Quality of life, care dependency and Paracetamol In advanced Dementia

Is paracetamol the panacea to improve quality of life?

PAULIEN H. VAN DAM

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Academic network for research in elderly care

The studies in this thesis took place in the University Network for the Care Sector South Holland (UNC-ZH). In this network, the Leiden University Medical Center (LUMC) collaborates structurally with 12 elderly care organisations in South Holland (Marente, Pieter van Foreest, Florence, Topaz, Argos Zorggroep, Saffier, Laurens, Zonnehuisgroep Vlaardingen, Woonzorgcentra Haaglanden, Aafje, ActiVite, Haagse Wijk- en Woonzorg).

Caregivers, policy makers, researchers, students, residents and relatives work together to improve the quality of care and quality of life for vulnerable older people. The UNC-ZH is a regional platform, inspirator and learning network for innovation in long-term care. Research, education and training, and practice are closely related.

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Voor hen die het niet meer weten of kunnen en hun naasten

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Chapter 1

General Introduction

Dementia

Worldwide, more than 55 million persons have dementia, the number increasing with nearly 10 million new cases each year.[1] In the Netherlands, 250,000-290,000 persons have dementia, 32-38% of whom live in a long-term care facility (LTCF).[2,3] Dementia is a neurodegenerative disease that mainly affects older adults and is often diagnosed when there are cognitive or behavioural (neuropsychiatric) symptoms.[1,4] These symptoms must interfere with daily activities or work, clearly represent a decline from previous levels of functioning, and they are not explained by delirium or depression.[4] Furthermore, the cognitive impairment has to be diagnosed based on history-taking from the patient and a knowledgeable informant, and an objective cognitive assessment. Finally, the cognitive impairment involves ≥ 2 of the following cognitive domains: I) impaired ability to acquire and remember new information, II) impaired reasoning and handling of complex tasks, poor judgment, III) impaired visuospatial abilities, IV) impaired language functions, and V) changes in personality and behaviour.[4] Recently, the term 'dementia' has been replaced with 'minor and major cognitive disorder' in the Diagnostic and Statistic Manual of Mental Disorders (DSM5),[5] but because Dutch guidelines still follow the above-mentioned criteria from the National Institute on Aging and the Alzheimer's Association[6], the term 'dementia' will be used throughout this thesis.

Quality of life

As dementia is a progressive neurological disease for which there is still no cure, the primary goal of caring for persons with dementia is optimizing their quality of life (QoL).[7] The World Health Organization (WHO) defines QoL as 'an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns.'[8]

Persons with dementia may not always be able to set their own goals and expectations. In this light, the WHO has defined goals for caregivers to improve dementia care, which include 'optimizing well-being' and 'understanding and managing behaviour changes'.[1]

According to Lawton, important domains of QoL in persons with dementia include competent cognitive functioning, the ability to perform activities of daily living (ADL), to engage in meaningful and social activities, and having balanced positive and negative emotions.[9] Ultimately, it is up to the persons with dementia themselves, which of these components are most important for their QoL, which characterizes the subjectivity of this topic.[7] When persons with dementia are no longer able to assess their own QoL, family, friends and professional caregivers need to be their voice, as they are most familiar with their values, goals and needs. There is a wide diversity of proxy-rated QoL assessment tools, reflecting the complexity of measuring QoL.[10,11] The QUALIDEM[12,13] is one of these tools and was identified and recommended previously as having

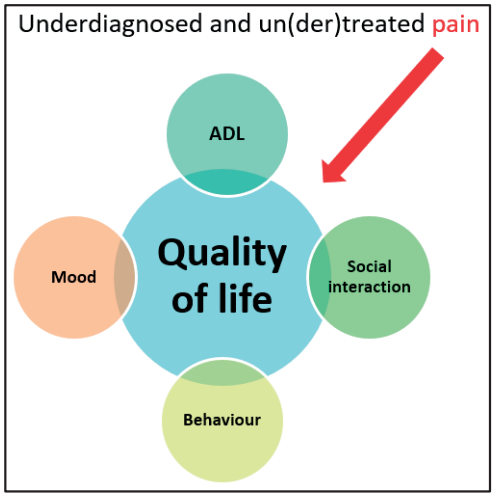
the most measurement properties reported, i.e. adequate evidence of construct and content validity, and satisfactory test-retest and inter-observer reliability.[11, 13, 14]

There is evidence that the QoL of persons with dementia does not always decline as the disease progresses.[15, 16] However, there are symptoms and signs accompanying the progressing disease that have an impact on QoL, i.e., functional decline,[17, 18] and neuropsychiatric symptoms such as depression, aggression and psychosis.[17-22] Also, the way in which QoL is measured (self-rating in persons with mild to moderate dementia and proxy-rating in persons with advanced dementia) may influence the outcome.[19, 21, 23] People surrounding persons with dementia face the challenge of optimizing these persons' QoL, and every factor identified to facilitate this, such as finding undiagnosed pain and treating it, is an added benefit.

Pain

Pain is common in persons with dementia living in LTCF: 30 to 80% regularly experiences acute or chronic pain.[24-27] Multiple causes can be found for this pain, often related to old age, and include musculoskeletal conditions, pressure ulcers and genitourinary infections.[25, 28, 29] The challenge is to identify those persons that are in pain and suffer from it. Ideal and the golden standard is that the persons self-report their pain. However, pain perception in persons with advanced dementia may be different and they are often no longer able to express pain adequately in terms of location, intensity and origin. Also, they are not always able to report the effect of pain treatment or potential adverse events.[25, 30] Consequently, pain in persons with advanced dementia is mainly observed and assessed by proxies (nursing staff, informal caregivers), but good assessment of pain is still not commonly implemented in practice in LTCF.[31] Although these assessments by proxies remain partly subjective, may vary between observers,[32] and differ from outcomes of self-reported pain assessments,[33] knowledge on the existence and intensity of pain is very important. Underdiagnosed and therefore untreated pain may have a negative impact on neuropsychiatric symptoms, i.e., aggression,[34, 35] agitation[36] and depression,[37, 38] social interaction,[39] ADL,[40, 41] appetite[42] and sleep.[43, 44] It may therefore have a major negative impact on the QoL of persons with advanced dementia (fig. 1).[26, 27, 45]

Fig. 1 Pain and quality of life



Pain treatment

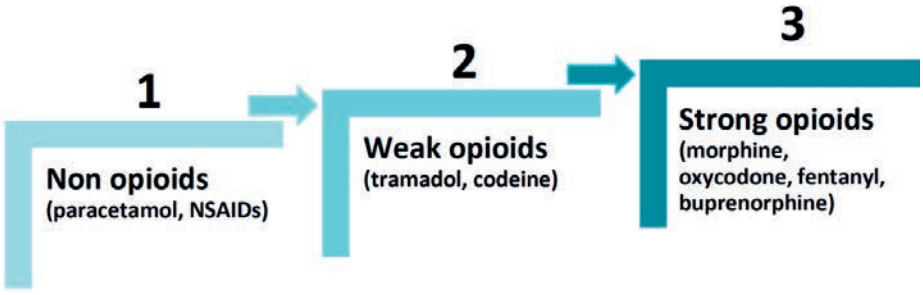
Non-pharmacological interventions

Pain management in persons with dementia can be challenging, since these persons often have comorbidities and a vulnerable brain, which increase the risk of adverse drug reactions. In this perspective, non-pharmacological interventions should be explored first when managing pain.[30] Several non-pharmacological interventions have been studied and been found effective on pain in persons with dementia, i.e. massage, exercise, music therapy and robotic care.[30, 46] These may work through providing distraction from pain and they also have been found effective on neuropsychiatric symptoms like depression and agitation.[30, 47] Pain and neuropsychiatric symptoms often co-exist and previous research has found evidence pointing towards behavioural interventions with a positive effect on pain and vice versa.[47] However, more research (solid randomized controlled trials) is needed to find out more about specific interventions such as singing, robotic care, aromatherapy and play activities, and to find the best frequency of offering an intervention for improving pain and neuropsychiatric symptoms in persons with dementia.[46, 47]

Pain treatment

To provide a good strategy to adequately treat pain in cancer patients, the WHO proposed an analgesic ladder in 1986. This ladder was later introduced in other patient groups outside cancer care and was composed of three steps: 1) mild pain: non-opioid analgesics such as paracetamol (also named acetaminophen) and nonsteroidal anti-inflammatory drugs (NSAIDs), 2) moderate pain: weak opioids with or without non-opioid analgesics, and 3) severe and persistent pain: strong opioids such as morphine, oxycodone, fentanyl and buprenorphine, with or without non-opioid analgesics (fig. 2).[48] Although this ladder was recently extended and adjusted by other authors, focusing more on QoL and on a bidirectional approach[49], part of step one (NSAIDs) and all of step 2 are usually skipped in older persons because of gastro-intestinal, cardiac, psychiatric and/or kidney side-effects.[50]

Fig. 2 World Health Organization Analgesic Ladder



Paracetamol in older persons

Paracetamol appears to be relatively safe and effective in treating mild to moderate pain in older persons, although the available evidence on safety and efficacy of paracetamol in an older population, especially long-term treatment, is limited.[51] While paracetamol is recommended as the first step in pain treatment and is most frequently used to treat mild to moderate pain among older persons with dementia,[52, 53] the working mechanism of paracetamol still remains partly unclear.[54] It is well known for its analgesic and antipyretic effects, but some people say they feel better when they take paracetamol. Is this because they had a fever, which is reduced by paracetamol and consequently they feel better? Or does paracetamol have other working mechanisms on well-being we do not yet know about? This is an interesting question, which to date remains unanswered. So far, paracetamol is step 1 of pain treatment, also in older persons, as the side-effects remain limited in low dosage (≤ 4 g per day for acute use and ≤ 3 g per day for chronic use). The recommended maximum daily dosage for paracetamol in older adults for use longer than 1 week is 2.5 g per day, except when a person has health problems such as liver insufficiency, a body weight ≤ 50 kg and/or use of more than 4 IU of alcohol per day.[55]

Effects of pain treatment

Previous research in persons with dementia has shown positive effects of paracetamol and opioids on sleep, at least in the first weeks of use,[56] social interaction,[39] agitation and psychosis,[57, 58] and depression,[59] and as a result also improvement of staff distress in LTCF.[60] Although strong opioids might be effective for persons with dementia and are increasingly prescribed,[61, 62] there are safety concerns that clinicians need to take into account.[63] Pain medication needs to be prescribed with caution, with special attention to monitoring efficacy and side-effects.

Care dependency and daily functioning

When a person is no longer able to fulfil their own needs, care dependency commences. With the progression of dementia, cognitive functions, such as memory, executive functions and planning/organizing, will deteriorate and help is needed from others.[64, 65] Initially from relatives and family, and at a later stage from professional caregivers. These declining cognitive functions often cause worsening of daily functioning.[66, 67] First affected are instrumental Activities of Daily Living (iADL; telephoning, shopping, preparing meals, taking care of household, travelling, taking medications and taking care of own finances),[68] followed by the basic ADL skills (dressing, bathing, toileting, transferring, incontinence and eating).[64, 69] The level of dependence in daily functioning has a direct negative relationship with the QoL,[70] morbidity and mortality[71, 72] and pain[73, 74] of a person with dementia. To maintain or improve their QoL, and to ameliorate distress of caregivers who take care of these persons, there is a need for points of reference to improve care dependency and daily functioning in persons with dementia.

Aims and outline of this thesis

Maintaining or improving the QoL of persons with advanced dementia is a huge challenge, mainly because it involves many factors. One of them is undiagnosed and therefore un(der) treated pain, which can be treated with pain medication. The populations in all studies used for this thesis consisted of persons with advanced dementia living in LTCF. The primary aim of this thesis is to investigate what the effect of paracetamol is on QoL and care dependency of persons with advanced dementia and low QoL living in LTCF. Other aims that are addressed in this thesis are to explore which persons with advanced dementia use different types of pain medications, how their pain medication use is associated with their QoL, and to investigate the effect of paracetamol on other outcomes such as neuropsychiatric symptoms, discomfort, pain and daily functioning.

Part I – Quality of life and pain medication in dementia

In *Chapter 2* of this thesis I) the characteristics of persons with advanced dementia living in LTCF with and without pain medication are compared, II) the QoL of these persons with and without pain, stratified by pain medication use (paracetamol, opioids, both paracetamol and opioids, or no pain medication), are compared, and III) the associations between the use of paracetamol and QoL of persons with advanced dementia living in LTCF are explored. The research questions of this chapter are:

1. What is the difference in characteristics between persons with advanced dementia living in LTCF with and without pain medication?
2. What is the association between the QoL, pain and use of pain medication (paracetamol, opioids, both paracetamol and opioids, no pain medication) of persons with advanced dementia living in LTCF?

Chapter 3 comprises the study protocol, aims and outline of the Quality of life and Paracetamol In advanced Dementia (Q-PID) study: to evaluate the effect of scheduled pain treatment with paracetamol on QoL, neuropsychiatric symptoms, pain, daily functioning and care dependency.

Chapter 4 shows the results of the main outcome measures of the Q-PID study. The research questions addressed in this chapter are:

1. What is the effect of regularly scheduled administration of paracetamol on QoL and discomfort of persons with advanced dementia living in LTCF?
2. What is the effect of regularly scheduled administration of paracetamol on pain and neuropsychiatric symptoms of persons with advanced dementia living in LTCF?

Part 2 – Care dependency, daily functioning, pain medication and QoL

Chapter 5 comprises results of the Q-PID study and investigates the effects of scheduled administration of paracetamol on care dependency and daily functioning of persons with advanced dementia living in LTCF. The following research question is addressed in this chapter:

1. What is the effect of regularly scheduled administration of paracetamol on care dependency and daily functioning in persons with advanced dementia living in LTCF?

Chapter 6 investigates care dependency and ADL functioning in persons with advanced dementia living in LTCF, and explores which factors are associated with care dependency and daily functioning. The research questions addressed in this chapter are:

1. How care dependent are persons with advanced dementia living in LTCF?
2. Which factors are associated with care dependency and daily functioning of persons with advanced dementia living in LTCF?

The final chapter, *Chapter 7*, presents the general discussion on the main results of the studies, considers the clinical implications of the findings, and provides recommendations for future research to improve the care for, and QoL of, persons with advanced dementia.

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Chapter 2

Quality of life and pain medication use in persons with advanced dementia living in long-term care facilities

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ABSTRACT

Objectives

In residents with dementia living in a long-term care facility (LTCF), un(der)treated pain may trigger behavioral disturbances, mood syndromes, and deterioration of physical functioning and self-maintenance. Because these factors can have considerable impact on the quality of life (QoL), this study aimed to (1) compare characteristics of persons with advanced dementia living in LTCFs with and without pain medication, (2) compare QoL in these persons with and without pain, stratified by type of pain medication use, and (3) explore associations between the use of paracetamol and QoL in persons with advanced dementia living in LTCFs.

Design and setting

This study analyzed baseline data from the COmmunication, Systematic assessment and treatment of pain, Medication review, Occupational therapy, and Safety (COSMOS) study; a multicenter, cluster randomized effectiveness-implementation clinical hybrid trial in 67 Norwegian LTCF clusters.

Participants

In total, 407 LTCF residents (rural and urban areas) aged ≥65 years, with Functional Assessment Staging scores of 5-7 (i.e. moderate to advanced dementia)

Main outcome measure

QoL as assessed by the 6 QUALIDEM (validated questionnaire to measure QoL in persons with dementia living in LTCF) domains applicable to persons with moderate to severe dementia. The association between QoL and paracetamol was estimated using linear mixed-effect models, adjusting for confounding variables.

Results

62.7% used pain medication (paracetamol, opioids, or both). QoL was lower in residents using pain medication, compared with those without pain medication [mean QUALIDEM score 68.8 (standard deviation 17.4) vs. 75.5 (standard deviation 14.6), respectively, $P < .001$]. Multilevel analysis showed that paracetamol use was not associated with QoL.

Conclusions and Implications

Persons with advanced dementia living in LTCF using pain medication have a lower QoL compared with those not using pain medication. These results are of key importance for the clinician because they stress the need for regular medication review and pain management. When measured cross-sectionally, use of paracetamol is not associated with increased QoL.

Trial registration

ClinicalTrials.gov NCT02238652

INTRODUCTION

According to the World Health Organization (WHO), at present 47.5 million people worldwide have dementia. This number is expected to increase to 75.6 million by 2030 and to 135.5 million by. 2050.[1] Pain is a common symptom among persons with dementia living in long-term care facilities (LTCFs), with a prevalence ranging from 40% to 60%.[2-5] A more accurate prevalence rate is difficult to establish, as persons with advanced stages of dementia cannot always express their feelings and needs (such as help for pain) compared with persons without dementia.[6-8] Therefore, undertreatment of pain remains a threat in this population. Moreover, un(der)treated pain may trigger behavioral disturbances (ie, aggression, apathy, agitation[5,6,9], mood syndromes (ie, depression) [10], and sleeping disorders[11,12] in persons with dementia. In addition, these symptoms may decrease the quality of life (QoL) of persons with dementia.[13-15]

QoL is defined by the WHO as *'individuals' perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns.'*[16] Because persons with dementia are often unable to show/explain their own goals, expectations, standards and concerns, healthcare professionals may need to maintain QoL for them. A major component of this latter aim is to adequately treat symptoms that may have an impact on QoL, such as pain.[17]

Several pain treatments have been evaluated regarding their influence on behavioral and mood problems of persons with dementia, irrespective of whether or not the person has pain. One such treatment is the use of paracetamol; the world's most frequently used analgesic and the first step of pain treatment in accordance with the WHO pain relief ladder.[18] One study showed that persons with dementia were less socially isolated and more active during the intervention period with paracetamol compared with the placebo period.[19] In another study on pain treatment conducted in Norway, agitation and depression rates dropped significantly in the intervention group who received pain medication in a stepwise way.[9,20,21] Moreover, staff distress diminished, because of a reduction in residents' agitation and apathy.[22] Finally, another study showed that pain treatment improved sleeping disturbances over a short period of time in persons with dementia and depression.[23]

Research on the relationship between pain, pain medication and QoL in persons with dementia is relatively scarce. Therefore, the aims of this study were to (1) compare characteristics of persons with advanced dementia living in LTCFs with and without pain medication, (2) compare QoL in these persons with and without pain, stratified by pain medication use (paracetamol, opioids, both paracetamol and opioids, or no pain medication), and (3) explore associations between the use of paracetamol and QoL in persons with advanced dementia living in LTCFs.

Our hypothesis was that persons with advanced dementia that use pain medication would have less pain and, consequently, would have a better QoL.

METHODS

Study Design

This study made a cross-sectional secondary analysis of data from baseline measurements of the COmmunication, Systematic assessment and treatment of pain, Medication review, Occupational therapy, and Safety (COSMOS) study; a multicenter, cluster randomized effectiveness-implementation clinical hybrid trial in 67 Norwegian LTCF clusters (conducted between August 2014 and December 2015).[24] The main purpose of that study was to ameliorate QoL of individuals both with and without dementia by improving advance care planning, adequate assessment and treatment of pain, implementing systematic medication reviews to reduce administration of unnecessary medication, and systematic organization of individual activities. The intervention lasted 4 months with a follow-up period of 9 months post-baseline.

The COSMOS trial was approved by the Regional Committee for Medical and Health Research Ethics, West Norway (REK 2013/1765), and registered at clinicaltrials.gov (NCT02238652).

Verbal and written informed consents were acquired in direct conversation with the resident (if possible) and his or her legal representative.

Inclusion criteria for this cross-sectional study were LTCF residents (in both rural and urban areas) aged ≥65 years, with Functional Assessment Staging (FAST) scores of 5-7 (ie, moderate, moderate severe and severe dementia).[25]

Patients with a life expectancy ≤6 months, or having schizophrenia were excluded.

Measurements

Information on age, sex, and marital status were collected by nurses. To extract data on pain medication use (paracetamol and opioids), the treating elderly care physician provided a "Topical Medication Overview" (ie, a sheet with only the current prescribed and used medications, including dose). This medication overview was provided in the same week as the other data were collected. Use of paracetamol and/or opioids was defined as the use of paracetamol, opioids or both on a continuous basis (ie, at least once a day).

The stage of dementia was obtained by the FAST measure.[25] This is a tool to assess functional deterioration in different stages of dementia.[26] FAST scores range from 1 (no objective or subjective functional decrement/normal aging) to 7 (severe dementia).

For the primary outcome, QoL, the validated questionnaire to measure QoL in persons with dementia living in LTCF (QUALIDEM), was used.[27,28] Moreover, of an established set of QoL instruments, it is considered to have the best-studied measurement properties.[29] The instrument consists of 8 subscale domains (care relationship, positive affect, negative affect, restless tense behavior, social relations, social isolation, feeling at home and occupation). For the present study 19 of 37 items were deleted as recommended by the authors of the QUALIDEM manual for people with advanced dementia.[30] Consequently, 6 domains were used for analysis (care relationship, positive affect, negative affect, restless tense behavior, social relationships and social isolation). To compare different domain scores and to calculate an overall mean score, the scores were rescaled to a maximum of 100 points per domain by dividing the score by the maximum score of the domain and multiplying by 100. In this way, the new value represents the original score as a percentage of the maximum value. An overall mean score (QUALIDEM 6-domain overall score, QUALIDEM-6D) was calculated by adding the domain scores, and dividing by 6 (the number of domains). Mean domain scores and an overall mean score range from 0 (worst QoL possible) to 100 (best QoL possible). This process of transformation has been successfully applied in previous studies.[31-33]

The Mobilization-Observation-Behavior-Intensity-Dementia-2 (MOBID-2) Pain Scale[34-36] is a 2-part tool used to measure pain intensity. This pain scale was developed to capture pain expressed verbally, with facial expression, and/or with showing defense by a person with dementia. The nurse grades the overall pain intensity with an overall score (ranging from 0 to 10). An overall score of ≥3 indicates that a resident has clinically relevant pain intensity.[34,35]

The Cornell Scale for Depression in Dementia, with 19 symptoms and signs distributed among 5 domains (mood-related signs, behavioral disturbance, physical signs, cyclic functions and ideational disturbance), was used to assess depressive symptoms.[37] A score >12 is indicative of probable major depressive disorder.[37]

Neuropsychiatric symptoms were measured by the Neuropsychiatric Inventory-Nursing Home version (NPI-NH).[38,39] It consists of 10 domains of behavior (delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, elation/euphoria, apathy/indifference, disinhibition, irritability/lability and aberrant motor behavior), and 2 types of neurovegetative changes (sleep and night-time behavior disorders and appetite and eating disorders). For each domain, frequency (rarely, sometimes, often, very often) and severity (mild, moderate, severe) are multiplied to form a domain score. The total NPI-NH score was calculated by adding all 12 domain scores,

ranging from 144 (extreme neuropsychiatric symptoms) to 0 (no neuropsychiatric symptoms). Furthermore, 8 domains were clustered into 3 factors, ie, Psychosis (delusion, hallucination), Agitation (agitation, disinhibition and irritability) and Affective Symptoms (depression, anxiety), as was carried out with Norwegian data[40], based on the study of Selbæk et al.[41]

The Physical Self-Maintenance Scale was used to assess physical functioning in terms of activities of daily living (ADL).[42] This encompasses 6 aspects (toilet, feeding, dressing, grooming, physical ambulation, and bathing) in which professional caregivers rate the level of self-maintenance. Total scores range from 0 (no physical self-maintenance) to 6 (complete physical self-maintenance).

Statistical Analysis

To compare characteristics of persons with and without pain medication and QoL for persons with and without pain, independent samples t-tests were used to compare numerical, normally distributed characteristics, whereas Mann-Whitney U-tests were used to compare numerical, non-normally distributed characteristics. Categorical characteristics were compared using χ^2 tests. The association between QoL and paracetamol use was estimated by linear mixed-effect models, using restricted maximum likelihood. To account for correlation among residents within LTCFs, we included a random intercept for LTCF units. Confounding was minimized by adjusting for opioid use, age, sex, stage of dementia, ADL functioning, neuropsychiatric behavior, mood and interaction between paracetamol and opioids.

For the QUALIDEM-6D and for each of the 6 QUALIDEM domains, 4 models were computed: (1) in the first model, the effect of paracetamol use on QoL was estimated; (2) the second model contained items from the first model plus confounding variables (age, sex, behavior, mood, stage of dementia); (3) in the third model opioid use was added; and (4)in the final model interaction between paracetamol and opioids was added.

Descriptive analyses were performed with SPSS statistical software, v 23 (IBM Corp., Armonk, NY), and linear mixed-effect analyses were performed with STATA/IC15 (StataCorp 2017 Stata Statistical Software, Release 15; StataCorp LLC, College Station, TX).

RESULTS

COSMOS data were available for 545 nursing home residents. Of these, 32 residents were excluded because of missing FAST scores, 86 were excluded as they had FAST scores of 1-4, and an additional 20 persons were removed due to missing QUALIDEM data.

Data for 407 persons with dementia were available for analysis (Table 1).

