoing artificial nutrition and hydration in nursing home patients with dementia: patients, decision making, and participants. *Alzheimer Dis Assoc Disord* 2004;18(3):154-162.
26. Teno JM, Gozalo PL, Mitchell SL et al. Does feeding tube insertion and its timing improve survival? *J Am Geriatr Soc* 2012;60(10):1918-1921.
27. Hendriks SA, Smalbrugge M, van Gageldonk-Lafeber AB, Galindo-Garre F, Schipper M, Hertogh CM, van der Steen JT. Pneumonia, intake problems, and survival among nursing home residents with variable stages of dementia in the Netherlands: Results from a prospective observational study. *Alzheimer Dis Assoc Disord*, 2016; Nov 15 [Epub ahead of print].
28. van der Maaden T, Hendriks SA, de Vet HC et al. Antibiotic use and associated factors in patients with dementia: a systematic review. *Drugs Aging* 2015;32(1):43-56.
29. van der Steen JT, Lane P, Kowall NW, Knol DL, Volicer L. Antibiotics and mortality in patients with lower respiratory infection and advanced dementia. *J Am Med Dir Assoc* 2012;13(2):156-161.
30. van der Steen JT. Prolonged life and increased symptoms vs prolonged dying and increased comfort after antibiotic treatment in patients with dementia and pneumonia. *Arch Intern Med* 2011;171(1):93-94.
31. van der Steen JT, Lane P, Kowall NW, Knol DL, Volicer L. Antibiotics and mortality in patients with lower respiratory infection and advanced dementia. *J Am Med Dir Assoc* 2012;13(2):156-161.
32. van der Maaden T, van der Steen JT, de Vet HC, Hertogh CM, Koopmans RT. Prospective Observations of Discomfort, Pain, and Dyspnea in Nursing Home Residents With Dementia and Pneumonia. *J Am Med Dir Assoc* 2015.
33. van Buul LW, van der Steen JT, Veenhuizen RB et al. Antibiotic use and resistance in long term care facilities. *J Am Med Dir Assoc* 2012;13(6):568-13.
34. Stewart AL, Teno J, Patrick DL, Lynn J. The concept of quality of life of dying persons in the context of health care. *J Pain Symptom Manage* 1999;17(2):93-108.
35. Goodman C, Froggatt K, Amador S, Mathie E, Mayrhofer A. End of life care interventions for people with dementia in care homes: addressing uncertainty within a framework for service delivery and evaluation. *BMC Palliat Care* 2015;14:42.
36. Jansen K, Schaufel MA, Ruths S. Drug treatment at the end of life: an epidemiologic study in nursing homes. *Scand J Prim Health Care* 2014;32(4):187-192.



Chapter 8

General discussion

INTRODUCTION

This thesis aims to contribute to the understanding of the clinical course of dementia in nursing home residents, in order to help optimize palliative care for nursing home residents across the dementia stages. We address the following objectives: 1) To explore changes in dementia severity, and how pneumonia and intake problems affect survival during nursing home stay. 2) To investigate the course of burdensome symptoms and treatment provided for these symptoms during nursing home stay. 3) To explore changes in care goals during nursing home stay, and to investigate end-of-life treatment decisions.

This final chapter discusses the findings of the studies described in the previous chapters. First, an overview of the main findings is presented, followed by an overview of the methodological considerations and reflections on the findings. Finally, we describe implications for practice and further research.

MAIN FINDINGS

Chapter 2, BANS-S

The Bedford Alzheimer Nursing-Severity Scale (BANS-S) assesses disease severity in people with Alzheimer's disease. Studying the hierarchy of the items in the scale can be useful to evaluate the progression of the disease and to provide information additional to the total score obtained by summing residents' responses. In our methodological study of the hierarchical properties of the items of the BANS-S, we found that the BANS-S met the criteria for an ordinal scale. We found that the residents had most difficulties with dressing and had less difficulty with eye contact. The order of the items was as follows: dressing, speech, muscles, mobility, eating, sleeping, and eye contact.

Chapter 3, Intercurrent health problems and survival

Our longitudinal survival study showed that pneumonia and intake problems frequently occurred during nursing home stay in all stages of dementia, and these are important risk factors for mortality. Our study found that almost 3 of every 10 residents developed at least one pneumonia in the first year, and for the residents who died (within the follow-up period of up to 3.5 year) the median survival time was just 5 weeks after the occurrence of the pneumonia. Even so, 3 out of 10 residents developed an intake problem in the first year and for the residents who died, the median survival time was just 4 weeks after the occurrence of the intake problems. Moreover, these health-problems were more important risk factors for mortality than the severity of the dementia. Further, compared to pneumonia, intake problems were a more important risk factor

for mortality, and were also more strongly related to more severe dementia in nursing home residents.

Chapter 4, Course of symptoms

In our longitudinal study about the course of symptoms, we found that residents frequently had pain and that this pain was frequently persistent during the disease trajectory, with a peak shortly before death. Agitation was even more common than pain. It also often persisted during the disease trajectory and decreased shortly before death. Shortness of breath was less common, and increased shortly before death. A positive significant longitudinal association was found between advanced dementia and pain, but not at the end of life, and there was no association with the other symptoms. Pain was treated mostly with acetaminophen (34%-52%), agitation was mostly treated non-pharmacologically (78%-92%). Parenteral opioids, morphine, and anxiolytics were prescribed substantially more frequently in the last week of life.

Chapter 5, Last week of life

In the last week of life we found that the distressing symptoms pain (52%), shortness of breath (35%), and agitation (35%) were common. Death from respiratory infections was associated with more burdensome symptoms than death from cardiovascular disorders or dehydration/cachexia. Distressing symptoms were mostly treated pharmacologically. Furthermore, quality of life in the last week was worse in residents with pain or agitation. The large majority of all residents (77%) received opioids and one-fifth (21%) received palliative sedation until death.

Chapter 6, Care goals and treatment orders

Our longitudinal study about care goals and treatment orders showed that overarching care goals were drawn up soon after admission and were reassessed, and treatment orders were discussed in more detail when the condition of the resident worsened. Treatment orders most frequently referred to resuscitation and hospitalization, and were predominantly do-not orders. The proportion of residents with palliative care goals did not change after pneumonia, but increased substantially after intake problems and in the period shortly before death. The most frequently reported reason for hospitalization was a fracture, especially in the group of residents with a do-not-hospitalize order.

Chapter 7, End-of-life treatment decisions

Chapter 7 describes that potentially burdensome life-prolonging treatments were rare in the last phase of life of nursing home with dementia in the Netherlands. Decisions to forgo potentially burdensome life-prolonging treatment shortly before death were made for almost half of the residents. Further, we found that only a small minority of the residents had a written advance directive upon admission.

METHODOLOGICAL CONSIDERATIONS

This section considers the methodological strengths and limitations of the studies presented in this thesis. The design of the study is discussed, and issues related to measurements are addressed.

Design of the study

The DEOLD study¹ is unique because of the long follow-up period from admission until death (or up to 3.5 years), and because it follows residents in variable stages of dementia. Every six months, elderly care physicians completed questionnaires that included a set of instruments that were suitable to assess care and were valid and reliable across nations and settings. All nursing home organizations were visited to instruct all physicians in an approximately one-hour training session shortly before data collection started. Recall bias may have been limited, because the elderly care physicians who were responsible for data collection could rely on both the chart and their own memory and on the nurses' chart and memory. Physicians also continuously registered health problems and their date of diagnosis, and registered the dates of hospitalization as well.

The strengths of this longitudinal observational study are that associations and individual changes could be studied over time. Another strength of the DEOLD study is the inclusion of residents in various stages of dementia, making the results representative for a wide population of nursing home residents with dementia.

The DEOLD study collected data from two cohorts. Data from the first cohort were collected both prospectively and retrospectively; data from the second cohort were collected retrospectively. In this thesis, we used both cohorts for the cross-sectional studies and we investigated the differences between the two cohorts. The populations differed in two ways only: prevalence of advanced dementia, which was present in 38% and 53% of residents respectively; and mean length of stay which was 10.5 months (range 0.2-37.7) and 30.2 months (range 0.2-178.4) respectively. We therefore reported the results for residents with advanced and less advanced dementia separately in the two cross-sectional studies.

The long follow-up period enabled us to investigate the full period from admission until death for many residents. We used 2 temporal perspectives for the analyses: the follow-up perspective from admission, and the follow-back perspective from the moment of death. Although this approach did result in more complex analyses, using both perspectives gives the best presentation of the clinical course.

Measurements

Pneumonia diagnoses were based on clinical judgment and in most cases not confirmed by X-ray. Using the physician's diagnosis only may have led to the inclusion of false positives; however, since this clinical judgement is consistent with usual diagnostic procedures in Dutch primary care and long-term care² and also elsewhere,³ it increases the relevance of our findings for clinical practice.

Self-report is the gold standard for assessing pain or other sources of suffering, but a main issue in assessing symptom burden in people with dementia in long-term care is that people with dementia are often incapable of expressing themselves verbally when they are uncomfortable or when they suffer from symptoms.⁴ In this study, physicians assessed whether pain, agitation and shortness were present or not, and reported the treatment that was provided for these symptoms. However, it is known that symptoms may be underrecognized in residents with dementia, so the prevalence of symptoms we found in our study may be an underestimation.

Further, to allow for longitudinal analyses, we collapsed the response options for frequencies of pain and shortness of breath into dichotomous outcomes: a symptom was present or not. This may have resulted in a loss of information. However, the full response options of frequencies showed patterns and stable distributions across assessments similar to the dichotomous response, so the risk of information bias is limited here.

REFLECTIONS ON THE FINDINGS

This section reflects on the results of this thesis in the order of the 3 main objectives.

Dementia severity, health problems and survival

Most studies in the field of dementia research use different terminology and different measurement instruments to define the stages of dementia, that is to say: to define how far a person's dementia has progressed.⁵⁻⁷ The terms 'advanced dementia'⁸, 'late dementia'⁵, 'end-stage of dementia' and 'severe dementia'⁹ are all used. For this reason, it is difficult to compare and to interpret these study findings.⁶ Our study population of nursing home residents with dementia was heterogeneous with regards to the severity of the disease. We found that the mean BANS-S score^{10,11} at baseline was 13.4 (SD = 4.3), and the mean BANS-S score in the last month of life was 15.9 (SD = 4.4), with a range from 7 to 28, covering the theoretical range. In addition to using and studying the BANS-S, we used the Global Deterioration Scale (GDS)¹² and the Cognitive Performance Scale (CPS)¹³ as indications for the severity of dementia in our study population. Upon admission, 88% had a GDS score of < 7, and 22% had CPS scores between

0 and 2, 44% scored 3 or 4, and 34% scored 5 or 6. We defined advanced dementia as having a GDS score of 7, *and* having a CPS score of 5 or 6. Only 9% of the residents had advanced dementia upon admission, and the proportion of residents with advanced dementia in the last month of life was 38%.

One of the key findings of this thesis is that dementia severity according to BANS-S, CPS and GDS is heterogeneous in our nursing home population and that more severe dementia is significantly associated with a higher mortality risk. However, incident pneumonia and intake problems were found to be prognostically much more unfavorable and therefore more important risk indicators for mortality than dementia severity. Residents frequently developed pneumonia and intake problems, and when they died within the follow-up period, it was often soon after the diagnosis of these health problems (median = 5 and 4 weeks respectively). The occurrence of pneumonia or an intake problem is an important signal of a worsening condition and should be regarded as an important trigger to consider a palliative care approach,¹⁴⁻¹⁶ whereas severity of the dementia is less relevant. Moreover, as all people with dementia admitted to a nursing home in the DEOLD study had in common that they were vulnerable with a short average survival time of 2 years after admission,¹ the moment of admission to a dementia special care unit of a nursing home can be regarded as a sufficiently important moment to start advance care planning and to consider a palliative care approach.

The course of burdensome symptoms and treatment provided for these symptoms
We found that residents frequently had burdensome symptoms upon admission and that these burdensome symptoms frequently persisted over the disease trajectory, with a peak shortly before death. Pain was a common symptom that frequently persisted during nursing home stay. However, symptom management for pain intensified only at the end of life. Almost one fifth of residents experienced both pain and agitation, but we found no (longitudinal) association between pain and agitation, although in previous studies it was hypothesized that pain is one of the underlying causes of behavioral symptoms.¹⁷⁻²² In a systematic review about associations between pain and neuropsychiatric symptoms, Van Dalen et al.²³ also found that available evidence does not support a strong association between pain and neuropsychiatric symptoms. In our study, more than half of the residents with persistent agitation received both antipsychotics and anxiolytics at more than one measuring point. This suggests that residents mostly used antipsychotics and/or anxiolytics for longer than 3 months. One might question if this is in line with guideline-recommendations of only short-term use.²⁴⁻²⁶ Although this thesis is based on observational research, the findings suggest that symptom management is suboptimal, and that there may be room for improvement. Perhaps more rigorous evaluation of the effect of provided treatment for burdensome symptoms is needed.

Overall, there was a gradual increase in the use of opioids and palliative sedation in the last days of life. Comparing our findings with the current literature, we found a lower percentage of palliative sedation compared with palliative care settings (21% versus 15 up to 60%), and a percentage comparable with van der Maaden et al. (22% in patients with dementia and pneumonia).²⁷ Van der Maaden et al. suggest that providing palliative sedation is a realistic option to enhance comfort in the days before death in patients with dementia and pneumonia. On the other hand, compared to other European studies in nursing homes and the general population, we found higher frequencies of palliative sedation in our population (21% versus 2.5-8.5%). This raises the question whether opioids and palliative sedation were administered appropriately. On the one hand, residents frequently had burdensome symptoms and the use of opioids and palliative sedation may therefore have been an appropriate treatment for them. On the other hand, opioids and palliative sedation were used frequently in the last days of life and people who are sedated may be more comfortable, but the process of dying may be accelerated.²⁷⁻²⁹ Future research in this area needs to focus on seeking the right balance between symptom relief and avoiding the mentioned side-effects of the use of palliative sedation in residents with dementia at the end of life.

Care goals and end-of-life treatment decisions

(Overarching) Care goals define upper and lower boundaries of medical care, and can give direction to future care and to treatment orders in the context of advance care planning in long-term care.^{30,31} We found that physicians and families often established overarching care goals during nursing home stay: 81% of the residents had an overarching care goal established in the first 8 weeks of admission, and 98% in the six months afterwards. Only a minority of the residents did not have an overarching care goal soon after admission. Overall, we found an upward trend during nursing home stay in the prevalence of overarching palliative care goals and especially a strong increase shortly before death. More specifically, 57% of all residents had an overarching palliative care goal (42% had a palliative care goal, and 15% had a symptomatic care goal) in the first weeks after admission, and this proportion increased very little during follow-up until shortly before death, when almost all residents had an overarching palliative care goal (45% had a palliative care goal, and 45% had a symptomatic care goal). The definitions of the care goals as used in the research, are defined and recommended by the Dutch association of elderly care physicians and social geriatricians "Verenso".³² One of the characteristics of palliative care is that it has no intention to shorten death or prolong life. In practice, however, in some cases it is desirable that a treatment has no life-prolonging effect, given the situation of the patient. Therefore, Verenso distinguishes a palliative and a symptomatic care goal. With a palliative care goal, treatment is aimed at well-being and comfort, irrespective of the life-prolonging effects of the treatment; with a symptomatic care goal, treatment is aimed at well-being, quality of life and comfort, but a life-prolonging effect of the treatment is considered undesirable. However,

this distinction is unknown in other countries than the Netherlands, and not well integrated in practice, as was observed in the DEOLD study by van Soest-Poortvliet et al.³³ in qualitative interviews. For example, physicians and nurses described a great variety in the denomination and contents of formulated and established care goals.³³ Therefore, we combined the palliative and the symptomatic care goals and used for the combined goals the term 'palliative care goal'.

Decisions about treatment orders were made alongside the discussions about the overarching care goals. Decisions about resuscitation and hospitalization, which refer to acute situations that can be anticipated, were the most frequently discussed treatment decisions in our study. They resulted frequently in 'do not' treatment orders for resuscitation and hospitalization. Once overarching care goals were established, we found that these were generally not redefined as long as the health condition of the residents remained stable. When the health condition of the residents worsened the overarching care goals were evaluated and redefined, and treatment orders were also rediscussed and agreed upon in more detail. As not all scenarios can be discussed beforehand, this way of advance care planning seems to suit practice and it fits with the clinical course of the disease, with the possible development of intercurrent and acute diseases. Our findings also suggest that advance care planning is strongly embedded in long-term care in the Netherlands, as advance care planning belongs to the 'core business' of elderly care medicine.³⁴⁻³⁷ In the Netherlands this is supported by an organization model with ample availability of specially trained elderly care physicians.^{35;38}

One of the questions to be answered about providing adequate palliative care for people with dementia concerns the optimal starting point of palliative care. It has been suggested that palliative care is suitable and important in the most advanced stages of dementia,^{8;39} but also earlier stages of dementia are suggested.⁴⁰ Van der Steen et al.,⁴¹ and van Riet-Paap et al.⁴² found a lack of consensus among experts on the applicability of palliative care. Hanson et al.⁶ in a recent review found that when a time period was mentioned for the palliative phase it varied considerably from a few years to the final month of life.^{6;9;40}

Our results suggest that when nursing home admission is necessary, a palliative approach is appropriate because pneumonia and intake problems, both occurring frequently in the first year after nursing home admission, are much more strongly related to mortality than dementia severity as measured by the BANS-S. This palliative approach can be or cannot be combined with treatment of intercurrent illnesses that may prolong life. This approach fits well in the recently proposed model of palliative care for people with dementia, published on behalf of The European Association for Palliative Care (EAPC; Figure 1).⁴³

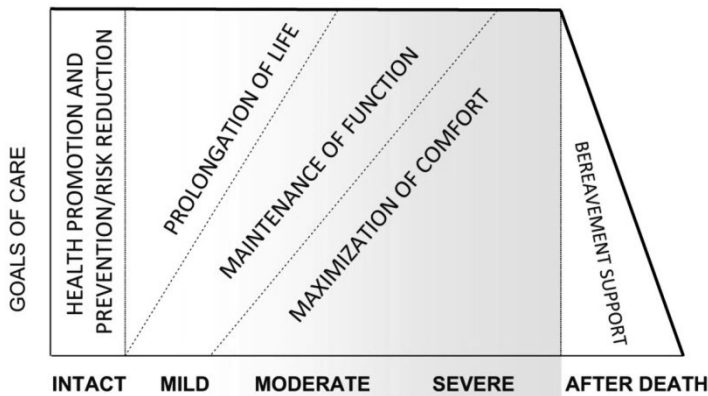


Figure 1: Model of changing care goals (van der Steen et al.; EAPC, 2014)⁴³

Our findings strongly suggest that establishing overarching care goals helps to prevent burdensome and potentially unnecessary treatment such as hospitalization. In the Netherlands quality of life is an important aspect in end-of-life decisions and outweighs life prolongation in treatment decisions. Consequently, forgoing burdensome medical interventions is acceptable for residents and their representatives as well as for physicians.^{44;45} We found that residents with dementia rarely undergo potentially burdensome life-prolonging treatment in the last phase of life, and we found that residents rarely died in hospitals. Medical care was almost always provided in accordance with earlier established (anticipatory) care goals. Overall the most frequently reported reasons for hospitalization were (hip) fractures (43%), while in the United States infection and pneumonia were found to be the most common reasons for hospitalization.⁴⁶ We found a higher prevalence of do-not-hospitalize orders, and a smaller proportion of patients who were hospitalized than in Belgium and the United States.^{47;48}

Decisions not to start (or sometimes to withdraw) treatment shortly before death mainly concerned decisions about artificial nutrition and hydration. This suggest that physicians and representatives of patients accept the reduction of food and fluids intake in this phase and consider this problem inherent in end stage dementia.^{15;49;50} Almost a quarter of the residents received antibiotics in the last week of life, while the effect of antibiotics on survival is probably limited in nursing home residents with advanced dementia.⁵¹ Antibiotics also do not seem to contribute to comfort in this phase, as van der Maaden et al.²⁷ found no difference in comfort for residents who were treated with and without antibiotics in their observational study, which suggests that the additional benefits of antibiotic treatment on comfort are marginal in the context of improved symptom relief.

We found that decisions to withdraw treatment mainly concerned the withdrawal of oral medications, including preventive medications, shortly before death. In particular the continuation of all kinds of preventive medications, almost up to the moment of death, raises the question whether the medication prescribed for this population is appropriate and in accordance with their overarching care goal (mostly palliative). Prescribing medication to residents with dementia should aim at comfort and management of symptoms (in line with the mostly palliative care goals), rather than focus on curative treatment and disease-specific outcomes. This topic warrants further research.

RECOMMENDATIONS FOR PRACTICE

The results of this dissertation have several implications for future practice.

