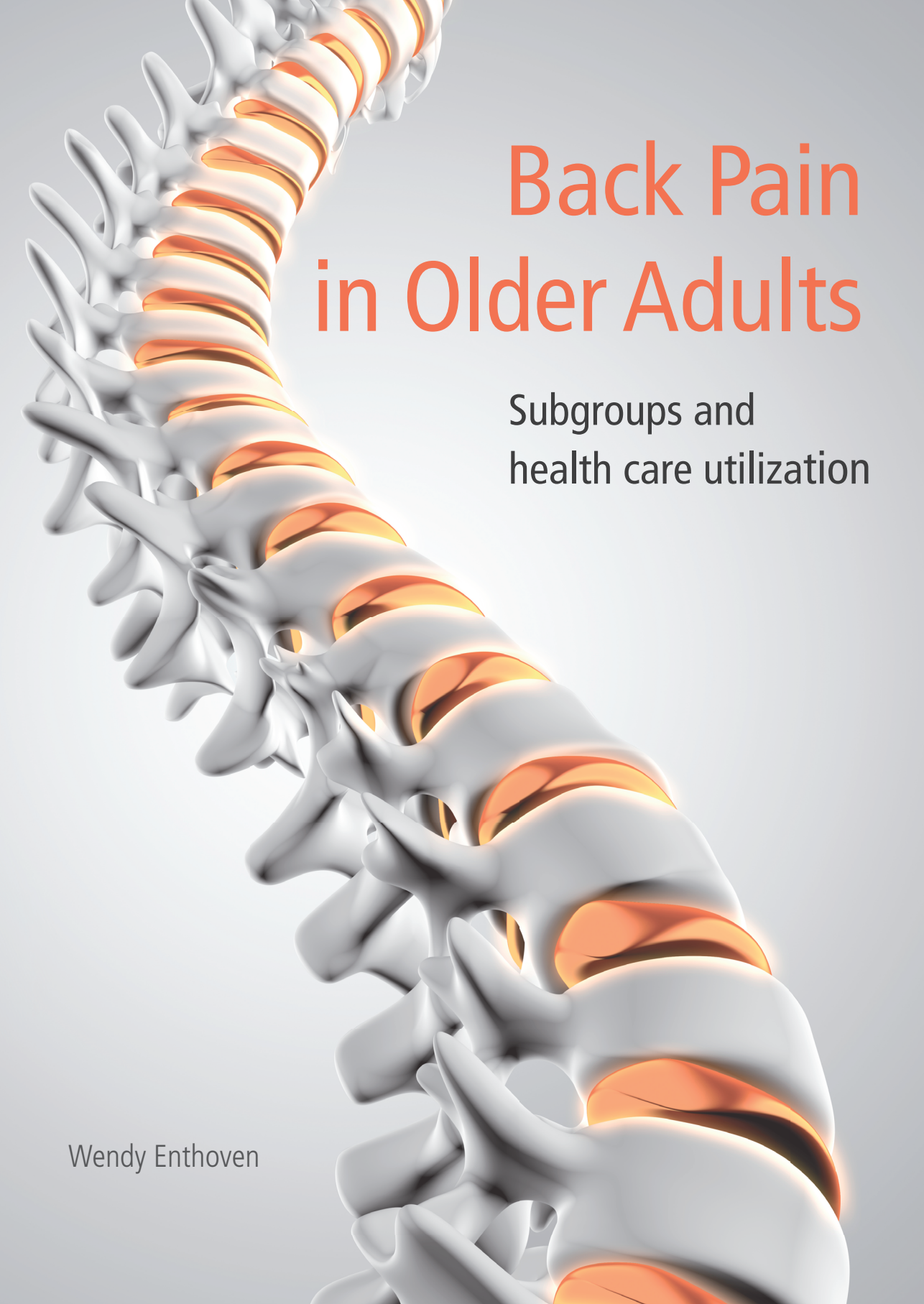

Back Pain in Older Adults

Subgroups and health care utilization

Wendy Enthoven

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Subgroups and Health Care Utilization

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Subgroups and Health Care Utilization

