UNDERSTANDING THE CLINICAL COURSE OF DEMENTIA

A search to optimize palliative care for nursing home residents

SIMONE A. HENDRIKS

Uitnodiging
voor het bijwonen van de openbare verdediging van mijn proefschrift

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Simone A. Hendriks
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Understanding the clinical course of dementia

A search to optimize palliative care for nursing home residents

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geboren te Haarlem
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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
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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. Dementia is one of the main causes of dependency and disability in older age, and it is associated with a reduced life expectancy. Eventually, the majority of people with dementia in western countries will be admitted to, and die in, a nursing home. 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.

In the last two decades, awareness that people with dementia need palliative care in the last phase of life has increased. 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.” 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. 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, 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. 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.
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. 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. 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.

A variety of instruments and scales are used in research to define the stages of dementia. 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. Another scale that differentiates more severe stages, is the continuous Bedford Alzheimer Nursing-Severity Scale (BANS-S). 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. 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, 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. 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. 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. In addition, nursing home residents with advanced dementia develop burdensome symptoms such as pain, agitation, and shortness of breath shortly before death. 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.\textsuperscript{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.\textsuperscript{10,31,32} Informing residents and families can help initiate a discussion about care goals,\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.6

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 study 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.
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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

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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 ≤ 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 al.\(^1\) 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 research\(^3\) 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, Ligtvoet 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 Ligtvoet 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.\textsuperscript{23} The diagnoses of dementias were based on international guidelines.\textsuperscript{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 administrated 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 \textit{Mokken}\textsuperscript{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,\textsuperscript{29} and the sum score can be used to order patients stochastically on the trait in most practical situations.\textsuperscript{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 $H^p$ (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 procedure\textsuperscript{31} and the item rest score regression. The scalability coefficient $H^p$ 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) \(0.3 \leq H < 0.4\): weak scale, (2) \(0.4 \leq H < 0.5\): medium scale, and (3) \(H \geq 0.5\): 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 \(\alpha\) 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.\(^\text{32}\)

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).\(^\text{15}\) Items involved in violations of the IIO assumption are removed from the questionnaire by the backward method.\(^\text{32}\) After IIO was established, the \(H^T\) coefficient was calculated to assess the precision of the item ordering.\(^\text{15}\) 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 (\(H = 0.47\)) and had a high reliability according to both reliability coefficients used (MS = 0.82 and Cronbach’s \(\alpha = 0.81\)). 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

<table>
<thead>
<tr>
<th>Item label</th>
<th>Alzheimer dementia (N = 164)</th>
<th>Other dementias (N = 186)</th>
<th>Complete group (N = 350)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean scores</td>
<td>H (SE)</td>
<td>Mean scores</td>
</tr>
<tr>
<td>1. Dressing</td>
<td>2.76</td>
<td>.58 (.04)</td>
<td>2.96</td>
</tr>
<tr>
<td>2. Sleeping</td>
<td>1.64</td>
<td>.31 (.06)</td>
<td>1.48</td>
</tr>
<tr>
<td>3. Speech</td>
<td>1.83</td>
<td>.37 (.06)</td>
<td>1.77</td>
</tr>
<tr>
<td>4. Eating</td>
<td>1.76</td>
<td>.49 (.05)</td>
<td>1.87</td>
</tr>
<tr>
<td>5. Mobility</td>
<td>1.76</td>
<td>.55 (.04)</td>
<td>2.11</td>
</tr>
<tr>
<td>6. Muscles</td>
<td>1.82</td>
<td>.50 (.05)</td>
<td>1.93</td>
</tr>
<tr>
<td>7. Eye contact</td>
<td>1.43</td>
<td>.47 (.05)</td>
<td>1.48</td>
</tr>
</tbody>
</table>

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

* 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

<table>
<thead>
<tr>
<th>Item label</th>
<th>Alzheimer dementia (N = 164)</th>
<th>Other dementias (N = 186)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean scores (Ordering)</td>
<td>H (SE)</td>
</tr>
<tr>
<td>1. Dressing</td>
<td>2.76 (1)</td>
<td>.58 (.04)</td>
</tr>
<tr>
<td>2. Sleeping</td>
<td>1.64 (5)</td>
<td>.29 (.06)</td>
</tr>
<tr>
<td>3. Speech</td>
<td>1.83 (2)</td>
<td>.37 (.06)</td>
</tr>
<tr>
<td>4. Eating</td>
<td>1.76 (4)</td>
<td>.45 (.05)</td>
</tr>
<tr>
<td>5. Muscles</td>
<td>1.82 (3)</td>
<td>.44 (.05)</td>
</tr>
<tr>
<td>6. Eye contact</td>
<td>1.43 (6)</td>
<td>.46 (.05)</td>
</tr>
</tbody>
</table>

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’ coefficient of .57 that suggests strong support for IIO (H’ > .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’ 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 ($H' = .59$). 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 al.\textsuperscript{11}) using classical test theory. They found that a Cronbach’s $\alpha$ 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 $\alpha$ 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.\textsuperscript{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\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{34} For example, speech is often affected early in frontotemporal dementia\textsuperscript{35,36} while it may be a later symptom in Alzheimer’s disease.\textsuperscript{37-39} However, whether this symptom is affected in vascular dementia or not depends on the location of the lesion.\textsuperscript{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.
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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

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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

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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 behavior6,7 More severe dementia may be associated with more pain8,9 and with more agitation10,11 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).
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

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

*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

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Assessment</th>
<th>Prevalence</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n; m)*</td>
<td>n</td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A1</td>
<td>(327; 7)</td>
<td>52</td>
<td>171</td>
</tr>
<tr>
<td>A2</td>
<td>(221; 30)</td>
<td>61</td>
<td>134</td>
</tr>
<tr>
<td>A3</td>
<td>(170; 36)</td>
<td>68</td>
<td>115</td>
</tr>
<tr>
<td>A4</td>
<td>(120; 18)</td>
<td>58</td>
<td>70</td>
</tr>
<tr>
<td>A5</td>
<td>(77; 9)</td>
<td>56</td>
<td>43</td>
</tr>
<tr>
<td>A6</td>
<td>(34; 3)</td>
<td>47</td>
<td>16</td>
</tr>
<tr>
<td>A&lt;†§</td>
<td>(162; 33)</td>
<td>67</td>
<td>108</td>
</tr>
<tr>
<td>A†</td>
<td></td>
<td></td>
<td>(211;6)</td>
</tr>
<tr>
<td>Agitation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A1</td>
<td>(328; 6)</td>
<td>57</td>
<td>188</td>
</tr>
<tr>
<td>A2</td>
<td>(221; 30)</td>
<td>58</td>
<td>128</td>
</tr>
<tr>
<td>A3</td>
<td>(170; 36)</td>
<td>62</td>
<td>105</td>
</tr>
<tr>
<td>A4</td>
<td>(120; 18)</td>
<td>57</td>
<td>68</td>
</tr>
<tr>
<td>A5</td>
<td>(77; 9)</td>
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<td>A6</td>
<td>(34; 3)</td>
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<td>A&lt;†§</td>
<td>(163, 30)</td>
<td>58</td>
<td>94</td>
</tr>
<tr>
<td>A†</td>
<td></td>
<td></td>
<td>(213; 4)</td>
</tr>
<tr>
<td>Shortness of breath</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A1</td>
<td>(327; 7)</td>
<td>19</td>
<td>62</td>
</tr>
<tr>
<td>A2</td>
<td>(219; 32)</td>
<td>18</td>
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</tr>
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<td>A3</td>
<td>(170; 36)</td>
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<td>(34; 3)</td>
<td>26</td>
<td>9</td>
</tr>
<tr>
<td>A&lt;†§</td>
<td>(163; 30)</td>
<td>28</td>
<td>46</td>
</tr>
<tr>
<td>A†</td>
<td></td>
<td></td>
<td>(213; 4)</td>
</tr>
</tbody>
</table>

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.

$\dagger$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 individuals 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.

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

$\dagger$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

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

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 after-death 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.