Table 1: Characteristics of and Measurements in the Total Group of Persons With Advanced Dementia, Stratified by Pain Medication Use

	Total (n = 407)	Pain Medication (n = 255)	No Pain Medication (n = 152)	P value
Mean age (SD), y	86.6 (7.3)	86.5 (7.2)	86.6 (7.4)	.878
Female (%)	294 (72.2)	189 (74.1)	105 (69.1)	.272
Marital status (%)				.605
- Unmarried	47 (12.3)	31 (11.8)	18 (11.8)	
- Married	101 (26.4)	62 (23.6)	40 (26.3)	
- Widow	234 (61.3)	159 (60.5)	80 (52.6)	
FAST score 7 (%)	86 (21.1)	62 (24.3)	24 (15.8)	.042*
QUALIDEM-6D 0-100 (SD)	71.3 (16.7)	68.8 (17.4)	75.5 (14.6)	< .001
- A Care relationship 0-100	76.9 (23.8)	74.6 (25.3)	80.9 (20.4)	.009
- B Positive affect 0-100	75.4 (22.4)	73.1 (22.7)	79.1 (21.3)	.010
- C Negative affect 0-100	67.0 (26.8)	63.2 (27.6)	72.9 (24.0)	.001
- D Restless tense behavior 0-100	59.6 (30.3)	55.3 (31.3)	66.0 (27.8)	.001
- F Social relationships 0-100	73.5 (21.4)	72.4 (21.5)	75.3 (20.9)	.196
- G Social isolation 0-100	75.2 (23.7)	73.4 (24.7)	78.4 (21.3)	.034
MOBID-2 overall pain intensity, 0-10 (SD)	2.5 (2.6)	3.2 (2.7)	1.4 (2.0)	< .001
MOBID-2 ≥3 (%)†	155 (43.3)	121 (54.0)	34 (25.4)	< .001
Cornell total score 36-0 (SD)	7.3 (6.1)	8.2 (6.6)	5.6 (5.2)	<. 001
NPI-Nursing Home total score, 0-144 (IQR)	12.0 (3.0-26.0)	13.0 (4.0-32)	9.0 (2.0-20.0)	.012
- Psychosis (delusion, hallucination) (0-24)	0.0 (0.0-3.0)	0.0 (0.0-4.0)	0.0 (0.0-1.0)	.035
- Agitation (agitation, disinhibition, irritability) (0-48)	3.0 (0.0-11.0)	4.0 (0.0-12.3)	2.0 (0.0-9.0)	.019
- Affective symptoms (depression, anxiety (0-24)	1.0 (0.0-6.0)	2.0 (0.0-8.0)	0.0 (0.0-4.5)	.016
Physical Self-maintenance Scale, 0-6 (IQR)	1.0 (0.0-1.0)	1.0 (0.0-1.0)	1.0 (0.0-2.0)	.003

* Compared with FAST 5/6 group

† Clinically relevant pain

SD = standard deviation; FAST = Functional Assessment Staging; QUALIDEM-6D = validated questionnaire to measure QoL in persons with dementia living in LTCF, 6-domain overall score; MOBID-2 = Mobilization-Observation-Behavior-Intensity-Dementia-2 pain scale; IQR = inter-quartile range

Mean age was 86.6 (standard deviation [SD] 7.3) years and 72.2% was female. Of all residents, 54.1% used paracetamol and 32.7% used 1 or more opioids on a continuous basis. Of these, there was a 25% overlap of participants using both paracetamol and opioids (62.7% used paracetamol, opioids or both). When stratified into 2 groups (using any pain medication daily and not using any pain medication), the mean age, sex and marital status did not differ between the 2 groups (Table 1). In the group that used pain medication, the percentage of residents with FAST scores of 7 was significantly higher (24.3%) than in those not using pain medication (15.8%); P = .042.

In the total group, the QUALIDEM-6D was 71.3 (SD 16.7). Of the 6 individual QUALIDEM domains, care relationship 76.9 (SD 23.8), positive affect 75.4 (SD 22.4), social relationships 73.5 (SD 21.4), and social isolation 75.2 (SD 23.7) scored above the QUALIDEM-6D mean. "Negative affect" and "restless tense behavior" scored below the QUALIDEM-6D mean (67.0 [SD 26.8] and 59.6 [SD 30.3], respectively).

Compared with the group without pain medication, those who used pain medication had significantly lower QUALIDEM scores on all domains, with the exception of "social relationships" (Table 1).

In the total group, (1) 43.3% had clinically relevant pain scores (MOBID-2 score ≥3) and (2) the MOBID-2 total pain score was (on average) 2.5 (SD 2.6)(Table 1). The group that used pain medication had a total pain score more than twice that of those not using pain medication [3.2 (SD 2.7) vs. 1.4 (SD 2.0), P < .001]; moreover, the proportion of clinically relevant pain scores showed a significant difference between these 2 groups (54.0% vs 25.4%, P < .001).

The mean Cornell total score of the total group was 7.3 (SD 6.1)(Table1). The mean Cornell score in the group that used pain medication was significantly higher [8.2 (SD 6.6)] than that of the group without pain medication [5.6 (SD 5.2)](Table 1).

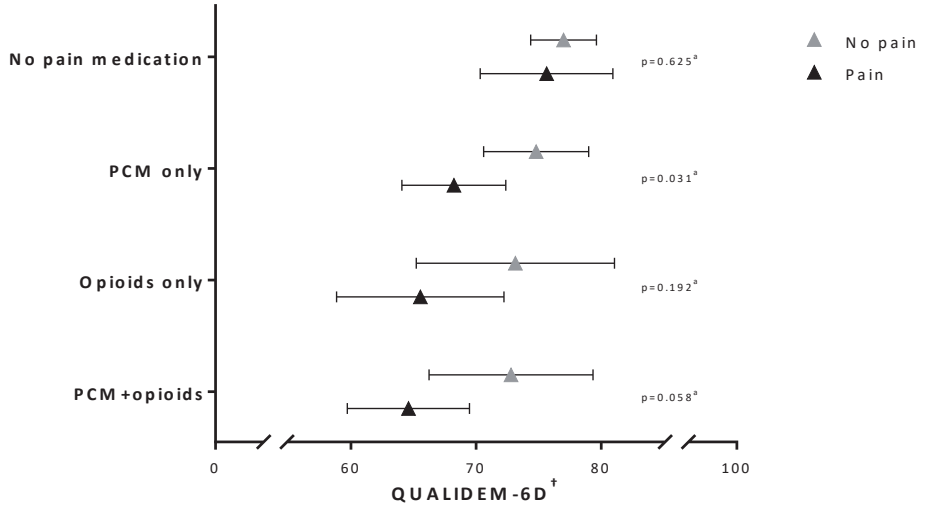
The median of the NPI-NH total score was 12.0 [interquartile range (IQR) 3.0-26.0]. The NPI-NH total score and the subscores on psychosis, agitation and affective symptoms, were significantly higher in the group with pain medication, than in the group without pain medication (Table 1).

The median ADL functioning on the Physical Self-maintenance Scale was 1.0 (IQR 0.0-1.0). The group without pain medication had better ADL functioning [1.0 (IQR 0.0-2.0)] compared with those using pain medication [1.0 (IQR 0.0-1.0)]; P = .003.

Figure 1 shows QoL of persons with dementia with and without pain, stratified by pain medication use. In the group with pain (MOBID-2 total score ≥3), persons with dementia that were using no pain medication had better overall QoL according to the QUALIDEM-6D [75.6 (SD 15.8)], compared with persons with paracetamol only [68.2 (SD 15.4)], opioids only [65.9 (SD 11.4)] and persons that used both paracetamol and opioids [64.6 (SD 18.6)]; P = .021. The group that used only paracetamol had significantly lower overall QoL when they were (still) in pain (68.2%), compared with having no pain (74.8%; P = .031).

Because there were no significant differences in QoL between the groups with and without pain using opioids, both opioids and paracetamol, or no pain medication, only the association between paracetamol and QoL was estimated. The final model of the linear mixed-effects model to estimate the association between paracetamol use and QoL is presented in Table 2. When adjusted for confounding variables and interaction between paracetamol and opioids, no significant association was found between paracetamol and overall QoL or in the 6 QoL subdomains.

Fig 1. Quality of life of persons with dementia with and without pain (MOBID-2 score ≥3), stratified by pain medication use



† Range 0-100
a Independent samples t-test
No pain medication no pain: n=100, pain: n=34
Paracetamol only no pain: n=57, pain: n=53
Opioids only no pain: n=18, pain: n=12
Paracetamol and opioids; no pain: n=28, pain: n=56
MOBID-2 = Mobilization-Observation-Behavior-Intensity-Dementia-2 pain scale
QUALIDEM-6D = validated questionnaire to measure QoL in persons with dementia living in LTCF, 6-domain overall score

Table 2. Final Linear Mixed-Effects Model of the Association Between Paracetamol Use and Quality of Life*

	Coefficient	Standard Error	z	P value	95% Confidence Interval	
QUALIDEM domains						
QUALIDEM-6D	-1.181	1.362	-0.87	.386	-3.850	1.488
A - Care relationship (SD)	-1.755	2.353	-0.75	.456	-6.367	2.857
B - Positive affect (SD)	-0.668	2.606	-0.26	.798	-5.775	4.440
C - Negative affect (SD)	-2.421	2.726	-0.89	.374	-7.764	2.922
D - Restless tense behavior (SD)	-3.639	2.969	-1.23	.220	-9.458	2.181
F - Social relationships (SD)	0.871	2.675	0.33	.745	-4.371	6.113
G - Social isolation (SD)	0.963	2.254	0.43	.669	-3.455	5.382

*Adjusted for opioid use, interaction between paracetamol and opioids, age, sex, stage of dementia, ADL functioning, neuropsychiatric behavior and mood
QUALIDEM-6D = validated questionnaire to measure QoL in persons with dementia living in LTCF, 6-domain overall score , SD = standard deviation

DISCUSSION

The main goal of this study was to gain insight into (1) differences in the characteristics of persons with advanced dementia with and without pain medication, (2) the QoL of these persons, and (3) the association between paracetamol use and QoL.

Contrary to our hypothesis, this study shows that, compared with the QoL of persons with dementia who did not use pain medication, the QoL of persons with dementia was lower when they use pain medication daily. This was the case for all QoL domains, with the exception of "social relationships". In addition, this study shows that (1) the pain score of persons with dementia using pain medication was more than twice as high as those without pain medication, and (2) that these individuals had a significantly lower ADL function.

Finally, the results show that paracetamol use was not independently associated with QoL of persons with dementia. Our results are of key importance for the clinician because they stress the need for regular medication review and pain management. Clinicians should not automatically assume that persons with dementia that are already using pain medication are relieved from their pain, or that they will be relieved from their pain once (any) pain medication is started. Periodical pain assessment and adjustment of pain medication prescriptions are important to diminish under- and over-prescription, and side-effects of pain medication as much as possible, to establish or maintain the best possible QoL in persons with advanced dementia.

In this study, the number of pain medications used is comparable to that of a previous study performed in Norway.[20] However, in the present study, the overall number of people having clinically relevant pain scores (MOBID-2 ≥3) was lower (43.3%) compared with the Norwegian study (> 55%). A possible explanation for this difference could be that, in the Norwegian study, only people with behavioral disturbances were included whereas in our study this was not the case. Pain could have caused these behavioral disturbances, leading to the higher number in the Norwegian study.

Our data on pain medication use and pain are also comparable with those of studies in other countries.[6,43] Moreover, the higher number of people using pain medication and still in pain, compared with those that use pain medication without pain, was also found in a study conducted in the United Kingdom .[44]

A major strength of the present study is that, to our knowledge, it is the first to explore the association between pain medication and QoL in this population. A recent study on the implementation of a stepwise multidisciplinary intervention concluded that effective pain management would be of vital importance to establish an optimal QoL.[45]

Another strength is that we used the 18-item QUALIDEM questionnaire, rather than the 37-item version, to measure QoL. As we only included people in severe stages of dementia and did not compare them with individuals in lower stages of dementia, we think that the 18-item version of the QUALIDEM is the most appropriate for our group of participants. Also, this avoids including items that are not applicable to be filled in by nurses about persons with advanced dementia, as was also applied in earlier studies.[43,46,47] Finally, we included all LTCF residents with FAST scores of 5-7 and aged ≥65 years irrespective of having pain or not, whereas other studies had stricter inclusion criteria besides (severe) dementia (eg, behavioral problems[20,36] or depression[23]).

A limitation of our study is that we used data from a study that was not specifically designed to address our research questions. For example, we only had information on what medication participants used at baseline, so we do not know how (adequately) the identification and assessment of pain were established before the baseline measurement, and consequently, how adequate the analgesic treatments were prescribed. Moreover, we had no information on what might have changed in the prescriptions of pain medication over time between baseline and the other measurement points at 4 and 9 months in the COSMOS study, so we were unable to examine the association between paracetamol use and QoL over time. Finally, another limitation of our study is that we could not control for the relative presence of painful conditions, because data on these were not present. This might have caused an underestimated QoL in the pain medication group, because simply having a painful condition could cause more pain and a lower QoL in a person with dementia and presumably there might have been more persons with a painful condition in the pain medication group than in the nonmedication group.

Our comparison of data on the QoL in persons with advanced dementia with and without pain revealed a lower QoL when an individual used paracetamol daily and was (still) in pain. For the other pain medication groups (opioids, opioids and paracetamol, and no pain medication) the same trend was seen; however, this difference was not significant. Either this trend could be based on coincidence, or the groups using opioids or both paracetamol and opioids were underpowered. A possible explanation for the lower QoL could be that a person experiences (unpleasant) side-effects (as seen with opioids in a recent study[48]), and/or the effects are insufficient. Also, the pain score of persons with dementia using pain medication in our study was more than twice as high as those without pain medication, which can be caused by badly dosed pain medication. Since this specific population is at increased risk for comorbidity, there is an increased chance of needing pain medication and being at risk to develop side-effects which can, in turn, decrease ADL function and QoL. This should be borne in mind by physicians when prescribing and evaluating pain medication in persons with advanced dementia.

Conclusions/Relevance

Persons with dementia living in LTCF who use pain medication have a lower QoL compared with persons with dementia who do not use any pain medication. These results are of key importance for the clinician because they stress the need for regular medication review and pain management. Periodical pain assessment and adjustment of pain medication prescriptions are important to diminish under and over prescription, and side-effects of pain medication as much as possible, to establish or maintain the best possible QoL in persons with advanced dementia. When measured cross-sectionally, the use of paracetamol is not associated with QoL. More research is needed to further explore the effects of paracetamol use on QoL over time.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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Chapter 3

Quality of life and Paracetamol In advanced Dementia (Q-PID): Protocol of a randomised double-blind placebo-controlled crossover trial

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ABSTRACT

Background

No proven effective interventions on quality of life (QoL) are available for persons with dementia in a long-term care facility (LTCF). However, several interventions are effective in diminishing mediators of QoL (i.e. challenging behaviour, depressed mood, sleeping disorders), including pain treatment. Un(der)diagnosed and un(der)treated pain is a serious and frequent problem in persons with dementia. Also, although pain is difficult to assess in this group, the impact on QoL is probably considerable. There is evidence that pain has a negative impact on behaviour, mood, functioning and social participation, and benefit may be derived from use of paracetamol. Therefore, in LTCF residents with advanced dementia, this study aims to evaluate the effect of scheduled pain treatment with paracetamol on QoL, neuropsychiatric symptoms, ADL function, pain, care dependency, and (change in) use of psychotropic and pain medication.

Methods

This randomised, double-blind, placebo-controlled crossover trial will include 95 patients with: 1) age ≥ 65 years, 2) advanced dementia (Reisberg Global Deterioration Scale 5-7), and 3) QUALIDEM score ≤ 70. Exclusion criteria are the regular use of pain treatment, allergies to the study drugs, severe liver insufficiency or disease, use of > 4 units of alcohol/day, weight < 50 kg, and/or concomitant use of flucloxacillin. The two treatment periods of six weeks each (paracetamol and corresponding placebo) will be separated by a washout period of seven days. Primary outcome is effect on QoL (QUALIDEM and DS-DAT) and secondary outcome is effect on neuropsychiatric symptoms, ADL function, pain, care dependency, and (change in) use of psychotropic and pain medication (all compared to baseline).

Discussion

If regular treatment with paracetamol proves to be beneficial for QoL, this could have major implications for daily practice in long-term care. Information from this study may help professionals in their decision making regarding the prescription of pain medication to improve the QoL of persons with dementia and a low QoL.

Trial registration

The trial was registered on the Netherlands Trial Register (NTR6766); http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=6766; Trial registration date: 20th October, 2017

Keywords: Quality of life, Paracetamol, Dementia, Nursing home, QUALIDEM

BACKGROUND

The main goal of caring for persons with dementia living in long-term care facilities (LTCF) is the maintenance and/or improvement of their quality of life (QoL)[1]. QoL in persons with dementia involves multi-dimensional wellbeing on various domains, all influenced by the severity of dementia as well as individual and environmental factors. QoL can be affected by cognitive and functional decline, as well as by behavioural and psychological symptoms of dementia, and the quality of care received[2]. The LTCFs of the University Network of the Care sector South Holland (UNC-ZH) give the highest priority to the challenge of making an individual's life with dementia bearable and to help achieve an optimal QoL.

Admission of a person with dementia to a LTCF is usually based on a combination of factors in many domains, in which care and treatment at home are insufficient to handle all the needs. The expected increase in the number of persons with dementia emphasises the need to cope with the difficulties that formal caregivers (elderly care physicians, nursing staff, paramedical staff) and informal caregivers (family/spouses) experience daily to maintain an optimal QoL in these individuals.

The appreciation and rating of an individual's QoL is (conceptually) something that a person should report themselves. However, although some persons with dementia can give self-reported ratings in earlier stages of the disease, in more advanced stages this competency is often lost and assessment of QoL then generally relies on proxy observations.

The prevalence of pain in persons with dementia is high; it is reported that 40-60% of this group regularly experiences pain; for example pain is reported in 32%, 43% and 57% of persons with dementia in Italy, the Netherlands and Finland, respectively [3]. Pain can have a negative influence on QoL in many ways; although pain is difficult to assess in persons with dementia, the impact on QoL is probably considerable. Studies have shown the beneficial effects of pain treatment in persons with dementia on outcomes other than the pain itself[4, 5]. Especially behavioural problems, sleeping and night-time behaviours, and social activities responded positively after active treatment with pain medication (irrespective of whether or not pain was present)[4-6]. In an earlier study, a secondary analysis suggested that pain management is also beneficial for mood (depression), apathy, staff distress, activities of daily living (ADL), appetite and eating disturbances[7, 8]; however, in this latter trial, the stepwise approach of treating pain was neither placebo-controlled nor blinded.

The complete mechanism of action of paracetamol, also known as acetaminophen, is still unclear[9]. Thus, the question remains whether paracetamol has only analgesic and antipyretic effects and, thereby, improves QoL, or whether it has another (yet unknown) independent

mechanism of action on well-being that has not yet been revealed. Over all, the effects of regular pain treatment (not only with paracetamol) on QoL in persons with dementia have not yet been studied[4, 6, 10-12].

This proposed study will help gain more insight into and knowledge on the effect of pain treatment on QoL, neuropsychiatric symptoms, ADL function, pain, care dependency, and (change in) use of psychotropic and pain medication. Hopefully, the results will help persons with dementia to achieve and/or sustain the highest possible QoL, by alleviating undesired symptomatology.

Aims of the Q-PID trial

The primary objective of the Q-PID trial is to evaluate the effect of scheduled administration of pain treatment with paracetamol on QoL of people with advanced dementia in LTCFs. Secondary aims are to evaluate the effects of regular pain treatment with paracetamol on neuropsychiatric symptoms, ADL function, pain, care dependency, and (change in) use of psychotropic and pain medication.

METHODS

Design and study population

This 13-week double-blind, randomised, placebo-controlled crossover trial, is designed to include 95 residents with advanced dementia, being admitted to LTCFs affiliated with the UNC-ZH. Inclusion criteria are 1) age ≥ 65 years, 2) advanced dementia (Reisberg Global Deterioration Scale (GDS) 5-7[13]) and 3) QUALIDEM score ≤ 70. This cut-off point is based on the median QUALIDEM total score that emerged from data of the STA-OP! study[14]. Exclusion criteria are the regular use of pain treatment [residents with paracetamol that is prescribed PRN (pro re nata, or 'as needed') are eligible only if the use of paracetamol in the previous week was ≤ 3 g/week with a maximum of 1 g/day], allergies to the study drugs (paracetamol or placebo), severe liver insufficiency or disease, use of > 4 units of alcohol/day, weight < 50 kg and/or concomitant use of flucloxacillin (because of possible interaction between paracetamol and flucloxacillin in women of advanced age, leading to an anion gap metabolic acidosis)[15].

Recruitment and consent

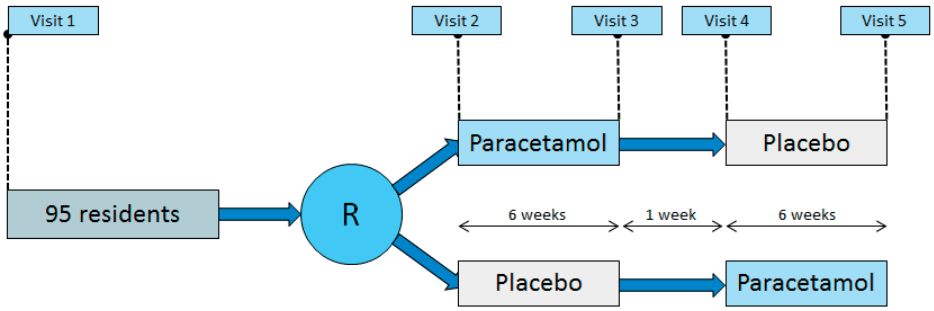
Eligible residents and their legal representatives will be selected by the treating elderly care physician on the basis of not using any pain medication, or using paracetamol PRN ≤ 3 g/week with a maximum of 1 g/day, after which the legal representative receives the patient information letter that explains the purpose/procedures of the proposed study, the tests and questionnaires required, and possible hazards that might be involved. The legal representative is asked to return the consent form to the researchers by mail, either with a consent, or with refusal for the

patient to participate. The patient information letter is re-send after non-response of the legal representative after four weeks. If the legal representative sends his/her consent, the researcher or research nurse contacts that legal representative by telephone to ensure that the right person has signed the form, and to answer any questions (if necessary). Once the researcher or research nurse has assured him/herself, then he/she also signs the consent form. A copy is added to the medical record of the patient in the nursing home. Thereafter, the resident is enrolled in the study. A case report form is kept of all participants in the study.

Treatment

Participants receive orally administered paracetamol (or placebo, if they are randomised into starting placebo first) at a daily dose of 3 g for four weeks (3 x 2 tablets of 500 mg each), followed by administration of 2.5 g/day for two weeks, according to recent protocols of chronic use of paracetamol in older people[16]. After a wash-out period of seven days, a second six-week administration period starts with corresponding placebo (or paracetamol if the participant started with placebo) (see Fig. 1). The placebo tablets resemble the paracetamol tablets in colour, size and composition, and contain quinine to give a bitter taste. All study medication is packed in similar medication baskets.

Fig. 1 Flowchart of the Q-PID crossover trial



R= randomisation
Visit 1: Screening for inclusion and exclusion criteria
Visit 2: Baseline measurements
Visit 3 and 4: Follow-up measurements
Visit 5: Final and closing measurements

Participants are allowed to use co-medication. If additional pain medication is needed during the study, administration of one extra gram paracetamol PRN per day can be accepted, provided that this is recorded in the patient's medication sheet and does not occur more than three times in one week. If more paracetamol or other pain treatment is needed, the participant will (temporarily) stop study medication, but the measurements will continue (if possible), following the intention-to-treat principle. For participants who are unable to swallow tablets, the study medication will be administered by their usual way of medication intake.

Randomisation, blinding and treatment allocation

After a screening visit by a research nurse, residents who are eligible for participation are randomised (1:1) into two groups (Fig. 1). Block randomisation (blocks of four) is used, generated by a computer random number generator in the pharmacy. Participants, informal caregivers, nursing staff, physicians, investigators and research nurses are blinded to treatment. The randomisation numbers combined with the allocated treatment arm (paracetamol/placebo or vice versa) are put in sealed envelopes and are under guidance of the researchers in case clarification of an allocation is needed. Only the study pharmacy of the Leiden University Medical Center knows which participant/code is allocated to which treatment arm. The researcher/research nurse shall only unblind the treatment allocation if this is relevant to the safety of the participant. In case of unblinding, the participant will quit study medication, but measurements will be continued (if possible) following the intention-to-treat principle. The same applies for participants quitting study medications for other reasons.

Research questions and hypotheses

1. What is the effect of regularly scheduled administration of pain treatment with paracetamol on QoL in LTCF residents with advanced dementia, compared to placebo? We hypothesise that undiscovered and un(der)treated pain, causing moderate to poor QoL (as assessed by the QUALIDEM and the DS-DAT), might be resolved by scheduled pain treatment, and thereby, improve overall QoL.
2. What is the effect of regularly scheduled administration of pain treatment with paracetamol on neuropsychiatric symptoms, ADL function and care dependency in LTCF residents with advanced dementia, compared to placebo? We hypothesise that resolving possibly undiscovered pain in persons with dementia will lead to decreased neuropsychiatric symptoms, better ADL functioning and less care dependency.
3. What is the effect of regularly scheduled administration of pain treatment with paracetamol on pain and use of psychotropic and pain medication in LTCF residents with advanced dementia, compared to placebo? As hypothesised in research question 1, regularly scheduled administration of pain might resolve undiscovered pain. Moreover, by evaluating pain using a measurement tool developed for the observation of people with dementia, we hypothesise this will increase the attention that nurses pay to pain. Finally, we hypothesise that use of psychotropic and (extra) pain medication will decrease due to paracetamol treatment.

Measurements

Prior to the study, the nursing staff receive training from the researchers on QoL and pain in persons with dementia, and receive instruction on how to observe pain. These skills can also be beneficial for patient care in LTCFs, even after this trial has ended.