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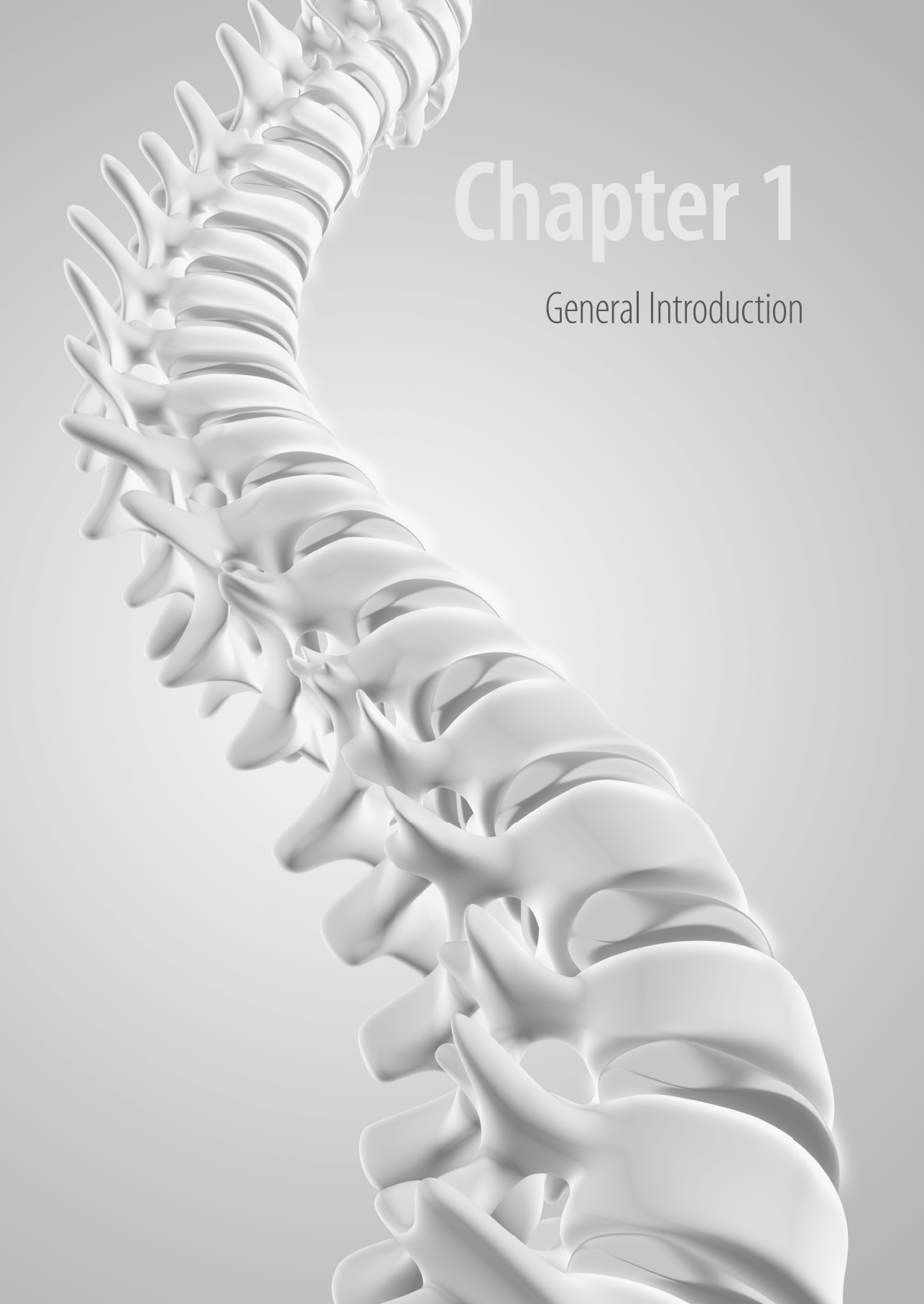

Chapter 1

General Introduction

BACK PAIN

Worldwide, back pain is a frequently occurring and disabling disease. The point prevalence of back pain is reported to be 11.9% in the general population[1] and back pain is a leading cause of years lived with disability.[2] Although many patients do not seek help for their back pain,[3-5] a considerable number of consultations in general practice are related to musculoskeletal complaints, including a large amount of back complaints.[6 7] Also in the Netherlands, back complaints reported to the general practitioner (GP) are the most common of all musculoskeletal complaints. The incidence of back pain without radiating pain in the leg is reported to account for 27 per 1000 patients - and these numbers have increased over time.[8] Moreover, the costs related to back pain are a substantial burden on society. For example, patients with back pain use almost twice as much health care as patients without back pain.[6]

OLDER ADULTS WITH BACK PAIN

In older adults benign or mild back pain is generally less frequent compared to younger age groups, but older adults experience more episodes with severe or disabling back pain.[9] With the aging population a greater number of people are likely to suffer from severe back pain in the future. Moreover, because the prevalence of seeking health care for back pain increases with age[6] these healthcare costs are also likely to increase in the future.[10] Another point is that, indirect costs resulting from lost work productivity also represent a large percentage of the overall costs associated with back pain,[11] because of retirement these indirect costs might be lower in the older population; this is probably why older adults with back pain are often excluded from randomized trials performed among back pain patients.[12] However, from the perspective of an aging population and increasing numbers of older patients with back pain, this is unfortunate. Furthermore, it seems that this trend will not improve over time, even though the proportion of older patients is rising.