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Treatment*%</th>
<th>Assessment</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain (n)</td>
<td></td>
<td>A1</td>
<td>A2</td>
</tr>
<tr>
<td>Non-pharmacological</td>
<td>27</td>
<td>26</td>
<td>24</td>
</tr>
<tr>
<td>Acetaminophen PRN</td>
<td>26</td>
<td>34</td>
<td>29</td>
</tr>
<tr>
<td>Acetaminophen</td>
<td>40</td>
<td>34</td>
<td>49</td>
</tr>
<tr>
<td>NSAID PRN</td>
<td>1</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>NSAID</td>
<td>13</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>Oral narcotic PRN§</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Oral narcotic¶</td>
<td>5</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>Parental narcotic PRN¶</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Parental narcotic¶</td>
<td>4</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Other</td>
<td>4</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>No therapy</td>
<td>16</td>
<td>11</td>
<td>11</td>
</tr>
</tbody>
</table>

Agitation (n) | | A1 | A2 | A3 | A4 | A5 | A6 | A<† | A†§ |
| Non-pharmacological | 86 | 86 | 88 | 78 | 92 | 88 | 85 | 50 | <0.001 |
| Trunk and limb restraints** | 11 | 5 | 4 | 4 | 4 | 3 | 3 | 13 | 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 | 8 | 8 | 5 | 3 | 0.305 |
| Other | 7 | 9 | 12 | 12 | 12 | 8 | 8 | 6 | 0.171 |
| No therapy¶ | 0 | 0 | 1 | 0 | 0 | 4 | 0 | 4 | |

Shortness of breath (n) | | A1 | A2 | A3 | A4 | A5 | A6 | A<† | A†§ |
| 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 | 4 | 0.965 |
| No therapy | 19 | 23 | 29 | 21 | 18 | 11 | 13 | 10 | 0.386 |

i = 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.

iP = .003, iP = .041, iP = .023, iP = .006, iP = .036, iP = .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.
I 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,\textsuperscript{8,27} because pain may be the underlying cause of behavioral symptoms.\textsuperscript{8,9} However, we found no significant association between pain and agitation. Absence of an association has been reported in more studies.\textsuperscript{12-15} Ahn and Horgas\textsuperscript{14} 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,\textsuperscript{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.\textsuperscript{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.\textsuperscript{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,\textsuperscript{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.\textsuperscript{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. 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 we 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


Chapter 5

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

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Nominated for the “Jaarprijs 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. A high symptom burden and inappropriate treatment at the end of life have been reported. 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.

Burdensome symptoms present frequently in the last phase of life, as Mitchell et al. 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. Agitation is less frequently studied but was reported in 20%-54% of nursing home residents with advanced dementia at the end of life.

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. So far, treatment has been mostly empirical or based on general palliative care guidelines, which are not tailored to dementia.

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. 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, 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. 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 7 and a Cognitive Performance Scale score of 5 or 6.

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. 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. Physicians reported how many hours before death opioid administration started. Palliative sedation was defined as continuous deep sedation or sleep until death. 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) scale, which was translated and tested in an independent Dutch population. 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 = variance in intercept/(variance in intercepts + 3.29). 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

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>(N = 330)</th>
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</thead>
<tbody>
<tr>
<td>Female, %</td>
<td>67</td>
</tr>
<tr>
<td>Age at death, mean (SD)</td>
<td>85.2 (7.4)</td>
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<tr>
<td>Advanced dementia, %</td>
<td>43</td>
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<tr>
<td>Type of dementia, %</td>
<td></td>
</tr>
<tr>
<td>Alzheimer disease</td>
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<td>Vascular</td>
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<td>Alzheimer and vascular</td>
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<td>Lewy body/ Parkinson disease</td>
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<td>Other types</td>
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<tr>
<td>Residence before admission, %</td>
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<td>Private home</td>
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<td>Residential home/ other nursing home</td>
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</tr>
<tr>
<td>General/ psychiatric hospital</td>
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<tr>
<td>Other</td>
<td>6</td>
</tr>
<tr>
<td>Physicians’ expectation of residents’ death, %</td>
<td></td>
</tr>
<tr>
<td>Expected</td>
<td>64</td>
</tr>
<tr>
<td>Expected, yet sooner than anticipated</td>
<td>22</td>
</tr>
<tr>
<td>Neither expected nor unexpected</td>
<td>3</td>
</tr>
<tr>
<td>Unexpected</td>
<td>11</td>
</tr>
</tbody>
</table>

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

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

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.](image)

**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)

<table>
<thead>
<tr>
<th>Type of Opioids</th>
<th>%a</th>
<th>Median</th>
<th>25th perc</th>
<th>75th perc</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patch fentanyl</td>
<td>12</td>
<td>60</td>
<td>30</td>
<td>60</td>
</tr>
<tr>
<td>Pump</td>
<td>10</td>
<td>90</td>
<td>60</td>
<td>180</td>
</tr>
<tr>
<td>Subcutaneous bolus injection</td>
<td>88</td>
<td>90</td>
<td>30</td>
<td>120</td>
</tr>
<tr>
<td>Tramadol drops</td>
<td>2</td>
<td>20</td>
<td>7</td>
<td>28</td>
</tr>
<tr>
<td>Controlled-release tablet</td>
<td>1</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Oxycodon tablet</td>
<td>0.4</td>
<td>40</td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>Drink</td>
<td>0.4</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Summed dosage (≥1 type of opioid)</td>
<td></td>
<td>90</td>
<td>52</td>
<td>150</td>
</tr>
</tbody>
</table>

OME = oral morphine equivalents.

Total 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)

<table>
<thead>
<tr>
<th>Sedation medication</th>
<th>%a</th>
<th>Median</th>
<th>25th perc</th>
<th>75th perc</th>
</tr>
</thead>
<tbody>
<tr>
<td>Midazolam</td>
<td>86</td>
<td>30</td>
<td>15</td>
<td>30</td>
</tr>
<tr>
<td>Morphineb</td>
<td>39</td>
<td>90</td>
<td>90</td>
<td>180</td>
</tr>
<tr>
<td>Diazepam</td>
<td>3</td>
<td>15</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>3</td>
<td>3</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Oxazepam</td>
<td>2</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Levomepromazine</td>
<td>2</td>
<td>50</td>
<td>50</td>
<td>50</td>
</tr>
</tbody>
</table>

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

mg/24h in oral morphine equivalents.

Table 5. Associations of symptoms with quality of life (QUALIda score)

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Coefficientb</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>5.5</td>
<td>3.5 to 7.5</td>
</tr>
<tr>
<td>Adjusted</td>
<td>4.0</td>
<td>2.1 to 6.0</td>
</tr>
<tr>
<td>Shortness of breath</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>0.1</td>
<td>-2.1 to 2.3</td>
</tr>
<tr>
<td>Adjusted</td>
<td>0.7</td>
<td>-1.2 to 2.6</td>
</tr>
<tr>
<td>Agitation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>6.6</td>
<td>4.6 to 8.6</td>
</tr>
<tr>
<td>Adjusted</td>
<td>6.1</td>
<td>4.2 to 8.1</td>
</tr>
</tbody>
</table>

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

Unstandardized regression coefficients from linear regression models.

Adjusted 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](image.png)

**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. 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). Furthermore, symptom prevalence did not differ between those with advanced dementia (in which CASCADE was limited) and less advanced dementia. 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). 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. Second, generalizability for the nation differed: DEOLD facilities performed “average” on general quality indicators, whereas CASCADE facilities performed better than average. 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.

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. In another Dutch study, dehydration/cachexia was a common cause of death as well. Dutch elderly care
physicians rarely provide tube feeding in case of intake problems, 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, 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. 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 recommendations 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 agitation and, therefore, possibly also overuse of anxiolytics, which were used mostly for agitation in line with Dutch guidelines for behavior problems. 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. 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. 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. 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. 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%)\textsuperscript{36} but lower compared with palliative care settings (15% to >60%).\textsuperscript{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.\textsuperscript{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,\textsuperscript{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


Chapter 6

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

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Cees M.P.M. Hertogh
Jenny T. van der Steen

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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-makers1;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 Scale\textsuperscript{28} score 5 or 6, and a Global Deterioration Scale\textsuperscript{29} score 7), and the most common type of dementia was Alzheimer’s disease (46%).\textsuperscript{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.\textsuperscript{30} The median length of stay until death was 8 months (25\textsuperscript{th} percentile = 4, 75\textsuperscript{th} percentile = 17 months).\textsuperscript{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.\textsuperscript{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. 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