During the study, demographic data are obtained by nursing staff. Severity of dementia is measured using the Reisberg GDS. This assessment tool rates the clinically identifiable stage of cognitive decline, with scores ranging from 1 (no cognitive decline) to 7 (very severe cognitive decline)[13]. Only persons with Reisberg GDS scores ≥ 5 at baseline will participate in this study. Table 1 represents the time schedule and an overview of the study measurements.

Table 1 Measurements and time schedule during the proposed study

	Visit 1 Screening	Visit 2 Baseline	Visit 3 6 weeks	Visit 4 7 weeks	Visit 5 13 weeks
Check inclusion/exclusion criteria	RN				
Demographic characteristics	Nurse				
Dementia (Reisberg GDS)	RN/nurse				
Comorbidity (FCI)		ECP			
Quality of life (QUALIDEM, DS-DAT)	Nurse	Nurse	Nurse	Nurse	Nurse
Neuropsychiatric symptoms (NPI-NH)		Nurse	Nurse	Nurse	Nurse
Functioning (Katz-15)		Nurse	Nurse	Nurse	Nurse
Care dependency (CDS)		Nurse	Nurse	Nurse	Nurse
Pain (MOBID-2)		Nurse	Nurse	Nurse	Nurse
(Co)-medication use		ECP	ECP	ECP	ECP
(Serious) Adverse Events ((S)AE's)		ECP	ECP	ECP	ECP

RN = Research nurse
Nurse = Professional care giver in nursing home
ECP = Elderly care physician

Primary outcome

Quality of life

At baseline and at follow-up, QoL will be measured with the QUALIDEM, which includes 37 items for observation by nurses on nine QoL domains (care relationships, positive affect, negative affect, restless tense, behaviour, positive self-image, social relations, social isolation, feeling at home, and having something to do)[17, 18]. This is a dementia-specific QoL measurement (initially developed for the Dutch population) and has satisfactory reliability and validity, also in other countries [17, 19] Only the 18 items that are also applicable for very severe dementia (GDS 7) will be included in this proposed study (as recommended by the authors in the QUALIDEM manual)[20]. These 18 items cover six QoL domains (care relationship, positive affect, negative affect, restless tense behaviour, social relations, and social isolation). The QUALIDEM is one of the few QoL instruments that focuses on the QoL domains that are considered important for persons with dementia, even in severe end-stage dementia, and is therefore a suitable instrument for the evaluation of QoL in persons with dementia [17, 19, 21, 22]. As it is recommended, we use the QUALIDEM together with the Discomfort Scale-Dementia of Alzheimer Type (DS-DAT; a measure to assess discomfort in dementia) to evaluate the influence of interventions and 24-h care on QoL in severe dementia[23]. The DS-DAT is a 9-item obser-

vational instrument that measures symptoms of discomfort of patients, regarding vocalisations, breathing, facial expression, and body movement. The Dutch version of the DS-DAT was found suitable to assess discomfort in nursing home residents that have severe dementia, and has proven to be valid and reliable[24-26].

Secondary outcomes

Neuropsychiatric symptoms

The Neuropsychiatric Inventory-Nursing Homes (NPI-NH) will be used to measure neuropsychiatric symptoms. The NPI-NH is based on a structured interview with an informant (in the proposed study: nursing staff) and consists of 10 domains of measuring behaviour (delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, elation/euphoria, apathy/indifference, disinhibition, irritability/lability and aberrant motor behaviour), and two types of measuring neuro-vegetative changes (sleep and night-time behaviour disorders and appetite and eating disorders)[27]. Each symptom is valuated with frequency and severity scores; the sum of these 12 scores provides a total score, ranging from 0 (no symptoms at all) to 144 (all symptoms at every moment). The Dutch version of the NPI-NH has high interrater agreement, good construct validity, and can be scored objectively[28, 29]. In addition to the frequency and severity scores, we also use the Caregiver Distress Scale of the NPI, which assesses the level of caregiver (occupational) distress associated with the patient's behavioural disturbances measured with the NPI, ranging from 0 (no distress) to 60 (very disruptive, major source of distress for staff)[30].

ADL functioning

The Katz ADL index is a reliable and valid instrument to measure ADL function[31]; it is also reliable and sensitive to change in persons with dementia[32]. The summary score of the Katz ADL index ranges from 0 (low function/fully dependent) to 15 (high function/fully independent) [33]. The questionnaire is filled out by the nursing staff.

Care dependency

Care dependency is measured with the Care Dependency Scale (CDS), that assesses care dependency of institutionalised residents based on 15 items[34]. It is filled in by nursing staff and has satisfactory reliability and validity[35, 36]. The total score ranges from 15 (completely dependent on care) to 75 (almost independent of care).

Pain

The Mobilization-Observation-Behaviour-Intensity-Dementia-2 (MOBID-2) pain scale is an observational pain tool for residents with advanced dementia[37, 38]. This assessment is based on observation of the resident's immediate pain behaviour related to the musculo-skeletal system, doing standardised and guided movements during morning care[12]. The intensity of pain is

rated by a nurse on a numerical rating scale, ranging from 0 (no pain) to 10 (pain as bad as it could possibly be)[39]. An overall score of ≥ 3 is indicative of a patient having clinically relevant pain[38, 40]. The MOBID-2 has good reliability and validity[41] and is responsive to change[12].

Psychotropic – and pain medication use

At baseline, a medication list is provided by the elderly care physician. In addition, copies of the drug registration forms are collected during the study period. Differences in use of psychotropic medication and/or use of (extra) pain medication during the study period are analysed as a secondary outcome measure.

Compliance

Compliance with study medication is registered on the drug registration form by the nurse each time paracetamol or placebo tablets are offered. Reasons for non-compliance are asked for and recorded. Additionally, a tablet count is performed after each intervention period. Non-compliance is defined as an adherence of < 90% as registered on the drug registration form (remaining tablet count of 24 or more, per period). Throughout the study, the nursing staff and physicians are asked to report (serious) adverse events and side effects of paracetamol/placebo use to the researchers on a structured questionnaire. At each study visit, we explicitly ask again for possible adverse events and side effects of paracetamol/placebo use that might not have been reported.

The study does not interfere in any way with standard care, diagnostics and treatment for persons with dementia.

Sample size calculation

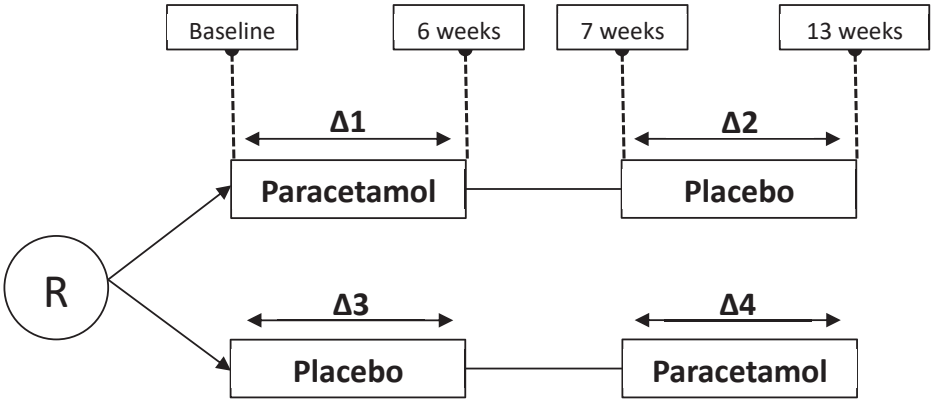
To detect an inter-individual difference of 10% on the QUALIDEM score with 80% power, and alpha 0.05, we calculated that a sample of 70 residents will be required. We assume an intra-individual standard deviation of 13 points, as derived from a previous study[42]. Estimating a dropout of 35% (mortality, loss to follow-up from other reasons, unwillingness to participate, existing pain, etc.) and invalid measurements of 5%, we plan to randomise 95 eligible patients.

Statistical analysis

Outcomes will be compared in four different time points: at baseline, and after 6, 7 and 13 weeks.. First, we examine the degree of an order effect, i.e. whether there is a significant difference between $\Delta 1$-$\Delta 2$ and $\Delta 4$-$\Delta 3$ (see Fig. 2 for the Δ-time frames). Unpaired T tests will be used for normally distributed numerical data, one-way ANOVA tests for not normally distributed data, and Chi-squared tests for categorical data. Second, we look for the existence of a period effect, i.e. whether the difference between $\Delta 2$ and $\Delta 4$ is significantly different from the difference between $\Delta 1$ and $\Delta 3$. Paired t-tests are used for normally distributed numerical data, Wilcoxon

signed-rank tests for no normal distributed data, and Chi-squared tests for categorical data. If no significant order effect or period effect is found, the mean/median outcomes of Δ1 and Δ4 are compared with the mean/median outcomes of Δ2 and Δ3, using paired t-tests for normally distributed numerical data, Wilcoxon signed-rank tests for not normally distributed data, and Chi-squared tests for categorical data. If any order or period effect is found, differences in QoL total and subdomain scores, neuropsychiatric symptoms, ADL functioning, care dependency, pain, and psychotropic and pain medication use are analysed with repeated (linear) mixed models, in which we adjust for order and period effect. Data will be presented quantitatively and processed using the SPSS package.

Fig. 2 Time frames (Δ) used in the statistical analysis



R= randomisation
Δ1= difference in outcomes between baseline and 6 weeks. Participant started with paracetamol.
Δ2= difference in outcomes between 7 weeks and 13 weeks. Participant started with paracetamol.
Δ3= difference in outcomes between baseline and 6 weeks. Participant started with placebo.
Δ4= difference in outcomes between 7 weeks and 13 weeks. Participant started with placebo.

DISCUSSION

This randomised, double-blind, placebo-controlled crossover study will provide knowledge on the effectiveness of six weeks of regularly scheduled pain treatment with paracetamol on QoL in persons with dementia living in LTCFs with low QoL, compared to placebo. Persons with dementia are at high risk of experiencing negative consequences of pain, such as behavioural problems (agitation, apathy), decrease in ADL functioning, sleep problems and depression.

Paracetamol is reported to be beneficial for social interaction[6] and behavioural disturbances[4, 12]. Since paracetamol is known for its analgesic effect, use of paracetamol might decrease the negative consequences of pain and, thereby, improve QoL in persons with dementia.

Paracetamol rarely causes side effects, which can include headache or allergy. In case of long-term use of paracetamol (i.e. months or years), or doses exceeding the maximum recommended dose (3-4 g/day) side effects can include liver damage, kidney damage and blood abnormalities. Any inconvenience for the residents (taste of the tablets, swallowing more tablets than the person is used to in one day) or the nursing staff (measurements taking up time), will not outweigh the benefits described above.

The crossover design has the advantage that (on average) 75% fewer participants are needed to achieve the same satisfactory power as studies that have parallel groups without crossover of treatments.[43] Also, the characteristics of the participants of the two randomised treatment groups are the same at baseline (the same person receives paracetamol and placebo, only the order of administration differs); therefore, confounding is minimised when comparing the two treatments. The washout period minimises the carryover of effects from one treatment period to another. Also, randomising the participants minimises any potential period effect (i.e. the effect of time and/or seasonal changes on a person's outcome) in the comparison of treatments[43]. A final benefit of this design is that, since participants receive both treatments, the results can be compared within one individual.

Within this vulnerable group of patients, there is always a risk of a high mortality rate and dropout during a study. Especially in a crossover study, this can be a problem, since participants are their own controls. Although this was taken into account when calculating the sample size, a high dropout could be a limitation of this study design (i.e. limiting the reliability of the results); although this also emphasises the difficulty of performing a study in this population. Another possible limitation is the percentage response of the consent that is requested from legal representatives by mail; we estimate that about 30% will be non-responders, and that about 50% of the responders will not allow the resident to participate in the study. Lastly, eligibility in this specific population is low, as (on average) ≥ 50% of persons with dementia already uses pain medication, the mortality rate between consent and screening can be high, and/or the residents might meet one or more of the exclusion criteria (e.g.severe psychiatric disease, low weight). Low eligibility was also shown in the DEP.PAIN.DEM study, in which 2200 patients had to be contacted in order to include just over 160 patients[5]. Based on ethical considerations, we will not specifically ask the elderly care physician to stop pain treatment in a patient in order to meet our eligibility criteria.

If the results of this proposed trial show that six weeks of paracetamol improves the QoL of persons with dementia and a low QoL, we need to be aware of the potential consequences for daily practice in long-term care. The message would certainly *not* be to give every person with dementia daily paracetamol. Recent increases in analgesic use in persons with dementia, especially in Scandinavian countries, have raised the question as to whether this was based on

sound individual evaluation and monitoring, or a reaction to reports on under-treatment [44]. It is likely (and has also been reported), that the effect of psychosocial interventions such as pleasant activities, exercise, as well as reminiscence and music therapy, is small or even absent if there is unnoticed or poorly managed pain [45]. Therefore, the message would be that nursing staff should regularly measure QoL in dementia, and that paracetamol for six weeks may be the first intervention to improve QoL of persons with advanced dementia and a low QoL.

Abbreviations

ADL: Activities of daily living; CDS: Care dependency scale; GDS: Global deterioration scale; LTCF: Long-term care facility; MOBID-2: Mobilization-Observation-Behaviour-Intensity-Dementia-2; NPI-NH: Neuro Psychiatric Inventory – Nursing Home version; PRN: pro re nata ('as needed'); QoL: Quality of life; Q-PID: Quality of life and Paracetamol In advanced Dementia; RN: Research nurse

DECLARATIONS

Ethics approval and consent to participate

The study will be conducted according to the principles of the Declaration of Helsinki (amended in October 2013), in accordance with the Medical Research Involving Human Subjects Act (WMO), the Guideline for Good Clinical Practice (May 1996), and in full conformity to any applicable state or local regulations. The study has been approved by the Medical Ethics Committee of the Leiden University Medical Center (ref. number P17.051). Written consent to participate will be obtained from the legal representative by mail and once more verified by telephone. Once the researcher or research nurse has assured him/herself that the right person has signed the form, and that questions (if present) have been answered, then he/she also signs the consent form. A copy is added to the medical record of the patient in the nursing home.

Consent for publication

Not applicable

Availability of data and material

Not applicable

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

PHvD, WPA, JG, BSH, and MAAC contributed to the study concept and design, and drafting and critical revision of the manuscript. All authors have read and approved the final version of the manuscript.

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Chapter 4

Does paracetamol improve quality of life, discomfort, pain and neuropsychiatric symptoms in persons with advanced dementia living in long-term care facilities? A randomised double-blind placebo-controlled crossover (Q-PID) trial

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ABSTRACT

Background

The objectives of this study are to determine the effects of regularly scheduled administration of paracetamol (acetaminophen) on quality of life (QoL), discomfort, pain and neuropsychiatric symptoms of persons with dementia living in long-term care facilities (LTCF).

Methods

A multicentre randomised double-blind placebo-controlled crossover trial for 13 weeks (January 2018 to June 2019) in 17 LTCFs across the west of the Netherlands. Inclusion criteria were age ≥ 65 years, (advanced) dementia and a moderate to low QoL, independent of the presence of pain (QUALIDEM ≤ 70). Exclusion criteria were the use of regular pain treatment, allergies to the study medication, severe liver disease, use of > 4 units of alcohol/day, weight < 50 kg and/or concomitant use of flucloxacillin. Participants received study medication (paracetamol/placebo) in two periods of 6 weeks each (1 week in between as a wash-out period). Randomisation decided in which order participants received paracetamol and placebo. Primary outcomes included QoL (QUALIDEM) and discomfort (DS-DAT); secondary outcomes included pain (MOBID-2) and neuropsychiatric symptoms (NPI-NH).

Results

Ninety-five LTCF residents (mean age 83.9 years [SD 7.6], 57.9% females) were included. Repeated linear mixed models showed no difference in mean differences of QUALIDEM (paracetamol +1.3 [95% CI -1.0-3.5], placebo +1.5 [95% CI -0.7-3.8]), DS-DAT (paracetamol: -0.1 [95% CI -1.4-1.2], placebo 0.6 [95 CI -0.7-1.8]), MOBID-2 (paracetamol 0.0 [95% CI -0.5-0.5], placebo -0.2 [-0.7-0.3]) and NPI-NH (paracetamol +1.5 [95% CI -2.3-5.4], placebo -2.1 [95% CI -6.0-1.7]) in favour of either paracetamol or placebo.

Conclusions

Compared to placebo, paracetamol showed no positive effect on QoL, discomfort, pain and neuropsychiatric symptoms in persons with advanced dementia with low QoL. It is important to find out more specifically which individual persons with advanced dementia could benefit from pain treatment with paracetamol, and for clinicians to acknowledge that a good assessment, monitoring and multidomain approach is vital for improving QoL in this vulnerable group.

Trial registration

Netherlands Trial Register (NTR6766); http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=6766; Trial registration date: 20th October, 2017

Key words: quality of life, dementia, paracetamol, QUALIDEM, long-term care facility

BACKGROUND

The expected increase in the number of persons with dementia in future decades[1] emphasises that caregivers need to be able to cope with the difficulties they experience daily in order to maintain optimal quality of life (QoL) in this population. The focus on QoL has become more and more pronounced in recent decades, but as the persons with dementia are mostly unable to adequately indicate how they experience their QoL, the intricate task of safeguarding it for them falls to the people around them.[2] In a long-term care facility (LTCF), there are even more (professional) caregivers who are responsible for the maintenance and/or improvement of the QoL of these persons.

Two of the principal goals proposed by the World Health Organization in their recent factsheet on dementia to improve the lives of persons with dementia are to optimise well-being and to identify and treat physical and psychological problems.[1] The latter category contains many factors that may be negatively associated with the QoL of a person with dementia, including the presence of depression, behavioural problems, pain, comorbidity, living alone and having needs that are unmet.[3,4] The strength and direction of these associations, however, vary considerably between individuals.[5] One of the mentioned factors, pain, can be treated. However, there is still a group of persons with dementia that have undiagnosed, and therefore untreated pain. Untreated, it may be associated with neuropsychological problems, e.g. behavioural problems (agitation, aggression, psychosis)[6-9] and depression.[9,10] On the other hand, in view of the large increase in opioids and paracetamol prescription in the past years[11-14], clinicians should be aware of side effects and overtreatment with pain medication in this population.

The use of pain medication has been proven effective on agitation[15,16], depression and apathy[17], sleep[18], and social interaction[19] in persons with dementia. Two relatively small trials with a crossover design were performed earlier to assess the effects of pain medication (paracetamol) in this target population. One included 25 participants (mean age 85.9 years, 88% female) living in LTCFs in which the authors concluded that paracetamol improved social interaction.[19] The second study included 39 participants (mean age 85.7, 87% female, mean Global Deterioration Score 5.7) living in LTCFs.[20] The researchers of this study found no significant difference in discomfort between the placebo and paracetamol groups. However, so far, no studies have investigated the effect of paracetamol on overall QoL of persons with dementia. The question remains whether paracetamol only has analgesic and antipyretic effects[21], or also other (unknown) effects that may influence QoL in persons with advanced dementia. Therefore, the present study aims to investigate the effect of regularly scheduled administration of paracetamol (acetaminophen) on QoL of persons with dementia with low QoL, independent of having pain, living in LTCFs. Furthermore, the effect of scheduled administration of paracetamol on discomfort, pain and neuropsychiatric symptoms will be assessed.[22]

METHODS

From January 2018 to June 2019 we performed a multicentre (block) randomised double-blind placebo-controlled crossover trial for 13 weeks in LTCFs connected to the University Network of the Care sector South Holland (UNC-ZH) in the west of the Netherlands.[22] The UNC-ZH is a collaboration between the Leiden University Medical Center (LUMC) and large care organisations in the west of the Netherlands. Its goal is to initiate, facilitate and perform care-related scientific research.[23]

Participants and enrolment

This study aimed to include 95 LTCF residents aged ≥ 65 years, with (advanced) dementia stage 5, 6 or 7 according to the Reisberg Global Deterioration Scale[24] and a moderate to low QoL, total score ≤ 70 on QUALIDEM-6-Domain total score (QUALIDEM-6D), independent of having pain. This cut-off point was derived from the median of the QUALIDEM-6D scores found in a previous Dutch study involving persons with dementia living in LTCFs.[25,26]

Exclusion criteria were use of regular pain treatment (residents who used paracetamol that was prescribed 'pro re nata', or 'as needed' (PRN) were eligible only if the use of paracetamol in the week previous to starting study medication was ≤ 3 g/week with a maximum of 1 g/day), allergies to the study medication (paracetamol or placebo), severe liver insufficiency or disease, use of > 4 units of alcohol/day, weight < 50 kg and/or concomitant use of flucloxacillin.[27]

Intervention

Study medication was produced and provided by the pharmacy of the LUMC. Participants received study medication in two periods of 6 weeks each with 1 week in between as a wash-out period. One period consisted of paracetamol, the other of placebo. In accordance with a Dutch guideline for chronic use of paracetamol in older persons, the dose of paracetamol in the first 4 weeks was slightly higher (3 times/day 1000mg) than the last two weeks of this period (2 times/day 1000 mg and 1 time/day 500 mg).[28] Placebo tablets were provided in the same amount and resembled the paracetamol tablets in appearance, taste and composition. The bitter taste was imitated by adding a low dose of quinine (without therapeutic activity) to the placebo substance. The study medication was packaged in identical jars and administered to the participants along with their other medication by nurses and nursing assistants that were allowed to administer medication, in the same way they were used taking their medication. When, however, pain treatment was needed, a single administration of paracetamol 1000 mg was allowed without consequences, but no more than 3 times/week. When more pain treatment was needed, the participant stopped study medication, but the measurements continued, following the intention-to-treat principle.

Randomisation, treatment allocation and blinding

Included participants were randomised in blocks of 4 by a random number generator in the pharmacy of the LUMC. Participants were randomised 1:1 into the paracetamol-placebo (AB) or the placebo-paracetamol (BA) treatment arm. Participants and their informal caregivers, researchers, research nurse and professional caregivers in the participating LTCFs were blinded to treatment allocation. Only the pharmacy of the LUMC knew which participant was allocated to which treatment arm.

Outcome measures

All data concerning the primary and secondary outcomes listed below were collected at baseline, 6 weeks, 7 weeks and 13 weeks. QoL, discomfort and pain were observed by the responsible nurse or nursing assistants, and neuropsychological symptoms were measured via interviews with the nurse/nursing assistant by a research nurse.

Primary outcomes

Quality of life and discomfort

The short 18-item version of the QUALIDEM was used to measure QoL. This version comprises six domains (care relationship, positive affect, negative affect, restless tense behaviour, social relationships and social isolation) that are also applicable to persons with very severe dementia.[29,30] In order to calculate a total mean score for QoL, the individual domain scores were re-calculated to a percentage score by dividing the domain score by its maximum achievable points multiplied by 100. Domain scores were then added up and divided by 6 to calculate an overall mean score, the QUALIDEM-6D. Both the domain scores and the overall mean score can range from 0 (worst QoL possible) to 100 (best QoL possible). These transformations have been applied successfully multiple times in previous studies.[12,31-33]

The Discomfort Scale-Dementia of Alzheimer Type (DS-DAT) was used to measure discomfort in persons with advanced dementia.[34] It consists of nine items of discomfort with a score ranging from 0 (no discomfort) to 27 (worst possible discomfort).

Secondary outcomes

Pain

The nurse/nursing assistant observed pain in the participants during morning care using the Mobilization-Observation-Behaviour-Intensity-Dementia-2 Pain scale (MOBID-2).[35,36] This observational instrument has been proven reliable, valid and very responsive to change of pain in persons with dementia.[35,37] While moving hands, arms and legs of the participant, turning the participant on both body sides on the bed and letting him/her sit on the edge of the bed, the nurse/nursing assistant rated pain intensity by observing facial expressions, vocalisations and defending behaviour. Subsequently the nurse/nursing assistant rated pain intensity by observa-

tion based on pain behaviour over the preceding week related to head/neck, chest/lungs/heart, upper abdomen, legs/pelvis/lower abdomen and skin/wounds. A total pain score ranging from 0 (no pain) to 10 (worst pain possible) was assigned to these observations. Scores ≥3 were seen as clinically relevant pain.[37]

Neuropsychiatric symptoms

Neuropsychiatric symptoms were measured with the Neuropsychiatric Inventory – Nursing Home version (NPI-NH).[38,39] This is an interview-based questionnaire completed by the nurse/nursing assistant and the research nurse, consisting of 13 items that are each scored for frequency and severity. Total scores range from 0 (no behavioural problems) to 144 (very severe behavioural problems).

Additional measurements at baseline

Demographic data were collected at the start of the study by the nursing staff and the treating elderly care physicians. The severity of dementia was measured with the Reisberg Global Deterioration Scale (GDS), which reflects the stage of progression of the disease from 1 (no cognitive decline) to 7 (very severe cognitive decline).[24] Comorbidity was assessed using the Functional Comorbidity Index, a list of 18 comorbid diseases that are associated with physical function.[40]

Compliance

The participants' compliance to study medication was tracked by counting residual study medication after each finished study period. A leftover tablet count of > 10% (> 24 missed tablets) per period was considered non-compliant. Also, the medication intake was registered on a medication registration form by the nurse/nursing assistant each time the (study) medication was administered. When participants refused study medication repeatedly, the nurse/nursing assistant informed the researchers and the study medication was discontinued on the medication administration form. The same applied to participants who had to stop because of starting (other) pain medication.

Sample size calculation

A sample size of 70 participants was calculated based on the detection of an inter-individual difference of 10% on the primary outcome measure QUALIDEM, with 80% power, and alpha 0.05. To account for an estimated dropout of 35% (mortality, loss to follow-up, (other) pain medication needed, etc.), enrolment of 95 participants was planned.