Information on patients' characteristics and their associations with back complaints is important for back pain management and may help identify factors that can have a beneficial influence on the course of back pain or treatment response. However, the characteristics of back pain in older patients probably differ from those in younger persons; for example, more severe back pain occurs more frequently in the higher age groups.[9] Furthermore, older patients more often have co-morbidities;[13] this can influence the back pain episode, resulting in a different course and prognosis of back pain complaints. Finally, older adults with musculoskeletal pain more often report difficulties in activities of daily living,[14] which can have a considerable impact on the independence of these patients.

SUBGROUPS

Defining subgroups in the heterogeneous population of back pain patients might help us to better inform and treat these patients. In this thesis, subgroups are identified in different ways and at various time points during follow-up in a population of older adults included in the BACE cohort study (figure 1).[15] Patients with neuropathic pain are identified using the 'Dolour Neuropathique four questions' (DN4) posed at baseline.[16] Non-recovery of patients is assessed at three months after baseline using self-reported recovery. Specific underlying pathology is assessed after one year to ensure that all underlying specific pathology has become apparent. Within this study population, trajectories are identified based on different courses of pain over time.

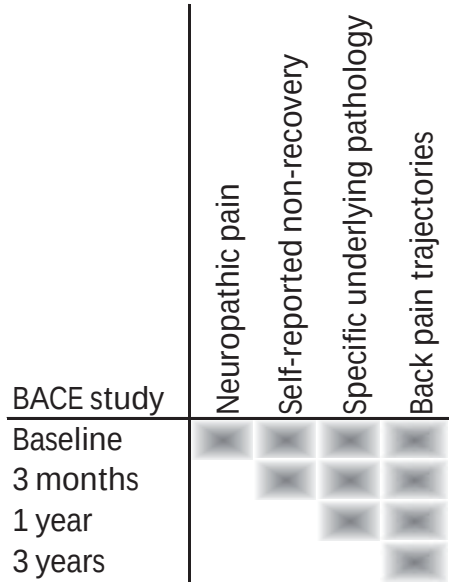

Figure 1. Different subgroups at different time points within the BACE study

Neuropathic pain

Neuropathic pain is defined as pain arising as a direct consequence of a lesion or disease affecting the somatosensory system, either at the peripheral or central level.[17] In back pain, although the mechanism of neuropathic pain is not fully understood, different mechanisms probably play a role in the development of neuropathic pain. It is suggested that back pain can be a 'mixed' type of pain, consisting of nociceptive and neuropathic components. Neuropathic pain may be caused by lesions of nociceptive sprouts in the degenerated intervertebral discs, by mechanical compression of the nerve root, or by action of inflammatory mediators from degenerated intervertebral discs.[18] Patients with neuropathic pain report a lower quality of life and have more functional disability compared to patients with nociceptive pain.[19] It is important to identify patients with neuropathic pain because conventional analgesic treatment may be less effective in this population,[20-22] and a different type of treatment may be more beneficial for them. Therefore, it is important to establish how many older patients with back pain experience neuropathic pain and to examine the characteristics of these patients.

Non-recovery

The majority of older patients in primary care have persistent symptoms of back pain.[23] This differs from back pain patients in general for whom the course of back pain is described as being favourable. Knowledge as to which patients will develop chronic back pain or experience more episodes of recurrent back pain will help healthcare professionals to better inform their patients. Therefore, we need to identify these predictive characteristics. Furthermore, if we can identify patients with a less favourable outcome, we may also develop better and more focused interventions for these patients in order to prevent this poor outcome.

Specific underlying pathology

A specific subgroup concerns patients with an underlying serious pathology that is the cause of their back pain. Although most patients with back pain have this condition without serious underlying pathology,[24-26] about 1-5% of back pain in primary care is caused by serious pathology.[27 28] This includes vertebral fractures, malignancies, infection, cauda equina syndrome and ankylosing spondylitis. Vertebral fractures are the most common underlying serious pathology in patients with back pain[25] and these fractures frequently occur among older patients.[24]

To identify these underlying causes of back pain, most clinical guidelines recommend to use so-called red flags.[29 30] These alarming symptoms, derived from history taking and/or physical examination, are suggested to have an association with serious pathology as a cause of back pain. Because the prevalence of serious pathology as a cause of back pain increases with age, red flags may be more important in patients aged over 55 years.[31] However, analysis of these red flags and their diagnostic value is scarce, especially among older adults with back pain.