<table>
<thead>
<tr>
<th>Care goal</th>
<th>Assessment</th>
<th>N</th>
<th>Life prolongation</th>
<th>Palliative</th>
<th>Preserve functioning</th>
<th>Other</th>
<th>No care goals</th>
<th>Change in palliative care goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>1</td>
<td>(326)</td>
<td>1</td>
<td>57</td>
<td>21</td>
<td>3</td>
<td>19</td>
<td>0.003</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>(221)</td>
<td>5</td>
<td>65</td>
<td>23</td>
<td>4</td>
<td>2</td>
<td>0.936</td>
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<tr>
<td></td>
<td>3</td>
<td>(172)</td>
<td>5</td>
<td>65</td>
<td>27</td>
<td>2</td>
<td>2</td>
<td>0.253</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>(122)</td>
<td>5</td>
<td>69</td>
<td>23</td>
<td>2</td>
<td>1</td>
<td>0.813</td>
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<tr>
<td></td>
<td>5</td>
<td>(76)</td>
<td>4</td>
<td>70</td>
<td>25</td>
<td>0</td>
<td>1</td>
<td>0.809</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>(34)</td>
<td>6</td>
<td>65</td>
<td>24</td>
<td>3</td>
<td>3</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>At the day of death</td>
<td>(211)</td>
<td>1</td>
<td>90</td>
<td>4</td>
<td>1</td>
<td>4</td>
<td>0.000</td>
</tr>
<tr>
<td>Neither problem</td>
<td>1</td>
<td>(158)</td>
<td>0</td>
<td>53</td>
<td>22</td>
<td>3</td>
<td>22</td>
<td>0.004</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>(115)</td>
<td>4</td>
<td>65</td>
<td>23</td>
<td>5</td>
<td>2</td>
<td>0.660</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>(92)</td>
<td>5</td>
<td>61</td>
<td>30</td>
<td>1</td>
<td>2</td>
<td>0.392</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>(67)</td>
<td>7</td>
<td>66</td>
<td>25</td>
<td>1</td>
<td>0</td>
<td>0.680</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>(42)</td>
<td>2</td>
<td>69</td>
<td>26</td>
<td>0</td>
<td>2</td>
<td>0.482</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>(18)</td>
<td>6</td>
<td>56</td>
<td>28</td>
<td>6</td>
<td>6</td>
<td>0.005</td>
</tr>
<tr>
<td></td>
<td>At the day of death</td>
<td>(74)</td>
<td>1</td>
<td>84</td>
<td>8</td>
<td>8</td>
<td>1</td>
<td>0.860</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>1</td>
<td>(86)</td>
<td>3</td>
<td>63</td>
<td>14</td>
<td>3</td>
<td>16</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>before</td>
<td>(78)</td>
<td>4</td>
<td>72</td>
<td>13</td>
<td>4</td>
<td>8</td>
<td>0.880</td>
</tr>
<tr>
<td></td>
<td>after</td>
<td>(73)</td>
<td>3</td>
<td>73</td>
<td>18</td>
<td>3</td>
<td>4</td>
<td>0.392</td>
</tr>
<tr>
<td></td>
<td>At the day of death</td>
<td>(57)</td>
<td>4</td>
<td>86</td>
<td>5</td>
<td>0</td>
<td>5</td>
<td>0.000</td>
</tr>
<tr>
<td>Intake problems</td>
<td>1</td>
<td>(102)</td>
<td>0</td>
<td>60</td>
<td>18</td>
<td>5</td>
<td>18</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>before</td>
<td>(100)</td>
<td>2</td>
<td>72</td>
<td>15</td>
<td>4</td>
<td>7</td>
<td>0.392</td>
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<tr>
<td></td>
<td>after</td>
<td>(94)</td>
<td>1</td>
<td>93</td>
<td>5</td>
<td>0</td>
<td>1</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>At the day of death</td>
<td>(81)</td>
<td>1</td>
<td>95</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>0.000</td>
</tr>
</tbody>
</table>

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.

³⁴ 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.

¹⁵ 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.

³⁰ 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.

¹⁷ 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.

²⁹ 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.

No significant differences at baseline in proportions of patients with palliative care goals (versus all other goals) between the subgroups.

No 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 (X² = 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 (X² = 4.902, P = 0.027).

The 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.

<p>| | | | | | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
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<th></th>
<th></th>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>96</td>
<td>Chapter 6</td>
<td></td>
<td></td>
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<td></td>
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<td></td>
</tr>
</tbody>
</table>
Table 2. Treatment orders around the developing of pneumonia and intake problems

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

*Fifteen 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. Although infection of the respiratory system may lead to critical decisions about treatment, 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. 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, discussion of the most common health problems and the most acute decisions is recommended when establishing a care plan. 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.

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. Elderly care physicians have a strong and often decisive influence on decision making and facilitate discussions on advance care planning and establishment of care plans. 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


Chapter 7

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

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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 study\(^1\) 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 care and also elsewhere, 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. 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. The terms ‘advanced dementia’, ‘late dementia’, ‘end-stage of dementia’ and ‘severe dementia’ are all used. For this reason, it is difficult to compare and to interpret these study findings. 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 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) 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...
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, 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, 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. In a systematic review about associations between pain and neuropsychiatric symptoms, Van Dalen et al. 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. 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). 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. 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. 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”. 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.\(^3\) in qualitative interviews. For example, physicians and nurses described a great variety in the denomination and contents of formulated and established care goals.\(^3\) 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).\(^43\)
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. 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. 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.

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. 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. Antibiotics also do not seem to contribute to comfort in this phase, as van der Maaden et al. 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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{32,61,62} Although Verenso (the Dutch association of elderly care physicians) has formulated the definitions of palliative and symptomatic care goals,\textsuperscript{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.\textsuperscript{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. 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, 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.
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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 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.
<At= 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 <At is in these cases also the baseline assessment, so that presence of pain was unknown before the <At assessment.
At= 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

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

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

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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 ≤ 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%. 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).
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, and two Dutch articles reported percentages of 77 and 79%.

![Graph showing antibiotic use in various settings.](image)

**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. 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. Another article reported that 43.1% of 102 feverish episodes in 193 patients were treated with antibiotics in Finland.
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. 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. Furthermore, a poor prognosis was associated with fewer antibiotics in a selection of European nursing homes, and in a Dutch study which assessed physicians' subjective predictions in a survey. 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. 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. 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. Patients who had been diagnosed with pneumonia previously, and were more ADL (activities of daily living)-dependent, were also less likely to receive antibiotics.