Palliative care across dementia stages

An important domain of palliative care is symptom management. Symptom management, however, appears to be suboptimal in nursing home residents with dementia. In case of persistent pain, symptom management intensified only at the end of life. And for agitation our data suggests that both antipsychotics and anxiolytics were prescribed frequently for much longer periods than the 3 months or 4 weeks recommended by guidelines respectively. These findings suggest that there is room for improvement, especially in the evaluation of treatment effects. To provide comfort and adequate symptom management, meticulous assessment and timely evaluation is needed. In addition to evaluation of symptom management, there may be also room for better evaluation of the use of medication for chronic conditions and comorbid diseases, because we found that decisions to withdraw oral drugs were made in particular shortly before death. Medications can be discontinued when they no longer have clear benefits for people with dementia in view of their care goals.⁵²⁻⁵⁶ The usefulness and benefits of medication for chronic conditions and comorbid diseases should be regularly reviewed and discussed with residents and their families.^{43;53;57-60}

We found that establishing overarching care goals is well embedded in long-term care in the Netherlands, because almost all residents had an overarching care goal soon after admission. Our findings strongly suggest that establishing overarching care goals helps residents and families to prepare for and anticipate expected health problems in the trajectory of dementia, because overarching care goals may help prevent burdensome, unnecessary treatment in acute situations. We found that residents with dementia rarely undergo potentially burdensome, life-prolonging treatment in the last phase of life, and we found that residents rarely die in hospitals. In the period just before death most nursing home residents had a palliative care goal. Benefits of

a palliative care approach in dementia are acknowledged by experts worldwide, but there is controversy about the best time to initiate a palliative care approach.^{6,41,42} Based on the findings of this thesis, a palliative care goal may be appropriate for all people with dementia who are vulnerable enough to be admitted to long-term care. Therefore, people with dementia and their families, as well as health care professionals and policy makers should be made more aware that admission to a nursing home is a sufficiently important signal to start a palliative care approach. Admission to a nursing home is an important moment for a discussion, tailored to the level of willingness, with residents and families about how to prepare for the final phase of life. Informing residents and families about the course of dementia, the short average survival time, burdensome symptoms that can occur and the occurrence of pneumonia and intake problems, which have a poor prognosis, may help formulate realistic overarching care goals.

Discussions about advance care planning provide the opportunity to plan and do things that are important for the resident, and for the resident and their families to maintain a sense of control. Explicit discussion of the desirability of prolongation of life as well as life-extending side-effects of medical treatments should not be avoided, especially when it is clear that prolongation of life is undesirable for the resident.^{32,61,62} Although Verenso (the Dutch association of elderly care physicians) has formulated the definitions of palliative and symptomatic care goals,³² this distinction is not well integrated in practice, as was observed in the DEOLD study by van Soest-Poortvliet et al. in qualitative interviews.³³ Therefore, tightening up the present framework of concepts is needed.

RECOMMENDATIONS FOR FURTHER RESEARCH

The results from this thesis provide clues for several recommendations for future research.

Symptom management

The majority of residents had burdensome symptoms during nursing home stay. Our observations call for further research to improve symptom management. Research should focus especially on how to best perform the evaluation of symptom management for pain and agitation, and on how to specify the optimal dosage of medication in terms of effect and side effects, especially in the last week(s) of life. Future research may employ observation on a day-to-day basis to better address effectiveness of symptom control and possible side effects. This will contribute to the development of practice guidelines for the treatment of burdensome symptoms in this specific patient population in palliative care.

Advance care planning

Research interest in attitudes and decision-making in the actual practice of advance care planning in people with dementia has increased.⁶³⁻⁶⁵ We explored changes in overarching care goals and changes in treatment orders during nursing home stay. An important aspect of advance care planning is the involvement of people with dementia and their families in decision-making. How is shared decision-making applied in daily practice and how is it perceived by residents and representatives? A next step would be to investigate how communication between physicians and residents with dementia and their representatives about advance care planning, including weighing the usefulness, benefits and life-extending side effects of medication, takes place. This will contribute to a better understanding of care processes and outcomes, and help improve the training of physicians and nurses in terms of communication skills and advance care planning. Another topic that deserves research attention is the appropriateness in daily practice of the used terminology 'palliative' and 'symptomatic', because the DEOLD study showed us that the terminology used by physicians and nurses is not uniform. Residents and their families are probably not familiar with this terminology at all.

In this thesis we investigated the clinical course of dementia in nursing home residents. Based on findings of the DEOLD study from 2007 to 2011 we concluded that a palliative care approach may be appropriate in a nursing home population with dementia. It should be noted that there is a strong policy tendency to postpone nursing home admission as long as possible. As a consequence, people with dementia will be living at home longer and will be treated in primary care. Implementing advance care planning as a standard element of good dementia care in general practice is challenging but necessary when people with dementia, also in more severe stages,^{6,64} will be living in their own home. In order to optimize palliative care for people with dementia in the community, better knowledge of the clinical course of the disease and the palliative care needs of people with dementia in primary care will therefore be important. A longitudinal observational study could be performed to investigate the course of intercurrent health problems, symptom burden, hospital transfers and causes of death. Understanding the clinical course in the primary care setting will help to support decision-making and advance care planning in this setting.

OVERALL CONCLUSION

Our study is unique in that we investigated the clinical course of dementia in long-term care for a long follow-up period, as well as the palliative care needs of residents with dementia with a wide range of dementia severity as determined by a formal measurement-instrument (BANS-S). A better understanding of the clinical course helps to shape adequate palliative care

for nursing home residents with dementia. The most important conclusion of this thesis is that awareness should be created that admission to a nursing home is a signal to start a palliative care approach. Exploring palliative care needs should start at, and be thoroughly evaluated during nursing home admission. Establishing overarching palliative care goals, timely recognition, medication evaluation, evaluation of treatment of burdensome symptoms, as well as appropriate communication between physicians, nurses and residents and their representatives about these topics will hopefully become routine practice. Further research should focus on the evaluation of symptom management, and uniform use of the terminology for care goals. Further, as people with dementia will be living at home longer, future research should focus on the clinical course and palliative care needs in people with dementia in primary care. This will be an important step toward more effective palliative care which will benefit people with dementia, their families and their professional caregivers.

REFERENCES

1. van der Steen JT, Ribbe MW, Deliëns L, Gutschow G, Onwuteaka-Philipsen BD. Retrospective and prospective data collection compared in the Dutch End Of Life in Dementia (DEOLD) study. *Alzheimer Dis Assoc Disord* 2014;28:88-94.
2. van der Steen JT, Mehr DR, Kruse RL, et al. Predictors of mortality for lower respiratory infections in nursing home residents with dementia were validated transnationally. *J Clin Epidemiol*. 2006;59:970-979.
3. Helton MR, Cohen LW, Zimmerman S, et al. The importance of physician presence in nursing homes for residents with dementia and pneumonia. *J Am Med Dir Assoc*. 2011;12:68-73.
4. Scherder E, Herr K, Pickering G, et al. Pain in dementia. *Pain*. 2009;145(3):276-8.
5. Koopmans RT, Ekkerink JL, van WC. Survival to late dementia in Dutch nursing home patients. *J Am Geriatr Soc* 2003;51:184-187.
6. Hanson E, Hellstrom A, Sandvide A et al. The extended palliative phase of dementia - An integrative literature review. *Dementia (London)* 2016.
7. Dementia Palliare: Interprofessional experiential learning solutions. The Best Practice Statement. Available at: www.uws.ac.uk/palliareproject. Accessed 2016.
8. Mitchell SL, Teno JM, Kiely DK et al. The clinical course of advanced dementia. *N Engl J Med* 2009;361:1529-1538.
9. Sampson EL. Palliative care for people with dementia. *Br Med Bull* 2010;96:159-174.
10. Volicer L, Hurley AC, Lathi DC, Kowall NW. Measurement of severity in advanced Alzheimer's disease. *J Gerontol* 1994;49:M223-M226.
11. Bellelli G, Frisoni GB, Bianchetti A, Trabucchi M. The Bedford Alzheimer Nursing Severity scale for the severely demented: validation study. *Alzheimer Dis Assoc Disord* 1997;11:71-77.
12. Reisberg B, Ferris SH, de Leon MJ, Crook T. The Global Deterioration Scale for assessment of primary degenerative dementia. *Am J Psychiatry* 1982;139:1136-1139.
13. Morris JN, Fries BE, Mehr DR et al. MDS Cognitive Performance Scale. *J Gerontol* 1994;49:M174-M182.
14. Hanson LC, Ersek M, Lin FC, Carey TS. Outcomes of feeding problems in advanced dementia in a nursing home population. *J Am Geriatr Soc* 2013;61:1692-1697.
15. Pasman HR, Onwuteaka-Philipsen BD, Ooms ME, van Wigcheren PT, van der Wal G, Ribbe MW. Forgoing artificial nutrition and hydration in nursing home patients with dementia: patients, decision making, and participants. *Alzheimer Dis Assoc Disord* 2004;18:154-162.
16. Levy C. Expectation Conversations About the Very Predictable Events in Advanced Dementia. *J Am Med Dir Assoc* 2015;16:724-727.
17. Corbett A, Husebo B, Malcangio M et al. Assessment and treatment of pain in people with dementia. *Nat Rev Neurol* 2012;8(5):264-274.
18. Achterberg WP, Pieper MJ, van Dalen-Kok AH et al. Pain management in patients with dementia. *Clin Interv Aging* 2013;8:1471-1482.
19. Pieper MJ, van Dalen-Kok AH, Francke AL et al. Interventions targeting pain or behaviour in dementia: A systematic review. *Ageing Res Rev* 2013;12(4):1042-1055.
20. van Dalen-Kok AH, Pieper MJ, de Waal MW, Lukas A, Husebo BS, Achterberg WP. Association between pain, neuropsychiatric symptoms, and physical function in dementia: a systematic review and meta-analysis. *BMC Geriatr* 2015;15(1):49.
21. Husebo BS, Ballard C, Cohen-Mansfield J, Seifert R, Aarsland D. The Response of Agitated Behavior to Pain Management in Persons with Dementia. *Am J Geriatr Psychiatry* 2014 Jul;22(7):708-17
22. Husebo BS, Ballard C, Aarsland D. Pain treatment of agitation in patients with dementia: a systematic review. *Int J Geriatr Psychiatry* 2011;26(10):1012-1018.

23. van Dalen-Kok AH, Pieper MJ, de Waal MW, Lukas A, Husebo BS, Achterberg WP. Association between pain, neuropsychiatric symptoms, and physical function in dementia: a systematic review and meta-analysis. *BMC Geriatr* 2015;15:49.
24. Verenso, the Dutch Association of Elderly Care Physicians and Social Geriatricians. Guideline: behaviour problems [in Dutch]. 2008. Available at: <http://www.verenso.nl/wat-doen-wij/vakinhoudelijke-producten/richtlijnen/probleemgedrag>. Accessed 2016.
25. Ballard CG, Gauthier S, Cummings JL et al. Management of agitation and aggression associated with Alzheimer disease. *Nat Rev Neurol* 2009;5:245-255.
26. Schneider LS, Tariot PN, Dagerman KS et al. Effectiveness of atypical antipsychotic drugs in patients with Alzheimer's disease. *N Engl J Med* 2006;355:1525-1538.
27. van der Maaden T, van der Steen JT, de Vet HC, Hertogh CM, Koopmans RT. Prospective Observations of Discomfort, Pain, and Dyspnea in Nursing Home Residents With Dementia and Pneumonia. *J Am Med Dir Assoc* 2016;17:128-135.
28. Anquinet L, Rietjens JA, Vandervoort A et al. Continuous deep sedation until death in nursing home residents with dementia: a case series. *J Am Geriatr Soc* 2013;61:1768-1776.
29. Rys S, Mortier F, Deliens L, Bilsen J. The practice of continuous sedation until death in nursing homes in Flanders, Belgium: a nationwide study. *J Am Geriatr Soc* 2014;62:1869-1876.
30. Nederlandse Vereniging van verpleeghuisartsen (NVVA). *Medische zorg met beleid*. Utrecht, NVVA, 1997.
31. Severijns MAB, Hertogh CPM, Stelt I van der. Medische besluitvorming bij dementerende patiënten. Een handreiking van de Nederlandse Vereniging van Verpleeghuisartsen. *Medisch Contact* 1997; 52: 1089-92.
32. Verenso, the Dutch Association of Elderly Care Physicians and Social Geriatricians. Guideline: Concepts and Requirements of Care in relation to end-of-life decisions in long-term care. [in Dutch]. 2007. Available from: <http://www.verenso.nl/assets/Uploads/Downloads/Handreikingen/Levensinde-beleidsversie-070607.pdf> Accessed 2016.
33. van Soest-Poortvliet MC, van der Steen JT, Gutschow G et al. Advance Care Planning in Nursing Home Patients With Dementia: A Qualitative Interview Study Among Family and Professional Caregivers. *J Am Med Dir Assoc* 2015;16(11):979-989.
34. Ruiter C de, Stelt I van der, Hertogh CPM, Delden JJM van. Advance care planning. Onze core business. *Tijdschrift voor ouderengeneeskunde* 2013;3:134-7.
35. Koopmans RT, Lavrijsen JC, Hoek JF, Went PB, Schols JM. Dutch elderly care physician: a new generation of nursing home physician specialists. *J Am Geriatr Soc* 2010;58:1807-1809.
36. Hertogh CM. Advance care planning and the relevance of a palliative care approach in dementia. *Age Ageing* 2006;35:553-555.
37. Hertogh CM, Ribbe MW. Ethical aspects of medical decision-making in demented patients: a report from the Netherlands. *Alzheimer Dis Assoc Disord* 1996;10:11-19.
38. Helton MR, Cohen LW, Zimmerman S, van der Steen JT. The importance of physician presence in nursing homes for residents with dementia and pneumonia. *J Am Med Dir Assoc* 2011;12:68-73.
39. Mitchell SL, Kiely DK, Hamel MB, Park PS, Morris JN, Fries BE. Estimating prognosis for nursing home residents with advanced dementia. *JAMA* 2004;291:2734-2740.
40. van der Steen JT. Dying with dementia: what we know after more than a decade of research. *J Alzheimers Dis* 2010;22:37-55.
41. van der Steen JT, Radbruch L, de Boer ME et al. Achieving consensus and controversy around applicability of palliative care to dementia. *Int Psychogeriatr* 2016;28:133-145.
42. van Riet-Paap PJ, Mariani E, Chattat R et al. Identification of the palliative phase in people with dementia: a variety of opinions between healthcare professionals. *BMC Palliat Care* 2015;14:56.

43. van der Steen JT, Radbruch L, Hertogh CM et al. White paper defining optimal palliative care in older people with dementia: a Delphi study and recommendations from the European Association for Palliative Care. *Palliat Med* 2014;28:197-209.
44. van der Steen JT, Kruse RL, Ooms ME et al. Treatment of nursing home residents with dementia and lower respiratory tract infection in the United States and The Netherlands: an ocean apart. *J Am Geriatr Soc* 2004;52:691-699.
45. The AM, Pasman R, Onwuteaka-Philipsen B, Ribbe M, van der Wal G. Withholding the artificial administration of fluids and food from elderly patients with dementia: ethnographic study. *BMJ* 2002;325:1326.
46. Givens JL, Selby K, Goldfeld KS, Mitchell SL. Hospital transfers of nursing home residents with advanced dementia. *J Am Geriatr Soc* 2012;60:905-909.
47. Lamberg JL, Person CJ, Kiely DK, Mitchell SL. Decisions to hospitalize nursing home residents dying with advanced dementia. *J Am Geriatr Soc* 2005;53:1396-1401.
48. Houttekier D, Vandervoort A, Van den Block L, van der Steen JT, Vander SR, Deliëns L. Hospitalizations of nursing home residents with dementia in the last month of life: Results from a nationwide survey. *Palliat Med* 2014.
49. Teno JM, Gozalo PL, Mitchell SL et al. Does feeding tube insertion and its timing improve survival? *J Am Geriatr Soc* 2012;60:1918-1921.
50. Mehr DR, van der Steen JT, Kruse RL, Ooms ME, Rantz M, Ribbe MW. Lower respiratory infections in nursing home residents with dementia: a tale of two countries. *Gerontologist* 2003;43 Spec No 2:85-93.
51. van der Steen JT, Lane P, Kowall NW, Knol DL, Volicer L. Antibiotics and mortality in patients with lower respiratory infection and advanced dementia. *J Am Med Dir Assoc* 2012;13:156-161.
52. Holmes HM, Hayley DC, Alexander GC, Sachs GA. Reconsidering medication appropriateness for patients late in life. *Arch Intern Med* 2006;166:605-9.
53. Holmes HM. Rational prescribing for patients with a reduced life expectancy. *Clin Pharmacol Ther* 2009;85:103-7.
54. Steinman MA, Hanlon JT. Managing medications in clinically complex elders. *JAMA* 2010;304:1592-1601.
55. Scott IA, Gray LC, Martin JH, Pillans PI, Mitchell CA. Deciding when to stop: towards evidence- based deprescribing of drugs in older patients. *Evid Based Med* 2013;18:121-4.
56. Scott IA, Anderson K, Freeman CR, Stowasser DA. First do no harm: a real need to deprescribe in older patients. *Med J Aust* 2014; 6;201:390-2.
57. Holmes HM, Sachs GA, Shega JW, Hougham GW, Cox HD and Dale W. Integrating palliative medicine into the care of persons with advanced dementia: identifying appropriate medication use. *J Am Geriatr Soc* 2008; 56: 1306-1311.
58. Arcand M, Roy-Petit J, Voyer G, Allard J and Ethier S. Should drugs be prescribed for prevention in the case of moderate or severe dementia. *La Revue de Gériatrie* 2007;32: 189-200.
59. Parsons C, Hughes CM, Passmore AP and Lapane KL. Withholding, discontinuing and withdrawing medications in dementia patients at the end of life: a neglected problem in the disadvantaged dying? *Drugs Aging* 2010; 27: 435-449.
60. Quill TE and Holloway R. Time-limited trials near the end of life. *JAMA* 2011; 306:1483-1484.
61. NVVA. Handreiking voor de besluitvorming over verpleeghuisgeneeskundig handelen bij dementerende patiënten. 1997. Utrecht. Explanation in English available from: Hertogh CMPM. Advance care planning and palliative care in dementia: a view from the Netherlands. In: Hughes JC, Lloyd-Williams M & GA Sachs. Supportive care for the person with dementia. Oxford, Oxford University Press, 2010, 271-81.
62. Gillick MR. Choosing appropriate medical care for the elderly. *J Am Med Dir Assoc* 2001;2:305-309.

63. van der Steen JT, van Soest-Poortvliet MC, Hallie-Heierman M et al. Factors associated with initiation of advance care planning in dementia: a systematic review. *J Alzheimers Dis* 2014;40:743-757.
64. Dening KH, Jones L, Sampson EL. Advance care planning for people with dementia: a review. *Int Psychogeriatr* 2011;23:1535-1551.
65. Mahin-Babaei F, Hilal J, Hughes JC. The basis, ethics and provision of palliative care for dementia: A review. *Maturitas* 2016;83:3-8.



Appendices

Appendix A. Online resource Figures (chapter 4)

Appendix B. Supplementary Table S1 (chapter 6)

Appendix C. Antibiotic use and associated factors in patients with dementia: A systematic review (article)

Appendix A. Online resource Figure 1 (chapter 4)

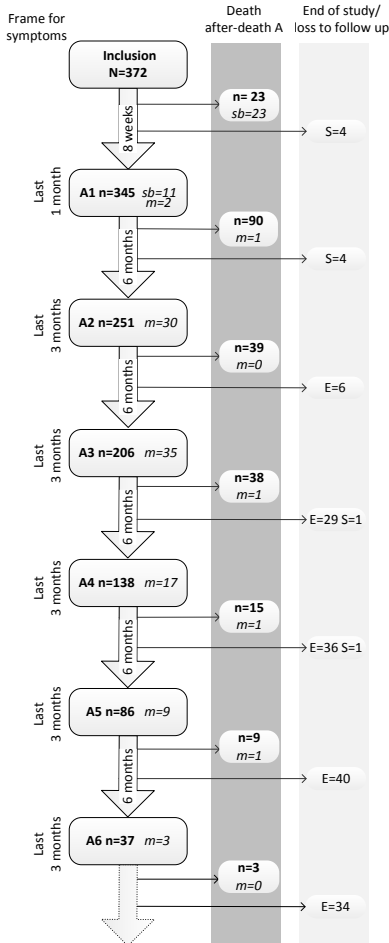


Figure 1 Number of residents per assessment

There were up to six regular assessments (baseline and semi-annual assessments), depending on timing of admission, and death.

n = number of residents per assessment; in the column "death": the number of residents who died in the period between 2 assessments.