Back pain trajectories

Defining different trajectories in the course of back pain may help to identify patients at risk for a non-favourable course of back pain. Although trajectories have been fitted for some populations with back pain,[32-36] they are not yet widely used to describe back pain patterns. Older adults may well show different course(s) of back pain compared to younger patients, especially since older age is associated with non-recovery.[36 37]

HEALTHCARE UTILIZATION

Older patients with chronic back pain have the highest healthcare costs; however, this association is mainly due to their increased number of co-morbidities.[38] Patients with a

fracture as underlying cause of back pain, and patients with neuropathic pain, also have higher healthcare costs.[38 39]

Analgesic therapy

A large percentage of all back pain patients receive analgesics after a first visit to their GP.[40] Of these, paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs) can be obtained either by prescription from a physician or over-the-counter. Analgesics are mostly prescribed to support patients to stay active, because staying active is an important element in a positive course of back pain. Older patients with back pain are more likely to be prescribed analgesics compared with younger adults with back pain.[41] With regard to the analgesic options, international guidelines for back pain usually recommend paracetamol as first choice, followed by NSAIDs.[42] This is mainly because the adverse side-effects of paracetamol are more favourable than those of NSAIDs. Nevertheless, because each class of medication is associated with (serious) adverse reactions it is important to consider the different types of analgesics. This applies particularly to older adults, who are more prone to adverse events due to co-morbidities and the use of co-medication.

One of the aims of this thesis is to describe the kind of analgesics (both prescribed and over-the-counter) among older adults with back pain.

Efficacy of NSAIDs

NSAIDs are a frequently used analgesic. Based on their working profile they can be divided into i) non-selective NSAIDs, which inhibit both cyclooxygenase 1 (COX-1) and 2 (COX-2), and ii) selective NSAIDs, which inhibit only the COX-2 enzyme. These COX enzymes play a key role in the synthesis of prostaglandins, which contribute to inflammation, pain and fever. Because NSAIDs inhibit the COX enzyme this inhibits the production of prostaglandins which, in turn, reduces inflammation, pain and fever. Both non-selective and selective NSAIDs are used in the treatment of pain. However, inhibition of these enzymes can also cause adverse events, since COX-1 produces prostaglandins that also support platelets, protect the stomach lining and may help maintain kidney function. Nonselective NSAIDs are also called 'traditional' NSAIDs and, compared to selective NSAIDs, carry a higher risk of gastro-intestinal adverse reactions,[43] such as gastritis or stomach bleeding, due to inhibition of both the COX enzymes. Although selective NSAIDs have fewer gastro-intestinal adverse reactions they are associated with cardiovascular risk.[44] Therefore, in view of this risk of serious adverse events, it is very important to establish whether these analgesics are really effective for back pain.

AIM AND OUTLINE OF THIS THESIS

The aim of this thesis is to describe: 1) the characteristics of older adults with back pain; 2) the various ways of identifying different types of patient subgroups, and their course and prognosis of back pain; and 3) healthcare use due to back pain in a population of older adults.

Most of the results described in this thesis are based on the BACE study population. The characteristics of these older adults with back pain are described in **chapter 2**. All these patients aged over 55 years were included after visiting their GP due to back pain.

Results on prevalence and associations of neuropathic pain in this cohort of older adults is presented and discussed in **chapter 3**. The number of patients and variables associated with non-recovery of their back pain after three months was assessed and reported in **chapter 4**. **Chapter 5** reports the assessment of underlying pathology as a cause for back pain in this population of older adults. Furthermore it discusses the diagnostic value of red flags to identify vertebral fractures in these patients. Based on the back pain course during 3 years, different trajectories were defined in this population. Also characteristics of patients in these different trajectories were identified and described in **chapter 6**.

Pain medication is often prescribed for patients with back pain. The use of these analgesics, both prescribed and over-the-counter are described in **chapter 7**. To determine the efficacy of NSAIDs for patients with chronic back pain, a Cochrane systematic review was performed and the results are reported in **chapter 8**.