Statistical analysis

At baseline, the characteristics and outcome measures in the two different treatment arms were compared using unpaired *t* tests for normally distributed numerical data, one-way ANOVA tests for non-normally distributed data, and chi-squared tests for categorical data.

The decision which statistical tests to use was based on whether the main outcome measure QUALIDEM showed an order and/or period effect. The calculation of these effects was extensively described in the protocol article of this study.[22] If no significant order and/or period effect was found, the two treatment groups, i.e. placebo and paracetamol, would be compared using paired *t* tests for normally distributed numerical data, Wilcoxon signed-rank tests for non-normally distributed data, and chi-squared tests for categorical data. In case of any order and/or period effect, repeated linear mixed models were used with adjustment for order and/or period effects.

Patient and public involvement

The topic of our study was identified by the Quality of life feedback group, in which care professionals of LTCFs participate. The members of the UNC-ZH (care organisations), combined with the client panel of older people from the LUMC and the QoL feedback group, felt that they needed feasible and evidence-based interventions that could help achieve optimal QoL in persons with (advanced) dementia. Therefore, they provided input to the researchers and the UNC-ZH to develop this study. The study was subsequently designed and performed in co-creation with these three groups.

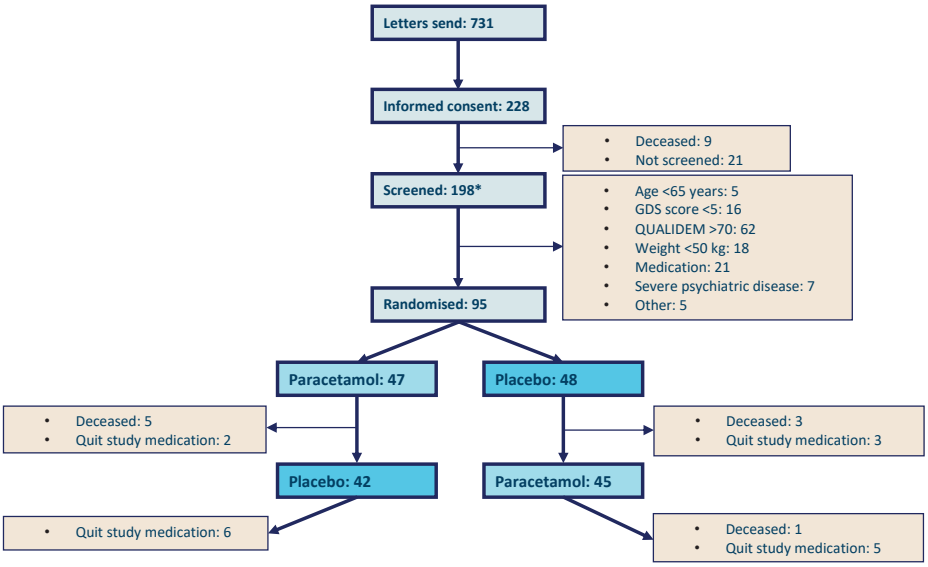
RESULTS

Enrolment and study flow

A total of 731 patient information letters were sent to legal representatives of eligible participants. Of these legal representatives, 228 consented to screening. Nine persons in this screening group died before enrolment/randomisation and 21 persons were not screened because the planned number of 95 participants was reached. One hundred ninety-eight eligible participants were eventually screened for inclusion and exclusion criteria. The main reasons for exclusion were a QUALIDEM > 70 (62 persons), using pain medication and/or medication interacting with study medication (21 persons), weight < 50 kg (18 persons) and a GDS score below 5 (16 persons). All reasons for exclusion can be found in Fig. 1. Finally, 95 LTCF residents with advanced dementia across 17 LTCFs (9 care organisations) in the west of the Netherlands were enrolled in this study; 47 in the paracetamol-placebo (AB) arm and 48 in the placebo-paracetamol (BA) arm.

During the study 9 participants died (not study-related), of whom 8 in the first study period.

Fig 1. Flowchart of the Q-PID trial



* Some overlap exists in the number of stated reasons for exclusion, because some persons met more than 1 exclusion criterium

Baseline characteristics of participants

The mean age of the participants was 83.9 years (SD 7.6), 57.9% were female, the majority had a GDS score of 6 (70.5 %) and the mean number of comorbidities according to the FCI in the total group was 2.7 (SD 2.0). These participant characteristics did not differ at baseline across both treatment arms (Table 1).

Primary outcomes

Quality of life

At baseline, the groups in the two treatment arms did not differ on QUALIDEM-6D total scores (AB arm: 58.1 [SD 13.1] vs. BA arm 57.0 [SD 13.8]; $p = 0.701$) and the six QUALIDEM domain scores (Table 1). The QUALIDEM-6D scores of each treatment arm during the study are shown in Fig. 2.

Order and period effects

Comparing the treatment effects of paracetamol on the QUALIDEM of both groups in both periods, i.e. the effect of paracetamol minus the effect of placebo, revealed a significant difference in mean differences of the QUALIDEM total scores between the two treatment arms (4.5

Table 1: Baseline characteristics and measurements of the total group, stratified by randomisation group

	Paracetamol-placebo ***N* = 47**	**Placebo-paracetamol** ***N* = 48**
Mean age (SD) in years	83.9 (7.5)	83.9 (7.7)
Female (%)	27 (57.4)	28 (58.3)
GDS score 7 (%)	10 (21.3)	10 (20.8)
FCI, 0-18 (SD)	2.9 ((1.9)	2.5 (2.1)
QUALIDEM-6D		
Total score 0-100 (SD)	58.1 (13.1)	57.0 (13.8)
A – Care relationship 0-100 (SD)	58.0 (22.3)	56.9 (23.0)
B – Positive affect 0-100 (SD)	69.6 (18.6)	68.4 (19.7)
C – Negative affect 0-100 (SD)	63.8 (28.0)	64.2 (25.0)
D – Restless tense behaviour 0-100 (SD)	37.9 (25.5)	39.8 (28.6)
F – Social relationships 0-100 (SD)	64.0 (21.2)	58.8 (20.9)
G – Social isolation 0-100 (SD)	55.1 (20.8)	53.7 (23.7)
DS-DAT, 0-27 (SD)	8.4 (4.9)	8.3 (6.0)
Pain (MOBID-2 ≥ 3) (%)	15 (33.3)*	15 (31.3)
MOBID-2 overall pain intensity, 0-10 (SD)	2.0 (2.4)	2.3 (3.0)
NPI-NH		
Total score, 0-144 (SD)	32.6 (21.0)	33.5 (18.9)
Psychosis 0-24 (SD)	3.7 (5.8)	3.7 (4.6)
Agitation 0-48 (SD)	10.7 (8.6)	11.9 (9.7)
Affective symptoms 0-24 (SD)	5.9 (6.2)	4.8 (5.7)
No psychotropic use† (%)	29 (61.7)**	19 (39.6)**

SD standard deviation, *GDS* Global deterioration Scale, *FCI* Functional Comorbidity Index), *QUALIDEM-6D* dementia-specific QoL measurement instrument, 6 domain version, *DS-DAT* Discomfort Scale-Dementia of Alzheimer Type, *MOBID-2* Mobilization-Observation-Behaviour-Intensity-Dementia-2 pain scale, *NPI-NH* Neuropsychiatric Inventory – Nursing Home version

*Missing, 2

**p value 0.031 (Pearson chi-Square)

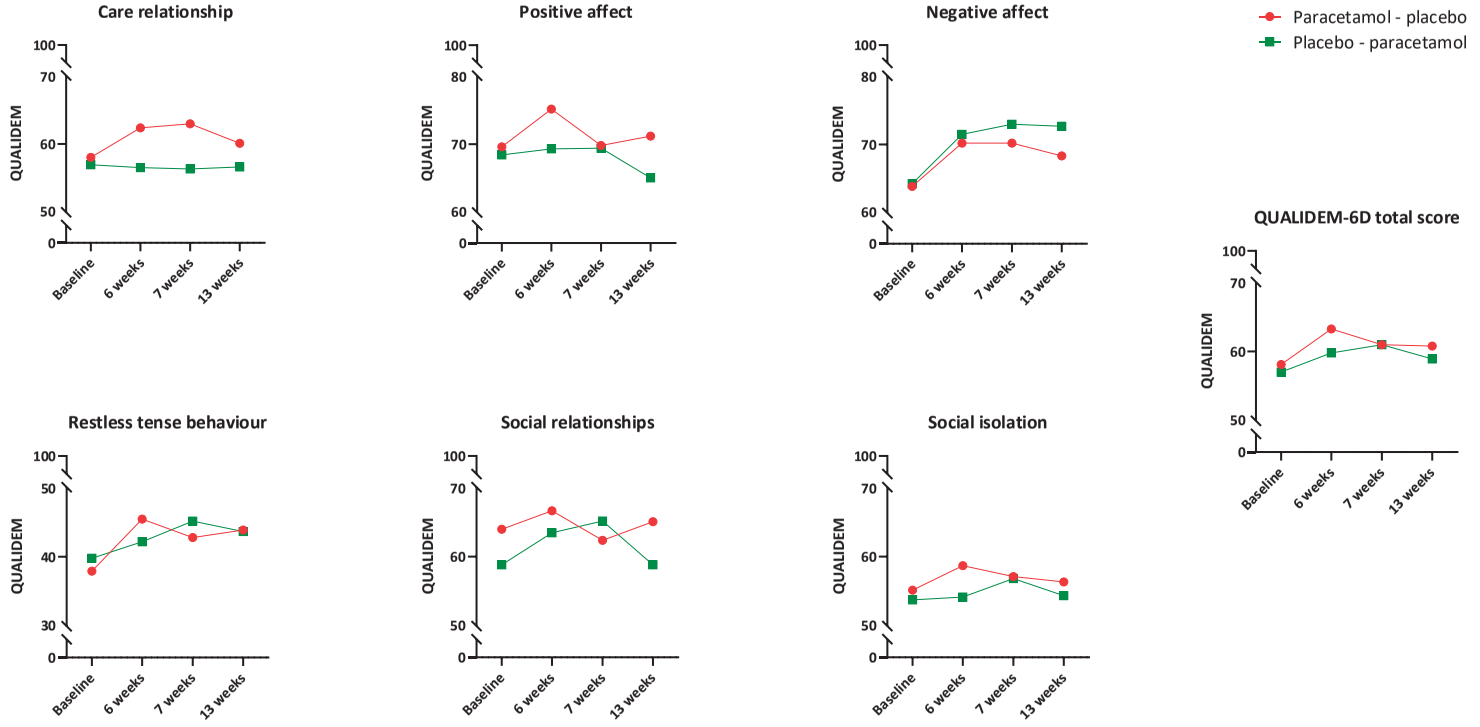
†Psychotropics: antipsychotics, antidepressants, anxiolytics, hypnotics and anti-dementia drugs

in the AB-arm and -4.8 in the BA-arm; $p = 0.008$), which means that there was an order effect in the main outcome measure QUALIDEM.

A strong period effect, i.e. the mean changes in both periods in the total group of participants were significantly different, was found for the QUALIDEM-6D total score (+3.8 in period 1 vs. -1.0 in period 2; $p = 0.004$), and the subdomain negative affect (6.7 in period 1 vs. -1.2 in period 2; $p = 0.005$).

Application of repeated linear mixed models subsequently showed no differences in the QUALIDEM-6D total scores and domain scores in favour of either paracetamol or placebo (Table 2).

Fig. 2 Mean QUALIDEM domain scores and mean QUALIDEM-6D total scores in the two treatment groups during the Q-PID study



QUALIDEM, questionnaire to measure QoL in persons with dementia, range 0 (worst QoL) to 100 (best QoL)
QUALIDEM-6D, 6-domain total score of the QUALIDEM questionnaire, range 0 (worst overall QoL) to 100 (best overall QoL)
Paracetamol – placebo, baseline to 6 weeks paracetamol, 7 weeks to 13 weeks placebo
Placebo – paracetamol, baseline to 6 weeks placebo, 7 weeks to 13 weeks paracetamol

Discomfort

The groups in the two treatment arms did not differ on DS-DAT total scores at baseline (AB arm 8.4 [SD 4.9] vs. BA arm 8.3 [SD 6.0]; $p = 0.970$). No difference was found in the treatment effects of paracetamol and placebo (paracetamol -0.04 [95% CI -1.3 – 1.3] vs. placebo 0.6 [95% CI -0.7 – 1.9])(Table 2).

Secondary outcomes

Pain

Mean MOBID-2 pain scores at baseline were similar in both treatment arms (AB arm 2.0 [SD 2.4] vs. BA arm 2.3 [SD 3.0]; $p = 0.531$)(Table 1). No difference in treatment effect on pain was found between both treatments (paracetamol: 0.0 [95% CI -0.5 – 0.5], placebo: -0.2 [95% CI -0.7 – 0.3])(Table 2).

Neuropsychiatric symptoms

At the start of the study there was no significant difference in NPI-NH total mean scores between the groups in the two treatment arms (AB arm 32.6 [SD 21.0] and BA arm 33.5 [SD 18.9]; $p = 0.822$) and the three subdomain scores (psychosis: 3.7 [SD 5.8] vs. 3.7 [SD 4.6], $p = 0.974$; agitation: 10.7 [SD 8.6] vs. 11.9 [SD 9.7], $p = 0.512$; affective symptoms: 5.9 [SD 6.2] vs. 4.8 [SD 5.7]; $p = 0.396$)(Table 1). No difference in treatment effect between paracetamol and placebo was found for the NPI-NH total mean score and the three subdomain scores (Table 2).

Compliance

Five participants quit study medication in the first period and 11 in the second study period. Reasons for quitting study medication were repeated refusal of study tablets (7 participants) and being in need of (other) pain medication (9 participants). Two participants from the latter group performed much better in the first period, and the nurses detected a clear deterioration in the second period. This caused them to contact the researchers to quit study medication and to continue paracetamol (although unsure which treatment arm the participant was in, the difference between the two periods was evident). After the study ended and after deblinding, these participants indeed turned out to be part of the AB treatment arm (first paracetamol, then placebo). At least two other patients did not stop study medication, but the nurses again saw a clear difference and when paracetamol was continued after the study ended, the participants performed better and were more relaxed.

In the first study period, the median compliance was 92.0% (IQR 80.7 – 100.0), taking into account participants who died and who stopped study medication during this period. Data for 14 participants on the number of residual tablets at the end of the first period was missing, due to the absence of the study medication jars on the LTCF units after the study period ended. In the second study period, the median compliance was 84.0% (IQR 67.5 – 98.1), taking into ac-

Table 2. Treatment effects of paracetamol and placebo on quality of life, discomfort, pain and neuropsychiatric symptoms. N = 95 (baseline) *N* = 86 (end of study)

	Intervention	Mean difference	95% CI	*p* value
QUALIDEM-6D†				
Total score	Paracetamol	1.3	-1.0 – 3.5	0.876
	Placebo	1.5	-0.7 – 3.8	
A – Care relationship	Paracetamol	2.9	-1.0 – 6.9	0.128
	Placebo	-1.4	-5.3 – 2.5	
B – Positive affect	Paracetamol	0.3	-3.7 – 4.3	0.872
	Placebo	0.7	-3.2 – 4.7	
C – Negative affect	Paracetamol	2.6	-1.4 – 6.6	0.919
	Placebo	2.9	-1.0 – 6.9	
D – Restless tense behaviour	Paracetamol	2.1	-3.1 – 7.3	0.955
	Placebo	2.3	-2.8 – 7.5	
F – Social relationships	Paracetamol	-1.1	-5.3 – 3.1	0.192
	Placebo	2.9	-1.3 – 7.0	
G – Social isolation	Paracetamol	0.9	-3.6 – 5.3	0.803
	Placebo	0.1	-4.3 – 4.5	
DS-DAT‡	Paracetamol	-0.04	-1.3 – 1.3	0.478
	Placebo	0.6	-0.7 – 1.9	
MOBID-2**	Paracetamol	0.0	-0.5 – 0.5	0.605
	Placebo	-0.2	-0.7 – 0.3	
NPI-NH††				
Total score	Paracetamol	1.5	-2.3 – 5.4	0.187
	Placebo	-2.1	-6.0 – 1.7	
Psychosis	Paracetamol	-0.3	-1.4 – 0.8	0.935
	Placebo	-0.3	-1.4 – 0.8	
Agitation	Paracetamol	1.2	-0.7 – 3.0	0.077
	Placebo	-1.2	-3.0 – 0.7	
Affective symptoms	Paracetamol	-0.3	-1.5 – 0.9	0.516
	Placebo	0.2	-0.9 – 1.4	

Repeated linear mixed models, adjusted for order and period effects, and psychotropic use

CI Confidence interval; *QUALIDEM-6D* dementia-specific QoL measurement instrument, 6 domain version, *DS-DAT* Discomfort Scale-Dementia of Alzheimer Type, *MOBID-2* Mobilization-Observation-Behaviour-Intensity-Dementia-2 pain scale, *NPI-NH* Neuropsychiatric Inventory – Nursing Home version

*Higher score means more pain

†Higher score means better QoL

‡Higher score means more discomfort

††Higher score means more neuropsychiatric symptoms

count participants who died and who stopped study medication during this, and previous study period. Compliance data for 18 participants was missing for the same reason as in period 1. The medication administration records showed better compliance than the residual tablet counting, indicating an imbalance between recording the study medication as 'given' and actually giving it.

DISCUSSION

The present study shows that paracetamol, compared to placebo, did not improve QoL, discomfort, pain and neuropsychiatric symptoms in persons with advanced dementia. It is important to take a closer look at the appropriateness of prescribing pain medication in these vulnerable persons. Also, doctors need to be aware that medication for sleep and neuropsychiatric symptoms has side effects and that (undertreated) pain may be the cause of sleep problems and/or neuropsychiatric symptoms, as has been described by others.[41]

Several strengths and limitations can be mentioned. First, to our knowledge, this is the largest crossover study with persons with dementia performed in LTCFs. The crossover design is an efficient study design that requires a substantially smaller sample size than trials with parallel groups[42,43], causing less variance between measurements. Consequently, up to four times less participants are needed to reach the same power as a parallel group study. In view of the target group, this was an important consideration in choosing the design for this study. Moreover, the crossover design is very suitable when a wash-out period longer than five times the halftime of the intervention can be fitted into the study design, so that no carry-over effects are expected after stopping or changing intervention. Also, confounding is minimised since the participants are their own controls and baseline characteristics will therefore be equal.

Prior to the study we were aware, due to previous experiences in research in this field, that only approximately 10% of all persons with dementia living in the participating LTCFs would be eligible to participate. Therefore, a lot of effort was needed and made in the present study to achieve the goal of enrolling 95 participants, which succeeded within the planned time frame. Furthermore, the study was performed within the care organisations that are member of the UNC-ZH, which assures a good research infrastructure.

Obviously, research in persons with advanced dementia living in LTCFs is complex and does not resemble research in a preconceived environment. One of the prerequisites to perform a crossover study is that the disease that will be studied is chronic and has a stable course. As we saw in our results, the entire group of participants performed worse in the second study period, irrespective of which treatment arm they were in. Therefore we used mixed effects models accounting for this period effect, rather than simply comparing the treatment groups crosswise. It may be possible that the dementia (and other comorbidities) deteriorated during the course of the study, which may have caused worse outcomes in the second period. We did not record the course of progression of the dementia and comorbidities during follow-up. It is also possible that the workload accompanying the present study caused the nurses/nursing assistants to be less motivated in the second period, contributing to the period effects found for the QUALIDEM and the NPI-NH.

Second, the time frames in which questionnaires needed to be completed at each time point were tight, so it was not always feasible to have the same nurse/nursing assistant complete the questionnaires at all time points for the same participant. Although we used questionnaires that are thoroughly validated, there is always a component of subjectivity, in which the connection between the person with dementia and the nurse/nursing assistant is important for how the questionnaires are completed.

Third to mention is the compliance of the study medication. The number of participants that quit study medication as reported by nursing staff was within our a priori estimated 'quit rate' (35% of 95 participants), but when counting the remaining tablets after each period, more participants appeared to have not received their study medication according to our definition of compliance (missed < 10% of tablets). Nevertheless, the median compliance in both periods was still 92.0% and 84.0%. The study medication could not be provided in the same unit-dose packages as the other medication, due to logistical problems between the separate preferred pharmacies in 17 nursing homes, and the additional costs associated with the organisation of this method/finances. This may have contributed for a large part to the non-corresponding compliance numbers of counting residual tablets after each period, and recorded numbers as signed on the medication administration forms.

Lastly, planning a sufficiently long enough wash-out period requires extensive knowledge on the working dynamics of the treatment. Although we accounted for the half-life of paracetamol (on average 2.7 h), participants may have experienced a beneficial psychological effect of paracetamol that lasted throughout the second period (hence the period effect that was found). Moreover, paracetamol may not be strong enough to treat all types of pain in persons with dementia, which may explain why no differences were found between paracetamol and placebo treatment in the complete group of participants.

Compared with the distribution of males/females found in earlier research among persons with advanced dementia living in LTCF (about 72% or more female[4,11,19,44]), our study had relatively fewer women (57.9%). An explanation for this could be that we included persons based on their QoL, and apparently relatively more males had a low QoL. Also, the mean NPI total score in our research population was higher than that found in other studies in persons with advanced dementia living in LTCF (33 in our study vs 12-16 in other studies[4,44]). QoL may be affected to a considerable degree by neuropsychiatric symptoms, which is probably what we saw in our research population, as we selected our participants on low QoL and found relatively more neuropsychiatric symptoms.

The present study aimed to increase QOL in persons with dementia that were or were not in pain with pain treatment. No positive effects of regularly scheduled administration of

paracetamol on QoL, discomfort, pain and neuropsychiatric symptoms in persons with advanced dementia were found, compared to placebo. However, there were individual cases that clearly derived benefit from paracetamol during and after the study. This could have important implications for future prescriptions of pain medication in persons with advanced dementia, and it raises questions on the statistical significance vs. the clinical relevance of the results. We showed that performing research in this vulnerable group living in LTCFs is a challenge, especially in finding the right balanced study design that accounts for this population, of which the characteristics (comorbidities and illness/death) can change quickly over a short amount of time. In addition, more research should be performed to find out which persons with dementia benefit from pain treatment, and which do not. Following this study, more attention should be paid to the compliance of medication that is administered outside a 'unit dose package' by a nurse/nursing assistant. Clinicians should be aware that good assessment and monitoring, and a multidomain approach instead of only prescribing pain medication, is vital for improving QoL in this vulnerable group.

CONCLUSIONS

In this study, paracetamol did not show positive effects on QoL, discomfort, pain and neuropsychiatric symptoms in persons with advanced dementia with low QoL. It is important to find out more specifically which persons with advanced dementia could individually benefit from pain treatment with paracetamol.

DECLARATIONS

Ethical approval and consent to participate

The study has been approved by the Medical Ethics Committee of the Leiden University Medical Center (ref. number P17.051).

The treating elderly care physician selected eligible residents. When residents did not use pain medication, or used paracetamol that was only prescribed PRN (pro re nata, or 'as needed'), a study information letter was sent to the residents' legal representative, explaining the purpose and procedures of the study. The legal representative was asked to return the consent form by mail, to indicate either consent or refusal to participate. Once consent was received, the resident was screened for eligibility to participate.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

PHD, WPA, BSH, and MAAC contributed to the study concept and design. PHD, WPA and MAAC were responsible for the planning, conduct and analysis of the data of the study. All authors contributed to the drafting and critical revision of this manuscript. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. All authors have read and approved the final version of the manuscript.

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Transparency statement

The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported. No important aspects of the study have been omitted, and any discrepancies from the study as originally planned have been explained.

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Chapter 5

The effect of paracetamol on care dependency and daily functioning in persons with advanced dementia living in long-term care facilities

Van Dam PH, Achterberg WP, Husebo BS, Caljouw MAA.

Under review

ABSTRACT

Background

Pain medication may have an impact on the quality of life (QoL) in persons with dementia, but may also influence care dependency and daily functioning. The aim of this study is to report on the effect of paracetamol on care dependency and daily functioning in persons with advanced dementia living in long-term care facilities.

Methods

The Quality of life and Paracetamol In advanced Dementia (Q-PID) study was a (block) randomized double-blind placebo-controlled crossover trial with paracetamol and placebo across seventeen long-term care facilities across 9 care organizations in the western region of the Netherlands. Participants were ≥ 65 years, had advanced dementia (Global Deterioration Scale 5-7) and low QoL (QUALIDEM-6D score ≤ 70). Measurements were performed by nursing staff at the start and at the end of each treatment period of six weeks. Repeated linear mixed models were used to compute differences between randomization groups, with adjustment for period and order effects, and psychotropic use.

Results

Ninety-five persons (mean age of 83.9 years, 57.4% female) were enrolled in the Q-PID study. The mean Care Dependency Scale total score was 37.8 (Standard Deviation [SD] 12.9) and the mean Katz-15 total score was 11.9 (SD 2.4). Repeated linear mixed models showed no difference in mean differences of care dependency (paracetamol -1.0 [95% Confidence Interval (CI) -2.4-0.3], placebo +0.1 [-1.3-1.5]) and daily functioning (paracetamol +0.2 [95% CI -0.2-0.6], placebo +0.1 [-0.3-0.4]).

Conclusions

Compared to placebo, no effect of scheduled administration of paracetamol was found on care dependency and daily functioning in persons with advanced dementia with low QoL. Future research should focus on which specific items of care dependency need special attention to improve the care for persons with advanced dementia. A multi-domain approach is needed to enhance and/or maintain QoL of persons with advanced dementia.