A = assessment

sb = short baseline assessment. In some cases, residents died before or shortly after the date on which the baseline assessment was scheduled, and therefore the physicians had no chance to complete the baseline assessment prospectively. For these residents we used shortened baseline assessments, to complete only the data of resident characteristics which we deemed not particularly vulnerable to recall bias.

m = missing whole assessment; The majority of the cases with a missing semi-annual assessment clustered in a few nursing homes, as a result of a period with insufficient physician staffing or frequent physician turnover. We agreed that these nursing homes provided after-death assessments only, and semi-annual assessments were no longer completed. This explains fewer after-death assessments (4) missed, as noted in the column "Death."

E= End of the study. As residents were admitted over time, this resulted in a variation of maximal duration of the individual follow up.

S= Loss to follow up

Appendix A. Online resource Figure 2 (chapter 4)

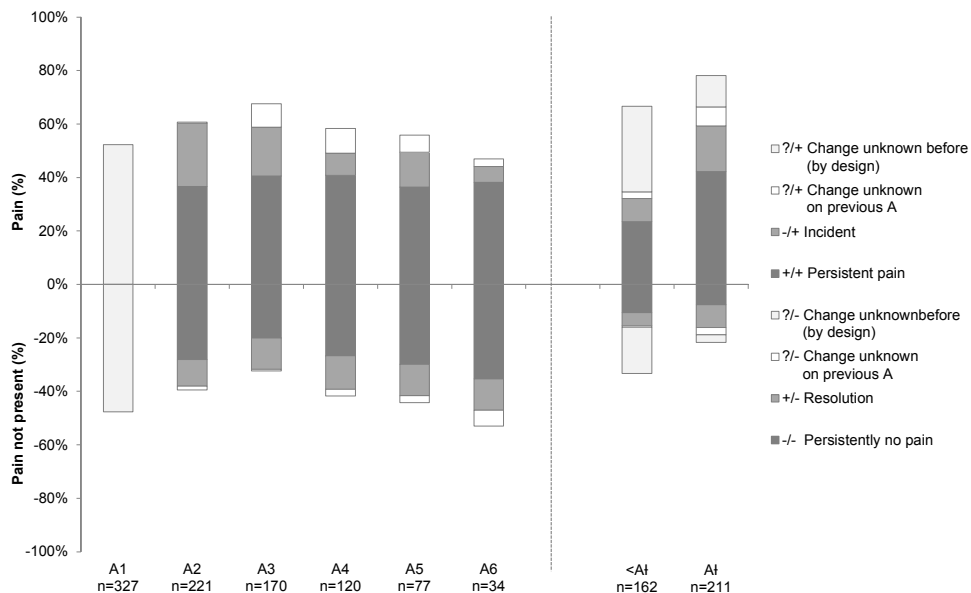


Figure 2. Prevalence of pain and the course over two consecutive assessments

The course of pain is illustrated with the proportion of incident pain, persistent pain, persistently no pain (absence of pain), and resolution of pain over two consecutive assessments, of all residents at the assessments concerned.

A1= baseline assessment, thus presentation of symptoms before A1 (before admission) is unknown, because of the design of the study in which we started data collection shortly after nursing home admission.

<A†= The last regular assessment before death is one of A1 to A6. Because 90 residents died after the baseline assessment (before the first semi-annual assessment), the <A† is in these cases also the baseline assessment, so that presence of pain was unknown before the <A† assessment.

A†=after-death assessment.

Appendix A. Online resource Figure 3 (chapter 4)

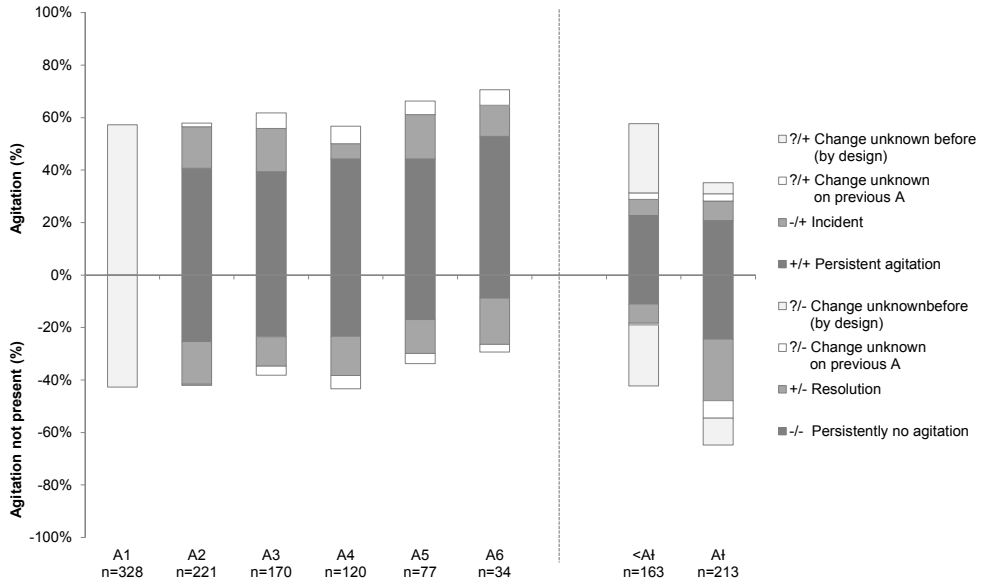


Figure 3. Prevalence of agitation and the course over two consecutive assessments

The course of agitation is illustrated with the proportion of incident agitation, persistent agitation, persistently no agitation (absence of agitation), and resolution of agitation over two consecutive assessments, of all residents at the assessments concerned.

A1= baseline assessment, thus presentation of symptoms before A1 (before admission) is unknown, because of the design of the study in which we started data collection shortly after nursing home admission.

<A†= The last regular assessment before death is one of A1 to A6. Because 90 residents died after the baseline assessment (before the first semi-annual assessment), the <A† is in these cases also the baseline assessment, so that presence of agitation was unknown before the <A† assessment.

A†=after-death assessment.

Appendix A. Online resource Figure 4 (chapter 4)

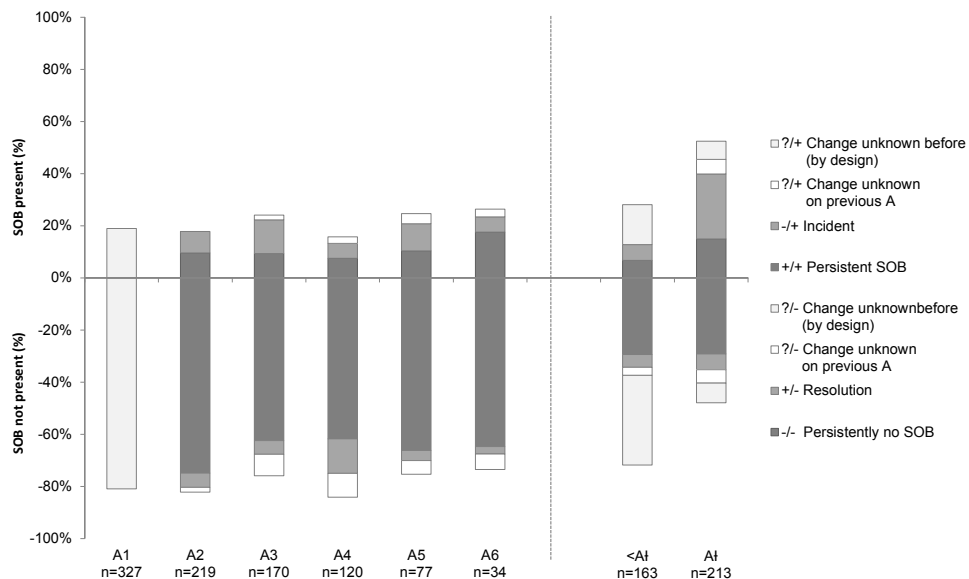


Figure 4. Prevalence of shortness of breath and the course over two consecutive assessments

The course of shortness of breath is illustrated with incident shortness of breath, persistent shortness of breath, persistently no shortness of breath (absence of shortness of breath), and resolution of shortness of breath over two consecutive assessments, of all residents at the assessments concerned.

A1= baseline assessment, thus presentation of symptoms before A1 (before admission) is unknown, because of the design of the study in which we started data collection shortly after nursing home admission.

<A†= The last regular assessment before death is one of A1 to A6. Because 90 residents died after the baseline assessment (before the first semi-annual assessment), the <A† is in these cases also the baseline assessment, so that presence of shortness of breath was unknown before the <A† assessment.

A†=after-death assessment.

SOB = shortness of breath.

Appendix B. Supplementary Table S1 (chapter 6)

Supplementary Table S1. Hospitalization during follow-up

Treatment order before hospitalization	n/N	%	Reason for hospitalization
Do-hospitalize	27/47	57	Hip fracture (n=7) ^{a,b,c} Anaemia Oral surgery ^a Ureteral stent replacement (n=5; 1 patient 5 times) ^d Ureteral stent replacement and fever (n=2; 1 patient 2 times) ^e Blood transfusion Abdominal aortic aneurysm Ileus (n=2; 1 patient 2 times) ^f Decompensation / dehydration 3rd degree AV-block and pacemaker (n=2) ^g Pneumonia ^g Gastrointestinal-bleeding and prepyloric ulcer ^b Missing (n=2) ^c
Do-not-hospitalize	10/47	21	Hip fracture (n=5) ^h Jaw fracture ^h Gastrointestinal-bleeding Carcinoma diagnostic bladder Bradycardia, pacemaker Pneumonia
No order	10/47	21	Hip fracture (n=4; 1 patient 2 times) ⁱ Rib and humerus fracture Gastrointestinal bleeding ^j Urosepsis Allergic reaction Pneumonia/cerebral infarct/hyponatremia/hyperglycaemia/poor intake Cataract operation
Missing	13		Hip fracture (n=7) Hip luxation (n=2; 1 patient 2 times) ^j Gastrointestinal-bleeding Pulmonary embolism Blood transfusion Cellulitis

Letters refer to patients who were hospitalized more than once, and refer to single hospitalization decisions.

^{a,b,c} Patient was hospitalized 2 times

^d Patient was hospitalized 5 times

^{e,f,g,h} Patient was hospitalized 2 times

ⁱ Patient was hospitalized 3 times

^j Patient was hospitalized 2 times



Appendices

Appendix C.

Antibiotic use and associated factors in patients with dementia:

A systematic Review

Tessa van der Maaden

Simone A. Hendriks

Henrica C. W. de Vet

Menno T. Zomerhuis

Martin Smalbrugge

Elise P. Jansma

Raymond T. C. M. Koopmans

Cees M. P. M. Hertogh

Jenny T. van der Steen

ABSTRACT

Background: Infections frequently occur in patients with dementia and antibiotics are often prescribed, but may also be withheld.

Objectives: The aim of this systematic review is to provide a systematic overview of the prevalence of antibiotic use, and factors associated with prescribing antibiotics in patients with dementia.

Data Sources: A systematic search of MEDLINE, EMBASE, PSYCINFO, CINAHL, and the Cochrane library databases until February 13, 2014 was performed, using both controlled terms and free-text terms.

Results: Thirty-seven articles were included. The point prevalence of antibiotic use in patients with dementia ranged from 3.3 to 16.6%. The period prevalence ranged from 4.4 to 88% overall, and from 23.5 to 94% in variable time frames before death; the median use was 52% (median period 14 days) and 48% (median period 22 days), respectively. Most patients with lower respiratory tract infections or urinary tract infections (77–91%) received antibiotic treatment. Factors associated with antibiotic use related to patients, families, physicians, and the healthcare context. More severe dementia and a poor prognosis were associated with less antibiotic use in various countries. Associations with aspiration and illness severity differed by country.

Conclusions and Implications: Antibiotic use in patients with dementia is substantial, and probably highly associated with the particular healthcare context. Future studies may report antibiotic use by infection type and stage of dementia, and compare cross-nationally.

Key Points

The prevalence of antibiotic use for patients with dementia is substantial, varies between countries, and depends on the particular healthcare setting

More severe dementia and a poor prognosis were related to fewer antibiotics in patients with dementia in various countries

Future studies investigating antibiotic prescription patterns should report antibiotic use by type of infection, stage of dementia, and goals of antibiotic treatment in multiple settings

INTRODUCTION

In 2010, 35.6 million people were estimated to have dementia worldwide and this number is expected to nearly double every 20 years.¹ Dementia patients are susceptible to infections, including respiratory tract infections (RTIs), urinary tract infections (UTIs), and skin and soft tissue infections,^{2,3} and decision makers such as physicians, patients, and families are often faced with complex treatment decisions, especially at the end of life.

Treatment decisions about antibiotics, specifically in patients with dementia, imply ethical considerations such as whether to accept potential burden caused by treatment, and weighing best interests against patient and family preferences.^{4,5} Furthermore, patients with dementia may be unable to express symptoms and complaints, and typical symptoms of the infection are often absent.^{6,7} Long-term care environments may involve specific challenges such as the absence of diagnostic resources, which complicates appropriate antibiotic treatment.^{8,9} These challenges in the treatment of infections for patients with dementia may lead to variability in antibiotic use. Eventually this can result in burdensome side effects and the development of antibiotic-resistant microbes, which pose a major health risk, especially in older and institutionalized populations.^{10,11}

Studies that report on withholding treatment in advanced stages of dementia often focus on cardiopulmonary resuscitation (CPR), artificial nutrition or hospitalization,¹²⁻¹⁴ which suggests that antibiotic use is frequently regarded as a routine treatment. In addition, patients, families, and professionals often do not realize that dementia is a life-limiting disease, which may result in the deployment of potentially burdensome medical interventions in dementia including intravenous antibiotics and fluids.¹⁵⁻¹⁸ Antibiotic use in dementia may vary across different countries and settings.^{19,20} However, an overview of the actual proportion of patients with dementia that receive antibiotic treatment worldwide in different settings and for various indications is lacking, as is a mapping of the factors associated with its use.

The objectives of this review are to provide a comprehensive overview of (i) the prevalence of antibiotic use in patients with dementia in general and for specific infections, and of (ii) factors associated with antibiotic treatment or withholding treatment in dementia, in various care settings and countries.

METHODS

Literature search

We performed systematic searches in the bibliographic databases PubMed, EMBASE.com, PsycINFO (via EB- SCO) and The Cochrane Library (via Wiley) from inception to February 13, 2014. Search terms included controlled terms from MeSH in PubMed, EMtree in EMBASE.com and thesaurus terms in PsycINFO as well as free-text terms. We used free-text terms only in The Cochrane Library. Search terms expressing 'dementia' were used in combination with search terms comprising 'antibiotics' (Online resource A). The references of the identified articles were searched for other relevant publications.

Inclusion criteria

Articles were included if they reported about antibiotic use in patients with dementia. We excluded articles if they were (i) not reporting about people with dementia or not referring to a population of which at least 50% had dementia; (ii) not containing empirical data such as in reviews, editorials, letters, and legal cases; (iii) case reports or $n = 1$ studies; (iv) not reporting about prevalence of antibiotic use or about factors associated with antibiotic use; (v) written in languages other than English, Dutch, French or German.

Selection process

Two reviewers (TM and EPJ) independently screened all potentially relevant titles and abstracts for eligibility. If possibly eligible, the full-text article was retrieved and evaluated. Differences in judgment were resolved through a consensus procedure. Data extraction was performed in duplicate by TM and three extra reviewers (SH, MZ, JTS), independently. We resolved any discrepancies in data extracted by discussion until consensus was reached. Data were extracted using a pilot-tested form that included design of the study, subject characteristics, setting, type of infection, diagnosis of the infection, severity of the dementia, prevalence of antibiotic use, and any factors associated with antibiotic use. When the same data about antibiotic prevalence were published in multiple publications, we used the data from the publication that matched our research question best, or, if indifferent, the first publication that reported on the largest possible appropriate selection of participants. We abstracted any factor that was examined for an association with antibiotic use, regardless of country and setting. We therefore abstracted all factors and subsequently categorized by content.

Assessment of methodological quality and usefulness

The methodological quality of the included articles was assessed using the Mixed Methods Appraisal Tool (MMAT),²¹ which enabled the appraisal of both quantitative and qualitative studies within their methodological domain resulting in comparable quality ratings. The quality ratings range from 0%, when none of four criteria are met, to 100% when all criteria are met.

In addition to the MMAT scoring, we developed and applied more specific criteria to rate the usefulness of included articles for the purpose of our review, and rated these as useful, somewhat useful or not useful (Online resource B). The MMAT scores and the usefulness of articles were assessed in duplicate and independently by TM and the three extra reviewers (SH, MZ, JTS) and disagreements were resolved by discussion. Articles that scored $\leq 25\%$ on the MMAT were excluded when evaluated as somewhat useful; articles evaluated as not useful were excluded regardless of the MMAT score.

RESULTS

The literature search generated a total of 1,867 references: 892 from PubMed, 843 from EMBASE.com, 114 from PsycINFO, 18 from the Cochrane Library, and an additional 10 references from reference lists. After removing duplicates, 1556 references remained. After screening titles and abstracts of references retrieved, 49 articles fulfilled the eligibility criteria, and quality and usefulness was adequate for 37 articles (Figure 1). Five studies were reported in more than one article, and we therefore report data from a total of 34 studies. We found 14 articles reporting about the prevalence of antibiotic use, overall or per infection, 13 articles examining the association of one or more factors with antibiotic use, and 10 articles that reported about both prevalence of antibiotic use and associated factors (Figure 1).

Prevalence of antibiotic use

Of the 24 articles that reported prevalence of antibiotic use (Online resource C), most (17) referred to nursing homes, long-term care facilities (LTCFs) or similar settings, and a few referred to a hospital setting (6), or home situation (1). Articles assessed the point prevalence of antibiotic use (3), period prevalence (7), antibiotic use in the last period before death (6) or antibiotic use during a specific infectious episode (8).

In nursing homes in Finland, Italy, and Canada, the point prevalence of antibiotic use ranged between 3.3 and 16.6%.^{19;22;23} The point prevalence depended on the setting; in an Italian study, it was 3.3% in nursing homes, and 15.2% in community-dwelling patients (Figure 2a and Online resource C).¹⁹

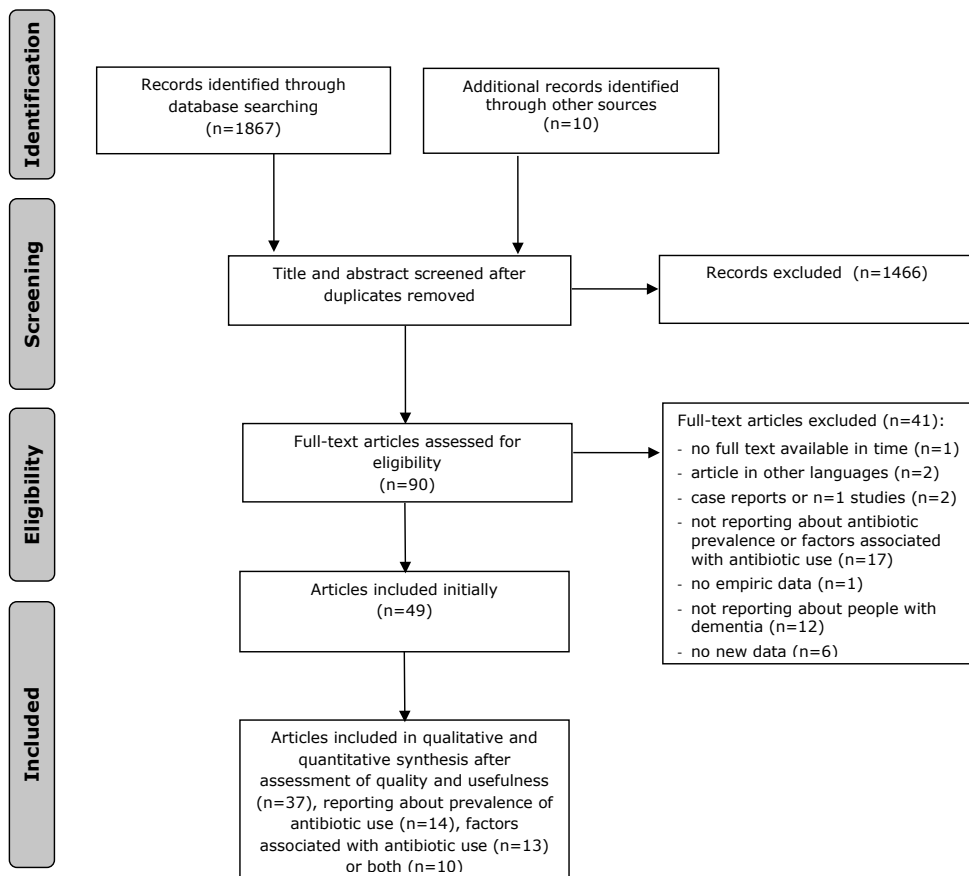


Figure 1. Flowchart of the search and selection procedure of studies.