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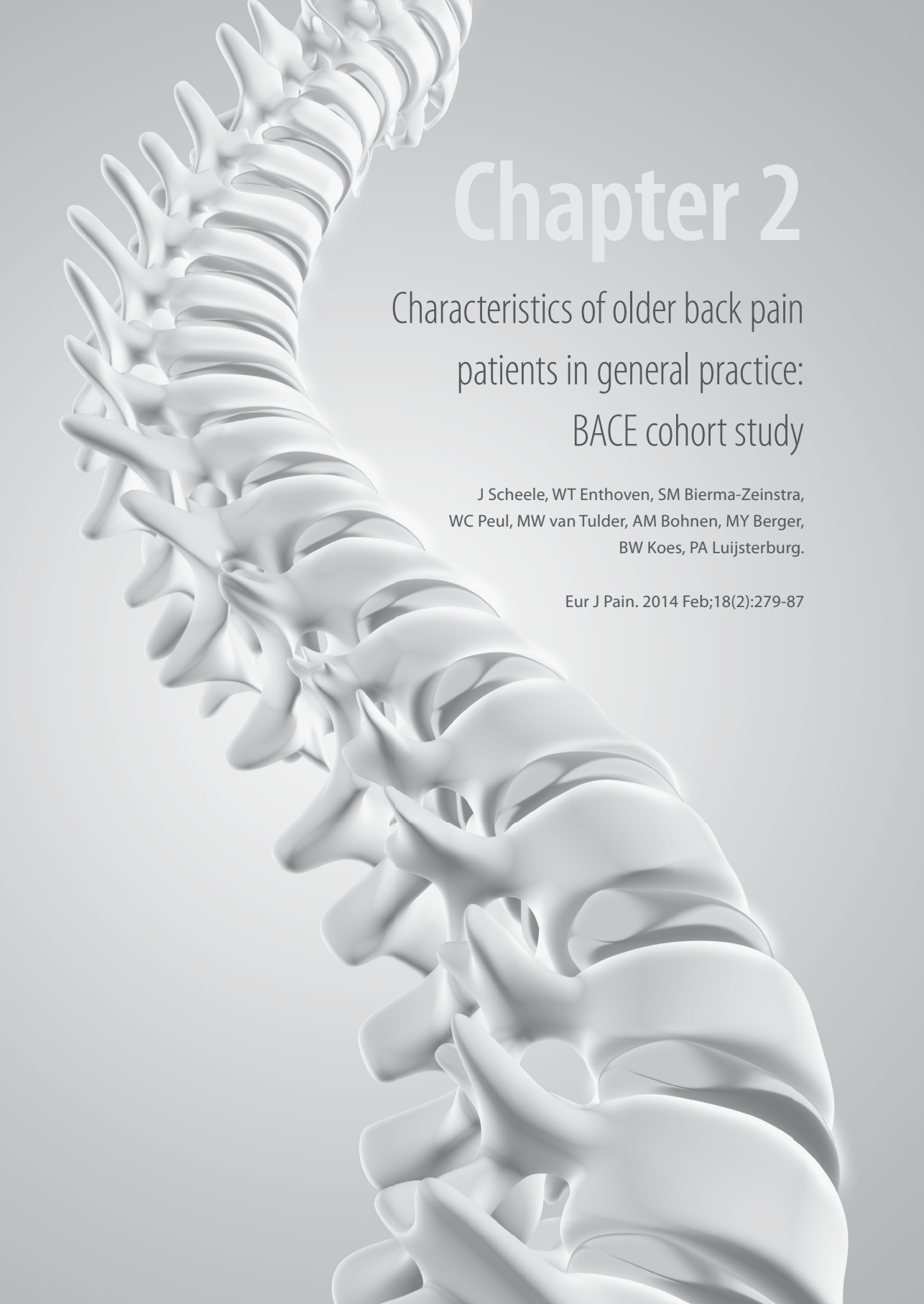

Chapter 2

Characteristics of older back pain patients in general practice: BACE cohort study

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ABSTRACT

Background

Although back pain is common among older people, limited information is available about the characteristics of these patients in primary care. Earlier research suggests that the severity of back symptoms increases with older age.

Methods

Patients aged >55 years visiting a general practitioner with a new episode of back pain were included in the BACE study. Information on patients' characteristics, characteristics of the complaint and physical examination were derived from the baseline measurement. Cross-sectional differences between patients aged >55–74 and ≥75 years were analysed using an unpaired *t*-test, Mann–Whitney *U*-test or a chi-square test.

Results

A total of 675 back pain patients were included in the BACE study, with a median age of 65 (interquartile range 60–71) years. Patients aged >55–74 years had a mean disability score (measured with the Roland Disability Questionnaire) of 9.4 (standard deviation (SD) 5.8) compared with 12.1 (SD 5.5) in patients aged ≥75 years ($p \leq 0.01$). The older group reported more additional musculoskeletal disorders and more often had low bone quality (based on ultrasound measurement of the heel) than patients aged >55–74 years. Average back pain severity over the previous week showed no difference ($p = 0.11$) between the age groups, but severity of back pain at the moment of filling in the questionnaire was higher ($p = 0.03$) in the older age group.

Conclusions

In this study, older back pain patients reported more disabilities and co-morbidity. However, the clinical relevance of these differences for the course of the back pain episode in older patients remains a subject for further research.