BACKGROUND

Pain has a considerable impact on care dependency and daily functioning in older persons living in Long-term care facilities (LTCF)[1,2], and may also lead to a lower quality of life (QoL).[3,4] Pain medication may diminish pain and thereby reduce the negative impact of pain on care dependency and daily functioning of persons with advanced dementia. Also, paracetamol may have a positive impact on wellbeing, as the working mechanism of paracetamol has not been completely clarified so far.[5] The Quality of life and Paracetamol In advanced Dementia (Q-PID) study assessed the effect of regularly scheduled administration of paracetamol (acetaminophen) on QoL, discomfort, pain, neuropsychiatric symptoms, care dependency and daily functioning of persons with advanced dementia and low QoL living in LTCF. Recently, the first results of the Q-PID study, i.e., the effect of paracetamol (acetaminophen) on QoL, discomfort, pain and neuropsychiatric symptoms, were published.[6] No treatment effect in favour of paracetamol was found on these four outcomes. Therefore the aim of this study is to investigate the effect of regularly scheduled paracetamol on care dependency and daily functioning in persons with advanced dementia with low QoL living in LTCF.

METHODS

The Q-PID study was a (block) randomized double-blind placebo-controlled crossover trial, performed between January 2018 and June 2019 in 17 LTCF across 9 care organizations in the western region of the Netherlands that are members of the University Network for the Care sector South Holland (UNC-ZH). Persons aged ≥ 65 years with advanced dementia (Global Deterioration Scale [GDS] score of 5-7) and low QoL (QUALIDEM-6D total score ≤ 70) were included in this study. Participants did not use pain medication daily and pain was not assessed prior to the study, assuring that participants were enrolled having low QoL. Each participant was randomized into one of the two randomization groups: one group received paracetamol for 6 weeks, followed by a 'wash-out' week without study medication and 6 weeks placebo. The second group received placebo for 6 weeks, followed by a 'wash-out' week without study medication and 6 weeks paracetamol. Demographic characteristics were collected by the elderly care physician and nursing staff at baseline. Measurements were performed by nursing staff at the start and right before the end of each treatment period (at baseline, and before the end of weeks 6, 7, and 13). Detailed information about the study design, the intervention, and the results on the outcomes of QoL, discomfort, pain and neuropsychiatric symptoms can be found elsewhere.[6,7]

Outcome measures

Care dependency

The Care Dependency Scale (CDS), which consists of components of care, was used to measure care dependency.[8-10] For each of the 15 items of the CDS, the nursing staff assessed the extent to which the person with dementia was able to perform a care task without assistance on a scale of 1 (completely dependent) to 5 (completely independent). The total score of the CDS ranges from 15 (completely care dependent) to 75 (completely care independent).

Daily functioning

(Instrumental) Activities of Daily Living (ADL) were measured with the Katz-15 scale, which comprises the six ADL items of the Katz-6 questionnaire (do you need help with bathing, dressing, using toilet, transfer to and from a chair, incontinence and ability to eat without help?)[11], seven items of the Lawton Instrumental Activities of Daily Living (LIADL; do you need help with using a telephone, shopping, preparing food, performing household tasks, travelling, taking medication and handling own finances?)[12], and two extra questions whether the person needs help with combing hair/shaving, and walking about.[13] The Katz-15 scale ranges from 0 (no help needed with (i)ADL tasks) to 15 (help needed in all 15 items of (i)ADL).

Pain

In the Q-PID study, pain was monitored at baseline, and after 6, 7, and 13 weeks using the Mobilization-Observation-Behaviour-Intensity-Dementia Pain Scale 2 (MOBID-2).[14-16] With this pain scale, nursing staff measured musculoskeletal pain during morning care, when guiding the person with dementia with movement of arms and legs, lying on both sides of the body, and sitting up on the bed (Part 1). MOBID-2 Part 2 consists of five items and assesses pain coming from head, skin, and internal organs. The nursing staff scored the pain of the person with dementia on a scale of 0 (no pain) to 10 (worst pain possible), based on the facial expression, vocalization, and defending behaviour during these movements. A score of ≥ 3 is regarded as clinically relevant pain.[14]

Statistical analysis

Differences between randomization groups were computed using unpaired *t* tests for normally distributed numerical data, one-way ANOVA tests for non-normally distributed data, and χ^2 tests for categorical data. Since order and period effects were found for the main outcome QoL, repeated linear mixed models were used, with adjustment for these effects plus the use of psychotropics, as the number of psychotropic users was statistically different at baseline in the randomization groups. For details on sample size calculation, see the protocol article of the Q-PID study.[7]

RESULTS

A total of 95 persons with a mean age of 83.9 years (SD 7.6) were enrolled in the Q-PID study. Data on care dependency and daily functioning were available for 94 persons (57.4% female) with a mean CDS total score of 37.8 (SD 12.9) and a mean Katz-15 total score of 11.9 (SD 2.4). The overall MOBID-2 pain score was 2.1 (SD 2.7) and 32.3% of the total group had clinically relevant pain (Table 1).

Table 1. Baseline characteristics of the total group, stratified by randomization group

	Paracetamol-placebo ***N* = 46**	**Placebo-paracetamol** ***N* = 48**
Mean age (SD) in years	83.8 (7.5)	83.9 (7.7)
Female (%)	26 (56.5)	28 (58.3)
GDS score 7 (%)	10 (21.7)	10 (21.3)
FCI, 0-18 (SD)	2.9 (2.0)	2.5 (2.1)
CDS, 15-75 (SD)	39.7 (13.7)	36.0 (11.9)
Katz-15, 0-15 (SD)	11.5 (2.5)	12.3 (2.2)
Pain (MOBID-2 ≥ 3) (%)	15 (33.3)	15 (31.3)
MOBID-2 overall pain intensity, 0-10 (SD)	2.0 (2.4)	2.3 (3.0)

SD = standard deviation; GDS score 7 = Global deterioration Scale stage 7 (most advanced dementia); FCI = Functional Comorbidity Index); MOBID-2 = Mobilization-Observation-Behaviour-Intensity-Dementia-2 pain scale; CDS = Care Dependency Scale (short version, higher score means less care dependency); Katz-15, daily functioning, higher score means more help needed with tasks

The characteristics of and measurements in the two randomization groups did not differ significantly at baseline, except regarding the number of persons who used psychotropics (antipsychotics, antidepressants, anxiolytics, hypnotics, and anti-dementia drugs); 37.0% in the paracetamol-placebo group vs. 60.4% in the placebo-paracetamol group (p = 0.023).

Nine participants deceased during the study, resulting in 86 participants remaining at the end of the study periods. Repeated linear mixed models, adjusted for order and period effects, and psychotropic use, showed no difference in mean differences of care dependency (paracetamol -1.0 [95% CI -2.4-0.3], placebo +0.1 [-1.3-1.5]) and daily functioning (paracetamol +0.2 [95% CI -0.2-0.6], placebo +0.1 [-0.3-0.4]), in favour of either paracetamol or placebo (table 2). Fig. 1 shows the course of care dependency and daily functioning during the Q-PID study.

DISCUSSION

The aim of this study was to investigate the effect of paracetamol on care dependency and daily functioning. No statistically significant treatment effect of scheduled administration of

Table 2. Treatment effects of paracetamol and placebo on care dependency and daily functioning*
N = 94 (baseline) *N* = 86 (end of study)

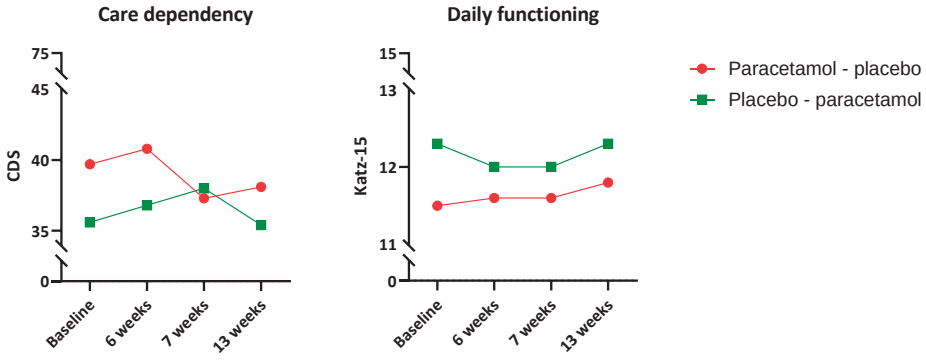
	Intervention	Mean difference	95% CI	*p* value
CDS†	Paracetamol	-1.0	-2.4 – 0.3	0.239
	Placebo	0.1	-1.3 – 1.5	
Katz-15‡	Paracetamol	0.2	-0.2 – 0.6	0.573
	Placebo	0.1	-0.3 – 0.4	

* Repeated linear mixed models, adjusted for order – and period effects, and use of psychotropics
† Higher score means less care dependency
‡ Higher score means worse daily functioning
CI = Confidence interval; CDS = Care Dependency Scale (short version); Katz-15 = ADL and iADL scale 15 items

paracetamol was found on care dependency and daily functioning in persons with advanced dementia with low QoL living in LTCF.

It is somewhat puzzling why we did not find an effect; one explanation may be the selection of patients. Participants were included in the Q-PID study based on having a low QoL and not using daily pain medication. The amount of pain was not a selection criterion and was unknown prior to inclusion in the study. We found that 31.9 % of the participants in the study had clinically relevant pain at baseline and the mean MOBID-2 pain score of all 94 participants was 2.1 (SD 2.7), which is below the threshold of 3 (clinically relevant pain). This is lower than the numbers of persons with advanced dementia with pain found in other studies.[1,17,18] Consequently, the range of improvement of pain was already low for two-thirds of our study population. Other studies have demonstrated that pain may have a negative impact on care dependency and ADL functioning.[1,2,6] As we found no significant improvement on pain, this might be a reason why care dependency and daily functioning did not improve either in the study. Moreover, prior to the Q-PID study, we hypothesized that when a person would feel better when paracetamol was taken, he/she may become less care dependent and have a better QoL. However, no positive effect of paracetamol on QoL and wellbeing was found. With the progression of dementia, it is possible that care dependency and daily functioning may not be influenced easily, especially in persons that are not in pain. Finally, only small changes over time were seen in both intervention groups, especially regarding ADL functioning and to a lesser extent also for care dependency. This was possibly based on natural variability in conjunction with the progression of the dementia, which may not be influenced by paracetamol (or placebo). These observed small changes over time of the Katz-15 (and CDS) may raise questions about the usefulness of these measures in clinical practice for persons with advanced dementia living in LTCF. The Katz-15 was designed to be used for research, the CDS to be used in nursing homes. Since the answers of the CDS are more defined with five options per item ('completely independent' to 'completely dependent'), this measure may provide more leads as to which specific interventions are needed to improve daily care for these persons, compared to the 'yes' or 'no' answers regarding which items the person needs help with.

Fig. 1 Mean CDS and Katz-15 total scores in the two treatment groups during the Q-PID study



CDS: Care Dependency scale, range 15 (completely care dependent) to 75 (completely care independent)
Katz-15: daily functioning, range 0 (completely independent functioning) to 15 (completely dependent functioning)
Paracetamol - placebo: baseline - 6 weeks paracetamol, 7 weeks - 13 weeks placebo
Placebo - paracetamol: baseline - 6 weeks placebo, 7 weeks - 13 weeks paracetamol

The most important strength to mention is that the Q-PID study is one of the biggest randomized double-blind placebo-controlled cross-over studies performed in LTCF among persons with advanced dementia, and that the number of drop-outs/withdrawals was within the prior estimated range. An important limitation was that a period effect was found, i.e., the total population performed better on QoL and neuropsychiatric symptoms in period 1 compared to period 2. This effect may have been caused by deterioration due to the disease, or by a Hawthorne effect for the first period (participation in a study in itself may lead to improvement).

CONCLUSIONS AND IMPLICATIONS

Compared to placebo, no effect of scheduled administration of paracetamol was found on care dependency and daily functioning in a group of 95 persons with advanced dementia with low QoL living in LTCF. It may be relevant for clinicians and nursing staff to find out more about the relationship between the different items of care dependency and existent pain, and which specific items of care dependency need special attention, to have points of reference to improve the care for, and thereby improve the QoL of, persons with advanced dementia. A multi-domain approach of professionals and informal caregivers is essential to reach this goal.

DECLARATIONS

Ethics approval and consent to participate

The study has been approved by the Medical Ethics Committee of the Leiden University Medical Center (ref. number P17.051) and was conducted according to the principles of the Declaration of Helsinki (amended in October 2013), in accordance with the Medical Research Involving Human Subjects Act (WMO), the Guideline for Good Clinical Practice (May 1996), and in full conformity to any applicable state or local regulations. The legal representative of possible participants was asked to return the consent form by mail/POST, to indicate either consent or refusal to participate. Once informed consent was received, the resident was screened for eligibility to participate.

Trial registration

Netherlands Trial Register (NTR6766); http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=6766; Trial registration date: 20/10/2017.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

None

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Authors' contributions

PHD, WPA, BSH, and MAAC contributed to study conception and design. PHD, WPA and MAAC were responsible for planning, conduct and analysis of the data of the study. All authors contributed to the drafting and critical revision of this manuscript. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. All authors have read and approved the final version of the manuscript.

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Chapter 6

Care dependency and daily functioning of persons with advanced dementia are associated with social relationships

Van Dam PH, Achterberg WP, Husebo BS, Caljouw MAA.

Submitted

ABSTRACT

Background

Cognitive deficits may lead to care dependency in persons with advanced dementia and interfere with their independence in activities of daily living (ADL). Also, higher levels of care dependency and functional disability are associated with a lower quality of life (QoL) in these persons. To find points of reference to improve care dependency and ADL, and thereby QoL, the objectives of this study are:

1. To examine care dependency and ADL functioning in persons with advanced dementia living in long-term care facilities (LTCF).
2. To explore which factors are associated with care dependency and ADL functioning of persons with advanced dementia living in LTCF.

Methods

Cross-sectional analysis of the Quality of life and Paracetamol In advanced Dementia (Q-PID) trial. Participants were ≥ 65 years old, had advanced dementia (Reisberg GDS 5-7) and a low QoL (QUALIDEM-6D total score < 70). Linear regression models were used to explore associated factors with care dependency and ADL functioning.

Results

Ninety-four persons with advanced dementia and mean age 83.8 years. Mean Care Dependency Scale (CDS) total score; 37.8 (Standard Deviation (SD) 12.9), mean Katz-15 total score; 11.9 (SD 2.4). Multiple linear regression models showed that GDS stage 7 was independently associated with higher care dependency (β -11.788, $p < 0.001$) and worse ADL functioning (β 1.312, $p = 0.027$). The QUALIDEM domain social relationships was independently associated with less care dependency (β 0.213, $p < 0.001$) and better ADL functioning (and β -0.031, $p = 0.008$).

Conclusions

Better social relationships are associated with less care dependency and better ADL functioning in persons with advanced dementia and low QoL living in LTCF. Very advanced dementia (GDS 7) is associated with higher care dependency and worse ADL functioning. It is important to acknowledge that care dependency and daily functioning can be improved by enhancing social relationships, even in the last stages of dementia.

Trial registration

Netherlands Trial Register (NTR6766); http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=6766; Trial registration date: 20th October, 2017

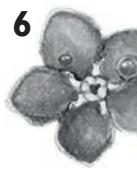
Key words: dementia, quality of life, care dependency, ADL functioning, long-term care facility

BACKGROUND

Dementia is a progressive deteriorating condition in which decline occurs in more than one cognitive domain (complex attention, executive function, learning and memory, language, perceptual-motor, or social cognition).[1] These cognitive deficits interfere with independence in activities of daily living (ADL) and lead to care dependency.[2] ADL comprises daily tasks such as feeding, bathing, dressing, grooming, moving, and toileting. Research indicates that not one specific cognitive domain is related to the deterioration of ADL and care dependency, but a combination of the degree of cognitive decline, a higher level of agitation and apathy, and higher physical comorbidity.[3-5] The progression of dementia could even lead to the need for 24-hour care and support provided by professional caregivers in a long-term care facility (LTCF).

As there is no cure for dementia, the main goal of caring for persons with dementia living in LTCF is the maintenance and improvement of quality of life (QoL).[6] Although the progression of Alzheimer's dementia in itself may not always lead to a decline in QoL[7], higher levels of care dependency and functional disability are associated with a lower QoL of persons with dementia.[8-10] Little is known about which factors are associated with care dependency and ADL functioning in persons with dementia who have a poor QoL. This knowledge is important to develop interventions for maintaining or improving their care dependency and daily functioning, and thereby their QoL. Therefore, the aims of this study are:

1. To examine care dependency and ADL functioning in persons with advanced dementia living in LTCF.
2. To explore which factors are associated with care dependency and ADL functioning of persons with advanced dementia living in LTCF.



METHODS

For this cross-sectional study, baseline data of the Quality of life and Paracetamol In advanced Dementia (Q-PID) study were used. The Q-PID study was a (block) randomized double-blind placebo-controlled crossover trial, performed between January 2018 and June 2019, and explored the effects of regularly scheduled paracetamol (acetaminophen) on QoL, discomfort, neuropsychological symptoms, pain, care dependency and ADL functioning in 95 persons with advanced dementia living in LTCFs. The participants who were included in the Q-PID study were ≥ 65 years old, had a low QoL (QUALIDEM[11] total score of ≤ 70), had advanced dementia (Reisberg Global Deterioration Scale (GDS)[12] 5 to 7), and did not use any scheduled pain medication. The QUALIDEM score of ≤ 70 was based on the median QUALIDEM total score that emerged from data of the STA-OP! Study.[13] Exclusion criteria were allergy to paracetamol

and/or quinin, weight < 50 kg, use of > 4 IU alcohol daily, and severe liver insufficiency. More detailed information about the Q-PID study and the first results were published elsewhere.[14, 15]

MEASUREMENTS

Demographic data

Data on age, sex, and dementia stage were collected by the nurse/nursing assistants working at the LTCF units of the participants. The stage of dementia has been established with the GDS.[12] The GDS defines 7 clinically identifiable and rateable stages of dementia according to clinical performance in daily functioning, cognition, personality, and emotions. Scores range from 1 (no cognitive decline) to 7 (very severe cognitive decline).

Care dependency and ADL functioning

The Care Dependency Scale (CDS) has been developed to measure care dependency in persons with dementia and persons with mental disabilities.[16] It consists of 15 items reflecting nursing dimensions of a person's level of care dependency and has been demonstrated to be reliable, producing valid data, and to have diagnostic accuracy in persons with dementia.[17-19] The level of care dependency for each item is scored on a scale of 1 (completely dependent) to 5 (completely independent). Consequently, total scores range from 15 (completely dependent) to 75 (completely independent).

ADL functioning was measured using the Katz-15, which is a combined instrument of six ADL items (Katz-6)[20], seven iADL items of the Lawton instrumental Activities of Daily Living index (LIADL)[21], and two additional questions about walking outside and brushing hair/shaving. The Katz-15 has been demonstrated to be a reliable and valid instrument to measure future health outcomes.[22] Scores range from 0 (no help needed with ADL) to 15 (help needed in all 15 items of (i)ADL).

Quality of life, discomfort, pain, and neuropsychiatric symptoms

The six-domain short version of the QUALIDEM (QUALIDEM-6D) was administrated by a nurse/nursing assistant to observe QoL.[23] This version is specifically designed to measure QoL in persons with advanced dementia and consists of 18 items that have been demonstrated to reflect the QoL of persons with dementia.[11, 24, 25] The six domains of the QUALIDEM (care relationship, positive affect, negative affect, restless tense behaviour, social relationships and social isolation) can be scored individually (ranging from 6 to 12 points per domain) and can be added up to a total score of 54 points. Making the scores of the domains and total score easier to compare, individual domains and the total score of the six domains together were recalculated to a score between 0 (lowest QoL) to 100 (highest QoL). This was performed by

dividing the obtained score by the total obtainable score in the item and multiplying it by 100, as was done in previous studies.[15, 26, 27]

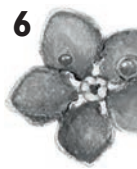
Discomfort was measured by using the Discomfort Scale - Dementia of Alzheimer Type (DS-DAT)[28], which consists of nine components of discomfort observed and scored by a nurse/nursing assistant. Pain was assessed based on the Mobilization-Observation-Behaviour-Intensity-Dementia (MOBID-2) Pain Scale[29, 30], where pain behaviour is observed by a nurse/nursing assistant during morning care on a scale from 0 (no pain) to 10 (worst pain). A score of ≥ 3 is considered clinical pain.[30] Neuropsychiatric symptoms were measured with the Neuropsychiatric Inventory – Nursing Home version (NPI-NH).[31, 32] In the analysis, total scores of all 12 items were calculated for each participant. Moreover, eight items were clustered into 3 separate domains, i.e. psychosis (psychosis, delusion, hallucination), agitation (agitation, disinhibition, irritability), and affective symptoms (depression, anxiety).

Comorbidity and medication use

The Functional Comorbidity Index (FCI) was used to assess comorbidity.[33] This index consists of 18 comorbid diseases that are known to have an impact on physical function. For this study, the use of antipsychotics, antidepressants, and benzodiazepines (psychotropics) was extracted from the topical medication overviews of all participants.

Statistical analysis

Descriptive statistics were expressed as means for normally distributed data and medians for non-normally distributed data. Univariate linear regression analysis was performed for each variable that was considered a probable associated factor with care dependency and/or ADL functioning. Variables with $p < 0.10$ in the univariate model plus age and sex were entered in a multivariate linear regression model. With a backward elimination procedure, all variables were deleted one by one (highest p values first) until only variables with $p < 0.003$ remained in the model (Bonferroni correction for multiple testing 0.05/16).[34]



Descriptive and linear regression analyses were performed with SPSS statistical software v 25.0 (IBM Corp., Armonk, NY).

RESULTS

Data on care dependency were available for 94 participants. Their mean age was 83.8 years of which 57.4% were females. Almost half of the participants used one or more psychotropics, their median FCI was 2.0 (interquartile range [IQR] 1.0-4.0), and very advanced dementia (GDS 7) was present in 21.3% of the study population (Table 1). Almost 80% of the total group

were completely or to a great extent dependent on care. The mean CDS total score was 37.8 (standard deviation [SD] 12.9) and mean Katz-15 total score was 11.9 (SD 2.4). Most care dependency, i.e., to a great extent or completely care dependent, was seen in learning ability (66.3%), eating and drinking (61.2%) and performing activities (59.3%). The items on which the population was least care dependent, i.e., to a great extent or completely independent, were communication (60.5%), maintaining body posture (58.1%) and mobility. (48.8%). The total group had a mean QUALIDEM-6D total score of 57.5 (SD 13.4), with the highest domain scores on positive affect (69.0, SD 19.1), negative affect (64.0, SD 26.4), and social relationships (61.3, SD 21.0)(Table 1). Almost one-third of the participants had clinically relevant pain, and the mean NPI-NH score was 33.0 points (SD 20.0).