The period prevalence of patients who received at least one course of antibiotics in a nursing-home setting was 4.4% in 3 days in a selection of European countries and Israel,²⁴ and 88% in a time span of 6 months in the US (Figure 2b and Online resource C).²⁵ The remaining five studies were conducted in hospitals in France, Israel, Canada, and the US, and antibiotic use ranged from 21.8% during the first 14 days of admission, to 86.2% during the stay in a hospital with a mean length of stay of 3.6 days. The median period prevalence in these articles was 52% for a median period of 14 days.²⁶⁻³⁰

The six articles that examined period prevalence of antibiotic use until death found percentages that ranged from 23.5% receiving antibiotics in the last 2 days of life at home in Japan,³¹ to 94% during terminal hospitalization in the US.³² The four remaining studies were conducted in Italian and US nursing homes or hospice agencies and antibiotic use was assessed in the last 6 months, 30 days or 14 days of life, and the last 7 days in hospice care, with a median prevalence of 48% for a median period of 22 days (Figure 2c and Online resource C).^{28-30;33-36}

Five articles reported about treatment for patients with lower respiratory infections (LRIs) or pneumonia, mostly diagnosed by clinical criteria (Figure 2d and Appendix C). Three US articles reported that 85.3–91.1% of patients received antibiotic therapy,³⁷⁻³⁹ and two Dutch articles reported percentages of 77 and 79%.⁴⁰⁻⁴¹

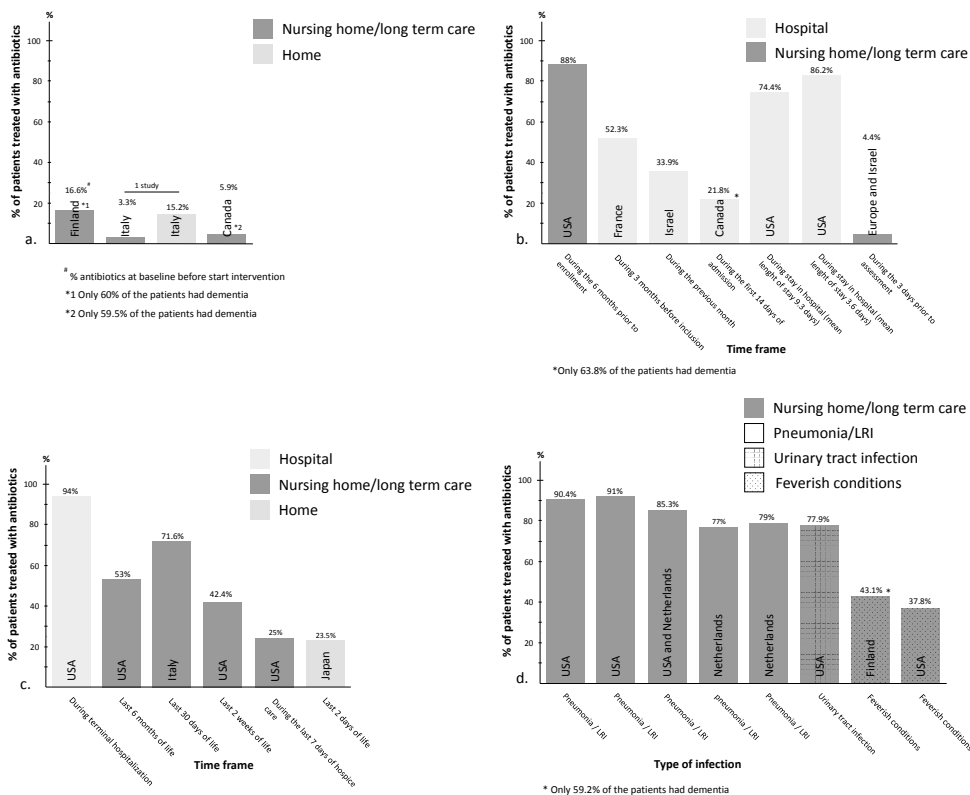


Figure 2. a. point prevalence of antibiotic use, b. period prevalence of antibiotic use, c. period prevalence of antibiotic use – last period before death, d. antibiotic use per infectious or feverish episode.

Antibiotic treatment of UTIs was provided in 77.9% of episodes in US nursing homes.⁶ An article that focused on treatment of feverish conditions reported that antibiotics were used in 37.8% of 172 feverish episodes in 104 patients in the US, of which 93 episodes were RTIs, 67 were UTIs, and 25 were systemic infections; all diagnoses were based on physical examinations.⁴² Another article reported that 43.1% of 102 feverish episodes in 193 patients were treated with antibiotics in Finland.⁴³

Factors associated with antibiotic use

Papers reported a total of 57 factors that were associated with antibiotic use and could be categorized into factors that related to (i) the patient's health status, (ii) persons involved in the decision making such as patients, physicians or families, and (iii) the healthcare context, such as country and setting (Tables 1, 2, 3). For only three articles, the search for factors associated with antibiotic use was the primary goal, and these articles investigated associations of multiple factors with antibiotic use for pneumonia in patients with dementia.^{37,41,44} Most articles tested one or a few factors that were or were not based on specific hypotheses.

Patient's health status

The majority of factors associated with antibiotic use in the included articles related to the patient's health status (27/57); four factors were reported in two or more articles, and showed consistent associations with fewer antibiotic treatments (Table 1—highlighted rows). The severity of dementia was studied in four articles and all found that patients with more severe dementia were less likely to receive antibiotics.^{33,39,41,44} Furthermore, a poor prognosis was associated with fewer antibiotics in a selection of European nursing homes,²⁴ and in a Dutch study which assessed physicians' subjective predictions in a survey.⁴⁵ The latter reported that three-quarters of the physicians would consider a mortality risk of 75–90% in spite of treatment sufficiently high to justify withholding antibiotics.⁴⁵ Lastly, illness severity and eating dependence, both pre-LRI and at the time of the treatment decision, were associated with fewer antibiotic treatments in two articles.^{39,41} Other factors were only examined in one study.

Eating dependency, drinking insufficiently and being dehydrated, both before a LRI and at the time of the treatment decision, and swallowing difficulty decreased the likelihood of antibiotic treatment in the US and the Netherlands.^{41,44} Patients who had been diagnosed with pneumonia previously,⁴¹ and were more ADL (activities of daily living)-dependent,³⁹ were also less likely to receive antibiotics.

A high body temperature in the US and the Netherlands,⁴⁴ and unstable vital signs in the US were positively related to antibiotic treatment for pneumonia.³⁷

Some articles showed contrasting results. Illness severity at the time of the treatment decision and 2 weeks before the treatment decision related to withholding antibiotics in the Netherlands,⁴¹ but in the US, indicators of more severe acute illness were associated with more antibiotic prescriptions,³⁹ or no association was found.⁴⁴ In addition, aspiration was associated with withholding antibiotics in the Netherlands,⁴¹ but in contrast, patients with suspected aspiration were more frequently treated with antibiotics in the US.³⁷

Persons involved in decision making

Articles that reported factors associated with persons involved in decision making assessed attitudes of patients, families, and physicians in hypothetical scenarios, or in real-life situations using qualitative designs (Table 2 and Online resource C, Table 3). Four studies, conducted in the US and Australia, found that 47% (71/152),⁴⁶ and 73% (159/218; 38/52)^{47,48} of subjects deciding for themselves were willing to accept antibiotics in general, or specifically for the treatment of pneumonia. Agreeing to antibiotics depended on the severity of the dementia with percentages ranging from 74% (62/84) choosing antibiotic treatment in the case of early Alzheimer's disease (AD) to only 25% (21/84) in the case of severe or late AD in a US study.⁴⁹

Three articles assessed attitudes of family members of patients with dementia using a hypothetical scenario, and reported that a majority (range 60–90%) preferred anti-biotic treatment. The highest percentage was found in a US study reporting that 90% (45/50) of spouses would choose antibiotics for their relative with dementia in case of a life-threatening infection.⁵⁰ In the case of critical illness (not further specified), 78% (40/51) of Chinese family care-givers would agree with antibiotic treatment for their relative with dementia.⁵¹ In a similar scenario, 60% (30/50) of relatives would agree to oral antibiotics in the UK.⁵²

Other studies explored attitudes of families and physicians using qualitative designs. A US focus group study pointed out that family members encountered difficulties viewing pneumonia as part of a 'natural death' for someone with dementia, and easily agreed to aggressive treatment including intravenous antibiotics. In fact, antibiotics were viewed as a comfort measure, rather than as a technological way of prolonging life.⁵³ Furthermore, a US survey study found that while spouses were reasonably comfortable to forgo life-sustaining treatments such as CPR and feeding tubes, of all treatments spouses were the most comfortable with the decision to agree to antibiotics and the least comfortable with the decision to forego antibiotics.⁵⁰

Table 1. Patient's health status factors associated with antibiotic use

Antibiotics	Factor*	Country	Setting	Limited to advanced dementia	Hypothetical	Before death	MMAT score	Usefulness	Study and year
Pneumonia and symptoms									
AB ↑	Unstable vital signs	US	1675 bed LTCF	+	-	-	50%	useful	Chen et al., 2006
AB ↑	High temperature	US and NL	NHS	-	-	-	50%	useful	Szafara et al., 2012
AB ↑	Suspected aspiration	US	1675 bed LTCF	+	-	-	50%	useful	Chen et al., 2006
AB ↑	NO aspiration	NL	NHS	-	-	-	75%	useful	van der Steen et al., 2002
AB ↑	Illness severity US	US	NHS	-	-	-	100%	useful	Mehr et al., 2003
AB ↑(US) AB ↓(NL)	Illness severity at time of the treatment decision and 2 weeks before the treatment decision	US and NL NL	NHS NHS	- -	- -	- -	50% 75%	useful useful	Mehr et al., 2003 van der Steen et al., 2002
AB =	LRI severity in severe dementia	US and NL	NHS	-	-	-	50%	useful	Szafara et al., 2012
Prognosis									
AB ↑	Approaching death (closer to death, determined in retrospect)	US	NHS	+	-	+	50%	useful	D'Agata and Mitchell, 2008
AB ↓	Poor prognosis (physician estimate at diagnosis) or ADEPT score	NL European countries and Israel	NHS NHS	- +	- -	- -	25% 75%	useful useful	van der Steen et al., 2009a [45] Onder et al., 2013
Health status/condition									
AB ↓	ADL dependency	US and NL	NHS	-	-	-	100%	useful	Mehr et al., 2003
AB ↓	Previous pneumonia	NL	NHS	-	-	-	75%	useful	van der Steen et al., 2002
AB =	General health condition: increased urine of fecal incontinence, increased mobility dependence, increased illness severity, increased discomfort	NL	NHS	-	-	-	75%	useful	van der Steen et al., 2002
AB =	Vaccination for influenza in prior winter	NL	NHS	-	-	-	75%	useful	van der Steen et al., 2002

Antibiotics	Factor*	Country	Setting	Limited to advanced dementia	Hypothetical	Before death	MM/AT score	Usefulness	Study and year
Dietary intake									
AB ↓	Swallowing difficulty	US and NL	NHS	-	-	-	50%	useful	Szafara et al., 2012
AB ↓	Eating dependence - pre-LRI and at the time of the treatment decision	US and NL	NL NHS	-	-	-	50%	useful	Szafara et al., 2012
AB ↓	Dehydration	NL	NHS	-	-	-	75%	useful	van der Steen et al., 2002
AB ↓	Insufficient drinking	NL	NHS	-	-	-	75%	useful	van der Steen et al., 2002
Dementia status									
AB ↓	Increased level of severity of the dementia	US	NH, transitional care unit, assisted living unit	-	-	+	75%	useful	Gjerdingen et al., 1999
AB ↓	More severe dementia	US and NL and NL	Chronic care facilities US NHS NL NHS	-	-	+	75%	useful	Evers et al., 2002
AB ↓							100%	useful	Mehr et al., 2003
AB ↓							50%	useful	Szafara et al., 2012
AB ↓							75%	useful	van der Steen et al., 2002
AB =	Psychogeriatric disease: Alzheimer dementia, mixed dementia	NL	NHS	-	-	-	75%	useful	van der Steen et al., 2002

Highlighted rows: Factors reported in two or more articles, Hypothetical: Factor from a study using a hypothetical scenario, Before death: Factor from a study examining antibiotic use in the period before death. AB↑ Positive association with antibiotic treatment, AB↓ Negative association with antibiotic treatment, AB= No association with antibiotic treatment, ADEPT: The Advanced Dementia Prognostic Tool, ADL: Activities of daily living, LRI: Lower respiratory infection, LTCF: Long term care facility, NH: Nursing home, NL: The Netherlands, US: United States of America.

Table 2. Person-related factors and associations with antibiotic use

Antibiotics	Factor	Country	Setting	Limited to advanced dementia	Hypothetical	Before death	MMAT score	Usefulness	Study and year
Patient attitudes									
AB ↑	Comfort of spouses with decision to forgo antibiotic was 40% and lowest of all treatment decisions	US	Aging and dementia research center	-	+	-	50%	somewhat useful	Mezey et al., 1996
AB ↑	Antibiotics are viewed as a comfort measure, not as a technologic means of prolonging life for someone with severe dementia	US	NHs	-	-	-	75%	useful	Forbes et al., 2000
AB ↑	Many family members do not view pneumonia as part of a 'natural death' for someone with dementia and agreed to hospitalization or to use of aggressive treatment in the nursing home, such as the use of IV antibiotics	US	NHs	-	-	-	75%	useful	Forbes et al., 2000
Physician attitudes									
AB ↓	Value of QoL in decision making	US and NL	NHs	-	-	-	50%	useful	Helton et al., 2006
AB ↓	Knowing nursing home patients (physician)	US and NL	NHs	-	-	-	50%	useful	Helton et al., 2006
AB ↓	Discussing treatment options with family timely	US and NL	NHs	-	-	-	50%	useful	Helton et al., 2006
AB ↓	Responsibility for treatment decision making NL vs US physicians	US and NL	NHs	-	-	-	50%	useful	Helton et al., 2006
AB ↓	Futility of treatment: physicians prefer not to treat when to do so seems futile	NL	NHs	-	-	-	25%	useful	van der Steen et al., 2009a [45]
AB ↓	Intention of hastening death	NL	NHs	-	-	-	25%	useful	van der Steen et al., 2005

Antibiotics	Factor	Country	Setting	Limited to advanced dementia	Hypothetical	Before death	MMAT score	Usefulness	Study and year
Patient demographics									
AB ↑	Primary language not English	US	LTCF	+	-	-	50%	useful	Chen et al., 2006
AB ↑	Gender (men)	US and NL	NHs	-	-	-	50%	useful	Szafara et al., 2012
AB ↑	US residents vs NL residents	US and NL	NHs	-	-	-	100%	useful	van der Steen et al., 2004
AB =	Sex	NL	NHs	-	-	-	75%	useful	van der Steen et al., 2002
Physician demographics									
AB =	Physicians' experience, age, gender or training status	NL	NHs	-	-	-	25%	useful	van der Steen et al., 2009a

AB↑ Positive association with antibiotic treatment, AB↓ Negative association with antibiotic treatment, AB= No association with antibiotic treatment, Highlighted rows: Factors reported in two or more articles, Hypothetical: Factor from a study using a hypothetical scenario, Before death: Factor from a study examining antibiotic use in the period before death, LTCF: Long term care facility, NH: Nursing home, NL: The Netherlands, US: United States of America, QoL: Quality of life, IV: Intravenous

Table 3. Healthcare contextual factors and associations with antibiotic use

Antibiotics	Factor	Country	Setting	Limited to advanced dementia	Hypothetical	Before death	MMAT score	Usefulness	Study and year
Advance directives									
AB ↓	A do not hospitalize (DNH) order	US	1 675 bed LTCF	+	-	-	50%	useful	Chen et al., 2006
AB ↓	Advance care planning	NL	NHs	-	-	-	50%	useful	van der Steen et al., 2002
Specifications of facilities									
AB ↑	Living alone	US	General internal medicine group practice	-	+	-	100%	somewhat useful	Lo et al., 1986
AB ↑	Number of psychogeriatric beds in the facility	NL	NHs	-	-	-	75%	useful	van der Steen et al., 2002
AB ↑	Home care vs nursing homes or hospital	Italy	NHs and home care services	+	-	-	75%	useful	Toscani et al., 2013
AB ↓	Treatment in the summer	NL	NHs	-	-	-	75%	useful	van der Steen et al., 2002
AB =	Nursing home situated in one of the three biggest NL cities	NL	NHs	-	-	-	75%	useful	van der Steen et al., 2002
AB =	Total number of beds or number of beds for somatic patients	NL	NHs	-	-	-	75%	useful	van der Steen et al., 2002
AB =	Religious affiliation of facility	NL	NHs	-	-	-	75%	useful	van der Steen et al., 2002
AB =	Level of policy making (availability of mission statement, quality policy, quality manual, and quality report on 4-point scale)	NL	NHs	-	-	-	75%	useful	van der Steen et al., 2002
AB =	Protocol or policy on (non) treatment available	NL	NHs	-	-	-	75%	useful	van der Steen et al., 2002

Antibiotics	Factor	Country	Setting	Limited to advanced dementia	Hypothetical	Before death	MMAT score	Usefulness	Study and year
Interventions and guidelines									
AB ↓	Intervention to reduce inappropriate use of antimicrobials in LTCFs using a team of experts visiting LTCFs	Finland	NHs and dementia units	-	-	-	75%	useful	Rummukainen et al., 2012
AB =	Recommendations by a palliative care team with the goal of enhancing patient comfort	US	Teaching hospital	-	-	-	50%	lessuseful	Ahronheim et al., 2000
Other									
AB =	Time - three death cohorts (1985-1990; 1991-1995; 1996-2000)	US	Chronic care facilities	-	-	+	75%	useful	Evers et al., 2002
AB =	Time - two time cohorts (1996-1998; 2006-2007)	NL	NHs	-	-	-	50%	useful	van der Steen et al., 2009b[40]

AB↑ Positive association with antibiotic treatment, AB↓ Negative association with antibiotic treatment, AB= No association with antibiotic treatment, Hypothetical: Factor from a study using a hypothetical scenario, Before death: Factor from a study examining antibiotic use in the period before death. ADEPT: The Advanced Dementia Prognostic Tool, ADL: Activities of daily living, LRI: Lower respiratory infection, LTCF: Long term care facility, NH: Nursing home, NL: The Netherlands, US: United States of America

A qualitative interview study that focused on the role of the physician found that physicians in the Netherlands have more patient contact and therefore know the patients and their relatives better than US physicians, and patient contact helped to start a timely discussion about treatment options for life-threatening infections. Ongoing care discussions before a 'crisis situation' occurs were thought to increase the odds of not choosing an aggressive treatment option.⁵⁴ Further, physicians preferred not to treat pneumonia when they considered treatment futile,⁴⁵ and curative treatment was sometimes forgone with an explicit intention to hasten death.⁵⁵

Healthcare context

The articles that described factors regarding the healthcare context indicated that patients living alone,⁴⁶ and at home, were more likely to receive antibiotics than nursing-home residents or hospital inpatients (Table 3).¹⁹ In Dutch nursing homes, the percentage of patients who received antibiotics for pneumonia increased with the number of psycho-geriatric beds in the facility.⁴¹ The total number of beds or the number of beds for somatic patients was unrelated to antibiotic use for patients with dementia. Furthermore, antibiotic prescriptions were not related to the religious affiliation of the facility, urbanization level, the level of policy making or the availability of a protocol or policy on treatment or non-treatment.⁴¹ Patients living in the Netherlands were less likely to receive antibiotic treatment than patients residing in the US.²⁰ Furthermore, patients who had a 'do not hospitalize' (DNH) order,³⁷ or an advance directive,^{41;56} were less likely to receive antibiotics.

Recommendations of a palliative care team aimed at improving comfort in a hospital did not affect antibiotic use in a US study.²⁶ In a recent Finnish article, an expert team comprising an infectious disease consultant and a geriatrician visited LTCFs and succeeded in reducing inappropriate use of antibiotics as UTI prophylaxis.²³ The factor time showed no association with antibiotic treatment, as observational studies in the US and the Netherlands found no change in antibiotic prescriptions over time in three and two death cohorts, respectively, between 1985 and 2007.^{33;40}

DISCUSSION

To our best knowledge, this is the first review that systematically assesses the prevalence of antibiotic use among patients with dementia, and factors associated with antibiotic prescriptions in this population. Antibiotic use is often substantial (median 48% within a median period of 14–30 days), but highly variable as the period prevalence ranged from 4.4 to 88%. However, in attitudinal studies, many patients, families, and physicians prefer to forgo treatment. We found that more severe dementia and a poor prognosis were consistently associated with using less antibiotics in various countries. Associations with aspiration, illness severity, and a number of healthcare contextual factors differed by country.

Strengths and limitations

We systematically identified, reviewed, and evaluated the literature concerning antibiotic use in patients with dementia. We considered the quality of the data in two ways, including only studies that met both general methodological criteria and usefulness criteria. The latter were developed because the first were rather unspecific and most studies were not primarily aimed at examining the prevalence of antibiotic use and factors associated with it, but provided data that could be useful to some extent to address the research question of this review. Studies that were somewhat useful were only included when they met the minimum criteria for acceptable methodological quality.