INTRODUCTION

Although back pain is a common health problem in older adult patients, back pain research focuses mainly on the working-age population. Patients aged >60 or 65 years are often excluded from studies.[1-3] It is suggested that older patients have a lower prevalence of back pain compared with the working population.[4 5] Some studies suggest that the prevalence of mild back pain decreases with increasing age, but that the prevalence of severe back pain increases with increasing age.[4] However, back pain in the older population remains the most common musculoskeletal disorder.[5] In the Netherlands, most back pain patients who seek medical care visit the general practitioner (GP); back pain without radiation is the sixth most prevalent complaint for which patients visit their GP, with a prevalence of 39.7 per 1000 registered patients per year.[6] Because back pain is a prevalent musculoskeletal complaint, also in older adults, it is important to gain insight into the characteristics of these patients. Although there are reports on the characteristics of back pain patients visiting their GP, information on older adults is lacking.[7 8] Compared with younger adults, the characteristics of back pain in older patients might differ because 1) older people have more co-morbidities;[9] 2) older people with musculoskeletal pain more often report difficulty in activities of daily living;[10 11] and 3) older people might have more severe back complaints.[4 12] Use of different age categories within the same study population enables the comparison of older and younger back pain patients on several patient and complaint characteristics. Information about patients' characteristics and their complaints in a relevant setting is important for back pain management and may help identify factors that can influence the course or treatment response of these back pain patients. Therefore, the aim of the present study was to describe the patients' characteristics and characteristics of the complaint, of back pain patients aged >55 years in general practice. The aim of the present study was also to investigate whether these characteristics differ between the age categories >55–74 and ≥75 years.

METHODS

Patient selection

The BACE study is a prospective observational cohort. Details of the study protocol are described elsewhere.[13] Patients aged >55 years were invited to participate in the BACE study if they consulted their GP with a new episode of back pain. An episode is considered 'new' if the patient had not visited a GP during the preceding 6 months for the same back complaint. All back complaints (defined as pain located in the region from the top of the shoulder blades to the first sacral vertebra) were included. Patients

were excluded if they were unable to fill in the questionnaire due to a language problem or cognitive disorders, or were unable to participate in the physical examination (wheelchair-bound patients). Patients were invited by their GP during the consultation or were retrospectively identified and approached within 2 weeks after the consultation in writing. In order to invite patients after consultation, medical patient records of the GPs were searched. A research assistant searched records using ICPC codes L02, L03, L84, L85 and L86. Hereafter, the GPs selected eligible patients using the inclusion and exclusion criteria. Only if the patient had visited the GP due to back complaints no more than 2 weeks before the search, the patient received a letter from the GP with an invitation to enter the study. The inclusion and exclusion criteria and rest of the study procedure remained the same. The only difference is the longer time period between GP consultation and inclusion to the study in this 'population which is identified in medical records'. The study protocol was approved by the Medical Ethics Committee of the Erasmus Medical Center, Rotterdam, the Netherlands.

Data collection

Baseline measurements included a questionnaire and a physical examination. The questionnaire and history taking during physical examination included questions on 1) patient characteristics: age, gender, education level, body mass index (BMI), marital status, employment status, smoking, measured as pack years (number of packs per day × years of smoking) and hazardous drinking, measured with the alcohol use disorders identification test (AUDIT-C);[14 15] 2) characteristics of the back complaint: duration of the current complaint, severity of back pain averaged during the previous week, and severity of back pain at the moment of filling in the questionnaire measured on an 11-point numerical rating scale (NRS 0–10),[16] disability measured with the Roland disability questionnaire (RDQ scale 0–24),[17] location of the back pain, cause of the back pain, history of back pain, back surgery in the past, radiating pain in the legs below the knee, severity of leg pain if present measured on an NRS (scale 0–10)[16] and morning stiffness of the back; 3) medical consumption: use of pain medication for back pain and care from a physical therapist; 4) psychological factors: quality of life measured with the Short Form-36, physical and mental component summary scale (SF-36 range 0–100),[18] depressive symptoms measured with the Center for Epidemiologic Studies Depression Scale (range 0–60),[19] kinesiophobia (fear-avoidance beliefs questionnaire, physical activity subscale range 0–28),[20] pain catastrophizing (pain catastrophizing scale, range 0–52),[21] and attitude and beliefs about back pain (back beliefs questionnaire, range 9–45);[22] and 5) co-morbidity, measured with the self-administered co-morbidity questionnaire.[23] The physical examination included 1) general examination of the body, such as pain during palpation of the paravertebral muscles, pain during palpation of the spinous processes and sacroiliac joint, and Heberden's or Bouchard's nodules; 2) range of motion of the