Table 1 Baseline characteristics of the total study population (*N* = 94)

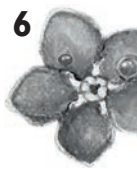
Mean age in years (SD)	83.8 (7.6)
Female (%)	54 (57.4)
Very severe dementia; GDS 7 (%)	20 (21.3)
Comorbidity; FCI, 0-18 (IQR)	2.0 (1.0-4.0)
Psychotropic use (%)	46 (48.9)
Care dependency; CDS, 15-75 (IQR)	37.8 (12.9)
Daily functioning; Katz-15, 0-15 (SD)	11.9 (2.4)
Quality of life; QUALIDEM-6D, 0-100 (SD)	
Total score	57.5 (13.4)
A – Care relationship	57.4 (22.6)
B – Positive affect	69.0 (19.1)
C – Negative affect	64.0 (26.4)
D – Restless tense behaviour	38.9 (27.0)
F – Social relationships	61.3 (21.0)
G – Social isolation	54.4 (22.3)
Discomfort; DS-DAT, 0-27 (SD)	8.3 (5.5)
MOBID-2 overall pain intensity, 0-10 (SD)	2.1 (2.7)
Pain; MOBID-2 total score ≥ 3 (%)	30 (31.9)
Neuropsychological symptoms; NPI-NH	
Total score, 0-144 (SD)	33.0 (20.0)
Psychosis, 0-24 (SD)	3.7 (5.2)
Agitation, 0-48 (SD)	11.3 (9.1)
Affective symptoms, 0-24 (SD)	5.4 (6.0)

SD, standard deviation; GDS, Global Deterioration Scale; FCI, Functional Comorbidity Index; Katz-15, daily functioning, higher score means more help needed with tasks, CDS, Care Dependency Scale, QUALIDEM-6D, dementia-specific QoL measurement instrument, 6-domain version; DS-DAT, Discomfort Scale-Dementia of Alzheimer Type; MOBID-2, Mobilization-Observation-Behaviour-Intensity-Dementia-2 pain scale; NPI-NH, Neuropsychiatric Inventory – Nursing Home version

Table 2 Univariate linear regression model for care dependency (CDS) and daily functioning (Katz-15) (*N* = 94)

	CDS		**Katz-15**	
	β	***p* value**	**β**	***p* value**
Age	0.220	0.213	0.021	0.520
Female	1.752	0.517	-0.061	0.903
Very severe dementia (GDS 7)	-14.788	**< 0.001**	1.759	**0.003**
Comorbidity; FCI total score	-0.171	0.801	0.174	0.174
Uses psychotropic(s)	-4.062	0.127	0.678	0.172
Quality of life; QUALIDEM-6D				
A – Care relationship	0.035	0.555	-0.003	0.805
B – Positive affect	0.231	**0.001**	-0.035	**0.007**
C – Negative affect	-0.011	0.831	0.001	0.898
D – Restless tense behaviour	0.123	**0.012**	-0.007	0.436
F – Social relationships	0.278	**< 0.001**	-0.038	**0.001**
G – Social isolation	0.111	**0.063**	-0.014	0.197
Discomfort; DS-DAT	-0.143	0.564	-0.015	0.749
MOBID-2 overall pain intensity	-0.611	0.219	0.062	0.497
Neuropsychological symptoms; NPI-NH				
Psychosis	0.343	0.182	-0.058	0.229
Agitation	-0.120	0.414	-0.004	0.881
Affective symptoms	0.084	0.708	-0.024	0.569

CDS, Care Dependency Scale; Katz-15, daily functioning; GDS, Global Deterioration Scale; FCI, Functional Comorbidity Index; QUALIDEM-6D, dementia-specific QoL measurement instrument, 6 domain version; DS-DAT, Discomfort Scale-Dementia of Alzheimer Type; MOBID-2, Mobilization-Observation-Behaviour-Intensity-Dementia-2 pain scale; NPI-NH, Neuropsychiatric Inventory – Nursing Home version



Care dependency – regression models

Table 2 shows the outcomes of the univariate linear regression models for care dependency. Five variables were associated with care dependency ($p < 0.10$), i.e. dementia severity (GDS 7) (β -14.788, $p < 0.001$), and the QUALIDEM domains positive affect (β 0.231, $p = 0.001$), restless tense behaviour (β 0.123, $p = 0.012$), social relationships (β 0.278, $p < 0.001$) and social isolation (β 0.111, $p = 0.063$). A multivariate linear regression model for CDS was performed with the preceding variables with $p < 0.10$ plus age and sex. The result of the final multivariate linear regression model is shown in Table 3. Dementia severity (GDS 7) and the QUALIDEM domain social relationships were independently associated with care dependency (β -11.713, $p < 0.001$ and β 0.213, $p < 0.001$, respectively). This means that the care dependency of persons with very severe dementia (GDS 7) is 11.713 points lower, i.e. higher care dependency compared to persons with moderate to severe dementia (GDS 5 and 6). Moreover, each percent scored higher on the social relationships domain of the QUALIDEM accounts for a 0.213 point rise on the CDS (less care dependency). Since the scores of the QUALIDEM domains are based on the obtained points divided by the total number of obtainable points multiplied by 100, a rise

of one point on the QUALIDEM domain social relationships is equal to 11.1% (1 of a total of 9 obtainable points), which means an improvement of 2.4 points (0.213 multiplied by 11.1) on the CDS according to the model.

Table 3 Final multivariate linear regression model of variables associated with care dependency (CDS) and daily functioning (Katz-15) (adj R^2 CDS; 0.32, Katz-15; 0.14)

	CDS		**Katz-15**	
	β	**p-value**	**β**	**p-value**
Very severe dementia; GDS 7	-11.713	**< 0.001**	1.312	**0.027**
QUALIDEM F – Social relationships	0.213	**< 0.001**	-0.031	**0.008**

CDS, Care Dependency Scale; Katz-15, daily functioning; GDS, Global Deterioration Scale; QUALIDEM, dementia-specific QoL measurement instrument, 6-domain version

ADL functioning – regression models

Dementia severity (GDS 7) (β 1.759, p = 0.003), and the QUALIDEM domains positive affect (β -0.035, p = .007) and social relationships (β -0.038, p = 0.001) were associated with ADL functioning in the univariate models. A multivariate linear regression model for the Katz-15 was performed with the preceding variables with $p < 0.10$ plus age and sex. In this final multivariate linear regression model, dementia severity (GDS 7) and QUALIDEM domain social relationships were independently associated with ADL functioning (β 1.312, p = 0.027 and β -0.031, p = 0.008, respectively), meaning that the Katz-15 total score of persons with most severe dementia (GDS 7) was 1.312 points higher (worse daily functioning). Moreover, every percent that is scored higher on the QUALIDEM domain social relationships accounts for a -0.34 point decrease (-0.031 multiplied by 11.1) on the Katz-15 total score (better daily functioning).

DISCUSSION

In this study, we explored which factors are associated with improvement or deterioration of care dependency and daily functioning in persons with advanced dementia who had a low QoL. This information could be a good point of reference to improve care dependency and daily functioning, and thereby QoL. On average, the score of the care dependency (37.8 out of 75 points) in our population was low and the mean score for daily functioning (11.9 out of 15 points on the Katz-15 instrument) was high, meaning that our study population was to a great extent dependent on care of others. Moreover, we found that good social relationships are associated with less care dependency and better daily functioning in persons with advanced dementia with low QoL and that having the most advanced stage of dementia (GDS 7) is associated with higher care dependency and worse daily functioning.

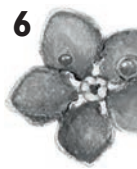
Care dependency, ADL functioning and QoL

According to Caljouw et al. the care dependency of persons with dementia living in LTCF may either deteriorate or improve over time.[35] However, the participants included in that study were more independent of care (higher CDS score) than those in our study. This may be caused by the difference in dementia (severity) between both study populations (76.8 vs. 100% dementia), i.e. the group with more (advanced) dementia displays a higher level of care dependency.

Garre-Olmo et al. found a direct relationship between the care dependency level and QoL, and between daily functioning and QoL, i.e. higher care dependency was directly correlated with a lower QoL, and better daily functioning was directly correlated with a higher QoL.[8] This is comparable to what we found in our study. It may also explain the much higher CDS score (lower care dependency) of 50.15 points that was found by Henskens et al., where QoL was neither an inclusion criterion, nor was it included as a factor that could be associated with care dependency.[5] Also, persons who were not able to complete a 6-minute walking test and/or were wheelchair bound were excluded from the Henskens study, indicating that the study population had better function and were less care dependent, as shown by their baseline results.

Social relationships

We have shown that good social relationships are associated with less care dependency and better daily functioning. Burge et al. also found that having daily contact with a proxy was strongly associated with a lower risk of deterioration of daily functioning, which implies that social relationships are important for maintaining ADL function[36], although not all participants in that study had (advanced) dementia. It is shown that it is possible to improve care dependency and daily functioning, and thus QoL of persons with dementia over time.[35, 37] However, to our opinion, social factors are important in improving the care for persons with advanced dementia. This may also imply that the care for persons with advanced dementia can be improved by offering interventions in which social interaction with e.g. relatives, family and care professionals may contribute to less care dependency and better functioning.



Strengths and limitations

This is one of the few studies exploring care dependency and ADL function and associated factors in persons with (very) advanced dementia. The very few studies that focused on this subject did not include social relationships, especially not those focussing on care dependency. Our data provide a new insight into the high care dependency of persons with advanced dementia having a low QoL.

Since this study is based on cross-sectional data, no conclusions can be drawn regarding causality, only associations. Moreover, the Q-PID study was not specifically designed for the aims of the current study, so variables that may also be associated with care dependency and ADL

functioning, such as measures of physical function, may be missing in our data. This could be a reason why the adjusted R^2s, which provide an insight into the goodness of fit of the models, were relatively low (0.32 and 0.14).

Clinical relevance

Knowledge on what persons with advanced dementia need to improve their care dependency and daily functioning, and thereby possibly improve their QoL, is important to provide the best possible care. Since care dependency and daily functioning are associated with social relationships, but also with pain[38, 39], it may be tentatively hypothesized that by improving social relationships, pain may be improved as well. This would shine a new light on factors that may influence pain in persons with advanced dementia and needs more attention in further research. Activities for persons with dementia that focus mainly on social relationships may be a good intervention to influence pain.

Conclusions and Implications

Better social relationships are independently associated with less care dependency and better daily functioning in persons with advanced dementia and low QoL living in LTCF. Very advanced dementia (GDS 7) is independently associated with higher care dependency and worse daily functioning. It is important to acknowledge that care dependency and daily functioning can be improved by enhancing social relationships, even in the latest stages of dementia. More (longitudinal) research is needed to improve our knowledge on the associations between and tailored interventions for care dependency, daily functioning, and pain.

LIST OF ABBREVIATIONS

ADL	Activities of Daily Living
CDS	Care Dependency Scale
DS-DAT	Discomfort Scale – Dementia of Alzheimer Type
FCI	Functional Comorbidity Index
GDS	Reisberg Global Deterioration Scale
LTCF	Long-term Care Facility
MOBID-2	Mobilization-Observation-Behaviour-Intensity-Dementia-2 pain scale
NPI-NH	Neuropsychiatric Inventory – Nursing Home version
QoL	Quality of Life
Q-PID study	Quality of life and Paracetamol In advanced Dementia study

DECLARATIONS

Ethics approval and consent to participate

The Q-PID study was conducted according to the principles of the Declaration of Helsinki (amended in October 2013), in accordance with the Medical Research Involving Human Subjects Act (WMO), the Guideline for Good Clinical Practice (May 1996), and in full conformity to any applicable state or local regulations. The study has been approved by the Medical Ethics Committee (ref. number P17.051). Informed consent was obtained from all legal representatives of the participants and where possible of the participants themselves.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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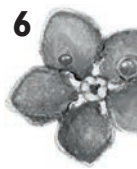

Authors' contributions

PHD, WPA, BSH, and MAAC contributed to the study concept and design. PHD and MAAC were responsible for the analysis of the data of the study. All authors contributed to the drafting and critical revision of this manuscript. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. All authors have read and approved the final version of the manuscript.

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Not applicable

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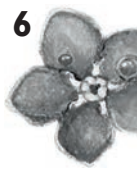

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Chapter 7

General Discussion

The aim of this thesis is to explore the characteristics and quality of life (QoL) of persons with advanced dementia living in long-term care facilities (LTCF) with and without pain medication, the association between QoL, pain and use of pain medication, and to study the effect of paracetamol on QoL, discomfort, pain, neuropsychiatric symptoms, care dependency and daily functioning in persons with advanced dementia living in LTCF. This chapter describes the main findings, the interpretation and critical discussion of findings and methodology, implications for practice and education, and recommendations for future research.

7.1 SUMMARY OF MAIN FINDINGS

Part I – Quality of life and pain medication in dementia

Part I in this thesis answers questions regarding the difference in characteristics and in QoL between persons with and without pain medication, the association between QoL, pain and use of pain medication (paracetamol, opioids, both paracetamol and opioids, or no pain medication), and the effect of regularly scheduled administration of paracetamol on QoL, discomfort, pain and neuropsychiatric symptoms in persons with advanced dementia living in LTCF.

The differences in characteristics and in QoL between persons with and without pain medication are described in **Chapter 2**. Cross-sectional data of the Communication, Systematic Assessment and Treatment of Pain, Medication Review, Occupational Therapy, and Safety (COSMOS) study - a multicenter, cluster randomized effectiveness-implementation clinical hybrid trial in 67 Norwegian LTCF clusters - were analyzed.[1] **Chapter 2** shows that persons with advanced dementia living in LTCF who used pain medication had 1) more advanced dementia (Functional Assessment Stage 7), 2) pain scores more than twice as high, 3) significantly worse daily functioning, 4) more depressive symptoms, and 5) more neuropsychiatric symptoms, compared with persons who did not use any pain medication. The QoL measured by the QUALIDEM-6D, the short 18-item 6-domain version of the QUALIDEM[2,3] specifically for persons with advanced dementia, was significantly lower in persons who used pain medication compared with persons who did not use any pain medication, except for the domain 'social relationships'.

The association between QoL, pain and use of pain medication (paracetamol, opioids, both paracetamol and opioids, or no pain medication) in persons with advanced dementia living in LTCF was also described in **Chapter 2**. The cross-sectional data of the COSMOS study showed that the group of persons with advanced dementia living in LTCF with clinically relevant pain (Mobilization-Observation-Behavior-Intensity-Dementia-2 [MOBID-2] total score ≥3) who did not use any pain medication daily had better overall QoL compared with persons who used paracetamol, opioids, or both paracetamol and opioids. In the group that used only paracetamol, the persons who were still in pain had a significantly lower QoL compared with persons with-

out pain. In the other three groups (no pain medication, opioids, and both paracetamol and opioids) no significant differences in overall QoL were seen between persons with and without pain. Because only the paracetamol group showed differences in QoL between persons with and without pain, the association between paracetamol use and QoL was estimated using linear mixed-effects models adjusting for confounding variables and interaction between paracetamol and opioids. No significant association was found between paracetamol use and overall QoL, or between paracetamol use and the 6 domains of the QUALIDEM.

Chapter 3 describes the protocol of the Quality of life and Paracetamol In advanced Dementia (Q-PID) study. This study was a randomized double-blind placebo-controlled crossover trial in 95 persons with advanced dementia living in LTCF across the west of the Netherlands. All participating organizations were members of the University Network for the Care sector South Holland (UNC-ZH). Only persons with low QoL (QUALIDEM-6D ≤70, the median QUALIDEM-6D total score in a general population of persons with dementia living in LTCF in the Netherlands in the STA-OP! study[4]) could participate in the study. Pain was not assessed prior to the study.

The effects of regularly scheduled administration of paracetamol on QoL, discomfort, pain and neuropsychiatric symptoms, as found in the Q-PID study, are described in **Chapter 4**. After conducting the study, repeated linear mixed models showed that paracetamol, compared to placebo, did not have a positive effect on QoL, discomfort, pain or neuropsychiatric symptoms. However, there were participants who clearly derived benefit from paracetamol during and after the study, according to their nursing staff. Although, on average, baseline pain scores on the Mobilization-Observation-Behaviour-Intensity-Dementia-2 (MOBID-2) pain scale in both treatment groups were lower than the score of ≥ 3 that is considered clinically relevant pain, more than 30% of the total group had a MOBID-2 pain score of ≥ 3 at baseline and did not use any pain medication (as this was an exclusion criterion). Data of the Q-PID study on the QoL revealed significant order – and period effects, which had consequences for the analyses and provided more food for thoughts regarding the design of the study. This subject will be elaborated on in the critical discussion (paragraph 7.2).

Part II – Care dependency, daily functioning, pain medication and QoL

Part II describes the effect of regularly scheduled administration of paracetamol on care dependency and daily functioning, and how care dependent persons with advanced dementia and low QoL living in LTCF are.

After adjusting for period and order effects, and psychotropic medication use, no effect of scheduled administration of paracetamol, compared to placebo, was found on care dependency

and daily functioning in a group of 95 persons with advanced dementia with low QoL living in LTCF. This was shown in the Q-PID study and is described in **Chapter 5**.

Cross-sectional data of the Q-PID study (baseline) were used to describe how care dependent the participants in the Q-PID study were and which factors were associated with care dependency and daily functioning (**Chapter 6**). The mean Care Dependency Scale (CDS) score was 37.8 (standard deviation 12.9). Almost 80% of the total group of persons with advanced dementia living in LTCF were completely or to a great extent dependent on care provided by professional caregivers. Most care dependency, i.e., to a great extent or completely care dependent, was seen in learning ability (66.3%), eating and drinking (61.2%) and performing activities (59.3%). The items on which the population was least care dependent, i.e., to a great extent or completely independent, were communication (60.5%), maintaining body posture (58.1%) and mobility (48.8%).

Five variables were associated with care dependency in the univariate linear regression models, as described in **Chapter 6**: dementia severity (Global Deterioration Scale [GDS] 7)[5], and QUALIDEM-6D domains positive affect, restless tense behavior, social relationships, and social isolation. The multivariate linear regression model, which consisted of these five variables plus age and sex , showed that dementia severity (GDS 7) and the QUALIDEM-6D domain social relationships were independently associated with care dependency, i.e., the care dependency of persons with very severe dementia (GDS 7) was much higher compared to persons with moderate to severe dementia (GDS 5 and 6), and better social relationships according to the QUALIDEM-6D domain social relationships were associated with less care dependency. Three variables were associated with daily functioning in the univariate linear regression models, i.e., dementia severity (GDS 7), and the QUALIDEM-6D domains positive affect and social relationships. The multivariate regression model was performed with these three variables plus age and sex , and showed that dementia severity (GDS 7) and the QUALIDEM-6D domain social relationships were independently associated with daily functioning - meaning worse daily functioning when having most severe dementia (GDS 7) compared to persons with moderate to severe dementia (GDS 5 and 6) - and better social relationships according to the QUALIDEM-6D domain social relationships was associated with better daily functioning.

7.2 INTERPRETATION AND CRITICAL DISCUSSION OF FINDINGS AND METHODOLOGY

Course and interpretation of QoL in persons with dementia

QoL is determined by many factors and comprises a persons' values and principles, which are different for each individual. Despite the complexity of QoL, and given the absence of a cure for

dementia, it has become increasingly important to measure QoL as a means of evaluating care and to understand the needs of the person being cared for.[6] The QoL may remain stable over time when measured longitudinally, even when the dementia progresses, as different studies found over a period of 12 to 24 months.[7-10] This would mean that QoL is generally not expected to change without intervention over the course of 13 weeks, which was the study period in the Q-PID study, in persons with (advanced) dementia. Nevertheless, we found a strong period effect in the second period compared to the first period of the Q-PID study, i.e., the average QoL of all participants was lower in the second period compared to the first study period of six weeks.

QoL assessment instruments in persons with advanced dementia

Several studies have reported on the differences in QoL when rated by a proxy (nursing staff and/or relatives) or by a person with dementia himself. When measured by proxy, QoL was rated lower in persons in the most advanced stage of dementia.[11-13] Moreover, in proxy assessments, QoL was rated lower compared to self-assessment.[14,15] Agitation[13], apathy[13] and caregiver distress[12] were negatively associated factors when rated by proxies, while care dependency[13], anxiety[16] and depressive symptoms[12,13,16] were negatively associated with QoL in self-assessments.

To assess QoL in persons with advanced dementia living in LTCF by nursing staff, the QUALIDEM instrument was chosen throughout the different chapters of this thesis. As a person with advanced dementia is not always able to understand and answer assessment questions, proxy ratings are necessary, but these are subjective because of the proxies' own values and opinions. The subjective nature of QoL has resulted in a large amount of assessment instruments, which were not all developed and evaluated for use in LTCF. However, to assess and evaluate care in LTCF, the best available option is to measure QoL of the person with dementia being cared for with the existing QoL instruments.

The QUALIDEM, an observational instrument for QoL measured by nursing staff that is based on the adaptation-coping model of Droës[17], was chosen in the different studies in this thesis. It has the widest set of measurement properties reported with satisfactory test-retest and inter-observer reliability, and content and construct validity, and was therefore the recommended observational instrument for assessing QoL in LTCF residents with dementia by Aspden et al.[6] Also, the usability of different QoL instruments was assessed recently in a systematic review by Hughes et al.[18] Again, the QUALIDEM instrument, together with the QUALID instrument[19], had the best psychometric evidence, with QUALIDEM having better ratings for most of the assessed items. Moreover, QUALIDEM was rated as the most accessible. Nevertheless, none of the existing assessment instruments for QoL, including QUALIDEM, take into account all the

individual values of the person with dementia, contain appropriate questions or have mixed self and proxy-rated assessments to complement each other.[18,20]

Versions of the Dutch QUALIDEM

To date, the QUALIDEM is used in three versions: the original 37-item version, the shorter 18-item version especially for persons with very advanced dementia[2], and an even shorter 8-item version that was established in 2020.[21] In the different studies of this thesis, we chose to use the 18-item version, since persons with very advanced dementia were included in all our studies and all participants needed to be assessed in the same way to obtain comparable scores. The 8-item version was not yet available when our studies were designed and conducted. However, it comprises some questions that are not applicable to persons with very advanced dementia, so it would not have been useful for evaluation purposes in the population in our studies.

Calculation of scores of the QUALIDEM instrument

Originally, the QUALIDEM 18-item instrument consists of 6 domains (care relationship, positive affect, negative affect, restless tense behavior, social relations, and social isolation) that are scored 0 to 3 points per item. Each domain contains a different number of items, so maximum domain scores range from 6 to 12 points. A total score of 0 to 54 can be obtained and higher scores mean higher QoL. As each domain has a different number of items and thus different total scores, the domains could not be easily compared within and between persons. This is why we recalculated each item score to a percentage of the total achievable points for the item. We then had scores between 0 (lowest QoL) to 100 (highest QoL) for each item. Domain scores were calculated by adding up the items scores and dividing this by the number of items in the domain. Subsequently, the QUALIDEM-6D total score was calculated by adding the domain scores and dividing the result by six (number of domains). By recalculating the scores, we improved the comparability of the scores between the participants and between the different domains without weighing. This form of recalculation of the QUALIDEM has already been done successfully in several other studies.[9,22-24] A first step to improve validity of proxy-rated QoL could be to weigh the different items in the domains of the QUALIDEM, adjusted to which items are perceived, preferably by the person with dementia himself, as affecting QoL most, as was done earlier for caregivers with the CarerQol.[25] The difficulty here is the inability of a person with advanced dementia to answer these questions, so the weighing would remain (partly) subjective.

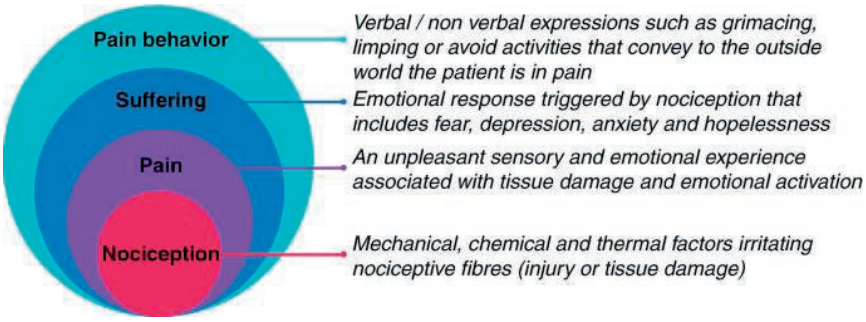
Pain

Aspects of pain

Pain, or 'an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage'[26], is a complex subjective experience that is not always adequately expressed by persons with dementia. According to one of the six key

notes that were added to this definition, vocalization is only one of many behaviors that express pain. When there is an inability to communicate, it does not mean the person does not experience pain.[27] Pain and nociception are different phenomena. Nociception, the neuropathophysiological mechanism of the body that detects a potentially harmful internal or external stimulus, is what triggers pain.[28] However, the latter has other dimensions, as proposed by Loeser.[29] These dimensions include suffering and pain behavior (Fig. 1). It is thus important to recognize all components of pain in a person, i.e., biological, emotional and social, and the suffering and behavior that result from it.[29]

Fig. 1 Loeser's pain model



Martin E. Pathophysiology of Pain. In: Pickering G, Zwakhalen S, Kaasalainen S, eds. Pain Management in Older Adults: A Nursing Perspective. Cham: Springer International Publishing; 2018:7 29.
Loeser JD. Perspectives on Pain. In: Turner P, Padgham C, Hedges A, eds. Clinical Pharmacology & Therapeutics: Proceedings of Plenary Lectures Symposia and Therapeutic Sessions of the First
World Conference on Clinical Pharmacology & Therapeutics London, UK, 3–9 August 1980. London: Palgrave Macmillan UK; 1980:313-316.

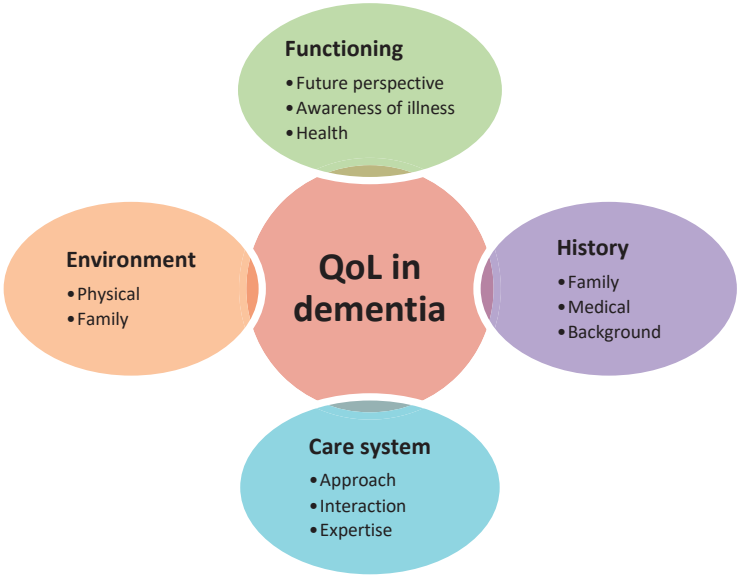
Pain and Quality of Life

Although pain has not been the main topic of the Q-PID study and this thesis, we did look at pain and its association with the use of pain medication and QoL in a population of Norwegian persons with advanced dementia living in LTCF in **Chapter 2**. When persons were still in pain, despite using pain medication, their QoL tended to be lower than the QoL of persons using pain medication not in pain, but this difference was only significant for paracetamol. This was presumably because of power issues with small groups, with the paracetamol group being the largest.

In our study that was described in **Chapter 2** of this thesis, all groups of pain medication users showed higher QoL on average when not in pain, compared to the persons who were still in pain despite using pain medication. This reflects findings in existing literature on the relationship between pain and QoL in persons with dementia.[30-32] Pain can negatively affect many factors that also affect QoL, i.e., depression[31,33], sleep[34,35], agitation[36-38], daily functioning[39] and care dependency[40]. There is an obvious overlap between pain and QoL, and the two cannot

be regarded separately when taking care of persons with advanced dementia. For this reason, physical well-being and health, which also include pain, are regularly reflected in various models and definitions of quality of life.[41-43] After researching the literature and practitioner meetings, the UNC-ZH also chose a QoL model of that identifies four domains (pillars) that can influence QoL. In this model, 'pain' comes under the element of Health, which is part of the domain 'Functioning'. (fig. 2).