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

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, but in the US, indicators of more severe acute illness were associated with more antibiotic prescriptions, or no association was found. In addition, aspiration was associated with withholding antibiotics in the Netherlands, but in contrast, patients with suspected aspiration were more frequently treated with antibiotics in the US.
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) 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 antibiotic 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 caregivers 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>
<thead>
<tr>
<th>Antibiotics</th>
<th>Factor*</th>
<th>Country</th>
<th>Setting</th>
<th>Limited to advanced dementia</th>
<th>Hypothetical</th>
<th>Before death</th>
<th>MMAT score</th>
<th>Usefulness</th>
<th>Study and year</th>
</tr>
</thead>
<tbody>
<tr>
<td>AB ↑</td>
<td>Unstable vital signs</td>
<td>US</td>
<td>1675 bed LTCF</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>50%</td>
<td>useful</td>
<td>Chen et al., 2006</td>
</tr>
<tr>
<td>AB ↑</td>
<td>High temperature</td>
<td>US and NL</td>
<td>NHs</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>50%</td>
<td>useful</td>
<td>Szafara et al., 2012</td>
</tr>
<tr>
<td>AB ↑</td>
<td>Suspected aspiration</td>
<td>US</td>
<td>1675 bed LTCF</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>50%</td>
<td>useful</td>
<td>Chen et al., 2006</td>
</tr>
<tr>
<td>AB ↑</td>
<td>NO aspiration</td>
<td>NL</td>
<td>NHs</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>75%</td>
<td>useful</td>
<td>van der Steen et al., 2002</td>
</tr>
<tr>
<td>AB ↑</td>
<td>Illness severity</td>
<td>US</td>
<td>NHs</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>100%</td>
<td>useful</td>
<td>Mehr et al., 2003</td>
</tr>
<tr>
<td>AB ↑(US)</td>
<td>Illness severity at time of the treatment decision and 2 weeks before the treatment decision</td>
<td>US and NL</td>
<td>NHs</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>50%</td>
<td>useful</td>
<td>Mehr et al., 2003</td>
</tr>
<tr>
<td>AB ↓(NL)</td>
<td>Illness severity at time of the treatment decision and 2 weeks before the treatment decision</td>
<td>NL</td>
<td>NHs</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>75%</td>
<td>useful</td>
<td>van der Steen et al., 2002</td>
</tr>
<tr>
<td>AB =</td>
<td>LRI severity in severe dementia</td>
<td>US and NL</td>
<td>NHs</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>50%</td>
<td>useful</td>
<td>Szafara et al., 2012</td>
</tr>
<tr>
<td>Prognosis</td>
<td>Approaching death (closer to death, determined in retrospect)</td>
<td>US</td>
<td>NHs</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>50%</td>
<td>useful</td>
<td>D’Agata and Mitchell, 2008</td>
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<tr>
<td>AB ↓</td>
<td>Poor prognosis (physician estimate at diagnosis) or ADEPT score</td>
<td>NL</td>
<td>European countries and Israel</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>25%</td>
<td>useful</td>
<td>van der Steen et al., 2009a [45]</td>
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<tr>
<td>AB ↓</td>
<td>Poor prognosis (physician estimate at diagnosis) or ADEPT score</td>
<td>NL</td>
<td>European countries and Israel</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>75%</td>
<td>useful</td>
<td>Onder et al., 2013</td>
</tr>
<tr>
<td>Health status/condition</td>
<td>ADL dependency</td>
<td>US and NL</td>
<td>NHs</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>100%</td>
<td>useful</td>
<td>Mehr et al., 2003</td>
</tr>
<tr>
<td>AB ↓</td>
<td>Previous pneumonia</td>
<td>NL</td>
<td>NHs</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>75%</td>
<td>useful</td>
<td>van der Steen et al., 2002</td>
</tr>
<tr>
<td>AB =</td>
<td>General health condition: increased urine of fecal incontinence, increased mobility dependence, increased illness severity, increased discomfort</td>
<td>NL</td>
<td>NHs</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>75%</td>
<td>useful</td>
<td>van der Steen et al., 2002</td>
</tr>
<tr>
<td>AB =</td>
<td>Vaccination for influenza in prior winter</td>
<td>NL</td>
<td>NHs</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>75%</td>
<td>useful</td>
<td>van der Steen et al., 2002</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>Factor*</td>
<td>Country</td>
<td>Setting</td>
<td>Limited to advanced dementia</td>
<td>Hypothetical</td>
<td>Before death</td>
<td>MMAT score</td>
<td>Usefulness</td>
<td>Study and year</td>
</tr>
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<td>-------------</td>
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</tr>
<tr>
<td>AB ↓</td>
<td>Swallowing difficulty</td>
<td>US and NL</td>
<td>NHs</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>50%</td>
<td>useful</td>
<td>Szafara et al., 2012</td>
</tr>
<tr>
<td>AB ↓</td>
<td>Eating dependence - pre-LRI and at the time of the treatment decision</td>
<td>US and NL</td>
<td>NHs</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>50%</td>
<td>useful</td>
<td>Szafara et al., 2012</td>
</tr>
<tr>
<td>AB ↓</td>
<td>Dehydration</td>
<td>NL</td>
<td>NHs</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>75%</td>
<td>useful</td>
<td>van der Steen et al., 2002</td>
</tr>
<tr>
<td>AB ↓</td>
<td>Insufficient drinking</td>
<td>NL</td>
<td>NHs</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>75%</td>
<td>useful</td>
<td>van der Steen et al., 2002</td>
</tr>
<tr>
<td>AB ↓</td>
<td>Increased level of severity of the dementia</td>
<td>US</td>
<td>NH, transitional care unit, assisted living unit</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>75%</td>
<td>useful</td>
<td>Gjerdingen et al., 1999</td>
</tr>
<tr>
<td>AB ↓</td>
<td>More severe dementia</td>
<td>US</td>
<td>Chronic care facilities</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>75%</td>
<td>useful</td>
<td>Evers et al., 2002</td>
</tr>
<tr>
<td>AB ↓</td>
<td>More severe dementia</td>
<td>US and NL</td>
<td>NHs</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>100%</td>
<td>useful</td>
<td>Mehr et al., 2003</td>
</tr>
<tr>
<td>AB ↓</td>
<td>More severe dementia</td>
<td>NL</td>
<td>NHs</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>50%</td>
<td>useful</td>
<td>Szafara et al., 2012</td>
</tr>
<tr>
<td>AB ↓</td>
<td>More severe dementia</td>
<td>NL</td>
<td>NHs</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>75%</td>
<td>useful</td>
<td>van der Steen et al., 2002</td>
</tr>
<tr>
<td>AB ↓</td>
<td>Psychogeriatric disease: Alzheimer dementia, mixed dementia</td>
<td>NL</td>
<td>NHs</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>75%</td>
<td>useful</td>
<td>van der Steen et al., 2002</td>
</tr>
</tbody>
</table>

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>
<thead>
<tr>
<th>Antibiotics</th>
<th>Factor</th>
<th>Country</th>
<th>Setting</th>
<th>Limited to advanced dementia</th>
<th>Hypothetical</th>
<th>Before death</th>
<th>MMAT score</th>
<th>Usefulness</th>
<th>Study and year</th>
</tr>
</thead>
<tbody>
<tr>
<td>AB ↑</td>
<td>Comfort of spouses with decision to forgo antibiotic was 40% and lowest of all treatment decisions</td>
<td>US</td>
<td>Aging and dementia research center</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>50%</td>
<td>somewhat useful</td>
<td>Mezey et al., 1996</td>
</tr>
<tr>
<td>AB ↑</td>
<td>Antibiotics are viewed as a comfort measure, not as a technologic means of prolonging life for someone with severe dementia</td>
<td>US</td>
<td>NHs</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>75%</td>
<td>useful</td>
<td>Forbes et al., 2000</td>
</tr>
<tr>
<td>AB ↑</td>
<td>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</td>
<td>US</td>
<td>NHs</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>75%</td>
<td>useful</td>
<td>Forbes et al., 2000</td>
</tr>
</tbody>
</table>

**Patient attitudes**

**Physician attitudes**

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

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

<table>
<thead>
<tr>
<th>Antibiotics Factor</th>
<th>Country</th>
<th>Setting</th>
<th>Limited to advanced dementia</th>
<th>Hypothetical</th>
<th>Before death</th>
<th>MMAT score</th>
<th>Usefulness</th>
<th>Study and year</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Advance directives</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AB ↓ A do not hospitalize (DNH) order</td>
<td>US</td>
<td>1675 bed LTCF</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>50%</td>
<td>useful</td>
<td>Chen et al., 2006</td>
</tr>
<tr>
<td>AB ↓ Advance care planning</td>
<td>NL</td>
<td>NHs</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>50%</td>
<td>useful</td>
<td>van der Steen et al., 2002</td>
</tr>
<tr>
<td><strong>Specifications of facilities</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AB ↑ Living alone</td>
<td>US</td>
<td>General internal medicine group practice</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>100%</td>
<td>somewhat useful</td>
<td>Lo et al., 1986</td>
</tr>
<tr>
<td>AB ↑ Number of psychogeriatric beds in the facility</td>
<td>NL</td>
<td>NHs</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>75%</td>
<td>useful</td>
<td>van der Steen et al., 2002</td>
</tr>
<tr>
<td>AB ↑ Home care vs nursing homes or hospital</td>
<td>Italy</td>
<td>NHs and home care services</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>75%</td>
<td>useful</td>
<td>Toscani et al., 2013</td>
</tr>
<tr>
<td>AB ↓ Treatment in the summer</td>
<td>NL</td>
<td>NHs</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>75%</td>
<td>useful</td>
<td>van der Steen et al., 2002</td>
</tr>
<tr>
<td>AB = Nursing home situated in one of the three biggest NL cities</td>
<td>NL</td>
<td>NHs</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>75%</td>
<td>useful</td>
<td>van der Steen et al., 2002</td>
</tr>
<tr>
<td>AB = Total number of beds or number of beds for somatic patients</td>
<td>NL</td>
<td>NHs</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>75%</td>
<td>useful</td>
<td>van der Steen et al., 2002</td>
</tr>
<tr>
<td>AB = Religious affiliation of facility</td>
<td>NL</td>
<td>NHs</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>75%</td>
<td>useful</td>
<td>van der Steen et al., 2002</td>
</tr>
<tr>
<td>AB = Level of policy making (availability of mission statement, quality policy, quality manual, and quality report on 4-point scale)</td>
<td>NL</td>
<td>NHs</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>75%</td>
<td>useful</td>
<td>van der Steen et al., 2002</td>
</tr>
<tr>
<td>AB = Protocol or policy on (non) treatment available</td>
<td>NL</td>
<td>NHs</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>75%</td>
<td>useful</td>
<td>van der Steen et al., 2002</td>
</tr>
<tr>
<td>Antibiotics Factor</td>
<td>Country</td>
<td>Setting</td>
<td>Limited to advanced dementia</td>
<td>Hypothetical</td>
<td>Before death</td>
<td>MMAT score</td>
<td>Usefulness</td>
<td>Study and year</td>
</tr>
<tr>
<td>--------------------</td>
<td>---------</td>
<td>---------</td>
<td>-------------------------------</td>
<td>-------------</td>
<td>-------------</td>
<td>-----------</td>
<td>------------</td>
<td>---------------</td>
</tr>
<tr>
<td><strong>Interventions and guidelines</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AB ↓</td>
<td>Finland</td>
<td>NHs and dementia units</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>75%</td>
<td>useful</td>
<td>Rummukainen et al., 2012</td>
</tr>
<tr>
<td>AB =</td>
<td>Recommendations by a palliative care team with the goal of enhancing patient comfort</td>
<td>US</td>
<td>Teaching hospital</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>50%</td>
<td>less useful</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AB =</td>
<td>Time – two time cohorts (1996-1998; 2006-2007)</td>
<td>NL</td>
<td>NHs</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>50%</td>
<td>useful</td>
</tr>
</tbody>
</table>

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. Further, physicians preferred not to treat pneumonia when they considered treatment futile, and curative treatment was sometimes forgone with an explicit intention to hasten death.