back and hip: anteflexion (finger–floor distance) and difference between left- and right-sided lateroflexion, left- and right-sided rotation of the upper body, left- and right-sided hip joint exorotation and endorotation; and 3) additional diagnostic tests: knee tendon reflex, difference in quadriceps strength, test of Lasegue,[24] difference in sensation between left and right feet, timed up and go test.[25] Laboratory test: C-reactive protein (CRP) level was determined during the physical examination. Increased CRP level was defined as CRP level >10 mg/L. Bone quality test: Bone quality was measured with the Lunar Achilles InSight (quantitative ultrasound measurement of the heel).[26] The bone quality is presented as a T-score, which is a comparison between the individual's bone quality index and a reference population mean, and expressed in standard deviation (SD) units difference. Low bone quality is defined as a T-score of > −2.5, which means that patients bone quality score was more than 2.5 SD lower than the population mean.[27]

Data analysis

First, the characteristics of the study population were reported using descriptive statistics and we compared the two inclusion methods used. Patients included directly during consultation were compared with those retrospectively identified and approached within 2 weeks after the consultation in writing on the following characteristics: age, gender, duration of current complaint, severity of back pain, level of disability, and duration between consultation and baseline measurements. Levene's test was used to assess the equality of variance for each variable. The chi-square test was used to compare categorical variables and an unpaired *t*-test to compare numerical variables. The Mann–Whitney *U*-test was used instead of the unpaired *t*-test for variables for which the *p*-value of the Levene's test was <0.01. Second, patients in the age category >55–74 years were compared with those aged ≥75 years on information from the baseline questionnaire and physical examination. In order to examine the differences between the age categories (>55–74 years vs. ≥75 years), the chi-square test was used to compare the categorical variables, and an unpaired *t*-test or Mann–Whitney *U*-test was used to compare the numeric variables. All analyses were performed using the SPSS version 17.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Population characteristics and selection

Of the 1402 back pain patients invited by 103 GPs to participate in this cohort study, 675 patients (48%) were included and 727 patients were excluded. Reasons for exclusion were as follows: not willing to participate ($n = 291$), not meeting the inclusion criteria ($n = 118$) or the patient did not respond ($n = 318$). Of the 675 included back pain patients,

105 were included during the consultation and 570 after they received a written invitation within 2 weeks after their consultation. Of these patients, 669 patients (99%) filled in the baseline questionnaire and 670 patients (99%) completed the physical examination. Patient selection is described in figure 1. The study population consisted of 274 men and 401 women, median age was 65 (interquartile range (IQR) 60–71) years and 479 (71%) were married. At baseline, median duration of back pain was 35 (IQR 20–100) days, and 156 (23%) patients had back pain lasting >3 months. Pain radiation in the legs below the knee was reported by 205 (30%) patients. Comparison of patients included during consultation and after the consultation revealed some differences. Patients included after a written invitation had slightly less severe back pain (mean 4.9; median 7; IQR 5–8) compared with those invited directly during the consultation (mean 6.5; median 5; IQR 3–7); also, they had a lower level of disability as measured with the RDQ (mean 9.5 and 11.3, respectively). However, these differences between the groups might be attributed to the difference in the (mean) number of days between consultation and completing the baseline measurement (the physical examination); i.e., 26 days for those with a written invitation and 8 days for those invited directly during consultation (table 1).