Fig. 2 Model of Quality of life in persons with dementia chosen by the University Network of the Care sector South Holland (UNC-ZH)



Interventions for pain

Paracetamol

As it is known for its antipyretic and analgesic working mechanism, and relatively minor side effects, paracetamol is found on all steps of the World Health Organization (WHO) analgesic ladder; as a sole intervention or together with non-steroidal pain medication (step 1), or as an adjuvant to opioids in moderate to strong pain (steps 2 and 3).[44,45] Although it is the most widely used painkiller, the mechanism of action of paracetamol is still partly unknown.[45] However, several studies found a positive effect of paracetamol in persons with dementia regardless of being in pain, e.g., on social interaction[46] and daily functioning[47]. This, together with the knowledge that pain could lead to low QoL, was the impetus for designing the Q-PID study. However, our inclusion criteria significantly differed from those of the studies of Chibnall et al.[46] and Sandvik et al.[47]: our main two inclusion criteria were having low QoL and using no pain medication regularly, whereas the participants in the study of Sandvik et al. were included based on signifi-

cant neuropsychiatric symptoms (agitation) and they could already be using pain medication at the start of the study. Also, the MOBID-2 pain score was 3.7 on average, which means clinically significant pain at the start of the study, and the pain scores decreased significantly in the first 8 weeks of paracetamol use.[47] In **Chapter 2** we saw that pain medication use and pain may be associated with a lower QoL, but QoL was not measured in the study of Sandvik et al. In the Q-PID study, participants did not use any pain medication at the start of the study, so use of pain medication did not affect low QoL. Also, pain scores of the participants of the Q-PID study were, on average, lower than 3 at baseline. If pain scores are higher at baseline, participants are more likely to improve significantly during treatment with pain medication, than when pain scores are already low at baseline. Unlike Chibnall et al. and Sandvik et al. we did not exclude persons with a short life expectancy or other severe illnesses in the Q-PID study.[46,47] This may have factored into the type and low QoL of persons who participated in the Q-PID study. A subanalysis of the group of persons who were in pain did not provide any additional insights, partly because of the small remaining sample size and the study was not powered for this.

Effect vs. side effect of pain medication

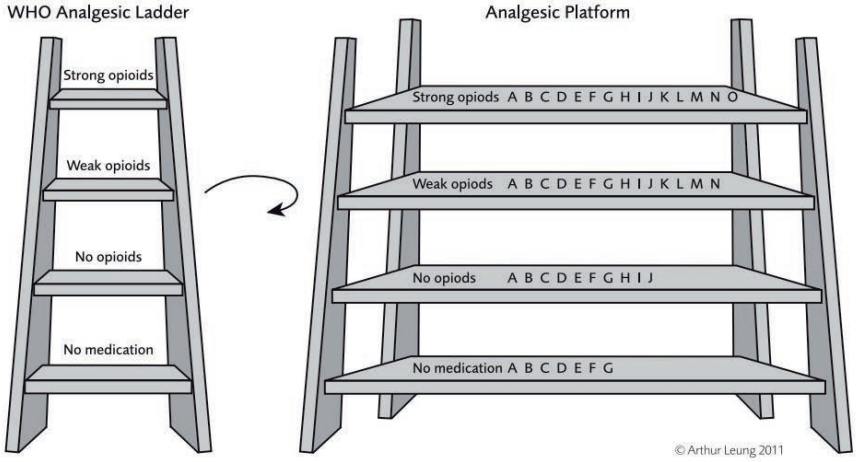
During the Q-PID study no side effects directly linked to the use of paracetamol were observed. Although existing literature confirms that paracetamol is generally well tolerated by persons with advanced dementia, the sample sizes were small and the follow-up to find rare adverse events was short, i.e., max. 13 weeks.[48] Opioids seem to have more side effects that may influence QoL, e.g., daytime sedation, agitation, dizziness, but again the available literature is insufficient.[48] In **Chapter 2** we found that persons who used pain medication and were still in pain, i.e., probable undertreatment of pain, had lower QoL than persons who used pain medication and did not have clinically significant pain. There seems to be a close balance between experiencing side effects and being undertreated for pain.

Analgesic ladder and non-pharmacological interventions

Whereas acute pain is mostly temporary and resolves when an injury to the body is healed, chronic pain has a longer duration (3-6 months) and can result in more and longer suffering and psychological consequences, which may lead to a lower QoL, as mentioned above.[28] As this suffering and pain behavior can persist, especially in persons with advanced dementia who are not able to express pain adequately, interventions with pain medication alone may not be sufficient for the management of pain as a whole, but only for nociception, i.e., the stimulus that leads to pain. This may be a reason why paracetamol alone did not improve the QoL, discomfort and neuropsychological symptoms in the Q-PID study. Several authors have proposed an adaptation of the 1986 WHO analgesic ladder, that focuses more on QoL by adding a fourth step (non-pharmacological interventions) and a bidirectional approach, i.e., the possibility to treat acute pain with the strongest analgesics as a first step and tone it down as soon as possible when pain relief is attained.[49,50]

Also, Leung et al. proposed a change of the concept analgesic ladder to an analgesic platform, where non-pharmacological interventions go hand in hand in every step of the ladder (Fig. 3).[51]

Fig. 3 Change of concept from the analgesic ladder to the analgesic platform



A—Physiotherapy and physical therapy | **B**—Mind–body integration (e.g. yoga, meditation and religious support) | **C**—Hypnosis and relaxation therapy | **D**—Acupuncture | **E**—Chiropractic | **F**—External rub/lotions | **G**—Other CAM options (Tai chi, Tui Na) | **H**—Muscle relaxants (e.g. cyclobenzaprine, baclofen and dantrolene) | **I**—Injectable agents (steroids, local anaesthetics) | **J**—Interpersonal reinforcement (e.g. support group) | **K**—Anticonvulsants (e.g. gabapentin, pregabalin and lamotrigine) | **L**—Antidepressants (e.g. tricyclics, SSRI, SNRI) | **M**—Compounds that act synergistically with opioids like cannabinoids (nabilone) | **N**—Cognitive behaviour therapy and psychological counselling | **O**—Surgical and neurosurgical procedures (e.g. spinal cord stimulation, deep brain stimulation, spinal delivery of opioids, ganglion ablation by phenol or electrofrequency, sympathectomy)

Care dependency and daily functioning

The group of persons with advanced dementia we followed for 13 weeks during the Q-PID study was very care dependent at baseline, i.e., almost 80% of the participants were completely or to a great extent dependent on care of others, and this care dependency lasted throughout the study. As discussed in **Chapter 4**, we found that both care dependency and daily functioning were associated with the most advanced stage of dementia, which is logically explained by the fact that persons in this stage of dementia all need extensive care from others[52], and being in need of care is included in the description of stage 7 of the Global Deterioration Scale[5]. Also, care dependency and daily functioning were associated with social relationships. We did not see any improvement in care dependency and daily functioning, probably because there was low average pain in the overall group, which is known to be an important factor to make care dependency, daily functioning and QoL worse.[40,53,54] In a group with relatively low pain scores, paracetamol alone may not be a right fit to improve care dependency and daily functioning, whereas other interventions like physiotherapy or exercises may be more successful.[55-57]

Limitations of research in LTCF in advanced dementia

Proxy assessment

As discussed before, the persons participating in the Q-PID study were unable to independently answer questions about their QoL and psychological and physical functioning, so the questionnaires had to be completed by nursing staff on the unit of the LTCF. The staff work in shifts and under pressure, so any extra work, such as filling out observational questionnaires, can be challenging.

Because nursing staff work in different shifts, we could not always ensure that the same person completed the questionnaires of one resident at all timeframes. This research was conducted in daily clinical practice, and we did not want to introduce any changes during the study, so we did not want to change shifts of caregivers to ensure that the same person completed the questionnaires every time. Despite the fact that the questionnaires we used were extensively tested for completion by different caregivers, there will always be a subjective component to proxy assessments, particularly when measuring QoL, where the background of proxy raters may be an important factor.[58]

Crossover design

The main reason for conducting a crossover study in LTCFs is that it only takes about a quarter of the number of participants to achieve the same power as a parallel study. It is efficient and less costly, because the variation between two measurements in one individual is much lower than between two individuals, and the comparison in the crossover study is made within one group rather than between two groups in a parallel study.[59] However, there are also disadvantages to a crossover study, for example a 'carry-over' effect, where one intervention is influenced by the other. To avoid this as much as possible, a wash-out period long enough for the previous intervention to have worn off can be introduced. Usually this means a wash-out period of more than 4 times the duration of action of the intervention.[59] The wash-out period in the Q-PID study was one week, which is considered more than enough, since the duration of action of paracetamol is six hours. Another limitation of a crossover study we encountered is the (natural) change over time that participants can show and that can interfere with the outcome. This 'period effect' can be prevented by randomization at the start of the study for the order in which the intervention will be conducted. Although randomization took place in the Q-PID study, we did find a strong 'period effect' for QoL and neuropsychiatric symptoms, i.e., better scores in the first study period. When the health situation of a participant deteriorates quickly, which we see regularly in this population of vulnerable older persons with (advanced) dementia, the characteristics of this person can change. This means more variation between two measurements and probably more participants are needed for the study to achieve sufficient power.

Administration of medication

During the Q-PID study, a striking phenomenon occurred, i.e., the study medication was signed off as having been given, however, after the study periods more study medication remained than there should have been according to the medication administration forms. So, compliance in practice was lower than the administration forms showed. To improve compliance, most medications that are administered in LTCF are delivered in special small bags called a 'baxter' system. All medication that should be administered at one time is in this bag. For several reasons, already discussed in **Chapter 3**, the study medication could not be included in this 'baxter' system during the Q-PID study. It seems that providing medication outside such a system still causes too much medication non-adherence, which should clearly be addressed during training of nursing staff responsible for administering medication. There will always be medications that are not allowed in the 'baxter' system, due to shelf life or supply, so improving medication quality and safety should be a clear point of focus for LTCFs.

7.3 IMPLICATIONS FOR PRACTICE AND EDUCATION

Several implications for practice and education result from the findings of this thesis. We found no effect of paracetamol alone on QoL, pain and care dependency, among other things, that was administered during daily practice to persons with advanced dementia living in LTCF. It seems important to approach individuals with a low QoL from a broad perspective and to combine multiple treatments or interventions to improve multiple factors. Possible ways to address this will be discussed below.

QoL as an individual perspective

Persons with advanced dementia often can no longer adequately articulate what they consider important in life, and they are often no longer concerned with best health, but rather psychological well-being and cognitive functioning as key factors determining their QoL.[60-62] Also, these factors can vary greatly between individuals and are also influenced by the setting a person lives in.[63,64] It is therefore important to define personal individual perspectives that are important for QoL early in life and in the stage of dementia, so relatives can follow these in dialogue with professional caregivers.[60] Once care is needed, it is essential that it is arranged as personally as possible, tailored to the person's own wishes and needs. The activities offered, either in the LTCF or at home, should also be personalized. In addition, it is important to look closely at the person's living environment and how it can be improved so that the person feels as comfortable as possible, even in the last phase of life.

Interventions for QoL

As we found in the Q-PID study, paracetamol alone is not a panacea to improve QoL in persons with advanced dementia, and certainly not when these individuals have relatively little pain. Evidence suggests that improving social relationships and engagement with activities are important factors in improving QoL, as well as anxiety, pain and depression.[65-67] This can be accomplished e.g., by offering meaningful individualized activities inside or outside the LTCF, cognitive stimulation and promoting physical activities.[68-70] These personalized interventions can be offered by activity coordinators, nursing staff or family and should be embedded in daily practice in LTCFs. Of course, if pain is observed, the above interventions can also be combined with adequate pain medication, starting with paracetamol.

Interventions targeting pain and neuropsychiatric symptoms

When pain is observed, a tailored intervention should be used, based on inhibiting nociception by administration of pain medication and providing distraction from the pain by offering activities such as massage, exercise and robotic care, thereby reducing suffering and improving QoL.[71] As pain can cause neuropsychiatric symptoms, treating pain can also ameliorate these symptoms and can thereby improve QoL. A stepwise multidisciplinary approach may be beneficial for both pain and neuropsychiatric symptoms and should be considered when pain is observed or neuropsychiatric symptoms occur.[72,73] Pain medication should be administered according to current guidelines, taking into account side effects, especially for opioids, and with frequent monitoring of effect and adjusting dosage and frequency accordingly.

Care dependency and daily functioning

It may be relevant for clinicians and nursing staff to find out more about the relationship between the different items of care dependency and existent pain, and which specific items of care dependency need special attention, to have points of reference to improve the care for, and thereby the QoL of, persons with advanced dementia. A multi-domain approach by professionals and informal caregivers is essential to reach this goal.

In **Chapter 6** we found that care dependency and daily functioning were associated with social relationships as part of QoL. This reinforces the view that it is important to focus on non-pharmacological interventions targeting social relationships and activities, and to teach nursing staff and family most important to maintain and improve QoL and care dependency are their presence and attention for persons with dementia.

Training nursing staff and family

First, good education is needed for nursing staff and family on what QoL means and what to look for to potentially improve QoL for a person with dementia. Being present is one of the most important factors, as mentioned above, but at the times they are not there, there are

still opportunities to offer activities to improve QoL. Since nursing staff often have a heavy workload, it is important that they learn how to offer activities requiring little effort in a low-threshold manner. They can even integrate activities in daily care. Second, teaching nursing staff and family to adequately recognize pain is important so that they can seek timely medical attention for pain treatment and look at offering activities that can reduce pain and pain behavior. Finally, more attention should be paid during training and continuing education to administering medication, especially medication outside a unit dose package. Unfortunately, it is still not uncommon for the medication inside and outside the unit dose package to be properly checked against the medication administration list and be given blindly, as we also found during the Q-PID study.

7.4 RECOMMENDATIONS FOR FUTURE RESEARCH

One possibility to achieve an even better and more individualized measurement of QoL, would be to create a weighted QoL measurement instrument, or use a weighing 'tariff' in an existing measurement instrument. Research should look at which factors are seen as more and less important for QoL, for example by involving a large group of older persons and asking their opinion on the most important factors for their QoL. Persons with mild dementia and informal caregivers of persons with advanced dementia can also be asked for their opinions on which factors are most important to them for the best QoL. Gathering this information can help create a weighted QoL score that is more individually oriented and can provide more accurate total scores, so that scores can be better compared between individuals, or the effect of an intervention on QoL in an individual at two or more timepoints can be better examined. This type of weighing by computing a 'tariff' has been done before, e.g., for measuring the QoL of informal caregivers (CarerQol instrument).[25] This 'tariff' was computed to take into account differences in dimensions of Care-related QoL and other factors like background and education to facilitate including informal care in economic evaluations. The latter seems less important in our population with advanced dementia in LTCF, but looking at the best way to weigh the different dimensions of the QUALIDEM-6D to form a total score may be important for individualizing care.

Future research should also focus on combined interventions targeting QoL, pain and care dependency. One of the pillars for these is the use of pharmacological interventions such as pain medication, but the biggest and most important pillars are non-pharmacological interventions, possibly combined with pharmacological treatment. The reinforcing effect of combining non-pharmacological and pharmacological treatments will have to be properly investigated in persons with advanced dementia living in LTCF.

OVERALL CONCLUSION

QoL in persons with advanced dementia is influenced by many factors, such as environment, background and psychological factors such as depression and agitation. This thesis provides evidence that administration of paracetamol or placebo alone is not effective, i.e., no 'panacea', for improving QoL, discomfort, pain, neuropsychiatric symptoms, care dependency and daily functioning in persons with advanced dementia living in LTCF. Personalizing interventions and combining pharmacological and non-pharmacological interventions are important, and we recognize that this will be challenging, but not impossible.

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Chapter 8

Summary

Worldwide, more than 55 million persons have dementia, the number increasing with nearly 10 million new cases each year. In the Netherlands, 250,000-290,000 persons have dementia, 32-38% of whom live in a long-term care facility (LTCF). As dementia is a progressive neurological disease for which there is still no cure, the primary goal of caring for persons with dementia is optimizing their quality of life (QoL).

Persons with dementia may not always be able to set their own goals and expectations. When persons with dementia are no longer able to assess their own QoL, family, friends and professional caregivers need to be their voice, as they are most familiar with their values, goals and needs.

There is evidence that the QoL of persons with dementia does not always decline as the disease progresses. However, there are symptoms and signs accompanying the progressing disease that have an impact on QoL, i.e., functional decline, and neuropsychiatric symptoms such as depression, aggression and psychosis. People surrounding persons with dementia face the challenge of optimizing these persons' QoL, and every factor identified to facilitate this, such as finding undiagnosed pain and treating it, is an added benefit.

Pain is common in persons with dementia living in LTCF: 30 to 80% regularly experiences acute or chronic pain. The challenge is to identify those persons that are in pain and suffer from it. Ideal and the golden standard is that the persons self-report their pain. However, pain perception in persons with advanced dementia may be different and they are often no longer able to express pain adequately in terms of location, intensity and origin. Also, they are not always able to report the effect of pain treatment or side effects of the treatment. Underdiagnosed and therefore untreated pain may have a negative impact on neuropsychiatric symptoms like aggression, agitation and depression, but also on social interaction, daily functioning, appetite and sleep. It may therefore have a major negative impact on the QoL of persons with advanced dementia.

So far, paracetamol is step 1 of pharmacological pain treatment, also in older persons, as the side-effects remain limited in low dosage (≤ 4 g per day for acute use and ≤ 3 g per day for chronic use). The working mechanism of paracetamol still remains partly unclear. It is well known for its effects on pain and fever, but some people say they feel better when they take paracetamol. Is this because they had a fever, which is reduced by paracetamol and consequently they feel better? Or does paracetamol have other working mechanisms on well-being we do not yet know about? This is an interesting question, which to date remains unanswered.

Main findings in this thesis

In part I of this thesis we explored the characteristics and the QoL of persons using different types of pain medication. We also studied the association between the QoL, pain and use of pain medication (paracetamol, opioids, both paracetamol and opioids, or no pain medication) in persons with advanced dementia living in LTCF. The differences in characteristics and in QoL between persons with and without pain medication are described in **Chapter 2**. Cross-sectional data of the Communication, Systematic Assessment and Treatment of Pain, Medication Review, Occupational Therapy, and Safety (COSMOS) study in 67 Norwegian LTCF clusters showed that persons who used pain medication had 1) more advanced dementia, 2) pain scores more than twice as high, 3) significantly worse daily functioning, 4) more depressive symptoms, and 5) more neuropsychiatric symptoms, compared to persons who did not use any pain medication. The QoL measured by the QUALIDEM-6D was significantly lower in persons who used pain medication compared to persons who did not use any pain medication, except for the domain 'social relationships'. The group of persons with advanced dementia living in LTCF with clinically relevant pain who did not use any pain medication daily had better overall QoL compared to persons who used paracetamol, opioids, or both paracetamol and opioids.

QUALIDEM-6D

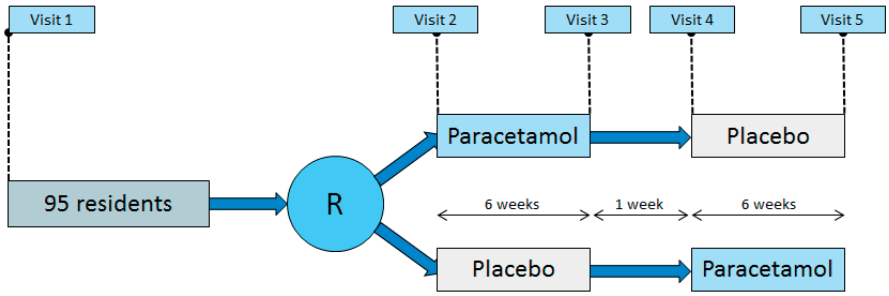
The QUALIDEM is a validated questionnaire, specifically developed to measure QoL in persons with dementia living in LTCF. The instrument consists of 8 subscale domains (care relationship, positive affect, negative affect, restless tense behaviour, social relations, social isolation, feeling at home and occupation). For the studies in this thesis 19 of 37 items were deleted as recommended by the authors of the QUALIDEM manual for people with advanced dementia. Consequently, six domains were used (care relationship, positive affect, negative affect, restless tense behaviour, social relationships and social isolation; QUALIDEM-6D).

Chapter 3 describes the protocol of the Quality of life and Paracetamol In advanced Dementia (Q-PID) study. This study was a randomized double-blind placebo-controlled crossover trial in 95 persons with advanced dementia living in LTCF across the west of the Netherlands. All participating organizations were members of the University Network for the Care sector South Holland (UNC-ZH). Only persons with low QoL (QUALIDEM-6D ≤70) could participate in the study. Pain was not assessed prior to the study. The effects of regularly scheduled administration of paracetamol on QoL, discomfort, pain and neuropsychiatric symptoms, as found in the Q-PID study, are described in **Chapter 4**. The data of the Q-PID study showed that paracetamol, compared to placebo, did not have a positive effect on QoL, discomfort, pain or neuropsychiatric symptoms. However, there were participants who clearly derived benefit from paracetamol during and after the study, according to the assessments of their nurses/nursing assistants.

The Q-PID study

The Q-PID study was a 13-week double-blind, randomised, placebo-controlled crossover trial. In a crossover trial participants receive all treatments with a wash-out period in between. In this study, participants were randomly assigned to start with paracetamol or placebo for six weeks. After a wash-out period of one week, a second six-week administration period started with placebo (or paracetamol if the participant started with placebo). The placebo tablets resembled the paracetamol tablets in colour, size and composition, and contained quinine to give a bitter taste (placebo-controlled). Researchers, research nurses, professional caregivers and participants did not know which participant was assigned to which treatment arm (double-blind). Only the study pharmacy of the Leiden University Medical Center knew which participant was allocated to which treatment arm.

The Q-PID study included 95 residents with advanced dementia, being admitted to long-term care facilities affiliated with the University Network of the care sector Zuid-Holland (UNC-ZH). Inclusion criteria were 1) age ≥ 65 years, 2) advanced dementia (Reisberg Global Deterioration Scale (GDS) 5-7) and 3) QUALIDEM score ≤ 70. Exclusion criteria were the regular use of pain treatment, allergies to the study drugs (paracetamol or placebo), severe liver insufficiency or disease, use of > 4 units of alcohol/day, weight < 50 kg and/or concomitant use of flucloxacillin.



Flowchart of the Q-PID crossover trial

R= randomisation

Visit 1: Screening for inclusion and exclusion criteria

Visit 2: Baseline measurements

Visit 3 and 4: Follow-up measurements

Visit 5: Final and closing measurements

Part II describes the effect of regularly scheduled administration of paracetamol on care dependency and daily functioning, and how care-dependent persons with advanced dementia and low QoL living in LTCF are. After adjusting for period and order effects, and psychotropic medication use, no effect of scheduled administration of paracetamol, compared to placebo, was found on care dependency and daily functioning in a group of 95 persons with advanced dementia with low QoL living in LTCF. This was shown in the Q-PID study and is described in **Chapter 5**.

Cross-sectional data of the Q-PID study (baseline) were used to describe how care dependent the participants in the Q-PID study were and which factors were associated with care dependency and daily functioning (**Chapter 6**). Almost 80% of the total group were completely or to a great extent dependent on care provided by professional caregivers. Most care dependency was seen in learning ability (66.3%), eating and drinking (61.2%) and performing activities (59.3%). The items on which the population was least care dependent, i.e., to a great extent or completely independent, were communication (60.5%), maintaining body posture (58.1%) and mobility (48.8%).