Some limitations should be acknowledged. First, detailed information about the diagnosis of infections and the specific reason to prescribe antibiotics was mostly lacking. Second, we included studies when more than 50% of subjects had dementia and some populations (4 of the 37 articles had less than 100% dementia) were therefore not homogeneous. Third, because investigating associations with antibiotic use was often not the primary goal of the studies, only a few factors were examined in multiple articles, leaving little opportunity to compare between countries and settings. Fourth, we are aware of the fact that the findings of studies conducted in the Netherlands in nursing-home settings contributed substantially to the factors we identified as associated with antibiotic use. This indicates the importance of studying the factors associated with antibiotic treatment in countries other than the Netherlands. Last, articles that reported on attitudes of family and patients regarding antibiotics were among the oldest articles included, and often applied a hypothetical scenario or a qualitative approach using focus groups. This leaves room for discussion about what would be chosen in actual practice, and how valuable these results are to represent attitudes towards withholding treatment with antibiotics today. Over the last decades, attitudes regarding providing antibiotics for comfort may have changed and the involvement of patients themselves and family may have gained importance.

Variability in antibiotic use

The prevalence of antibiotic use varied widely between studies. Although the designs of the prevalence studies varied, antibiotic prescription patterns in practice probably also varied widely. Part of this variability is likely caused by little evidence being available on effects to guide practice. Furthermore, the decision about antibiotics may depend on country, setting, and on whether the patient is perceived as approaching the end of life. For example, we found that antibiotics were frequently prescribed in the last 30 days of life in Italy, but, in contrast, the point prevalence of antibiotic use in an earlier period was surprisingly low.^{19;34}

Country and setting

Studies comparing different countries after pooling individual patient data examined the situation in the US and in the Netherlands. The few studies in other countries did not compare directly with other countries. Antibiotic use in general nursing-home populations varies between European countries; the mean point prevalence of antibiotic use ranged from 1.1% in Latvia to 15.9% in Finland.⁵⁷ Although this report lacks data about the prevalence in patients with dementia specifically, antibiotic use may be as variable, or perhaps even more variable in these patients.

US nursing-home residents, compared with Dutch residents, were more likely to receive antibiotics for pneumonia. Comparing both countries, the same factor operated in different directions: severity of the infection was associated with fewer antibiotics in the Netherlands, but increased antibiotic use in the US. Differences in training of physicians and differences in the organization of care may explain this. Dutch elderly care physicians follow a 3-year vocational training in elderly care medicine that includes training in advance care planning and decision making in end-of-life care.^{54;58} Further, elderly care physicians in the Netherlands are employed by the nursing home which is their principal site of practice. They therefore meet with their patients regularly, while, in many other countries and settings, care in the nursing home is provided by the general practitioner.^{58;59} Fewer physician contacts potentially result in less certainty about treatment decisions and family preferences, even after adjustment for country.⁶⁰ Physicians' experiences with treatment of patients with dementia, and with a focus on palliative care and withholding treatments, may also play a role.

Patients treated at home were more likely to receive antibiotics for an infection compared with patients in a hospital or nursing-home setting.^{19;56} It was suggested that the use of antibiotics at home may be higher due to urinary catheters, which were five times more common in patients living at home.¹⁹ Furthermore, patients eligible for home care may have specific indications that relate to antibiotic use, such as infections or pressure sores. In many countries, hospitalization of patients with dementia and pneumonia is common and typically involves intravenous antibiotic treatment.⁶¹⁻⁶³ Treatments such as parenteral antibiotics—which may be the only treatment option for patients with intake problems—may not be available in a home-care or nursing-home setting, depending on the country, which implies that a decision for antibiotics sometimes parallels a decision to hospitalize.

Although few studies assessed cross-national variation in attitudes towards antibiotic treatment for patients with dementia, these attitudes and decision making probably differ. This is supported by variability in treatment decisions between physicians in different countries using hypothetical scenarios regarding chronically ill older patients. For example, 897 physicians from seven countries selected a treatment option from supportive care only to maximum care including admission to

the intensive care unit for an 82-year-old man with a gastrointestinal bleeding, and US physicians were among the most aggressive while Australian colleagues were the most conservative.^{64,65}

Decision making about antibiotic treatment

Most family members of patients with dementia would agree to antibiotic treatment for an infection. Many experience emotional difficulties including guilt when deciding to refrain from life-sustaining treatments,¹⁷ but being involved in decision making is not always regarded as a burden.⁶⁶ To avoid routinely prescribing antibiotics, one of the parties involved should initiate the discussion of withholding curative treatment.⁶⁷ Not only whether treatment options are being discussed, but also how they are addressed may make a difference. For example, in a US survey study, a detailed written explanation about pneumonia to inform community-dwelling older people about treatment options surprisingly led to more of the subjects choosing antibiotics in the case of severe dementia and pneumonia.⁶⁸ In practice, the physician's attitude may be important. That is, an attitude which is more passive and deferential to family preferences may result in more aggressive treatment (antibiotics and hospitalization), in contrast to an attitude to treat based on what is perceived by the physician to be in the best interest of the patient. This was observed in a study in which physicians in both the US and the Netherlands indicated that timely discussion of treatment options may decrease the risk of starting inappropriate treatment of pneumonia,⁵⁴ emphasizing the importance of timely and effective communication between all parties involved in decision making.

Effects of antibiotic treatment: ethical considerations

The rationales behind withholding antibiotic treatment for terminally ill patients with dementia or incompetent patients and palliative use of antibiotics are the subject of an ethical debate in the literature.^{15,69-74} As the dementia progresses, the general treatment goal may shift from life prolongation to maintenance of function, and eventually to maximization of comfort.⁷⁵ However, the evidence base to guide treatment decisions about use of antibiotics consistent with these goals is small. In advanced dementia, antibiotics may prolong life in only a small minority of patients,⁷⁶ but hydration status affected survival even more profoundly than antibiotic treatment in nursing-home residents, many of whom had dementia.⁴⁴ Antibiotics might also relieve the symptoms of pneumonia in the absence of other proper treatment to relieve symptoms,⁷⁷ and may be prescribed to provide comfort.⁴¹ However, it remains unclear whether antibiotics actually enhance comfort, and if they do, whether such benefit outweighs the potential burden of antibiotic treatment in severely ill patients with dementia. Furthermore, one may consider that the patient, when cured of the infection, is still exposed to the deterioration of the dementia.^{78,79} When the goal of antibiotic treatment is not to provide comfort, and treatment is not expected to decrease mortality risk,^{42,76} some question its usefulness. Others claim that, regardless of the underlying illness and potentially negative consequences, withholding a drug that is effective in a disease treatment is always inappropriate.⁸⁰

In decision making about providing antibiotics, prescribers may also consider their decision from a public health point of view and include the emergence of antibiotic resistance into their considerations to start or withhold treatment.⁶⁹ However, antibiotic resistance and inappropriate antibiotic use did not emerge as a factor from the studies we included in this review. This is not surprising, considering the novelty of the topic of antibiotic resistance, the limited awareness about it in, for example, the nursing home setting, and difficulty applying general knowledge about resistance in the community in individual cases in clinical practice.^{11;69}

Implications

This review identifies several gaps in knowledge about the prevalence of antibiotic use in patients with dementia, as well as about factors associated with use of antibiotics in this population. The majority of articles focused on overall antibiotic use, or antibiotic use for RTIs, mostly in institutionalized patients (long-term care; hospital). Information about other common infections such as UTIs and skin infections, and about community-dwelling patients, is virtually lacking. Furthermore, few studies focused specifically on patients with advanced or end-stage dementia, and the factors investigated in these studies were not always the same as those assessed in studies that included all stages of dementia. Moreover, we found no studies that examined if factors associated with antibiotic use differed by dementia stage. Future studies should address these gaps, and distinguish types of infections and stages of dementia. We suggest a cross-national study in which a standardized set of factors as identified from our review is examined simultaneously and systematically, to further investigate antibiotic prescription patterns and how these may vary between countries and settings.

Little is known about attitudes and decision making in real practice situations. Qualitative studies using individual interviews or ethnographic designs may assess attitudes among patients, family, healthcare workers, and physicians, and other factors that are important in decision making around antibiotics in practice. Observational studies about antibiotic use in patients with dementia should include the goal of antibiotic treatment, and investigate associations with function, survival, comfort, and quality of life in different settings to contribute to a more evidence-based approach in antibiotic use.

Conclusion

This review suggests that decision making about starting or withholding antibiotic treatment remains a challenge, involves ethical considerations, and is strongly influenced by the particular healthcare context. Treatment with antibiotics is sometimes withheld, but considerations about this, and perhaps whether use or non-use is considered at all, depend on country, setting, and family and physician preferences. This review provides a basis for further research and an international discussion among stakeholders about the ethical and practical considerations of withholding antibiotic treatment in patients with dementia.

Supplementary Data

Online resource A, B and C can be found after the references.

REFERENCES

1. Prince M, Bryce R, Albanese E, et al. The global prevalence of dementia: a systematic review and metaanalysis. *Alzheimers Dement* 2013;9:63–75.
2. Mitchell SL, Teno JM, Kiely DK, et al. The clinical course of advanced dementia. *N Engl J Med* 2009;361:1529–38.
3. Vandervoort A, Van den Block L, van der Steen JT, et al. Nursing home residents dying with dementia in Flanders, Belgium: a nationwide postmortem study on clinical characteristics and quality of dying. *J Am Med Dir Assoc* 2013;14:485–92.
4. Hurley AC, Volicer L. Alzheimer Disease: “It’s okay, Mama, if you want to go, it’s okay”. *JAMA* 2002;288:2324–31.
5. van der Steen JT, Ooms ME, Ribbe MW, et al. Decisions to treat or not to treat pneumonia in demented psychogeriatric nursing home patients: evaluation of a guideline. *Alzheimer Dis Assoc Disord* 2001;15:119–28.
6. D’Agata E, Loeb MB, Mitchell SL. Challenges in assessing nursing home residents with advanced dementia for suspected urinary tract infections. *J Am Geriatr Soc* 2013;61:62–6.
7. Scherder E, Herr K, Pickering G, et al. Pain in dementia. *Pain* 2009;145:276–8.
8. Loeb M, Simor AE, Landry L, et al. Antibiotic use in Ontario facilities that provide chronic care. *J Gen Intern Med* 2001;16:376–83.
9. Zimmer JG, Bentley DW, Valenti WM, et al. Systemic antibiotic use in nursing homes. A quality assessment. *J Am Geriatr Soc* 1986;34:703–10.
10. Croft AC, D’Antoni AV, Terzulli SL. Update on the antibacterial resistance crisis. *Med Sci Monit* 2007;13:RA103–18.
11. van Buul LW, van der Steen JT, Veenhuizen RB, et al. Antibiotic use and resistance in long term care facilities. *J Am Med Dir Assoc* 2012;13:568–13.
12. Jox RJ, Denke E, Hamann J, et al. Surrogate decision making for patients with end-stage dementia. *Int J Geriatr Psychiatry* 2012;27:1045–52.
13. Mitchell SL, Teno JM, Intrator O, et al. Decisions to forgo hospitalization in advanced dementia: a nationwide study. *J Am Geriatr Soc* 2007;55:432–8.
14. Rurup ML, Onwuteaka-Philipsen BD, Pasman HR, et al. Attitudes of physicians, nurses and relatives towards end-of-life decisions concerning nursing home patients with dementia. *Patient Educ Couns* 2006;61:372–80.
15. Congedo M, Causarano RI, Alberti F, et al. Ethical issues in end of life treatments for patients with dementia. *Eur J Neurol* 2010;17:774–9.
16. Mitchell SL, Kiely DK, Hamel MB. Dying with advanced dementia in the nursing home. *Arch Intern Med* 2004;164:321–6.
17. Sachs GA, Shega JW, Cox-Hayley D. Barriers to excellent end-of-life care for patients with dementia. *J Gen Intern Med* 2004;19:1057–63.
18. Morrison RS, Siu AL. Mortality from pneumonia and hip fractures in patients with advanced dementia. *JAMA* 2000;284(19):2447–8.
19. Toscani F, Di GP, Villani D, et al. Treatments and prescriptions in advanced dementia patients residing in long-term care institutions and at home. *J Palliat Med* 2013;16:31–7.
20. van der Steen JT, Kruse RL, Ooms ME, et al. Treatment of nursing home residents with dementia and lower respiratory tract infection in the United States and The Netherlands: an ocean apart. *J Am Geriatr Soc* 2004;52:691–9.
21. Pace R, Pluye P, Bartlett G, et al. Testing the reliability and efficiency of the pilot Mixed Methods Appraisal Tool (MMAT) for systematic mixed studies review. *Int J Nurs Stud* 2012;49:47–53.

22. Daneman N, Gruneir A, Newman A, et al. Antibiotic use in long-term care facilities. *J Antimicrob Chemother* 2011;66:2856–63.
23. Rummukainen ML, Jakobsson A, Matsinen M, et al. Reduction in inappropriate prevention of urinary tract infections in long-term care facilities. *Am J Infect Control* 2012;40:711–4.
24. Onder G, Liperoti R, Foebel A, et al. Polypharmacy and mortality among nursing home residents with advanced cognitive impairment: results from the SHELTER study. *J Am Med Dir Assoc* 2013;14:450–12.
25. Blass DM, Black BS, Phillips H, et al. Medication use in nursing home residents with advanced dementia. *Int J Geriatr Psychiatry* 2008;23:490–6.
26. Ahronheim JC, Morrison RS, Morris J, et al. Palliative care in advanced dementia: a randomized controlled trial and descriptive analysis. *J Palliat Med* 2000;3:265–73.
27. Catic AG, Berg AI, Moran JA, et al. Preliminary data from an advanced dementia consult service: integrating research, education, and clinical expertise. *J Am Geriatr Soc* 2013;61:2008–12.
28. Malyuk RE, Wong C, Buree B, et al. The interplay of infections, function and length of stay (LOS) in newly admitted geriatric psychiatry patients. *Arch Gerontol Geriatr* 2012;54:251–5.
29. Nourhashemi F, Gillette S, Cantet C, et al. End-of-life care for persons with advanced Alzheimer disease: design and baseline data from the ALFINE study. *J Nutr Health Aging* 2012;16:457–61.
30. Reisfeld S, Paul M, Gottesman BS, et al. The effect of empiric antibiotic therapy on mortality in debilitated patients with dementia. *Eur J Clin Microbiol Infect Dis* 2011;30:813–8.
31. Hirakawa Y, Masuda Y, Kuzuya M, et al. End-of-life experience of demented elderly patients at home: findings from DEATH project. *Psychogeriatrics* 2006;6:60–7.
32. Ahronheim JC, Morrison RS, Baskin SA, et al. Treatment of the dying in the acute care hospital. Advanced dementia and meta-static cancer. *Arch Intern Med* 1996;156:2094–100.
33. Evers MM, Purohit D, Perl D, et al. Palliative and aggressive end-of-life care for patients with dementia. *Psychiatr Serv* 2002;53:609–13.
34. Di Giulio P, Toscani F, Villani D, et al. Dying with advanced dementia in long-term care geriatric institutions: a retrospective study. *J Palliat Med* 2008;11:1023–8.
35. D’Agata E, Mitchell SL. Patterns of antimicrobial use among nursing home residents with advanced dementia. *Arch Intern Med* 2008;168:357–62.
36. Albrecht JS, Gruber-Baldini AL, Fromme EK, et al. Quality of hospice care for individuals with dementia. *J Am Geriatr Soc* 2013;61:1060–5.
37. Chen JH, Lamberg JL, Chen YC, et al. Occurrence and treatment of suspected pneumonia in long-term care residents dying with advanced dementia. *J Am Geriatr Soc* 2006;54:290–5.
38. Givens JL, Jones RN, Shaffer ML, et al. Survival and comfort after treatment of pneumonia in advanced dementia. *Arch Intern Med* 2010;170:1102–7.
39. Mehr DR, van der Steen JT, Kruse RL, et al. Lower respiratory infections in nursing home residents with dementia: a tale of two countries. *Gerontologist* 2003;43:85–93.
40. van der Steen JT, Meuleman-Peperkamp I, Ribbe MW. Trends in treatment of pneumonia among Dutch nursing home patients with dementia. *J Palliat Med* 2009;12:789–95.
41. van der Steen JT, Ooms ME, Ader HJ, et al. Withholding anti-biotic treatment in pneumonia patients with dementia: a quantitative observational study. *Arch Intern Med* 2002;162:1753–60.
42. Fabiszewski KJ, Volicer B, Volicer L. Effect of antibiotic treatment on outcome of fevers in institutionalized Alzheimer patients. *JAMA* 1990;263(23):3168–72.
43. Visapaa J. Significant changes in the terminal care of aged patients in the long-term care in Helsinki. *Scand J Soc Med* 1998;26:53–5.
44. Szafara KL, Kruse RL, Mehr DR, et al. Mortality following nursing home-acquired lower respiratory infection: LRI severity, antibiotic treatment, and water intake. *J Am Med Dir Assoc*. 2012;13:376–83.
45. van der Steen JT, Helton MR, Ribbe MW. Prognosis is important in decisionmaking in Dutch nursing home patients with dementia and pneumonia. *Int J Geriatr Psychiatry* 2009;24:933–6.

46. Lo B, McLeod GA, Saika G. Patient attitudes to discussing life- sustaining treatment. *Arch Intern Med* 1986;146:1613–5.
47. Low JA, Chan DKY, Hung WT, et al. Treatment of recurrent aspiration pneumonia in end-stage dementia: preferences and choices of a group of elderly nursing home residents. *Intern Med J* 2003;33:345–9.
48. Reilly RB, Teasdale TA, McCullough LB. Projecting patients' preferences from living wills: an invalid strategy for management of dementia with life-threatening illness. *J Am Geriatr Soc* 1994;42:997–1003.
49. Gjerdingen DK, Neff JA, Wang M, et al. Older persons' opinions about life-sustaining procedures in the face of dementia. *Arch Fam Med* 1999;8:421–5.
50. Mezey M, Kluger M, Maislin G, et al. Life-sustaining treatment decisions by spouses of patients with Alzheimer's disease. *J Am Geriatr Soc* 1996;44:144–50.
51. Kwok T, Twinn S, Yan E. The attitudes of Chinese family caregivers of older people with dementia towards life sustaining treatments. *J Adv Nurs* 2007;58:256–62.
52. Potkins D, Bradley S, Shrimanker J, et al. End of life treatment decisions in people with dementia: carers' views and the factors which influence them. *Int J Geriatr Psychiatry* 2000;15:1005–8.
53. Forbes S, Bern-Klug M, Gessert C. End-of-life decision making for nursing home residents with dementia. *J Nurs Scholarsh* 2000;32:251–8.
54. Helton MR, van der Steen JT, Daaleman TP, et al. A cross- cultural study of physician treatment decisions for demented nursing home patients who develop pneumonia. *Ann Fam Med* 2006;4:221–7.
55. van der Steen JT, van der Wal G, Mehr DR, et al. End-of-life decision making in nursing home residents with dementia and pneumonia: Dutch physicians' intentions regarding hastening death. *Alzheimer Dis Assoc Disord* 2005;19:148–55.
56. Parsons C, McCorry N, Murphy K, et al. Assessment of factors that influence physician decision making regarding medication use in patients with dementia at the end of life. *Int J Geriatr Psychiatry* 2013. 29:281–90.
57. ESAC. Report on point prevalence survey of antimicrobial prescription in European nursing homes, 2009. 2010.
58. Koopmans RT, Lavrijsen JC, Hoek JF, et al. Dutch elderly care physician: a new generation of nursing home physician specialists. *J Am Geriatr Soc* 2010;58:1807–9.
59. Hoek JF, Ribbe MW, Hertogh CM, et al. The role of the specialist physician in nursing homes: the Netherlands' experience. *Int J Geriatr Psychiatry* 2003;18:244–9.
60. Helton MR, Cohen LW, Zimmerman S, et al. The importance of physician presence in nursing homes for residents with dementia and pneumonia. *J Am Med Dir Assoc* 2011;12:68–73.
61. Li Q, Zheng NT, Temkin-Greener H. Quality of end-of-life care of long-term nursing home residents with and without Dementia. *J Am Geriatr Soc* 2013;61:1066–73.
62. Givens JL, Selby K, Goldfeld KS, et al. Hospital transfers of nursing home residents with advanced dementia. *J Am Geriatr Soc* 2012;60:905–9.
63. Lamberg JL, Person CJ, Kiely DK, et al. Decisions to hospitalize nursing home residents dying with advanced dementia. *J Am Geriatr Soc* 2005;53:1396–401.
64. Alemayehu E, Molloy DW, Guyatt GH, et al. Variability in physicians' decisions on caring for chronically ill elderly patients: an international study. *CMAJ* 1991;144:1133–8.
65. Molloy DW, Guyatt GH, Alemayehu E, et al. Factors affecting physicians' decisions on caring for an incompetent elderly patient: an international study. *CMAJ* 1991;145:947–52.
66. Jacobs VE, van Zuthem HJ, van Delden JJ. Experiences of guardians of psychogeriatric patients regarding decision not to treat. *Ned Tijdschr Geneesk* 2000;144:378–81.
67. van der Steen JT, van Soest-Poortvliet MC, Hallie-Heierman M, et al. Factors associated with initiation of advance care planning in dementia: a systematic review. *J Alzheimers Dis* 2014;40:743–57.