Healthcare context
The articles that described factors regarding the healthcare context indicated that patients living alone, and at home, were more likely to receive antibiotics than nursing-home residents or hospital inpatients (Table 3). In Dutch nursing homes, the percentage of patients who received antibiotics for pneumonia increased with the number of psycho-geriatric beds in the facility. 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. Patients living in the Netherlands were less likely to receive antibiotic treatment than patients residing in the US. Furthermore, patients who had a ‘do not hospitalize’ (DNH) order, or an advance directive, 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. 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. 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.

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. 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. 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. Fewer physician contacts potentially result in less certainty about treatment decisions and family preferences, even after adjustment for country. 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. 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. 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. 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. 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, for example, the nursing home setting, and difficulty applying general knowledge about resistance in the community in individual cases in clinical practice.

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


44. 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.


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

<table>
<thead>
<tr>
<th>Set</th>
<th>Search terms</th>
<th>Items</th>
</tr>
</thead>
<tbody>
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<td>#4 NOT (Animals[mh] NOT humans[mh])</td>
<td>679</td>
</tr>
<tr>
<td>#4</td>
<td>#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])</td>
<td>837</td>
</tr>
<tr>
<td>#3</td>
<td>#1 AND #2</td>
<td>891</td>
</tr>
<tr>
<td>#1</td>
<td>“Dementia”[Mesh] OR dement*[tiab] OR alzheimer*[tiab]</td>
<td>152189</td>
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Online resource B Usefulness criteria

<table>
<thead>
<tr>
<th>Useful</th>
<th></th>
</tr>
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<tbody>
<tr>
<td>Quantitative research</td>
<td>• the starting point of the study corresponds well with our research question</td>
</tr>
<tr>
<td></td>
<td>• the population is representative</td>
</tr>
<tr>
<td></td>
<td>• the method to determine antibiotic use is little or not error prone</td>
</tr>
<tr>
<td></td>
<td>• the results are reported clearly</td>
</tr>
<tr>
<td>Qualitative research</td>
<td>• the starting point of the study corresponds well to our research question</td>
</tr>
<tr>
<td></td>
<td>• the results are reported clearly</td>
</tr>
<tr>
<td></td>
<td>• appropriate subjects or informants are used</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Somewhat useful</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Quantitative research</td>
<td>• the starting point of the study only partially corresponds to our research question</td>
</tr>
<tr>
<td></td>
<td>• the population is (very) selective</td>
</tr>
<tr>
<td></td>
<td>• the method to determine antibiotic use is error prone (e.g. interview without referring to patient’s chart)</td>
</tr>
<tr>
<td></td>
<td>• the results are reported poorly</td>
</tr>
<tr>
<td>Qualitative research</td>
<td>• the starting point of the study only partially corresponds with our research question</td>
</tr>
<tr>
<td></td>
<td>• the results are reported poorly</td>
</tr>
<tr>
<td></td>
<td>• inappropriate subjects or informants are used (too few or too homogeneous)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Not useful</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• 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</td>
</tr>
</tbody>
</table>
### 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

<table>
<thead>
<tr>
<th>Study</th>
<th>MMAT score</th>
<th>Usefulness</th>
<th>Country</th>
<th>Design study</th>
<th>Setting</th>
<th>Population/enrollment criteria</th>
<th>Number of subjects</th>
<th>Severity of dementia</th>
<th>Time frame</th>
<th>Antibiotic therapy</th>
<th>Factor associated with the use of antibiotics</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Rummukainen et al., 2012</td>
<td>75%</td>
<td>Useful</td>
<td>Finland</td>
<td>Observational prospective study</td>
<td>Older patients (dementia 60%)</td>
<td>39 NHs and dementia units</td>
<td>1221</td>
<td>Not specified</td>
<td>n.a</td>
<td>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</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2005-2008</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>In 2008: 7.8% (90/1158) received antibiotics as UTI prophylaxis and 1.7% (20/1158) were on acute RTI treatment</td>
<td></td>
</tr>
<tr>
<td>2. Toscani et al., 2013</td>
<td>75%</td>
<td>Useful</td>
<td>Italy</td>
<td>Multicenter prospective observational cohort study</td>
<td>Patients with a FAST score of ≥7 with and expected survival of ≥2 weeks according to their primary doctor's clinical judgment</td>
<td>34 NHs and home care services</td>
<td>410; 245 nursing home residents; 165 home care service</td>
<td>Most advanced stage of dementia (FAST score 7 or higher)</td>
<td>n.a</td>
<td>8.1% (33/410) of all patients received antibiotics</td>
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<td>2007-2009</td>
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<td></td>
<td>AB ↑ Home care vs nursing homes or hospital</td>
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</tr>
<tr>
<td>3. Daneman et al., 2011</td>
<td>75%</td>
<td>Somewhat useful</td>
<td>Canada</td>
<td>Point-prevalence study</td>
<td>Residents ≥ 66 years old who had completed a Continuing Care Reporting System Long Term Care assessment (dementia: 59.5%)</td>
<td>361 LTCFs</td>
<td>37371</td>
<td>Not specified</td>
<td>n.a</td>
<td>5.9% (2190/37119) were receiving antibiotics at the time of their index assessment</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>MMAT score</td>
<td>Usefulness</td>
<td>Country</td>
<td>Design study</td>
<td>Setting</td>
<td>Population/enrollment criteria</td>
<td>Number of subjects</td>
<td>Severity of dementia</td>
<td>Time frame</td>
<td>Antibiotic therapy</td>
<td>Factor associated with the use of antibiotics</td>
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<td>4. Blass et al., 2008</td>
<td>25%</td>
<td>Useful</td>
<td>US</td>
<td>Prospective cohort study</td>
<td>3 NHs</td>
<td>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</td>
<td>125</td>
<td>Advanced dementia, not further specified</td>
<td>6 months prior to enrollment</td>
<td>88% (110/125) received antibiotic therapy at baseline (spanning the 6 months prior to enrollment)</td>
<td></td>
</tr>
<tr>
<td>5. Onder et al., 2013</td>
<td>75%</td>
<td>Useful</td>
<td>Czech republic, England, Finland, Germany, Italy, the Netherlands, Israel</td>
<td>Longitudinal observational study</td>
<td>57 NHs</td>
<td>Older adults with advanced cognitive impairment residing in NHs</td>
<td>822</td>
<td>Severe cognitive impairment (CPS scores between 5.4 and 5.8)</td>
<td>The three days prior to assessment</td>
<td>4.4% (36/822) received antibiotics</td>
<td>AB = Poor prognosis (physician estimate at diagnosis) or ADEPT score</td>
</tr>
<tr>
<td>6. Ahronheim et al., 2000</td>
<td>50%</td>
<td>Somewhat useful</td>
<td>US</td>
<td>RTC</td>
<td>1 teaching hospital</td>
<td>Patients with advanced dementia who where hospitalized for acute illness.</td>
<td>Total: 99 patients (190 hospital admissions); Intervention: 48 (92 hospital admissions); Control: 51 (98 hospital admissions)</td>
<td>FAST stage 6d-7b: Total: 47 (47.5%); Intervention: 26 (54.2%); Control: 21 (41.2%);</td>
<td>During stay in hospital</td>
<td>74.4% (142/190) of admissions received systemic antibiotic treatment during their stay</td>
<td>AB = Recommendations by a palliative care team with the goal of enhancing patient comfort</td>
</tr>
</tbody>
</table>