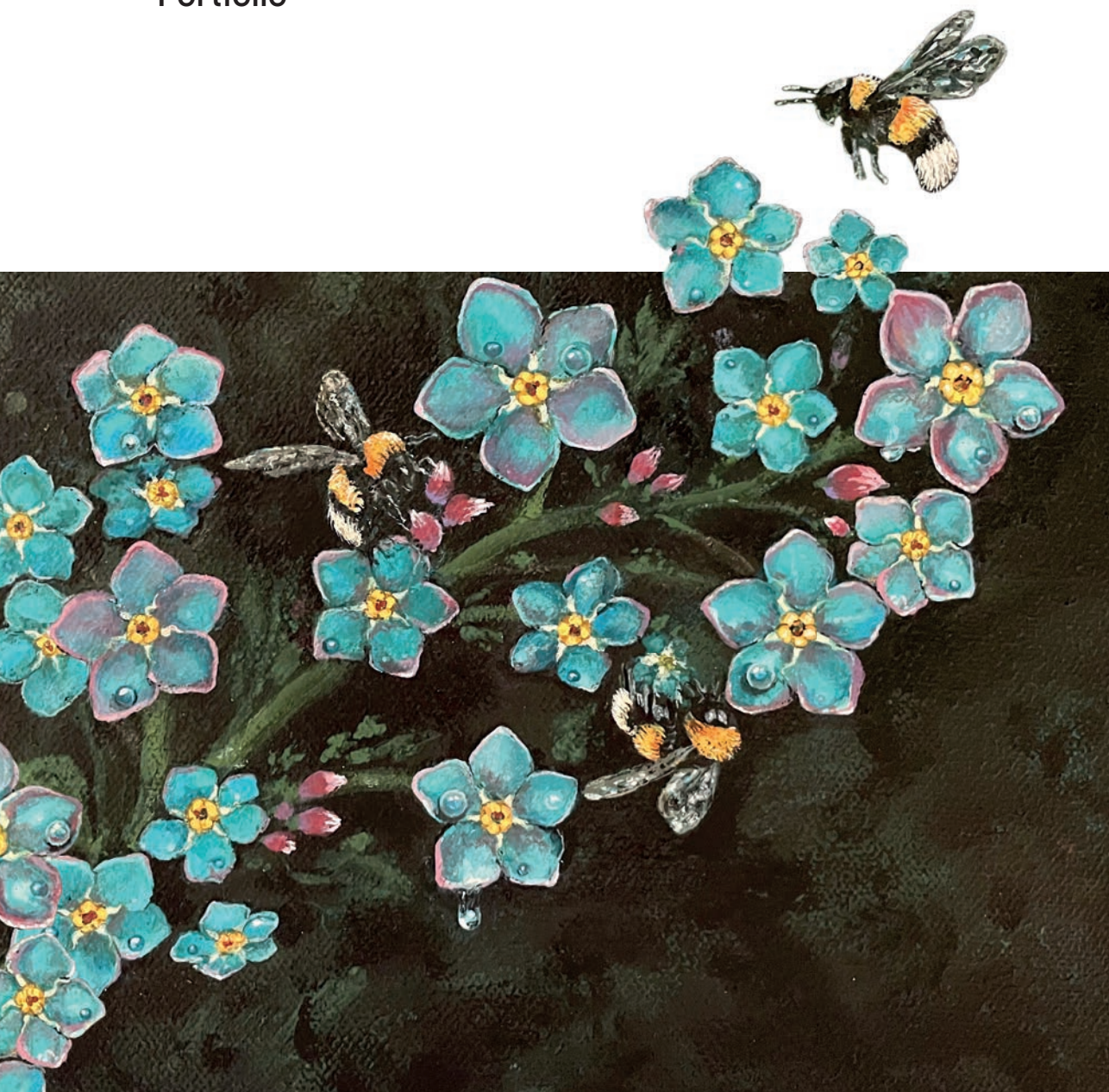
The care dependency of persons with very severe dementia (GDS 7) was much higher compared to persons with moderate to severe dementia (GDS 5 and 6), and better social relationships according to the QUALIDEM-6D domain social relationships were associated with less care dependency (**Chapter 6**). Dementia severity (measured by the Global Deterioration Scale - GDS 7) and the QoL domain 'social relationships' were independently associated with daily functioning meaning worse daily functioning when having very severe dementia (GDS 7) compared to persons with moderate to severe dementia (GDS 5 and 6) and better social relationships were associated with better daily functioning.

Overall conclusion

QoL in persons with advanced dementia is influenced by many factors, such as environment, background and psychological factors such as depression and agitation. This thesis provides evidence that administration of paracetamol or placebo alone is not effective, i.e., no 'panacea', for improving QoL, discomfort, pain, neuropsychiatric symptoms, care dependency and daily functioning in persons with advanced dementia living in LTCF. Personalizing interventions, collaboration between different health care workers and family/friends, and combining pharmacological and non-pharmacological interventions are important to maintain the best QoL possible, and we recognize that this will be challenging, but not impossible.

Chapter 9

Nederlandse samenvatting
Dankwoord
Curriculum Vitae
Portfolio



NEDERLANDSE SAMENVATTING

Wereldwijd lijden meer dan 55 miljoen mensen aan dementie en dit aantal stijgt met bijna 10 miljoen nieuwe gevallen per jaar. In Nederland hebben 250.000-290.000 mensen dementie, waarvan 32-38% in een verpleeghuis woont. Aangezien dementie een neurologische ziekte is die erger wordt in de tijd en waarvoor nog geen genezing bestaat, is het belangrijkste doel van de zorg voor mensen met dementie het optimaliseren van hun kwaliteit van leven.

Mensen met dementie zijn niet altijd meer in staat hun eigen doelen en verwachtingen in het leven aan te geven. Wanneer zij niet langer in staat zijn hun eigen kwaliteit van leven te beoordelen, moeten familie, vrienden en professionele zorgverleners hun spreekbuis zijn, aangezien zij het meest vertrouwd zijn met hun normen, waarden en behoeften.

Er zijn aanwijzingen dat de kwaliteit van leven van mensen met dementie niet altijd afneemt naarmate de ziekte vordert. Er zijn echter wel klachten en symptomen die in beeld komen bij het voortschrijden van de ziekte en die van invloed zijn op de kwaliteit van leven, namelijk functionele achteruitgang en neuro-psychiatrische symptomen zoals depressie, agressie en psychose. Het is voor naasten van mensen met dementie een uitdaging de kwaliteit van leven van deze personen zo optimaal mogelijk te houden, en elke factor die hierbij kan helpen, zoals het opsporen en behandelen van pijn, heeft een toegevoegde waarde.

Pijn komt vaak voor bij mensen met dementie die in een verpleeghuis wonen; 30 tot 80% ervaart regelmatig acute of chronische pijn. De uitdaging is die personen te vinden die pijn hebben en eraan lijden. Ideaal en de gouden standaard is dat de personen hun pijn zelf rapporteren. De pijngewaarwording bij mensen met gevorderde dementie kan echter anders zijn en zij zijn vaak niet meer in staat pijn adequaat uit te drukken wat betreft locatie, intensiteit en oorsprong. Ook zijn zij niet altijd in staat het effect van pijnbehandeling of mogelijke bijwerkingen te melden. On(der)gediagnosticeerde en onbehandelde pijn kan een negatieve invloed hebben op neuro-psychiatrische symptomen, zoals agressie, agitatie en depressie, maar ook op sociale interactie, dagelijks functioneren, eetlust en slaap. Deze kunnen vervolgens weer leiden tot een slechtere kwaliteit van leven.

Tot nu toe is paracetamol stap 1 van de pijnbehandeling, ook bij ouderen, omdat de bijwerkingen beperkt blijven bij een lage dosering (≤ 4 g per dag voor kortdurend gebruik en ≤ 3 g per dag voor chronisch gebruik). Het werkingsmechanisme van paracetamol blijft tot nu toe gedeeltelijk onduidelijk. Paracetamol staat bekend om zijn werking bij pijn en koorts, maar sommige mensen zeggen dat ze zich beter voelen of beter slapen als ze paracetamol innemen. Is dat omdat zij koorts hadden, die door paracetamol wordt verminderd en zij zich daardoor beter voelen? Of heeft paracetamol andere werkingsmechanismen op het welzijn die we nog niet kennen? Dit is een interessante vraag, die tot op heden onbeantwoord blijft.

Belangrijkste bevindingen in dit proefschrift

In deel I van dit proefschrift onderzochten we de eigenschappen en de kwaliteit van leven van mensen met gevorderde dementie die verschillende soorten pijnmedicatie gebruiken. We keken daarnaast ook naar het verband tussen de kwaliteit van leven, pijn en het gebruik van pijnmedicatie (paracetamol, opioïden, zowel paracetamol als opioïden, of geen pijnmedicatie). De verschillen in eigenschappen en in kwaliteit van leven tussen personen met en zonder pijnmedicatie worden beschreven in **Hoofdstuk 2**. De data uit de Communication, Systematic Assessment and Treatment of Pain, Medication Review, Occupational Therapy, and Safety (COSMOS) studie werd hiervoor gebruikt; een studie in 67 Noorse verpleeghuizen. **Hoofdstuk 2** laat zien dat personen die pijnmedicatie gebruikten 1) de meest gevorderde dementie (Functional Assessment Stage 7), 2) meer dan twee keer zo hoge pijnscores, 3) significant slechter dagelijks functioneren, 4) meer depressieve symptomen en 5) meer neuro-psychiatrische symptomen hadden, vergeleken met mensen die geen pijnmedicatie gebruikten. De kwaliteit van leven gemeten met de QUALIDEM-6D, een meetinstrument specifiek voor het meten van kwaliteit van leven door zorgmedewerkers bij mensen met gevorderde dementie, was significant lager bij mensen die pijnmedicatie gebruikten in vergelijking met personen die geen pijnmedicatie gebruikten, behalve voor het domein 'sociale relaties'. De groep personen die klinisch relevante pijn hadden en niet dagelijks pijnmedicatie gebruikten, hadden een betere kwaliteit van leven in vergelijking met personen die paracetamol, opioïden of zowel paracetamol als opioïden gebruikten.

QUALIDEM-6D

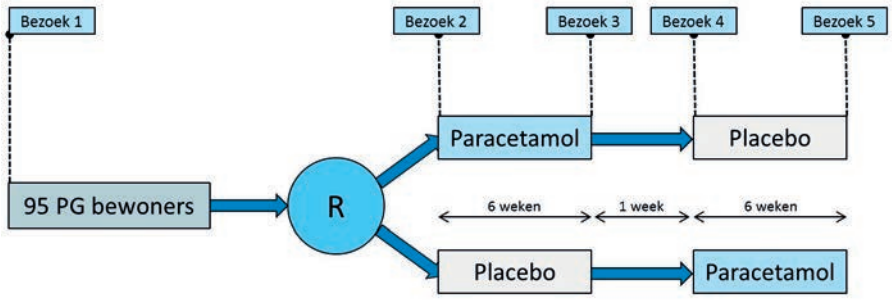
De QUALIDEM is een gevalideerde vragenlijst die special werd ontwikkeld om kwaliteit van leven te meten bij mensen met dementie die in een verpleeghuis wonen. De vragenlijst bestaat uit 8 domeinen (zorgrelatie, positief affect, negatief affect, rusteloos gespannen gedrag, sociale relaties, sociale isolatie, zich thuis voelen en daginvulling). Voor de studies in dit proefschrift werden 19 van de 37 vragen uit deze vragenlijst gehaald, zoals wordt aangeraden door de ontwikkelaars van deze vragenlijst bij mensen met gevorderde dementie. Er bleven hierdoor 6 domeinen over (zorgrelatie, positief affect, negatief affect, rusteloos gespannen gedrag, sociale relaties en sociale isolatie; QUALIDEM-6D).

Hoofdstuk 3 beschrijft het studieprotocol van de studie Quality of life and Paracetamol In advanced Dementia (Q-PID). Deze studie was een gerandomiseerde dubbelblinde placebogecontroleerde cross-over studie bij 95 personen met gevorderde dementie die in verpleeghuizen woonden in het westen van Nederland. Alle 9 deelnemende zorgorganisaties waren lid van het Universitair Netwerk voor de Care sector Zuid-Holland (UNC-ZH). Alleen personen met een lage kwaliteit van leven (QUALIDEM-6D ≤70) konden deelnemen aan de studie. Pijn werd voorafgaand aan de studie niet beoordeeld. Een cross-over studie wil zeggen dat alle deelnemers zowel paracetamol als placebo kregen, maar dat er werd geloot voor de volgorde (eerst 6 weken paracetamol en daarna placebo, of andersom).

Het Q-PID onderzoek

Het Q-PID onderzoek was een 13-weekse dubbelblind, gerandomiseerd, placebogecontroleerd cross-over onderzoek. Bij een cross-over onderzoek krijgen alle deelnemers alle behandelingen met een 'uitwasperiode' er tussen, zodat het effect van de behandeling in de vorige periode verdwenen is. In deze studie werd er geloot (gerandomiseerd) voor de volgorde van de behandelingen met paracetamol en placebo. De helft van de deelnemers startte met 6 weken paracetamol en de andere helft met placebotabletten. Na een week geen medicatie (de uitwasperiode) kreeg de groep die gestart was met paracetamol nu placebo en andersom. De placebotabletten waren geheel gelijk aan de paracetamoltabletten qua kleur, vorm en smaak, alleen bevatten ze geen werkzame stof (placebogecontroleerd). De onderzoekers, onderzoeksverpleegkundigen, verzorging en deelnemers wisten niet welke behandeling in welke periode werd gegeven aan de deelnemers (dubbel-blind). Alleen de apotheek van het Leids Universitair Medisch Centrum (LUMC) wist deze volgorde.

Het Q-PID onderzoek includeerde 95 bewoners met matige tot gevorderde dementie, die woonden in verpleeghuizen die verbonden waren aan het Universitair Netwerk voor de care sector Zuid-Holland (UNC-ZH). Criteria om te mogen meedoen aan het onderzoek waren 1) leeftijd ≥ 65 jaar, 2) matige tot gevorderde dementie (Reisberg Global Deterioration Scale (GDS) 5-7) en 3) QUALIDEM-6D score ≤ 70. Criteria om niet te mogen meedoen aan het onderzoek waren het regelmatig gebruik van pijnmedicatie, allergie voor de studiemedicatie (paracetamol of placebo), ernstig leverfalen, gebruik van > 4 eenheden alcohol per dag, gewicht < 50 kg en/of gelijktijdig gebruik van het antibioticum flucloxacilline.



Flowchart van het Q-PID onderzoek
PG bewoners: psychogeriatrische bewoners
R: randomisatie (loting)
Bezoek 1: screening inclusie – en exclusiecriteria
Bezoek 2: metingen vóór start studie
Bezoek 3 and 4: follow-up metingen
Bezoek 5: Laatste metingen

De effecten van dagelijkse toediening van paracetamol op kwaliteit van leven, discomfort, pijn en neuro-psychiatrische symptomen, als resultaat van de Q-PID-studie, zijn beschreven in **Hoofdstuk 4**. Na uitvoering van de Q-PID studie bleek dat paracetamol, in vergelijking met placebo, geen positief effect had op kwaliteit van leven, discomfort, pijn en neuropsychiatrische symptomen. Er waren echter deelnemers die duidelijk baat hadden bij paracetamol tijdens en na de studie, naar de mening van hun verzorging.

Deel II van dit proefschrift beschrijft het effect van dagelijkse toediening van paracetamol op zorgafhankelijkheid en dagelijks functioneren, en hoe zorgafhankelijk personen met gevorderde dementie en lage kwaliteit van leven wonend in een verpleeghuis waren. Er werd geen effect gevonden van dagelijkse toediening van paracetamol, vergeleken met placebo, op zorgafhankelijkheid en dagelijks functioneren, zoals beschreven in **Hoofdstuk 5**.

De data van de baseline gegevens van de Q-PID studie werd gebruikt om te beschrijven hoe zorgafhankelijk de deelnemers aan de Q-PID studie waren en welke factoren samenhingen met hun zorgafhankelijkheid en dagelijks functioneren (**Hoofdstuk 6**). Bijna 80% van de totale groep was geheel of grotendeels afhankelijk van zorg van professionele zorgverleners. De meeste zorgafhankelijkheid werd gezien bij het vermogen om nieuwe dingen aan te leren (66,3%), eten en drinken (61,2%) en het uitvoeren van activiteiten (59,3%). De items waarop de groep het minst zorgafhankelijk was, waren communicatie (60,5%), handhaven van goede lichaamshouding (58,1%) en mobiliteit (48,8%).

Het in **Hoofdstuk 6** uitgevoerde rekenmodel voor zorgafhankelijkheid laat zien dat de zorgafhankelijkheid van personen met zeer gevorderde dementie veel hoger was in vergelijking met personen met matige tot ernstige dementie, en dat betere sociale relaties geassocieerd waren met minder zorgafhankelijkheid. Het rekenmodel voor dagelijks functioneren laat zien dat zeer gevorderde dementie en het QUALIDEM-6D domein 'sociale relaties' onafhankelijk geassocieerd waren met dagelijks functioneren, dat wil zeggen slechter dagelijks functioneren bij personen met de meest vergevorderde dementie in vergelijking met personen met matige tot ernstige dementie, en dat betere sociale relaties volgens het QUALIDEM-6D domein 'sociale relaties' geassocieerd waren met beter dagelijks functioneren.

Conclusie

De kwaliteit van leven van mensen met gevorderde dementie wordt beïnvloed door vele factoren zoals de omgeving, wat ze hebben meegemaakt in hun leven en psychologische factoren zoals depressie en agitatie. Dit proefschrift laat zien dat toediening van paracetamol of placebo alleen niet effectief is, d.w.z. geen 'wondermiddel' is, voor het verbeteren van kwaliteit van leven, welbevinden, pijn, neuro-psychiatrische symptomen, zorgafhankelijkheid en dagelijks functioneren bij mensen met gevorderde dementie die in een verpleeghuis wonen. Meer ge-

personaliseerde interventies, nauwe samenwerking tussen naasten en hulpverleners, en een combinatie van medicamenteuze en niet-medicamenteuze interventies zijn essentieel voor een zo optimaal mogelijke kwaliteit van leven, ons realiserend dat dit een uitdaging zal zijn, maar geen onmogelijke opgave.

DANKWOORD

Een promotietraject gaan doen iets voor mij? Ik dacht van niet, tot ik er aan begon en nu durf ik zelfs te zeggen dat ik er een beter mens door geworden ben. Ik heb deze reis echter zeker niet alleen gemaakt en zonder de hulp van een aantal mensen had het mij ook niet gelukt.

Wilco: regelmatig kritisch, altijd eerlijk en mij waar nodig een duw in de juiste richting gevend, maar ook zeer benaderbaar bij problemen of onzekerheden, wat ik enorm heb gewaardeerd en nog steeds waardeer. Monique, wat heb ik enorm veel aan jou gehad met je altijd kritische blik en meedenken bij het onderzoek dat we samen hebben gedaan. Ook het samen regelen van symposia en andere organisatorische bezigheden bij een aantal congressen waren aan ons wel besteed. Bettina, thank you so much for your efforts in supporting my research and receiving me at SEFAS in Bergen. I felt very welcome and will definitely return.

Maaike: jouw onvoorwaardelijke steun en altijd bemoedigende woorden en knuffels hebben mij er in moeilijke tijden absoluut doorheen gesleept. Ik ben dan ook super trots dat jij als mijn paranimf naast mij wil staan op de dag van mijn verdediging. Yvonne, als fijne collega en sparringpartner, staat aan mijn andere zijde, waarvoor dank.

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Dagrun Slettebo, Reidun Sandvik, Reidun Kjome and all the PhD candidates and postdocs at SEFAS: thank you for being so kind and welcoming to me and I hope I will work with you again in the future!

Dank aan de fijne collega's bij SOOL voor de organisatorische ondersteuning (Victor Chel, Aletta Koldewijn, Eline van der Meij) en mijn mentoren vanuit de opleiding tot specialist ouderengeneeskunde; Saskia van Eck, Annemarie Moll en Jeroen Janssens. Jullie waren kritisch waar nodig, maar hebben mij altijd ondersteund op mijn weg. Jan Wijnia, Arthur Ruigrok, Peter Amesz, Tamira Breedijk, Gerard-Jan Blauw, Monica van Eijk en Dianne Kroon: bedankt voor jullie wijze lessen en begeleiding als opleiders tijdens mijn verschillende stages. Door jullie werd het vak ouderengeneeskunde nóg leuker.

Ik wil tot slot ActiVite bedanken voor het meedenken en de gegeven steun in het afronden van mijn promotietraject. Hierdoor kon ik naast mijn drukke werk als specialist ouderengeneeskunde ook tijd vrijmaken om de laatste loodjes af te ronden.

CURRICULUM VITAE

Paulien van Dam werd geboren op 3 april 1987 in Alphen aan den Rijn. Na haar gymnasium op het Scala Collega in Alphen aan den Rijn, welke zij in 2005 behaalde, was de keuze voor een vervolgstudie snel gemaakt: geneeskunde. Deze studie volgde zij van 2005 tot eind 2011 aan de Universiteit van Leiden. Tijdens de zorgstage op de afdeling Neurologie van het Groene Hart Ziekenhuis in Gouda en een keuzestage ouderengeneeskunde in het Diaconessenhuis in Leiden werd haar aandacht voor een breed specialisme getrokken, met in het bijzonder de oudere patiënt. Echter, in die tijd was huisarts worden nog de wens.

Haar artsencarrière startte zij bij GGZ Rivierduinen op de gesloten - en open kliniek Rijnaarde in Alphen aan den Rijn, alwaar zij ervaring opdeed met volwassenenpsychiatrie. Vervolgens ging zij bij Mé-doc aan de slag als basisarts in een verpleeghuis, waar zij allereerst terecht kwam bij zorgorganisatie De Zellingen in Capelle aan den IJssel. Het werk als arts in de ouderengeneeskunde voelde als een warm bad en hier werd de wens tot het worden van huisarts omgesmolten naar de wens om specialist ouderengeneeskunde te worden. Na nog enkele maanden ervaring te hebben opgedaan met de ziekte van Huntington bij Topaz, locatie Overduin in Katwijk, begon zij de opleiding tot specialist ouderengeneeskunde in september 2014 bij Lelie Zorggroep, verbonden aan de SOOL in Leiden. Hier werkte zij op twee locaties met bewoners met het syndroom van Korsakov en psychogeriatrische problematiek. Het tweede deel van haar eerste opleidingsjaar volgde zij op de somatiek en psychogeriatrie bij Zorgwaard in Oud-Beijerland.

Waar Paulien tijdens haar wetenschapsstage voor geneeskunde nog niet enthousiast raakte voor het doen van onderzoek, gebeurde dit wel tijdens de keuzestage Wetenschap in het tweede jaar van de opleiding tot specialist ouderengeneeskunde. Onder begeleiding van Monique Caljouw en Wilco Achterberg deed zij onderzoek naar de zorggerelateerde kwaliteit van leven van mantelzorgers na geriatrische revalidatie. Hierover werd een mooi artikel in de JAMDA gepubliceerd, waarvoor Paulien in 2017 ook de Jan Stoopprijs won. In maart 2016 startte Paulien een AIOTO-SO traject: de opleiding tot specialist ouderengeneeskunde gecombineerd met een promotietraject, waardoor het opleidingstraject met minimaal 3 jaar werd verlengd. Er volgden drie onderzoeksperiodes van een jaar, afgewisseld met stages in o.a. het ziekenhuis (ouderengeneeskunde Bronovo ziekenhuis in Den Haag), de geriatrische revalidatie (Alrijne Zorggroep), eerstelijn (ouderengeneeskunde Bronovo ziekenhuis in Den Haag) en een afsluitende stage somatiek en psychogeriatrie (Alrijne Zorggroep locatie Leythenrode in Leiderdorp).

Tijdens de onderzoeksperiodes gaf Paulien les aan derdejaars studenten geneeskunde over het doen van wetenschappelijk onderzoek in de ouderengeneeskunde. Ook ging Paulien tweemaal naar Bergen in Noorwegen, alwaar zij ervaringen uitwisselde met Noorse collega-onderzoekers en Noorse onderzoeksdata bestudeerde. In 2020 ontving Paulien voor het artikel gebaseerd

op deze Noorse data over het gebruik van pijnmedicatie en kwaliteit van leven bij mensen met gevorderde dementie wederom de Jan Stoopprijs.

Op 26 december 2020 mocht Paulien zich specialist ouderengeneeskunde noemen en ging zij aan het werk bij ActiVite, waar zij met veel plezier ervaring op deed in de psychogeriatrie en de eerstelijn, en volgde zij de opleiding tot WZD-functionaris. In februari 2023 maakte zij de overstap naar Topaz360° in Leiden; een behandelpraktijk voor ouderen volledig gericht op de eerstelijn.

PORTFOLIO

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2017 Quality of Life of Informal Caregivers After Geriatric Rehabilitation. van Dam PH, Achterberg WP, Caljouw MA. Care-Related J Am Med Dir Assoc. 2017 Mar 1;18(3):259-264. doi: 10.1016/j.jamda.2016.09.020. Epub 2016 Nov 9. PMID: 27838337.

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2018 24th NKG Oslo (poster presentations: P053 - Pain Medication Use and Quality of Life in Persons With Advanced Dementia, P179 - Quality of life and Paracetamol In advanced Dementia (Q-PID trial))

2018 Nursing Home Research International Working Group, Rome (poster presentations: P26 - Quality of Life and Paracetamol In advanced Dementia (Q-PID): protocol of a randomised double blind placebo-controlled crossover trial, P27 - Quality of life and

pain medication use in persons with advanced dementia: a cross-sectional analysis of the COSMOS trial)

2021 25th NKG Reykjavik (online oral presentation in symposium: S116-3 - Effect of paracetamol on quality of life, wellbeing, pain and neuropsychiatric problems of persons with advanced dementia living in long-term care facilities: a randomised double-blind placebo-controlled crossover trial)

2022 26th NKG Odense (oral presentation in symposium: S34 - Does paracetamol improve quality of life, discomfort, functioning, care dependency, pain and neuropsychiatric symptoms in persons with advanced dementia?)

Scientific oral presentations Netherlands

2017 Verenso Jaarcongres, winnaar Jan Stoopprijs 2017 met het artikel 'Quality of Life of Informal Caregivers After Geriatric Rehabilitation'

2019 ZonMW congres Goed Gebruik Geneesmiddelen (GGG)

2019 UNC-ZH 15 jarig jubileum symposium Kwaliteit van leven bij dementie

2020 SANO Wetenschapsdag

2020 Verenso jaarcongres, winnaar Jan Stoopprijs 2020 met het artikel 'Quality of Life and Pain Medication Use in Persons With Advanced Dementia Living in Long-Term Care Facilities'

2021 Verenso symposium Wetenschappelijk onderzoek in het verpleeghuis Randstad Zuid

2021 SANO Wetenschapsdag

2021 V&VN Jaarcongres

2021 Kenniscafé UNC-ZH over implementatie onderzoeksresultaten Q-PID

Courses

2016 PhD Introductory Meeting

2016 Basiscursus Regelgeving en Organisatie voor Klinisch onderzoekers (BROK)

2018 Basic Methods and Reasoning in Biostatistics

2018 Speedreading

2019 Analysis of Repeated Measurements