68. Ainslie N, Beisecker AE. Changes in decisions by elderly persons based on treatment description. *Arch Intern Med* 1994;154(19):2225–33.
69. Marcus EL, Clarfield AM, Moses AE. Ethical issues relating to the use of antimicrobial therapy in older adults. *Clin Infect Dis* 2001;33:1697–705.
70. Brody H, Campbell ML, Faber-Langendoen K, et al. Withdrawing intensive life-sustaining treatment—recommendations for compassionate clinical management. *N Engl J Med* 1997;336:652–7.
71. Wanzer SH, Adelstein SJ, Cranford RE, et al. The physician's responsibility toward hopelessly ill patients. *N Engl J Med* 1984;310:955–9.
72. Parsons C, Hughes CM, Passmore AP, et al. Withholding, discontinuing and withdrawing medications in dementia patients at the end of life: a neglected problem in the disadvantaged dying? *Drugs Aging* 2010;27:435–49.
73. Chen LK, Chou YC, Hsu PS, et al. Antibiotic prescription for fever episodes in hospice patients. *Support Care Cancer* 2002;10:538–41.
74. Stiel S, Krumm N, Pestinger M, et al. Antibiotics in palliative medicine—results from a prospective epidemiological investigation from the HOPE survey. *Support Care Cancer* 2012;20:325–33.
75. van der Steen JT, Radbruch L, Hertogh CM, et al. White paper defining optimal palliative care in older people with dementia: a Delphi study and recommendations from the European Association for Palliative Care. *Palliat Med* 2014;28:197–209.
76. van der Steen JT, Lane P, Kowall NW, et al. Antibiotics and mortality in patients with lower respiratory infection and advanced dementia. *J Am Med Dir Assoc* 2012;13:156–61.
77. van der Steen JT, Pasma HR, Ribbe MW, et al. Discomfort in dementia patients dying from pneumonia and its relief by antibiotics. *Scand J Infect Dis* 2009;41:143–51.
78. Schwaber MJ, Carmeli Y. Antibiotic therapy in the demented elderly population: redefining the ethical dilemma. *Arch Intern Med* 2008;168:349–50.
79. Hertogh CM, Ribbe MW. Ethical aspects of medical decision- making in demented patients: a report from the Netherlands. *Alzheimer Dis Assoc Disord* 1996;10:11–9.
80. Rozzini R, Trabucchi M. Antibiotic therapy in elderly persons affected by severe dementia. *Arch Intern Med* 2008;168:2497–8

Online resource A

Search strategy in PubMed as of February 13, 2014 (read from bottom-up).

Set	Search terms	Items
#5	#4 NOT (Animals[mh] NOT humans[mh])	679
#4	#3 NOT ("addresses"[Publication Type] OR "biography"[Publication Type] OR "comment"[Publication Type] OR "directory"[Publication Type] OR "editorial"[Publication Type] OR "festschrift"[Publication Type] OR "interview"[Publication Type] OR "lectures"[Publication Type] OR "legal cases"[Publication Type] OR "legislation"[Publication Type] OR "letter"[Publication Type] OR "news"[Publication Type] OR "newspaper article"[Publication Type] OR "patient education handout"[Publication Type] OR "popular works"[Publication Type] OR "congresses"[Publication Type] OR "consensus development conference"[Publication Type] OR "consensus development conference, nih"[Publication Type])	837
#3	#1 AND #2	891
#2	"Anti-Bacterial Agents"[Pharmacological Action] OR "Anti-Bacterial Agents"[Mesh] OR antibiotic*[tiab] OR anti-bacterial[tiab]	600355
#1	"Dementia"[Mesh] OR dement*[tiab] OR alzheimer*[tiab]	152189

Online resource B Usefulness criteria

Useful	
Quantitative research	<ul style="list-style-type: none"> the starting point of the study corresponds well with our research question the population is representative the method to determine antibiotic use is little or not error prone the results are reported clearly
Qualitative research	<ul style="list-style-type: none"> the starting point of the study corresponds well to our research question the results are reported clearly appropriate subjects or informants are used
Somewhat useful	
Quantitative research	<ul style="list-style-type: none"> the starting point of the study only partially corresponds to our research question the population is (very) selective the method to determine antibiotic use is error prone (e.g. interview without referring to patient's chart) the results are reported poorly
Qualitative research	<ul style="list-style-type: none"> the starting point of the study only partially corresponds with our research question the results are reported poorly inappropriate subjects or informants are used (too few or too homogeneous)
Not useful	
	<ul style="list-style-type: none"> Articles are rated as not useful when one or several of the criteria scores so poorly that the results of the article are of no value for our review

Online resource C

Table 1. Overall antibiotic use (data referring to Figures 2a-c), and factors associated with use of antibiotics (Tables 1-3 in the article) Detail on the 37 included articles

Study	MIMAT score	Usefulness	Country	Design study	Setting	Population/enrollment criteria	Number of subjects	Severity of dementia	Time frame	Antibiotic therapy	Factor associated with the use of antibiotics
1. Rummukainen et al., 2012	75%	Useful	Finland	Observational prospective study 2005-2008	39 NHs and dementia units	Older patients (dementia 60%)	1221	Not specified	n.a	Baseline (2005): 16.6% (203/1221) of residents received antibiotics; 14.5% (177/1221) as UTI prophylaxis; 2.1% (26/1221) or for an acute UTI treatment In 2008: 7.8% (90/1158) received antibiotics as UTI prophylaxis and 1.7% (20/1158) were on acute RTI treatment	AB ↓Intervention to reduce inappropriate use of antimicrobials in LTCFs using a team of experts visiting LTCFs
2. Toscani et al., 2013	75%	Useful	Italy	Multicenter prospective observational cohort study 2007-2009	34 NHs and home care services	Patients with a FAST score of ≥7 with and expected survival of ≥2 weeks according to their primary doctor's clinical judgment	410; 245 nursing home residents; 165 home care service	Most advanced stage of dementia (FAST score 7 or higher)	n.a	8.1% (33/410) of all patients received antibiotics 3.3% (8/245) nursing home residents received antibiotics	AB ↑Home care vs nursing homes or hospital
3. Daneman et al., 2011	75%	Somewhat useful	Canada	Point-prevalence study 2009	361 LTCFs	Residents ≥ 66 years old who had completed a Continuing Care Reporting System Long Term Care assessment (dementia: 59.5%)	37371	Not specified	n.a	15.2% (23.7/165) of home care service patients received antibiotics 5.9% (2190/37119) were receiving antibiotics at the time of their index assessment	



Period prevalence											
Study	MIMAT score	Usefulness	Country	Design study	Setting	Population/enrollment criteria	Number of subjects	Severity of dementia	Time frame	Antibiotic therapy	Factor associated with the use of antibiotics
4. Blass et al., 2008	25%	Useful	US	Prospective cohort study 2000-2004	3 NHs	Patients with advanced dementia who (1) met hospice guidelines for persons with dementia, (2) were receiving hospice or palliative care, or (3) had a rapidly declining health status and a high likelihood of dying within 2 months	125	Advanced dementia, not further specified	6 months prior to enrollment	88% (110/125) received antibiotic therapy at baseline (spanning the 6 months prior to enrollment)	
5. Onder et al., 2013	75%	Useful	Czech republic, England, Finland, Germany, Italy, the Netherlands, Israel	Longitudinal observational study	57 NHs	Older adults with advanced cognitive impairment residing in NHs	822	Severe cognitive impairment (CPS scores between 5.4 and 5.8)	The three days prior to assessment	4.4% (36/822) received antibiotics	AB ↓ Poor prognosis (physician estimate at diagnosis) or ADEPT score
6. Ahronheim et al., 2000	50%	Somewhat useful	US	RTC	1 teaching hospital	Patients with advanced dementia who were hospitalized for acute illness.	Total: 99 patients (190 hospital admissions); Intervention: 48 (92 hospital admissions); Control: 51 (98 hospital admissions)	FAST stage 6d-7b Total: 47 (47.5%) Intervention: 26 (54.2%) Control: 21 (41.2%) FAST stage 7c-7f Total: 52 (52.5%) Intervention: 22 (45.8%) Control: 30 (58.8%)	During stay in hospital	74.4% (142/190) of admissions received systemic antibiotic treatment during their stay Intervention: 79.3% (73/92) of admissions received systemic antibiotic treatment during their stay Control: 70.4% (69/98) of admissions received systemic antibiotic treatment during their stay	AB = Recommendations by a palliative care team with the goal of enhancing patient comfort

7. Catic et al., 2013	Somewhat useful	50%	US	Pilot study 2012	1 hospital	Patients aged 65 and older, admitted to any clinical service for 48 hours or less, GDS 7 and English-speaking proxy	Total: 29 Control: 24 Intervention: 5	Advanced dementia. BANS-S scores: 20.1 (1.7)	During stay in hospital mean length of stay 3.6 days	86.2% (25/29) received IV antibiotics
8. Nourhashemi et al., 2012	Somewhat useful	50%	France	Prospective observational study 2004-2007	Geriatric wards of 2 hospitals	Patients with Alzheimer disease identified after hospitalization on geriatric wards	112	Severe dementia (MMSE < 10)	During 3 months before inclusion	52.3% (56/107) received antibiotic therapy during the 3 months before inclusion (mean duration 10.00 ±6.70 days)
9. Malyuk et al., 2012	Somewhat useful	75%	Canada	Retrospective naturalistic study 2003-2007	1 geriatric Psychiatry teaching hospital	Elderly patients with chronic mental illness or dementia (dementia: 63.8%)	Group A: 85; Group C: 305 Total: 390	Moderate dementia: 29.5%; severe dementia: 33.8%	Within 14 days of admission	31.7% (33/104) were still receiving antibiotics at inclusion 21.8% (85/390) received antibiotics within 14 days of admission
10. Reisfeld et al., 2011	Somewhat useful	50%	Israel	Retrospective cohort study 2005-2007	1 700-bed community hospital	Hospitalized patients with gram-negative bacteremia, with dementia and a bed-ridden functional status.	378 patients	Not specified	During the previous month	33.9% (128/378) received antibiotic treatment during the previous month



Overall antibiotic use – last period before death

Study	MIMAT score	Usefulness	Country	Design study	Setting	Population/enrollment criteria	Number of subjects	Severity of dementia	Time frame	Antibiotic therapy	Factor associated with the use of antibiotics
11. Evers et al., 2002	75%	Useful	US	Retrospective study 1985-2000	Chronic care facilities	Patients who died with dementia who were brought for clinical autopsy	279	Clinical dementia rating score(CDR) range 0-5: Mild dementia, CDR 0.5- 1: 52 patients Moderate dementia 2: 42 patients Severe, 3 to 5: 185 patients	Last 6 months of life	53% (148/279) received antibiotics in the last 6 months of life 40% (21/52) of patients with mild dementia received antibiotics in the last 6 months of life 60% (25/42) of patients with moderate dementia received antibiotics in the last 6 months of life	AB ↓More severe dementia (Increased scores at Clinical Dementia Rating Scale) AB = Time – three death cohorts (1985-1990; 1991-1995; 1996-2000)
12. Albrecht et al., 2013	75%	Useful	US	Survey study 2007	1545 hospice agencies	Patients discharged from hospice (alive or death) during the 3-month period beginning 4 months before the agency interview.	Total 4733; dementia 450	Not specified	The last 7 days of hospice care	55% (102/185) of patients with severe dementia received antibiotics in the last 6 months of life 25% (109/450) received antibiotics in the last 7 days of hospice care	

13. D'Agata and Mitchell, 2008	50%	Useful	US	Prospective cohort study 2003-2006	21 NHs Nursing home residents aged 60 and older, with a length of stay 30 days or longer	214	CPS score 5 or 6 and GDS score of 7. Severely cognitively impaired, with 162 (75.7%) scoring 0 on the Test for Severe Impairment.	Last 2 weeks of life	66.4% (142/214) of residents received at least 1 course of antibiotics during an average of 32.2 days of follow up 42.4% received at least 1 course of antibiotics within the 2 weeks before death	AB ↑ Approaching death (closer to death, determined in retrospect)
14. Di Giulio et al., 2008	75%	Useful	Italy	Retrospective exploratory study 2004-2005	7 LTCFs (>200 beds) Patients diagnosed with severe cognitive impairment	141	Severe cognitive impairment, FAST stages: 7c: 50% (71/141) 7d: 30% (43/141) ≥7e: 19% (27/141)	Last 30 days of life	51.5% received at least 1 dose of antibiotics within the 8 weeks before death 71.6% (101/141) received antibiotics in the last 30 days of life (85% had fever or urinary tract infection)	
15. Hirakawa et al., 2006	50%	Useful	Japan	Multicenter observational study 2002-2004	Home; decedents were using 16 study clinics belonging to the society with diagnoses of all illnesses	98	Score of ≥ 1 on a scale of 6 levels of which 0 is not demented.	Last 2 days of life	23.5% (23/98) of the patients dying with dementia received antibiotics in the last 2 days of life	



16. Ahronheim et al., 1996	50%	Somewhat useful	US	Retrospective chart review study	1 teaching hospital	Patients 65 and older who died with a diagnosis of advanced dementia	80	Advanced dementia (at least 2 of: MMSE < 5, complete dependence with respect to transfer, feeding and continence, a DNR order or an assessment performed by a psychiatrist or geriatrician documenting a diagnosis of severe dementia, a documented chronic progressive decline in cognitive function or a non-physician note documenting severe dementia)	During terminal hospitalization	94% (75/80) received antibiotics during their terminal hospitalization 73% (58/80) received empiric antibiotic therapy (no documented source of infection) 65% (52/80) received non-empiric antibiotic therapy (antibiotics ordered specifically for positive blood, urinary, or tissue test results, or other fluid culture, or for an infiltrate on a chest x-ray film)
----------------------------	-----	-----------------	----	----------------------------------	---------------------	--	----	--	---------------------------------	---

Table 2. Antibiotic use per infectious episode (data referring to Figure 2d), and associated factors with use of antibiotics (Tables 1-3)

Study	MMAT score	Usefulness	Country	Design study	Setting	Population/enrollment criteria	Number of subjects	Severity of dementia	Type of infection	Diagnosis infection	Antibiotic therapy	Factor associated with the use of antibiotics
17. Fabiszewski et al., 1990	75%	Useful	US	Prospective cohort	1 hospital (3 25-bed intermediate medical care units)	Patients who where hospitalized for long-term care and had dementia	75 of 104 patients developed 172 episodes of fever	BAMS-S: Antibiotic group (n=37) 15.4 (0.8); Palliative group (n=38): 17.6 (0.7)	Fever	Fever was defined as an unexplained rectal temperature elevation to 38.9°C or higher or a temperature of 37.7°C or higher that persists for more than 24 hours. Temperatures were measured when signs of potential temperature elevation were observed by caregivers.	37.8% (65/172) of fevers was treated with antibiotics 69.6% (64/92) of fevers in the antibiotic group was treated with antibiotics	
18. Givens et al., 2010	75%	Useful	US	Prospective cohort study 2003-2006	21 NHs	Nursing home residents aged 60 and older, with a length of stay 30 days or longer, cognitive impairment due to dementia	Of 323 residents 133 residents developed 225 pneumonia	BAMS-S scores: 23.9 (2.3)	Pneumonia	Clinical criteria, chest radiograph when available	91.1% (205/225) of pneumonia episodes was treated with antibiotics 55.1% (124/225) oral 15.6% (35/225) IM 20.4% (46/225) IV	
19. D'Agata et al., 2013	75%	Useful	US	Prospective study 2009-2011	25 NHs	NH residents with advanced dementia, 65 years and older, English-speaking proxy, GDS score of 7.	266 of who 72 experienced 131 episodes	BAMS-S scores: 21.8 (2.4)	Urinary tract infection	Clinical criteria	77.9% (102/131) episodes UTI's were treated with antibiotics	



20. Chen et al., 2006	50%	Useful	US	Retrospective cohort study 2001-2003	1 675 bed LTCF	Residents aged 65 and older who died with advanced dementia	Of 240 residents 154 patients developed pneumonia 229 suspected pneumonia episodes during the last 6 months of life	Advanced dementia (CPS ≥5)	Pneumonia	Clinical criteria	90.4% (207/229) of pneumonia episodes was treated with antibiotics of which IV 29%, IM 25%, PO 37%, in case of more than one type, the strongest is reported	AB ↑ Unstable vital signs (respiratory rate ≥ 30 breaths/min, temperature ≥ 101.1F, heart rate ≥ 125 beats/min, systolic blood pressure <90 mmHg.) AB ↑ Suspected aspiration AB ↑ Primary language not English
21. Mehr et al., 2003	100%	Useful	US and NL	2 Prospective cohort studies 1995-1998	36 NHs	Nursing home residents who were 60 and older, were in the nursing home at least 2 weeks before the illness and had a LRI	701	Severe dementia: USA – AB+: 37.6%, AB-: 53.4%	LRI	Clinical criteria diagnosed by trained project nurses	85.3% (598/701) received antibiotic treatment 27.8% (195/701) received parenteral antibiotic treatment	AB ↓ A do not hospitalize (DNI) order AB ↑ Illness severity (e.g. rapid pulse, respiratory distress, high temperature) AB ↓ Illness severity at time of the treatment decision and 2 weeks before the treatment decision AB ↓ ADL dependency
												AB ↓ More severe dementia (Increased scores at the Cognitive Performance Scale)

22. van der Steen et al., 2002	Useful	NL	Observational cohort study 1996-1998	61 NHs	Nursing home residents who (1) had a psychogeriatric disease (almost always dementia); (2) reside in the nursing home for at least 4 weeks; and (3) be diagnosed as having pneumonia by the physician.	706	BANS-S score 17.5 (4.8) - subgroup of 635 patients treated without antibiotics or treated with antibiotics for curative reasons	Pneumonia	Clinical criteria	77% (544/706) of episodes was treated with antibiotics	<p>AB ↑ No aspiration</p> <p>AB ↑ Number of psychogeriatric beds in the facility</p> <p>AB ↓ Illness severity at time of the treatment decision and 2 weeks before the treatment decision</p> <p>AB ↓ Previous pneumonia</p> <p>AB ↓ Dehydration</p> <p>AB ↓ Insufficient drinking (<1500 mL daily, previous 7 days)</p> <p>AB ↓ Eating dependence - pre-LRI and at the time of the treatment decision (requires assistance/fully dependent)</p> <p>AB ↓ More severe dementia (Increased scores at the Bedford Alzheimer Nursing Severity Scale)</p> <p>AB ↓ Advance care planning</p> <p>AB ↓ Treatment in the summer</p> <p>AB = Psychogeriatric disease: Alzheimer dementia, mixed dementia</p> <p>AB = Sex</p> <p>AB = General health condition: increased urine of fecal incontinence, increased mobility dependence, increased illness severity, increased discomfort</p> <p>AB = Vaccination for influenza in prior winter</p> <p>AB = Nursing home situated in one of the three biggest NL cities</p> <p>AB = Total number of beds or number of beds for somatic patients</p> <p>AB = Religious affiliation of facility</p> <p>AB = Level of policy making (availability of mission statement, quality policy, quality manual, and quality report on 4-point scale)</p> <p>AB = Protocol or policy on (non) treatment available</p>
--------------------------------	--------	----	---	--------	--	-----	---	-----------	-------------------	--	--



23. van der Steen et al., 2009b[40]	25%	Useful	NL	Prospective cohort study 2006-2007	54 NHs	Nursing home residents from psychogeriatric wards	72	BANS-S scores: 17.1 (4.7)	Pneumonia	Clinical criteria	79% (57/72) of episodes was treated with antibiotics	AB = Time – two time cohorts (1996-1998; 2006-2007)
24. Visapaa, 1998	50%	Somewhat useful	Finland	Chart review 1976 and 1985	3 Long Term Care institutions for permanent care	Patients > or ≥65 (dementia: 59.2%)	191 in 1985, 177 for analysis of the last week, 102 febrile patients in the last week of life	59.2% dementia, severity not specified	Feverish conditions	Not specified	43.1% (44/102) received antibiotics to treat feverish conditions in the last 7 days of life	

Table 3. Attitudes towards antibiotic use using a hypothetical scenario (data referring to the text in the Results, and Tables 1-3)