**Notes:**
- **MMAT score** represents the Modified Medical Category Activities of Daily Living score.
- **Usefulness** indicates the perceived usefulness on a scale from 1 (not useful) to 100 (very useful).
- **Country** specifies the location of the study.
- **Setting** describes the type of setting where the study was conducted.
- **Population/enrollment criteria** outlines the criteria used for selecting participants.
- **Number of subjects** refers to the total number of participants in the study.
- **Severity of dementia** describes the stage or severity level.
- **Time frame** indicates the duration of the study.
- **Antibiotic therapy** details the percentage of subjects receiving antibiotic therapy.
- **Factor associated with the use of antibiotics** lists the factors identified in the study.
<table>
<thead>
<tr>
<th>Study</th>
<th>Usefulness</th>
<th>Criteria</th>
<th>Design</th>
<th>Setting</th>
<th>Population</th>
<th>Setting</th>
<th>Criteria</th>
<th>Setting</th>
<th>Population</th>
<th>Setting</th>
<th>Criteria</th>
<th>Setting</th>
</tr>
</thead>
<tbody>
<tr>
<td>7. Catic et al., 2013</td>
<td>50%</td>
<td>Somewhat useful</td>
<td>Pilot study 2012</td>
<td>1 hospital</td>
<td>Patients aged 65 and older, admitted to any clinical service for 48 hours or less, GDS 7 and English-speaking proxy</td>
<td>Total: 29</td>
<td>Advanced dementia. BANS-5 scores: 20.1 (1.7)</td>
<td>During stay in hospital mean length of stay 3.6 days</td>
<td>86.2% (25/29) received IV antibiotics</td>
<td></td>
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</tr>
<tr>
<td>8. Nourhashemi et al., 2012</td>
<td>50%</td>
<td>Somewhat useful</td>
<td>Prospective observational study 2004-2007</td>
<td>Geriatric wards of 2 hospitals</td>
<td>Patients with Alzheimer disease identified after hospitalization on geriatric wards</td>
<td>Total: 112</td>
<td>Severe dementia (MMSE &lt; 10)</td>
<td>During 3 months before inclusion</td>
<td>52.3% (56/107) received antibiotic therapy during the 3 months before inclusion (mean duration 10.00 ±6.70 days)</td>
<td></td>
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</tr>
<tr>
<td>9. Malýuk et al., 2012</td>
<td>75%</td>
<td>Somewhat useful</td>
<td>Retrospective naturalistic study 2003-2007</td>
<td>1 geriatric Psychiatry teaching hospital</td>
<td>Elderly patients with chronic mental illness or dementia (dementia: 63.8%)</td>
<td>Group A: 85; Group C: 305</td>
<td>Moderate dementia: 29.5%; severe dementia: 33.8%</td>
<td>Within 14 days of admission</td>
<td>21.8% (85/390) received antibiotics within 14 days of admission</td>
<td></td>
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</tr>
<tr>
<td>10. Reisfeld et al., 2011</td>
<td>50%</td>
<td>Somewhat useful</td>
<td>Retrospective cohort study 2005-2007</td>
<td>1 700-bed community hospital</td>
<td>Hospitalized patients with gram-negative bacteraemia, dementia and a bed-ridden functional status.</td>
<td>Group A: 378 patients with dementia and gram-negative bacteraemia</td>
<td>Not specified</td>
<td>During the previous month</td>
<td>33.9% (128/378) received antibiotic treatment during the previous month</td>
<td></td>
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</tr>
<tr>
<td>Study</td>
<td>MMAT score</td>
<td>Usefulness</td>
<td>Country</td>
<td>Design study</td>
<td>Setting</td>
<td>Population/enrollment criteria</td>
<td>Number of subjects</td>
<td>Severity of dementia</td>
<td>Time frame</td>
<td>Antibiotic therapy</td>
<td>Factor associated with the use of antibiotics</td>
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<tr>
<td>11. Evers et al., 2002</td>
<td>75%</td>
<td>Useful</td>
<td>US</td>
<td>Retrospective study</td>
<td>Chronic care facilities</td>
<td>Patients who died with dementia who were brought for clinical autopsy</td>
<td>279</td>
<td>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</td>
<td>Last 6 months of life</td>
<td>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  55% (102/185) of patients with severe dementia received antibiotics in the last 6 months of life</td>
<td>AB = Time – three death cohorts (1985-1990; 1991-1995; 1996-2000)</td>
<td></td>
</tr>
<tr>
<td>12. Albrecht et al., 2013</td>
<td>75%</td>
<td>Useful</td>
<td>US</td>
<td>Survey study 2007</td>
<td>1545 hospice agencies</td>
<td>Patients discharged from hospice (alive or death) during the 3-month period beginning 4 months before the agency interview.</td>
<td>Total 4733; dementia 450</td>
<td>Not specified</td>
<td>The last 7 days of hospice care</td>
<td>25% (109/450) received antibiotics in the last 7 days of hospice care</td>
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<tr>
<td>Study Reference</td>
<td>Country</td>
<td>Study Type</td>
<td>Setting</td>
<td>Number</td>
<td>Patients</td>
<td>Details</td>
<td>Last 2 weeks of life</td>
<td>Last 30 days of life</td>
<td>Notes</td>
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<tr>
<td>D'Agata and Mitchell, 2008</td>
<td>US</td>
<td>Prospective cohort study</td>
<td>Nursing home residents aged 60 and older, with a length of stay 30 days or longer</td>
<td>21 NHs</td>
<td>214</td>
<td>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.</td>
<td>66.4% (142/214) of residents received at least 1 course of antibiotics during an average of 322 days of follow up</td>
<td>42.4% received at least 1 course of antibiotics within the 2 weeks before death</td>
<td>51.5% received at least 1 dose of antibiotics within the 8 weeks before death</td>
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<tr>
<td>Di Giulio et al., 2008</td>
<td>Italy</td>
<td>Retrospective exploratory study</td>
<td>Patients diagnosed with severe cognitive impairment</td>
<td>7 LTCFs (≥200 beds)</td>
<td>141</td>
<td>Severe cognitive impairment, FAST stages: 7c: 50% (71/141), 7d: 30% (43/141), ≥7e: 19% (27/141)</td>
<td>71.6% (101/141) received antibiotics in the last 30 days of life (85% had fever or urinary tract infection)</td>
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<tr>
<td>Hirakawa et al., 2006</td>
<td>Japan</td>
<td>Multicenter observational study</td>
<td>Decedents aged 65 years or older who died at home.</td>
<td>Home; decedents were using 16 study clinics belonging to the society with diagnoses of all illnesses</td>
<td>98</td>
<td>Score of ≥ 1 on a scale of 6 levels of which 0 is not demented.</td>
<td>23.5% (23/98) of the patients dying with dementia received antibiotics in the last 2 days of life</td>
<td>AB↑ Approaching death (closer to death, determined in retrospect)</td>
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<tr>
<td>16. Ahronheim et al., 1996</td>
<td>Somewhat useful</td>
<td>US</td>
<td>Retrospective chart review study</td>
<td>Patients 65 and older who died with a diagnosis of advanced dementia</td>
<td>80</td>
<td>Advanced dementia (at least 2 of: MMSE &lt; 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)</td>
<td>During terminal hospitalization</td>
<td>94% (75/80) received antibiotics during their terminal hospitalization</td>
<td>73% (58/80) received empiric antibiotic therapy (no documented source of infection)</td>
<td>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)</td>
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</tbody>
</table>
Table 2. Antibiotic use per infectious episode (data referring to Figure 2d), and associated factors with use of antibiotics (Tables 1-3)

<table>
<thead>
<tr>
<th>Study</th>
<th>Usefulness</th>
<th>Country</th>
<th>Design study</th>
<th>Setting</th>
<th>Population/enrollment criteria</th>
<th>Number of subjects</th>
<th>Severity of dementia</th>
<th>Type of infection</th>
<th>Diagnosis infection</th>
<th>Antibiotic therapy</th>
<th>Factor associated with the use of antibiotics</th>
</tr>
</thead>
<tbody>
<tr>
<td>17. Fabiszewski et al., 1990</td>
<td>75% Useful</td>
<td>US</td>
<td>Prospective cohort</td>
<td>Hospital for long-term care and had dementia</td>
<td>75/104 patients developed 172 episodes of fever</td>
<td>75.8% (69/172) of fever was treated with antibiotics</td>
<td>69.6% (64/92) of fever in the antibiotic group was treated with antibiotics</td>
<td>93 of 172 episodes were urine, 67 were UTI, and 25 were systemic infections</td>
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<tr>
<td>18. Givens et al., 2010</td>
<td>75% Useful</td>
<td>US</td>
<td>Prospective cohort study</td>
<td>Nursing home residents aged 65 and older, with a length of stay 30 days or longer, cognitive impairment due to dementia</td>
<td>133 residents developed 225 episodes of pneumonia</td>
<td>91.1% (205/225) of pneumonia episodes was treated with antibiotics</td>
<td>55.1% (124/225) IV</td>
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<tr>
<td>19. D’Agata et al., 2013</td>
<td>75% Useful</td>
<td>US</td>
<td>Prospective study</td>
<td>Nursing home residents with advanced dementia, 65 years and older, with a length of stay ≥ 90 days</td>
<td>131 episodes UTI were treated with antibiotics</td>
<td>77.9% (102/131) episodes UTI were treated with antibiotics</td>
<td>20.4% (26/128) IV</td>
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<tr>
<td>Study (Year)</td>
<td>Usefulness</td>
<td>Country</td>
<td>Study Design</td>
<td>Setting</td>
<td>Population</td>
<td>Clinical Criteria</td>
<td>Antimicrobial Treatment</td>
<td>Comments</td>
<td></td>
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<tr>
<td>Chen et al., 2006</td>
<td>50% Useful</td>
<td>US</td>
<td>Retrospective cohort study</td>
<td>1,675 bed LTCF 2001-2003</td>
<td>Residents aged 65 and older who died with advanced dementia</td>
<td>Of 240 residents 154 patients developed 229 suspected pneumonia episodes during the last 6 months of life</td>
<td>Advanced dementia (CPS ≥5)</td>
<td>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</td>
<td>A8 † Unstable vital signs (respiratory rate ≥ 30 breaths/min, temperature ≥ 101.1°F, heart rate ≥ 125 beats/min, systolic blood pressure &lt; 90 mmHg)</td>
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<tr>
<td>Mehr et al., 2003</td>
<td>100% Useful</td>
<td>US and NL</td>
<td>2 Prospective cohort studies</td>
<td>36 NHs 1995-1998</td>
<td>Nursing home residents who were 60 and older, were in the nursing home at least 2 weeks before the illness and had a LRI</td>
<td>701 Nursing home residents who were 60 and older, were in the nursing home at least 2 weeks before the illness and had a LRI</td>
<td>Severe dementia: USA – AB+: 37.6%, AB-: 53.4%</td>
<td>LRI Clinical criteria diagnosed by trained project nurses 85.3% (598/701) received antibiotic treatment 27.8% (195/701) received parenteral antibiotic treatment</td>
<td>A8 † Illness severity (e.g. rapid pulse, respiratory distress, high temperature) A8 † Illness severity at time of the treatment decision and 2 weeks before the treatment decision A8 † ADL dependency A8 † More severe dementia (increased scores at the Cognitive Performance Scale)</td>
<td></td>
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</tr>
<tr>
<td>22. van der Steen et al., 2002</td>
<td>Useful NL Observational cohort study</td>
<td>61 NHs</td>
<td>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.</td>
<td>706 BANS-S score 17.5 (4.8) - subgroup of 635 patients treated without antibiotics or treated with antibiotics for curative reasons</td>
<td>Pneumonia Clinical criteria</td>
<td>77% (544/706) of episodes was treated with antibiotics</td>
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<tr>
<td>75% Useful</td>
<td>1996-1998</td>
<td>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.</td>
<td>706 BANS-S score 17.5 (4.8) - subgroup of 635 patients treated without antibiotics or treated with antibiotics for curative reasons</td>
<td>Pneumonia Clinical criteria</td>
<td>77% (544/706) of episodes was treated with antibiotics</td>
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</tbody>
</table>

AB ↑ No aspiration
AB ↑ Number of psychogeriatric beds in the facility
AB ↓ Illness severity at time of the treatment decision and 2 weeks before the treatment decision
AB ↓ Previous pneumonia
AB ↓ Dehydration
AB ↓ Insufficient drinking (<1500 mL daily, previous 7 days)
AB ↓ Eating dependence - pre-LRI and at the time of the treatment decision (requires assistancefully dependent)
AB ↓ More severe dementia (increased scores at the Bedford Alzheimer Nursing Severity Scale)
AB ↓ Advance care planning
AB ↓ Treatment in the summer
AB = Psychogeriatric disease: Alzheimer dementia, mixed dementia
AB = Sex
AB = General health condition: increased urine of fecal incontinence, increased mobility dependence, increased illness severity, increased discomfort
AB = Vaccination for influenza in prior winter
AB = Nursing home situated in one of the three biggest NL cities
AB = Total number of beds or number of beds for somatic patients
AB = Religious affiliation of facility
AB = Level of policy making (availability of mission statement, quality policy, quality manual, and quality report on 4-point scale)
AB = Protocol or policy on (non) treatment available
<table>
<thead>
<tr>
<th>Ref.</th>
<th>Author(s)</th>
<th>Usefulness</th>
<th>Design</th>
<th>Setting</th>
<th>Sample Size</th>
<th>Main Outcome Measure</th>
<th>Clinical Criteria</th>
<th>Antibiotics</th>
</tr>
</thead>
<tbody>
<tr>
<td>23.</td>
<td>van der Steen et al., 2009b</td>
<td>Useful NL</td>
<td>Prospective cohort study</td>
<td>Nursing home residents from psychogeriatric wards</td>
<td>54 NHs</td>
<td>BANS-S scores: 17.1 (4.7)</td>
<td>Pneumonia</td>
<td>79% (57/72) of episodes was treated with antibiotics</td>
</tr>
<tr>
<td>24.</td>
<td>Visapaa, 1998</td>
<td>Somewhat useful Finland</td>
<td>Chart review 1976 and 1985</td>
<td>Long Term Care institutions for permanent care</td>
<td>3 patients &gt; or ≥65 (dementia: 59.2%)</td>
<td>Feverish conditions</td>
<td>Not specified</td>
<td>43.1% (44/102) received antibiotics to treat feverish conditions in the last 7 days of life</td>
</tr>
</tbody>
</table>
### Table 3. Attitudes towards antibiotic use using a hypothetical scenario (data referring to the text in the Results, and Tables 1-3)

#### Family

<table>
<thead>
<tr>
<th>Study</th>
<th>MMAT score</th>
<th>Usefulness</th>
<th>Country</th>
<th>Design study</th>
<th>Setting</th>
<th>Population/enrolment criteria</th>
<th>Number of subjects</th>
<th>Severity of dementia</th>
<th>Hypothetical scenario</th>
<th>Prefer antibiotic therapy</th>
<th>Factor associated with the use of antibiotics</th>
</tr>
</thead>
<tbody>
<tr>
<td>25. Kwok et al., 2007</td>
<td>25%</td>
<td>Useful</td>
<td>China</td>
<td>Interview study using a hypothetical scenario</td>
<td>Family caregivers of older people with dementia</td>
<td>3 NH, 1 day care center, 1 psychiatric and 4 LTC wards</td>
<td>51 patients and family caregivers (response 57%)</td>
<td>Most patients had moderate to severe dementia and were residing in nursing homes</td>
<td>Dementia and critical illness or coma</td>
<td>In critical illness: 78% (40/51) and in coma: 61% (31/51) would agree to treatment with antibiotics</td>
<td></td>
</tr>
<tr>
<td>26. Potkins et al., 2000</td>
<td>25%</td>
<td>Useful</td>
<td>UK</td>
<td>Survey study</td>
<td>Relatives of people with dementia</td>
<td>2 old age psychiatry assessment units and 1 LTCF</td>
<td>50 patients and their relatives</td>
<td>Most had severe dementia – Clinical Dementia Rating Scale (CDR): 8 stage 1, 11 stage 2, 31 stage 3</td>
<td>Life-threatening infection</td>
<td>52% (26/50) would agree to IV antibiotics 60% (30/50) would agree to oral antibiotics</td>
<td></td>
</tr>
<tr>
<td>27. Mezey et al., 1996</td>
<td>50%</td>
<td>Somewhat useful</td>
<td>US</td>
<td>Interview and survey study using hypothetical scenarios</td>
<td>Spouse caregivers of Alzheimer's disease patients, evaluated at the Aging and Dementia Research Center (ADRC), who had a minimum St 4 on the GDS</td>
<td>50 spouses</td>
<td>Not specified</td>
<td>Critical illness – not further specified</td>
<td>Critical illness: 90% (45/50) would agree to receive antibiotic treatment</td>
<td>AB ↑ Comfort of spouses with decision to forgo antibiotic was 40% and lowest of all treatment decisions</td>
<td></td>
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</tbody>
</table>