Family										
Study	MMAT score	Usefulness	Country	Design study	Setting	Population/enrollment criteria	Number of subjects	Severity of dementia	Hypothetical scenario	Factor associated with the use of antibiotics
25. Kwok et al., 2007	25%	Useful	China	Interview study using a hypothetical scenario	3 NH, 1 day care center, 1 psycho geriatric and 4 LTC wards	Family caregivers of older people with dementia	51 patients and family caregivers (response 57%)	Most patients had moderate to severe dementia and were residing in nursing homes	Dementia and critical illness or coma	In critical illness: 78% (40/51) and in coma: 61% (31/51) would agree to treatment with antibiotics
26. Potkins et al., 2000	25%	Useful	UK	Survey study	2 old age psychiatry assessment units and 1 LTCF	Relatives of people with dementia	50 patients and their relatives	Most had severe dementia – Clinical Dementia Rating Scale (CDR): 8 stage 1, 11 stage 2, 31 stage 3)	Life-threatening infection	52% (26/50) would agree to IV antibiotics 60% (30/50) would agree to oral antibiotics
27. Mezey et al., 1996	50%	Somewhat useful	US	Interview and survey study using hypothetical scenarios	1 Aging and Dementia Research Center	Spouse caregivers of Alzheimer's disease patients, evaluated at the Aging and Dementia Research Center (ADRC), who had a minimum Stage 4 on the GDS	50 spouses	Not specified	Critical illness – not further specified	Critical illness: 90% (45/50) would agree to receive antibiotic treatment AB ↑ Comfort of spouses with decision to forgo antibiotic was 40% and lowest of all treatment decisions
Patient										
Study	MMAT score	Usefulness	Country	Design study	Setting	Population/enrollment criteria	Number of subjects	Severity of dementia	Hypothetical scenario	Prefer antibiotic therapy
28. Reilly et al., 1994	75%	Useful	US	Survey study	Community	Community dwelling elderly people aged 60 and older	218 (response 69%)	Moderately advanced Alzheimer's disease	Moderately advanced Alzheimers disease, and no longer able to care for yourself independently, but still recognize and interact with your family or friends. You develop an acute medical illness, such as pneumonia, which maybe reversible with medical treatment.	73% (159/218) would accept antibiotic treatment



29. Gjerdingen et al., 1999	75%	Useful	US	Survey/interview study 1996-1997	3 NHs; 1 transitional care unit; 1 assisted living unit	Individuals 65 years and older who had normal cognitive function, received healthcare at home, or who resided at a nursing home, transitional care unit, or assisted-living unit.	84 – response 70%	n.a.	Different levels of dementia: Personality changes that make you unpleasant 1. Cannot remember how to do everyday things 2. Cannot recognize loved ones 3. Cannot care for yourself at all and cannot communicate	% of individuals that would prefer antibiotics with different levels of dementia 1. 74% (62/84) 2. 55% (46/84) 3. 37% (31/84) 4. 25% (21/84)	AB ↓ Increased level of hypothetical severity of the dementia (4 levels): -Personality changes that make you unpleasant -Cannot remember how to do everyday things -Cannot recognize loved ones -Cannot care for yourself at all and cannot communicate
30. Low et al., 2003	75%	Useful	Australia	Descriptive cross-sectional interview study 2000	6 NHs	Nursing home residents more than 65-years old, Short Portable Mental Status Questionnaire (SPMSQ) of 3 or less, Geriatric Depression Scale (GDS-15) score of less than 6	52 – response 88%	Severe dementia (hypothetical scenario)	Recurrent aspiration pneumonia and end-stage dementia (Imagine in a state having severe dementia, having problems with feeding and swallowing and, as a result, have had several episodes of pneumonia requiring admission to a hospital. Question: if faced with the above scenario would they agree to treatment with antibiotics?)	73.1% (38/52) would agree to treatment with antibiotics, 1.9% (1/52) was unsure	
31. Lo et al., 1986	100%	Somewhat useful	US	Survey study with a questionnaire and a hypothetical scenario	General Internal Medicine Group Practice	Three groups: (1) 28 patients younger than 65 years, with cancer, angina pectoris, congestive heart failure, COPD, stroke, cirrhosis, or chronic renal failure; (2) 69 patients, 65 years of age and older with these diagnoses; (3) 55 patients, 65 years or older, with none of these diagnoses	28 (group 1), 69 (group 2), 55 (group 4) 152 (total, response 76%)	Not specified	Severe dementia: patients were asked to suppose they had such severe memory loss that they could not identify people, were confused about where they were, and were unable to care for themselves with no chance of recovery.	47% (71/152) would accept antibiotics and hospitalization for pneumonia	AB ↑ Living alone

Table 4. Factors associated with use of antibiotics (only) (data referring to Tables 1-3)

Study and year	MIMAT score	Usefulness	Country	Design study	Setting	Population/enrollment criteria	Number of subjects	Limited to advanced dementia	Before death	Hypothetical	Factor associated with the use of antibiotics
32. Forbes et al., 2000	75%	useful	US	Descriptive and qualitative study	NHs	Family members of residents with moderately, severe or very severe dementia, as measured by the CPS, and having decision-making responsibility for the resident, spoke English, did not have lengthy travel.	28 family members	-	-	-	AB ↑ Antibiotics are viewed as a comfort measure, not as a technologic means of prolonging life for someone with severe dementia AB ↑ Many family members do not view pneumonia as part of a 'natural death' for someone with dementia and agreed to hospitalization or to use of aggressive treatment in the nursing home, such as the use of IV antibiotics
33. van der Steen et al., 2004	100%	useful	US and NL	Prospective cohort studies	NHs	Psychogeriatric disease, residence in the nursing homes for at least 4 weeks, and pneumonia as judged by the attending physician.	701 residents (US) and 551 residents (NL)	-	-	-	AB ↑ US residents vs NL residents
34. Szafara et al., 2012	50%	useful	US and NL	Observational, prospective cohort studies	NHs	Psychogeriatric disease, residence in the nursing homes for at least 4 weeks, and having symptoms compatible with an LRI (respiratory, systemic signs and symptoms as well as results of chest radiographs. Without morphine use.	1044 residents (US) and 513 residents (NL)	-	-	-	AB ↑ - High temperature >38.3_C AB ↓ Swallowing difficulty AB ↓ Eating dependence - pre-LRI and at the time of the treatment decision (requires assistance/fully dependent) AB ↓ More severe dementia (increased scores at the Bedford Alzheimer Nursing Severity Scale, or increased scores at the Cognitive Performance Scale) AB ↑ Gender (men) AB = LRI severity in severe dementia (a prognostic score for 14-day mortality risk)

35. Helton et al., 2006	50%	useful	US and NL	Qualitative semistructured interview study	NHs	Physicians who care for nursing home patients, who represented a wide range of clinical experience, worked in both rural and urban settings, and varied in their care approaches at the end of life.	12 physicians (US) and 12 physicians (NL)	-	-	-	AB ↓ Value of QoL in decision making AB ↓ Knowing nursing home patients (physician) AB ↓ Discussing treatment options with family timely AB ↓ Responsibility for treatment decision making NL vs US physicians AB ↓ Intention of hastening death
36. van der Steen et al., 2005	25%	useful	NL	Prospective cohort study	NHs	Psychogeriatric disease, residence in the nursing homes for at least 4 weeks, pneumonia as judged by the attending physician, and with a physician's decision not to treat with antibiotics.	165 patients	-	-	-	AB ↓ Poor prognosis (physician estimate at diagnosis) or ADEPT score AB ↓ Futility of treatment: physicians prefer not to treat when to do so seems futile AB = Physicians' experience, age, gender or training status
37. van der Steen et al., 2009a[45]	25%	useful	NL	Survey study	NHs	Physicians in nursing homes from all over the Netherlands, who diagnosed newly a pneumonia in their next patient with dementia	69 physicians	-	-	-	AB ↓ Poor prognosis (physician estimate at diagnosis) or ADEPT score AB ↓ Futility of treatment: physicians prefer not to treat when to do so seems futile AB = Physicians' experience, age, gender or training status

AB↑
 AB↓
 AB=
 BANS-S:
 ADEPT:
 ADL:
 Before death:
 FAST:
 Hypothetical:
 IV:
 LRI:
 LTC:
 LTCF:
 MMSE:
 NH:
 NL:
 QoL:
 US:

Positive association with antibiotic treatment
 Negative association with antibiotic treatment
 No association with antibiotic treatment
 Bedford Alzheimer Nursing Severity-Scale
 The Advanced Dementia Prognostic Tool
 Activities of daily living
 Factor from a study examining antibiotic use in the period before death
 Functional Assessment Staging Test
 Factor from a study using a hypothetical scenario
 Intravenous
 Lower respiratory infection
 long term care
 Long term care facility
 Mini-Mental State Examination
 Nursing home
 The Netherlands
 Quality of life
 United States of America





Summary

SUMMARY

Chapter 1

To improve their quality of life people with dementia need adequate palliative care, and there are still many questions to answer about providing adequate palliative care. One of these questions concerns the optimal starting point of palliative care across dementia stages. The identification of the palliative phase and palliative care needs in dementia is a point of discussion, and opinions vary among health care professionals.

Understanding the clinical course of dementia forms the foundation of physician prognostication and supports palliative care actions, decision-making, and advance care planning. Although the majority of people with dementia are eventually admitted to and die in long-term care facilities, we lack a thorough understanding of the clinical course of dementia, palliative care needs and decision-making in long-term care settings. Available knowledge is mostly based on retrospectively collected data, limited to the dying-phase, or limited to nursing home residents with advanced dementia.

Therefore, the overarching goal of this thesis is to achieve a better understanding of the clinical course of dementia in people in various stages of dementia in Dutch nursing homes, to help optimize palliative care for nursing home residents across the dementia stages. To address the objectives of this thesis, data from the Dutch End of Life in Dementia (DEOLD) study were used.

Chapter 2

In chapter 2, Mokken models were fitted to the Bedford Alzheimer Nursing-Severity Scale (BANS-S) to study its psychometric properties. Since Alzheimer is a progressive disease, studying the hierarchy of the items in the scale can be useful to evaluate the progression of the disease. We found that the BANS-S met the criteria for an ordinal scale. The probability of having problems with an item with a higher mean score (higher in the hierarchy) was higher for residents with more severe dementia than for residents with less severe dementia. This result is relevant because many scales do not discriminate between residents with more severe dementia. Furthermore, it should also be taken into account that the data were from baseline measurements and that the population at this point did not always have severe dementia. Further research should be done to determine whether the dementia patterns found for this population apply to the course of the dementia for individuals and to evaluate the responsiveness of the scale to individual changes.

Chapter 3

Chapter 3 describes the incidence of pneumonia and intake problems and how these health problems affect survival. Further, this chapter shows whether pneumonia and intake problems mediated the relationship between dementia severity and death. Using longitudinal data is important to characterize the disease dynamics. We found that pneumonia and intake problems were not limited to, or typical of, advanced dementia. Moreover, these health problems were important risk factors for mortality in nursing home residents in all stages of dementia. Developing pneumonia and intake problems are important signals to consider palliative care actions. The high risk of developing pneumonia and intake problems, and the poor survival of residents with dementia in a long-term care facility even shortly after admission, call for a palliative care approach and an active focus on advance care planning upon nursing home admission, or preferably earlier.

Chapter 4

Chapter 4 describes the longitudinal changes in symptoms and provided treatment during nursing home stay. There is a lack of knowledge about how specific symptoms are managed over time in a nursing home population with dementia in variable stages. We found that burdensome symptoms frequently developed during the disease trajectory. Agitation was persistent and the most common symptom, yet it decreased at the end of life. Pain was also common and persistent and increased in the last week of life. Shortness of breath was less common, but it often persisted and increased at the end of life. No significant longitudinal association was found between pain and agitation. A positive significant longitudinal association was found between advanced dementia and pain, but not at the end of life and there was no association with other symptoms. Parenteral opioids, morphine, and anxiolytics were prescribed substantially more frequently at the end of life. Symptom control may be suboptimal from admission, and a stronger focus on symptom control is needed at an earlier stage than the end of life.

Chapter 5

Chapter 5 describes the last week of life of nursing home residents, focusing in detail on treatment provided for the most important burdensome symptoms. Pain was the most common symptom (52%), followed by agitation (35%), and shortness of breath (35%). Opioids were the most commonly provided treatment for residents in pain and residents with shortness of breath. Agitation was mainly treated with anxiolytics. Death from respiratory infections was associated with the largest symptom burden, in comparison with death from cardiovascular disorders or dehydration/cachexia. Furthermore, quality of life in the last week was worse in residents with pain or agitation. The large majority of all residents (77%) received opioids and one-fifth (21%) received palliative sedation until death. Symptom management at the end of life may be improved, with regard to weighing of effects and side effects.

Chapter 6

Chapter 6 describes the changes in care goals and treatment orders around the occurrence of pneumonia and intake problems, and whether hospitalization was in line with earlier agreed upon do-not-hospitalize orders. Overarching care goals were drawn up soon after admission and were reassessed and discussed in more detail when the condition of the resident worsens. The proportion of residents with palliative care goals and do-not-treat orders rose during follow-up, especially before death. The proportion of people with palliative care goals was similar after pneumonia, and increased after intake problems and in the period shortly before death (last six months of life). The most frequently reported reason for hospitalization was a fracture, especially in the group of residents with a do-not-hospitalize order. Overarching care goals that anticipate expected health problems in the trajectory of dementia and that anticipate the most acute decisions may help prevent burdensome, unnecessary treatment and avoidable transfers to the hospital.

Chapter 7

Chapter 7 describes end-of-life treatment decisions for residents in the last phase of life. We found that only a minority of the residents had a written advance directive upon admission. Potentially burdensome life-prolonging treatments were rare in residents with advanced dementia and less advanced dementia. Decisions not to start or to withdraw treatment shortly before death mainly related to artificial nutrition and hydration, and medication. Physicians and families often establish a palliative care goal, because they may feel that a palliative care approach is more appropriate at the end of life in nursing home residents with dementia.

Chapter 8

The general discussion in this chapter provides a summary of the study's most important results, and it addresses a number of methodological considerations about the design of the study and issues related to measurements. Reflections on the study's findings highlight that 1) Although dementia stages were heterogeneous in long-term care, people with dementia who were admitted to a nursing home have in common that they are vulnerable with a short survival time after admission. Especially incident pneumonia and intake problems are prognostically unfavorable. 2) Residents frequently have burdensome symptoms that persist over the disease trajectory. Because treatments are frequently continued and changed only at the end of life, the question is raised whether symptom management is adequately evaluated during nursing home stay. 3) Establishing overarching care goals is well embedded in long-term care in the Netherlands, and this way of advance care planning seems to suit actual practice and fits with the clinical course of the disease. Further, residents with dementia rarely undergo potentially burdensome life-prolonging treatment in the last phase of life, but decisions to withdraw oral (preventive) drugs are made shortly before death.

Implications of the study's results for care practice include: 1) More rigorous and timely evaluation is needed to provide comfort and adequate symptom management. 2) The usefulness and benefits of (preventive) medication should be reviewed regularly and discussed with residents and their families. 3) Awareness should be created among people with dementia and their families, as well as among health care professionals and policy makers that admission to a nursing home is a sufficiently important signal to start a palliative care approach. Informing residents and families about the course of dementia may help formulate realistic overarching care goals. 4) Explicit discussions about the desirability of prolongation of life and the life-extending side-effect of medical treatment may also be helpful to formulate care goals.

Suggestions for further research focus on the evaluation of symptom management, and on uniform use of the terminology for care goals. Further, future research should focus on the clinical course of the disease and the palliative care needs of people with dementia in primary care.

Establishing overarching care goals, timely evaluations of symptom management, and conversations about the (un)desirability of life prolongation and the usefulness of (preventive) medication will hopefully become routine practice, in order to optimize palliative care in nursing home residents with dementia.



Nederlandse samenvatting

NEDERLANDSE SAMENVATTING

Hoofdstuk 1

Dementie is een van de grootste uitdagingen voor de gezondheid wereldwijd en een aanzienlijk aantal mensen en hun families zullen het lot van dementie treffen. Dementie is een progressieve en levensbekortende ziekte en belastend voor zowel de mensen met dementie als hun naasten. Daarom is er behoefte aan adequate palliatieve zorg om de kwaliteit van leven te kunnen verbeteren. Palliatieve zorg is een benadering die de kwaliteit van het leven van mensen en hun naasten behoud of verbetert door het voorkomen en verlichten van lijden. Dit wordt onder andere gedaan door middel van vroegtijdige signalering en zorgvuldige beoordeling en behandeling van pijn en andere problemen van lichamelijke, psychosociale en spirituele aard. Tot nu toe zijn er nog veel vragen onbeantwoord gebleven over het inzetten van optimale palliatieve zorg voor mensen met dementie. Eén van deze vragen gaat erover in welke fase in het ziekteverloop gestart zou moeten worden met palliatieve zorg. Het startpunt van het inzetten van palliatieve zorg is vooralsnog namelijk een punt van discussie, omdat de meningen tussen beroepsbeoefenaren in de gezondheidszorg verdeeld zijn. Dit heeft onder andere te maken met het feit dat men verschillende concepten van palliatieve zorg hanteert en dat velen dit begrip nog steeds als palliatief-terminale zorg opvatten.

Inzicht in het klinisch beloop van dementie vormt de basis voor een arts om prognoses te kunnen geven en is ondersteunend bij het inzetten van palliatieve zorgacties, besluitvorming en vroegtijdige zorgplanning. Hoewel de meerderheid van de mensen met dementie uiteindelijk wordt opgenomen en overlijdt in een verpleeghuis, is er maar beperkte kennis beschikbaar over het klinisch beloop van dementie, de palliatieve zorgbehoeften en de besluitvorming bij verpleeghuisbewoners. De huidige kennis is vooral gebaseerd op retrospectief verzamelde gegevens, dan wel gegevens die beperkt zijn tot de stervende-fase, dan wel beperkt zijn tot verpleeghuisbewoners met zeer gevorderde dementie. Vooralsnog zijn er geen representatieve nationale gegevens beschikbaar over intercurrente aandoeningen en de kans op overlijden in relatie tot de ernst van de dementie, over symptoombestrijding, en over besluitvorming rondom behandelingen gedurende de verpleeghuis opname. Daarom is het hoofddoel van dit proefschrift om beter inzicht te krijgen in het klinisch beloop van dementie in Nederlandse verpleeghuizen, om bij te kunnen dragen aan het optimaliseren van de palliatieve zorg. Om de vraagstellingen in dit proefschrift te kunnen beantwoorden zijn gegevens van de Dutch End of Life in Dementia (DEOLD) studie gebruikt.

Hoofdstuk 2

In hoofdstuk 2 wordt beschreven hoe “Mokken modellen” gerealiseerd zijn om de psychometrische eigenschappen van de Bedford Alzheimer Nursing-Severity Scale (BANS-S) te bestuderen. De BANS-S beoordeelt de ernst van de dementie en aangezien dementie een progressieve ziekte is, is het waardevol om de hiërarchie van de items van de schaal (“in hoeverre is iemand in staat om zich zelfstandig aan te kunnen kleden”, “om zelfstandig te kunnen eten”, “spraakvermogen”, “vermogen om oog contact te hebben”, “slaap-waak ritme”, “staat van de spieren”) te bestuderen om uiteindelijk de progressie van de ziekte te kunnen evalueren. We hebben vastgesteld dat de BANS-S aan de criteria voor een ordinale schaal voldoet. Dit bleek uit het feit dat de kans op het hebben van problemen bij een item met een hogere moeilijkheidsgraad groter was voor bewoners met een vergevorderd stadium van dementie dan voor mensen met een minder vergevorderd stadium van dementie. Deze bevindingen zijn belangrijk omdat veel schalen geen onderscheid kunnen maken tussen mensen met een vergevorderd stadium van dementie. Daarnaast moet er wel rekening mee worden gehouden dat deze studie gebaseerd is op de gegevens van de baselinemeting en slechts een heel klein deel van de onderzoekspopulatie een vergevorderd stadium van dementie had vlak na opname in het verpleeghuis. Verder zal er nog longitudinaal onderzoek gedaan moeten worden om te onderzoeken of het gevonden beloop in deze studiepopulatie ook van toepassing is op het beloop van een individu.

Hoofdstuk 3

Hoofdstuk 3 beschrijft de incidentie van pneumonieën en intake problemen en hoe deze gezondheidsproblemen van invloed zijn op de overleving. Verder wordt er gekeken naar de relatie tussen deze gezondheidsproblemen, het stadium van de dementie en de kans op overlijden. Voor het beantwoorden van de onderzoeksvragen werd er gebruik gemaakt van longitudinaal onderzoek. We hebben vastgesteld dat pneumonieën en intake problemen niet met name voorkomen bij mensen in een vergevorderd stadium van dementie, maar ook regelmatig voorkomen bij mensen met een minder vergevorderd stadium van dementie. Bovendien blijken zowel het krijgen van een pneumonie als een intake probleem belangrijke risicofactoren te zijn voor sterfte bij verpleeghuisbewoners. Dit geldt voor alle verpleeghuisbewoners met dementie, dus ongeacht in welk stadium van dementie zij verkeren. Het ontwikkelen van pneumonieën en intake problemen zijn daarom belangrijke signalen om een palliatieve zorgbenadering te overwegen. Het hoge risico op het ontwikkelen van zowel een pneumonie als een intake probleem, als ook de beperkte overlevingsduur, zelfs kort na opname, pleiten voor een palliatieve zorgbenadering en aandacht voor vroegtijdige zorgplanning bij opname in het verpleeghuis, of bij voorkeur al in de thuissituatie.

Hoofdstuk 4

Hoofdstuk 4 beschrijft de longitudinale veranderingen in belastende symptomen en de ingezette symptoombestrijding gedurende de opname in het verpleeghuis. Pijn was veelvoorkomend (variërend tussen 47%-68% bij de halfjaarlijkse metingen) met een toename tot 78% in de laatste week van het leven. Pijn was vaak persistent aanwezig (in 36%-41% van alle bewoners). Agitatie was het meest voorkomend (57%-71%), en ook vaak persistent (39%-53%), maar met een afname van de prevalentie tot 35% in de laatste week van het leven. Kortademigheid kwam minder frequent voor (16%-26%), met een toename tot 52% in de laatste week van het leven. Pijn was niet significant geassocieerd met agitatie. De symptoombestrijding die werd ingezet gedurende de verpleeghuisopname bleef over het algemeen onveranderd, veelal aan het einde van het leven werd de symptoombestrijding aangepast. Pijn werd veelal behandeld met paracetamol (34%-52%), en aan het einde van het leven met parenterale opioïden (44%). Agitatie werd over het algemeen niet-farmacologisch behandeld (78%-92%) en aan het einde van het leven werden anxiolytica het meest voorgeschreven (62%). In het algemeen werden bronchodilatoren het meest voorgeschreven voor kortademigheid (29%-67%), maar aan het einde van het leven was dit morfine (69%).

Pijn en agitatie komen dus reeds vanaf opname frequent voor en kunnen persistent zijn bij verpleeghuisbewoners met dementie. Onze bevindingen suggereren dat symptoombestrijding pas aangepast wordt aan het einde van het leven. Dit roept de vraag op of symptoombestrijding suboptimaal is, en of er ruimte voor verbetering mogelijk is in het evalueren van de symptoombestrijding gedurende de opname in het verpleeghuis.

Hoofdstuk 5

Hoofdstuk 5 beschrijft de laatste week van het leven van verpleeghuisbewoners met dementie, waarbij de focus ligt op belastende symptomen en de behandeling daarvan. Pijn was het meest voorkomende symptoom (52%), gevolgd door agitatie (35%) en kortademigheid (35%). Pijn werd over het algemeen behandeld met tenminste één type opioïd (73%), evenals kortademigheid over het algemeen werd behandeld met een opioïd (71%). Voor agitatie werden voornamelijk anxiolytica voorgeschreven (57%). Op de dag van overlijden, kreeg 77% van de verpleeghuisbewoners opioïden met een mediaan van 90 mg/24h (orale equivalenten) en bij 21% werd palliatieve sedatie toegepast. Pijn en agitatie waren geassocieerd met een lagere kwaliteit van leven. Overlijden aan een respiratoire infectie was geassocieerd met de grootste symptomen last.

Onze bevindingen laten dus zien dat symptomen vaak aan het einde van het leven voor komen bij verpleeghuisbewoners met dementie, ondanks het voorschrijven van opioïden aan de meerderheid van de bewoners. Wat betreft de balans tussen het effect en de bijwerkingen

van de symptoombestrijding, zijn mogelijk de doseringen suboptimaal. Toekomstig onderzoek zou kunnen bestaan uit een observationeel van dag-tot-dag onderzoek om de effectiviteit van symptoombestrijding en de mogelijke bijwerkingen beter te kunnen beoordelen.

Hoofdstuk 6

In hoofdstuk 6 worden de veranderingen in de behandeldoelen en het anticiperend beleid rondom het optreden van pneumonieën en intake problemen beschreven en wordt in kaart gebracht of ziekenhuisopname in lijn is met eerder overeengekomen anticiperend beleid. Behandeldoelen en anticiperend beleid wordt gemaakt in het kader van advance care planning binnen het verpleeghuis. Advance care planning is anticiperende besluitvorming over de toekomstige zorg met alle belanghebbenden, waarin doelen en grenzen voor toekomstige behandelingen worden vastgesteld. Hierbij wordt rekening gehouden met de voorkeuren van de patiënt, en de levensverwachting van de patiënt. We hebben vastgesteld dat overkoepelende behandeldoelen al snel na opname afgestemd en geëvalueerd werden en in meer detail besproken werden als de toestand van de bewoner verslechterde. Het aantal mensen met een palliatief beleid en een beleid om af te zien van een behandeling ("niet-reanimeren", "geen ziekenhuisopname", "geen antibiotica") nam toe gedurende de follow-up periode, met name vlak voor overlijden. Het aantal mensen met een palliatieve beleid was vergelijkbaar na een longontsteking, maar steeg na intake problemen en in de periode kort voor overlijden (laatste zes maanden van het leven). De meest voorkomende oorzaak van een ziekenhuisopname was een botbreuk, met name in de groep bewoners waarbij was afgesproken om niet in te sturen naar het ziekenhuis. Uit onze bevindingen blijkt dat een overkoepelend behandelbeleid dat anticipeert op te verwachten gezondheidsproblemen in het traject van dementie, kan helpen bij het nemen van beslissingen tijdens acute situaties en om belastende en onnodige behandeling te helpen voorkomen, zoals opname in het ziekenhuis.

Hoofdstuk 7

Hoofdstuk 7 beschrijft beslissingen ten aanzien van behandelingen die al dan niet worden ingezet bij het naderende levenseinde. We hebben vastgesteld dat slechts een minderheid van de bewoners een schriftelijke wilsverklaring bleek te hebben bij opname. Potentieel belastende levensverlengende behandelingen werden slechts zelden ingezet noch bij bewoners met vergevorderde dementie, noch bij bewoners met minder gevorderde dementie. Beslissingen ten aanzien van het niet starten of stoppen van een behandeling werden voornamelijk vlak voor het overlijden gemaakt en hadden voornamelijk betrekking op kunstmatige voeding, hydratatie en medicatie. Dat artsen en familieleden vaak kozen voor een palliatief beleid, heeft mogelijk te maken met hun gevoel dat een palliatieve zorgbenadering het meest passend is bij verpleeghuis bewoners met dementie aan het einde van hun leven.

Hoofdstuk 8

In de algemene discussie wordt een overzicht gegeven van de belangrijkste resultaten van de studie. Daarnaast worden een aantal methodologische overwegingen met betrekking tot de opzet van de studie besproken en kwesties ten aanzien van de metingen die zijn verricht. De reflecties op de bevindingen van de studie zijn in het kort: 1) Het stadium van dementie waarin verpleeghuisbewoners verkeren is verschillend, maar de verpleeghuisbewoners met dementie hebben gemeen dat ze kwetsbaar zijn en dat de tijd totdat ze overlijden over het algemeen kort is. 2) Bewoners hebben vaak belastende symptomen die langdurend kunnen aanhouden, opmerkelijk is dat onze bevindingen suggereren dat de symptoombestrijding die wordt ingezet vaak pas aan het einde van het leven wordt aangepast. Dit roept de vraag op of er ruimte is voor verbetering van het evalueren van de symptoombestrijding. 3) Het overkoepelend behandelbeleid wordt over het algemeen kort na opname besproken en vastgelegd en deze manier van vroegtijdige zorgplanning lijkt goed te passen bij de praktijk en het klinisch beloop van de ziekte. Verder ondergaan bewoners met dementie zelden potentieel belastende en levensverlengende behandelingen in de laatste fase van het leven, maar daarentegen wordt (preventieve) medicatie veelal doorgegeven tot kort vóór overlijden.

Aanbevelingen voor de praktijk zijn onder meer: 1) Zorgvuldige en tijdige evaluaties van symptoombestrijding zijn nodig om adequate symptoombestrijding te geven en daarmee het comfort te verhogen. 2) Het nut en de voordelen van (preventieve) medicatie moet regelmatig met de bewoners en hun familie besproken en geëvalueerd worden. 3) De bewustwording dat opname in een verpleeghuis een belangrijk signaal is om een palliatieve zorgbenadering te starten moet worden vergroot bij mensen met dementie en hun familie, alsook bij zorgverleners en beleidsmakers. Het informeren van bewoners en families over het beloop van dementie kan helpen bij het formuleren van realistische overkoepelende behandeldoelen. 4) Het expliciet bespreken van de wenselijkheid van levensverlenging en levensverlengende bijwerkingen van medische behandelingen kan zinvol zijn om behandeldoelen te formuleren.

Verder onderzoek zou zich moeten richten op de evaluatie van symptoombestrijding en op de communicatie in het kader van advance care planning. Verder verdient het de aanbeveling dat toekomstig onderzoek zich richt op het klinisch beloop en palliatieve zorg behoeften van mensen met dementie die thuis wonen.

Het afstemmen van overkoepelende behandeldoelen, regelmatige evaluaties van symptoombestrijding en gesprekken over de (on) wenselijkheid van levensverlengende behandelingen worden hopelijk onderdeel van de dagelijkse praktijk, om de palliatieve zorg voor verpleeghuisbewoners met dementie te optimaliseren.





Dankwoord

DANKWOORD

De afgelopen jaren hebben in het teken gestaan van onderzoek doen en opleiding volgen. Daarbij waren de laatste loodjes toch ècht het zwaarst, maar nu is het dan eindelijk zover: mijn boekje is af! Dit proefschrift was uiteraard niet tot stand gekomen zonder de medewerking, hulp en steun van velen. Daarom wil ik er een aantal graag in het bijzonder noemen.

Allereerst gaat mijn dank uit naar alle mensen en zorginstellingen die hebben meegewerkt aan het verzamelen van de data. Dit project was niet mogelijk geweest zonder jullie bijdrage hierin.

De leden van de beoordelingscommissie: prof. dr. B.D. Unwuteaka-Philipsen, prof. dr. R.C.T.M. Koopmans, prof. dr. C. Leget, prof. dr. F.R.J. Verhey en dr. S.J. Swart, ben ik zeer erkentelijk voor het lezen en beoordelen van mijn manuscript.

Graag wil ik mijn promotor Cees Hertogh en mijn copromotoren Jenny van der Steen en Martin Smalbrugge bedanken voor al hun inbreng, begeleiding en vertrouwen in mij. Jullie hebben er alle drie op jullie eigen wijze voor gezorgd dat ik door dit traject ben heen gerold.

Cees, ik heb enorm veel respect voor jouw kennis, kunde en passie voor je vak. Bedankt dat je mij vaak hebt uitgedaagd om het één en ander toch nog eens vanuit een andere invalshoek te belichten. Mijn proefschrift heeft hierdoor veel meer diepgang gekregen.

Jenny, jij stond aan de basis van dit project en jouw deskundigheid en ervaring heeft de inhoud van dit proefschrift naar een hoger niveau gebracht. Ik heb veel respect voor jouw consciëntieusheid, drive en tomeloze inzet. Ik heb veel van jou geleerd op onderzoeksgebied en vond het erg prettig met je samenwerken door je laagdrempeligheid en bereikbaarheid.

Martin, jij weet met je scherpe blik de essentie naar boven te halen en houdt altijd het doel voor ogen: een wetenschappelijke bijdrage aan verbetering van de praktijk. Deze kwaliteiten zijn van grote meerwaarde geweest voor dit proefschrift. Ik heb veel respect voor jouw veelzijdigheid en onuitputbare energie. Dankjewel voor je pragmatische insteek als het nodig was en voor het feit dat je altijd bereid bent om met me mee te denken.

Naast de projectgroep leden zijn er nog een aantal co-auteurs die ik graag wil bedanken voor hun inhoudelijke en waardevolle input van mijn artikelen: Francisca Galindo-Garre, Ladislav Volicer, Rianne van Gageldonk, Maarten Schipper, Raymond Koopmans, Bregje Unwuteaka-Philipsen en Luc Deliens. Rianne van Gageldonk wil ik daarnaast nog bedanken voor de begeleiding en gastvrijheid bij het RIVM. In het bijzonder noem ik nog Francisca Galindo-Garre, omdat ik je wil bedanken voor je onmisbare bijdrage aan de statistische analyses en je begeleiding bij mijn opleiding epidemiologie.

Mijn promotietraject is verweven geweest met mijn opleiding tot specialist ouderengeneeskunde. De SBOH wil ik bedanken voor het creëren van de mogelijkheden om een gecombineerd promotie- en opleidingstraject te volgen.

Verder wil ik ook Jos van Berkel hier bedanken. Jos, je bent 5 jaar lang mijn mentor geweest en een betere kon ik mij niet wensen. Ik kon altijd bij je binnen lopen en sparren over van alles en nog wat, waardoor ik weer vol goede moed je kamer uit kon lopen.

Floor en Kyra, jullie zijn vanaf de eerste dag van de opleiding betrokken geweest bij het wel en wee tijdens mijn traject en wat ontzettend leuk dat we nu ook (regio)collega's zijn! Maar bovenal, wat fijn dat we nog steeds zo'n goede band hebben.

Mijn (oud) kamer- en afdelingsgenootjes Sandra, Janine, Kirstin, Nienke, Mirjam, Laura, Tessa en Marijke bedankt voor alle gezelligheid, goede gesprekken, adviezen, congresreisjes samen, en het kunnen meeleven met elkaars hoogte- en dieptepunten. En ik wil ook zeker Salomé en Bernadette bedanken voor hun inzet en hulp en de vele gesprekjes tussendoor. Daarnaast waren en zijn er natuurlijk vele andere collega's uit zowel het onderzoek als het werkveld die ik hierbij wil bedanken voor hun belangstelling en fijne samenwerking.

Sandra en Janine, dank jullie wel voor alle inhoudelijke input, steun en waardevolle gesprekken. Wat ontzettend leuk en mooi om na al dat sparren, meedenken, kletsen en nog eens kletsen over de meest uit een lopende dingen, met jullie als paranimfen dit promotietraject te mogen volbrengen.

Mijn (schoon)familie en vrienden wil ik bedanken voor alle belangstelling, interesse en gezelligheid buiten het werk om. Dit boekje maakt nu wellicht duidelijk waar ik me de afgelopen jaren mee bezig heb gehouden.

Zonder de steun van mijn ouders had ik hier uiteraard niet gestaan. Jullie hebben er altijd alles voor over gehad om het mij en Matthijs goed te laten hebben en dat is meer dan gelukt! Lieve pap, als ik van iemand heb geleerd om hard te werken en niet op te geven dan bij jij dat wel. Lieve mam, een zorgzamere moeder dan jij is er niet.

Lieve, lieve Bernard. Je bent mijn grote steun en toeverlaat geweest. Dankjewel voor ... alles. Wat ben ik dankbaar om samen met jou door het leven te mogen gaan!





Curriculum Vitae

CURRICULUM VITAE

Curriculum Vitae (Nederlands)

Simone Hendriks werd op 26 juni 1985 in Haarlem geboren. Na het behalen van haar gymnasium diploma aan het Mendelcollege in Haarlem, begon zij in 2003 met de studie geneeskunde aan de Vrije Universiteit in Amsterdam. Ze studeerde af in december 2009, waarna ze als basisarts in het verpleeghuis is gaan werken. In september 2010 startte zij met de opleiding tot specialist ouderengeneeskunde bij Gerion in Amsterdam. Vanaf maart 2012 combineerde zij haar opleiding met promotieonderzoek, waarvan de resultaten in dit proefschrift beschreven zijn. Daarnaast studeerde zij in april 2014 af als epidemioloog en in september 2016 heeft zij haar opleiding tot specialist ouderengeneeskunde afgerond. Sinds september 2016 is zij voor vier dagen in de week als specialist ouderengeneeskunde werkzaam, in voornamelijk de ambulante setting, bij Geriant in Noord-Holland. Daarnaast werkt zij voor één dag in de week als docent wetenschappelijke vorming bij Gerion en is zij betrokken bij de onderzoeksafdeling Huisartsgeneeskunde & Ouderengeneeskunde van het VUmc.



Curriculum Vitae (English)

Simone Hendriks was born on 26th of June 1985 in Haarlem, the Netherlands. After completing her secondary education at the Mendelcollege in Haarlem, she studied Medicine at VU University Amsterdam. She received her degree in December 2009. Hereafter, she started as physician in a nursing home, and in September 2010 she started with a traineeship Elderly Care Medicine at Gerion Amsterdam. In 2012 she started the PhD-project described in this thesis, at the Department of General Practice & Elderly Care Medicine, at the EMGO Intitute for Health and Care Research / VU University Medical Center in Amsterdam. She was registered as an epidemiologist in 2014, and she was registered as a physician elderly care in September 2016. Since September 2016 she works four days a week as an elderly care physician at Geriant, a care organization providing medical care for people with dementia and providing consultations for people with complex care who live at home. Additionally, she works as a teacher for scientific education at Gerion and works at the Department of General Practice & Elderly Care Medicine at the VU University Medical Center in Amsterdam.

Publications

Hendriks SA, Smalbrugge M, Deliëns L, Koopmans RTCM, Onwuteaka-Philipsen BD, Hertogh CM, Van der Steen JT. End-of-life treatment decisions in nursing home residents dying with dementia in the Netherlands. *Int J Geriatr Psychiatry* 2016; Dec 29 [Epub ahead of print].

Hendriks SA, Smalbrugge M, Hertogh CM, Van der Steen JT. Changes in care goals and treatment orders around the occurrence of health problems and hospital transfers in dementia: A prospective study. *J Am Geriatr Soc* 2016; Nov 21 [Epub ahead of print].

Hendriks SA, Smalbrugge M, van Gageldonk-Lafeber AB, Galindo-Garre F, Schipper M, Hertogh CM, van der Steen JT. Pneumonia, intake problems, and survival among nursing home residents with variable stages of dementia in the Netherlands: Results from a prospective observational study. *Alzheimer Dis Assoc Disord* 2016; Nov 15 [Epub ahead of print].

Hendriks SA, Smalbrugge M, Galindo-Garre F, Hertogh CM, van der Steen JT. From admission to death: Prevalence and course of pain, agitation, and shortness of breath, and treatment of these symptoms in nursing home residents with dementia. *J Am Med Dir Assoc* 2015 Jun 1;16(6):475-81.

Awarded the "Jaarprijs palliatieve zorg 2015".

van der Maaden T, Hendriks SA, de Vet HC, Zomerhuis MT, Smalbrugge M, Jansma EP, Koopmans RT, Hertogh CM, van der Steen JT. Antibiotic use and associated factors in patients with dementia: a systematic review. *Drugs Aging* 2015 Jan;32(1):43-56.

Hendriks SA, Smalbrugge M, Hertogh CM, van der Steen JT. Dying with dementia: symptoms, treatment, and quality of life in the last week of life. *J Pain Symptom Management* 2014 Apr;47(4):710-20.

Awarded the "Jan Stooprij" for the best article 2013 young talented researchers. Nominated for the "Jaarprijs palliatieve zorg 2014."

Galindo-Garre F, Hendriks SA, Volicer L, Smalbrugge M, Hertogh CM, van der Steen JT. The Bedford Alzheimer nursing-severity scale to assess dementia severity in advanced dementia: a nonparametric item response analysis and a study of its psychometric characteristics. *Am J Alzheimers Dis Other Demen* 2014 Feb;29(1):84-9

International Presentations

The 9th World Research Congress of the EAPC, in Ireland, Dublin, 2016

Poster presentation: "End-of-life treatment decisions in patients dying with dementia in the Netherlands"

2nd Nursing Home Research International Working Group (NHRIWG), in France, Toulouse, 2015

Oral presentation: "Pneumonia and intake problems: inherent to advanced dementia?"

Poster presentation: "Discussions about care goals and treatment orders anticipating future scenarios in dementia in long-term care: a prospective study"

68th Annual Scientific Meeting of The GSA, in the USA, Orlando, 2015

Oral presentation: "Advance care planning in dementia in long-term care. Are hospitalizations in accordance with ACP?"

Poster presentation: "Care goals and end-of-life treatment decisions in dying with dementia in the Netherlands"

11th Congress of the EUGMS, in the Netherlands, Oslo 2015

Poster presentation: "Pneumonia and intake problems not only inherent to advanced dementia"

10th Congress of the EUGMS, in the Netherlands, Rotterdam 2014

Oral presentation: "From admission to death: prevalence and course of pain, agitation, and shortness of breath, and treatment of these symptoms in nursing home residents with dementia"

13th World congress of the EAPC, Czech Republic, Prague, 2013

Oral presentation: "Dying with dementia: symptoms, treatment and quality of life in the last week of life"