#### Patient

<table>
<thead>
<tr>
<th>Study</th>
<th>MMAT score</th>
<th>Usefulness</th>
<th>Country</th>
<th>Design study</th>
<th>Setting</th>
<th>Population/enrolment criteria</th>
<th>Number of subjects</th>
<th>Severity of dementia</th>
<th>Hypothetical scenario</th>
<th>Prefer antibiotic therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>28. Reilly et al., 1994</td>
<td>75%</td>
<td>Useful</td>
<td>US</td>
<td>Survey study</td>
<td>Community dwelling elderly people aged 60 and older</td>
<td>218 (response 69%)</td>
<td>Moderately advanced Alzheimer's disease</td>
<td>Moderately advanced Alzheimer 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</td>
<td>73% (159/218) would accept antibiotic treatment</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Useful/N.</td>
<td>US/Country</td>
<td>Methodology</td>
<td>Participants</td>
<td>% Responders</td>
<td>Question</td>
<td>Results</td>
<td></td>
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<tr>
<td>Gjerdingen et al., 1999</td>
<td>75%</td>
<td>Useful US</td>
<td>Survey/interview study</td>
<td>3 NHs, 1 transitional care unit; 1 assisted living unit</td>
<td>84 – response n.a.</td>
<td>% of individuals that would prefer antibiotics with different levels of dementia</td>
<td>70%</td>
<td>1. Personality changes that make you unpleasant 2. Cannot remember how to do everyday things 3. Cannot recognize loved ones 4. Cannot care for yourself at all and cannot communicate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low et al., 2003</td>
<td>75%</td>
<td>Useful Australia</td>
<td>Descriptive cross-sectional interview study</td>
<td>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</td>
<td>52 – response</td>
<td>Severe dementia (hypothetical scenario)</td>
<td>88%</td>
<td>Recurrent aspiration pneumonia and end-stage dementia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lo et al., 1986</td>
<td>100%</td>
<td>Somewhat useful US</td>
<td>Survey study with a questionnaire and a hypothetical scenario</td>
<td>General Internal Medicine Group Practice</td>
<td>28 (group 1), 69 (group 2), 55 (group 4)</td>
<td>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.</td>
<td>76%</td>
<td>47% (71/152) would accept antibiotics and hospitalization for pneumonia</td>
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</tbody>
</table>
### Table 4. Factors associated with use of antibiotics (only) (data referring to Tables 1-3)

<table>
<thead>
<tr>
<th>Study and year</th>
<th>MMAT score</th>
<th>Usefulness</th>
<th>Country</th>
<th>Design study</th>
<th>Setting</th>
<th>Population/enrollment criteria</th>
<th>Number of subjects</th>
<th>Limited to advanced dementia</th>
<th>Before death</th>
<th>Hypothetical</th>
<th>Factor associated with the use of antibiotics</th>
</tr>
</thead>
<tbody>
<tr>
<td>32. Forbes et al., 2000</td>
<td>75% useful</td>
<td>US</td>
<td>Descriptive and qualitative study</td>
<td>NHs</td>
<td>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.</td>
<td>28 family members</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>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</td>
<td></td>
</tr>
<tr>
<td>33. van der Steen et al., 2004</td>
<td>100% useful</td>
<td>US and NL</td>
<td>Prospective cohort studies</td>
<td>NHs</td>
<td>Psychogeriatric disease, residence in the nursing homes for at least 4 weeks, and pneumonia as judged by the attending physician.</td>
<td>701 residents (US) and 551 residents (NL)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>AB † US residents vs NL residents</td>
<td></td>
</tr>
<tr>
<td>34. Szafara et al., 2012</td>
<td>50% useful</td>
<td>US and NL</td>
<td>Observational, prospective cohort studies</td>
<td>NHs</td>
<td>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.</td>
<td>1044 residents (US) and 513 residents (NL)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>AB † - High temperature &gt;38.3°C AB † Swallowing difficulty AB † Eating dependence - pre-LRI and at the time of the treatment decision (requires assistancefully 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)</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Country</td>
<td>Sample Size</td>
<td>Study Type / Description</td>
<td>Key Findings</td>
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<tr>
<td>Helton et al., 2006</td>
<td>US and NL</td>
<td>24</td>
<td>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.</td>
<td>- AB ↓ Value of QoL in decision making</td>
<td></td>
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<tr>
<td>van der Steen et al., 2005</td>
<td>NL</td>
<td>165</td>
<td>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.</td>
<td>- AB ↓ Intention of hastening death</td>
<td></td>
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<tr>
<td>van der Steen et al., 2009a[45]</td>
<td>NL</td>
<td>69</td>
<td>Physicians in nursing homes from all over the Netherlands, who diagnosed newly a pneumonia in their next patient with dementia</td>
<td>- AB ↓ Poor prognosis (physician estimate at diagnosis) or ADEPT score</td>
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**Abbreviations:**
- AB↑: Positive association with antibiotic treatment
- AB↓: Negative association with antibiotic treatment
- AB≡: No association with antibiotic treatment
- BANS-S: Bedford Alzheimer Nursing Severity-Scale
- ADEPT: The Advanced Dementia Prognostic Tool
- ADL: Activities of daily living
- Before death: Factor from a study examining antibiotic use in the period before death
- FAST: Functional Assessment Staging Test
- Hypothetical: Factor from a study using a hypothetical scenario
- IV: Intravenous
- LRI: Lower respiratory infection
- LTC: long term care
- LTCF: Long term care facility
- MMSE: Mini-Mental State Examination
- NH: Nursing home
- NL: The Netherlands
- QoL: Quality of life
- US: United States of America
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)

36. van der Steen et al., 2005
25% useful NL Prsopective 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

37. van der Steen et al., 2009a
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

- Poor prognosis (physician estimate at diagnosis) or ADEPT score
- Futility of treatment: physicians prefer not to treat when to do so seems futile

- No association with antibiotic treatment
- Positive association with antibiotic treatment
- Negative association with antibiotic treatment

- BANS-S: Bedford Alzheimer Nursing Severity-Scale
- ADEPT: The Advanced Dementia Prognostic Tool
- ADL: Activities of daily living
- Before death: Factor from a study examining antibiotic use in the period before death
- FAST: Functional Assessment Staging Test
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- MMSE: Mini-Mental State Examination
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- NL: The Netherlands
- QoL: Quality of life
- US: 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
<table>
<thead>
<tr>
<th>R1</th>
<th>Nederlandse samenvatting</th>
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</table>
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 ziekteproces gestart zou moeten worden met palliatieve zorg. Het startpunt van het inzetten van palliatieve zorg is vooral namelijk een punt van discussie, omdat de meningen tussen beroepsbeoefenaren in de gezondheidszorg verdeeld zijn. Dit heeft onder ander 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. Vooral nog zijn er geen representatieve nationale gegevens beschikbaar over intercurrente aandoeningen en de kans op overlijden in relatie tot de ernst van de dementie, over symptoombehandeling, en over besluitvorming rondom behandelingen gedurende de verpleeghuisopname. 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 Dementie (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 waardvol om de hiërarchie van de items van de schaal (“in hoeverre is iemand in staat om zich zelfstandig aan te 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 ordinaal 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 longitudinal 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 vroegtijds 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 persistender aanwezig (in 36%-41% van alle bewoners). Agitatie was het meest voorkomend (57%-71%), en ook vaak persistend (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 persistender 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 behandeling 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 langdurig 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 voor 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 beleids-makers. 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 medicijnse behandeling 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

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CURRICULUM VITAE

Curriculum Vitae (Nederlands)

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


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”

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”
UNDERSTANDING THE CLINICAL COURSE OF DEMENTIA
A search to optimize palliative care for nursing home residents

Simone A. Hendriks

Uitnodiging
voor het bijwonen van de openbare verdediging
van mijn proefschrift

UNDERSTANDING THE CLINICAL COURSE OF DEMENTIA
In de aula van de Vrije Universiteit
Koelelaan 1105 te Amsterdam
maandag 10 april 2017
om 11.45 uur
Volgens de wet is van dit als wetenschappelijk arbeid aan te wijzen.