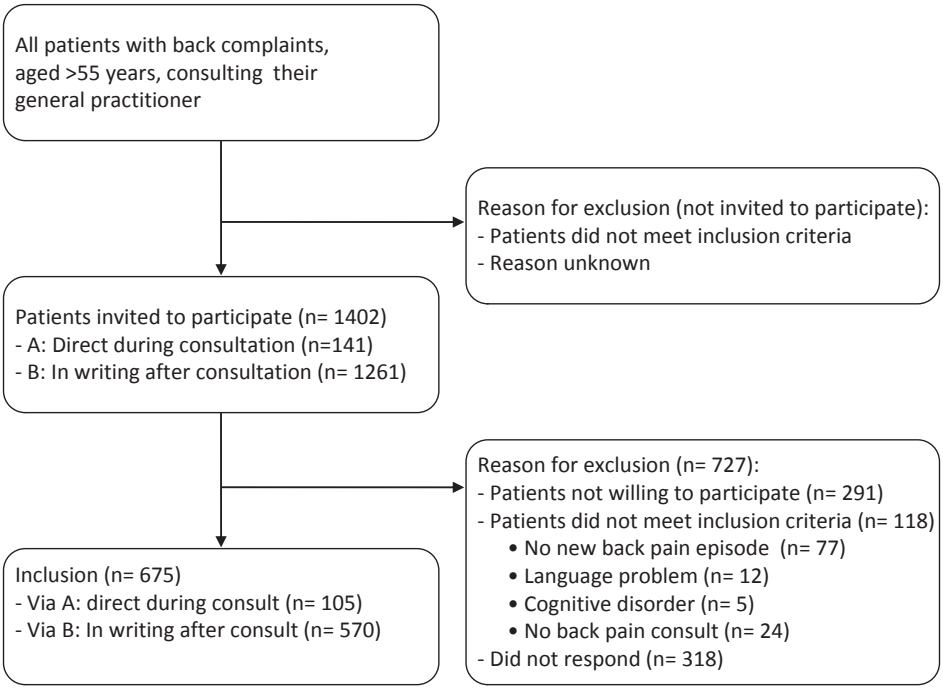

Figure 1. Flow chart of the study

Table 1. Comparison of the inclusion methods

	Direct during consultation (n=105) n (%)	In writing after consultation (n= 570) n (%)	Total (n=675) n (%)
Number of days between consultation and baseline measurements: median (IQR)	8 (6-13)	26 (20-33)	23 (16-31)**
Patient characteristics			
Age in years: mean ± SD	66.8 ± 7.3	66.3 ±7.7	66.4 ±7.6
Male	50 (48)	224 (39)	274 (41)
Low education level	43 (41)	236 (41)	279 (41)
Married	70 (67)	409 (72)	479 (71)
Paid job	24 (23)	153 (27)	177 (26)
Characteristics of the complaint			
Duration of back pain > 3 months	32 (31)	124 (21.8)	156 (23)
Severity of back pain (NRS average previous week): mean ± SD	6.5 ± 2.1	4.9 ± 2.7	5.2 ± 2.7**
Radiating pain in the legs below the knee	27 (26)	178 (31)	205 (30)
Disability (RDQ): mean ± SD	11.3 ± 5.7	9.5 ± 5.8	9.8 ± 5.8**

** p< 0.01

IQR: interquartile range (presented as 25-75 IQR), SD: standard deviation, NRS: numeric rating scale, RDQ: Roland Disability Questionnaire

Age groups: patient and complaint characteristics

Table 2 presents the patients and complaint characteristics per age category. The percentage of patients retrospectively identified and approached within 2 weeks after the consultation was the same in both age categories (84%). Significantly more patients aged ≥75 years had a lower education level compared with the younger group (58% and 38%, respectively). The older group had a lower percentage of smokers (5% and 21%, respectively) and of hazardous drinking (32% and 53%, respectively) than patients in the age category >55–74 years. However, these differences might be explained by the healthy survival effect, whereby those with a healthy lifestyle live longer than those with an unhealthy lifestyle. In 67% of the patients, the back pain was located in the lumbar spine. The (mean) severity of back pain in the previous week showed no significant differences between the two groups: 5.1 (SD 2.7) for patients aged >55–74 years and 5.6 (SD 2.5) for patients aged ≥75 years. In contrast, (mean) back pain severity at the moment of filling in the baseline questionnaire was significantly different between the groups ($p < 0.05$); (mean) 4.5 (SD 2.5) for patients aged >55–74 years and 5.1 (SD 2.5) for patients aged ≥75 years. There was a significant difference in disability between the two groups: 9.4 (SD 5.8) for the younger patients and 12.1 (SD 5.5) for patients aged ≥75 years, indicating that older patients experienced more disability due to back pain. Regarding medical consumption, 483 (72%) of all patients took pain medication for their back pain, with no significant dif-

Table 2. Characteristics of the back pain patients (n=675).

	>55-74 years (n=566) n (%)	≥ 75 years (n=109) n (%)	Total (n=675) n (%)
Number of days between consultation and baseline measurements: median (IQR)	23 (17-31)	23 (15-29)	23 (16-31)
Patient characteristics			
Male	237 (42)	37 (34)	274 (41)
Education level:			
Low	216 (38)	63 (58)	279 (41)**
Middle	246 (44)	29 (27)	275 (41)
High	98 (17)	16 (15)	114 (17)
Body mass index: mean ± SD	27.6 ± 4.7	27.1 ± 4.5	27.5 ± 4.7
Marital status: married	426 (75)	53 (49)	479 (71)**
Paid job	177 (31)	0	177 (26)**
Smoking	117 (21)	5 (5)	122 (18)**
Hazardous drinking (AUDIT-C)	298 (53)	35 (32)	333 (49)**
Characteristics of the complaint			
Duration of back pain:			
< 1 week	55 (10)	7 (6)	62 (9)
1 week-6 weeks	229 (40)	44 (40)	273 (40)
6 weeks-3 months	94 (17)	10 (9)	104 (15)
> 3 months	129 (23)	27 (25)	156 (23)
Average back pain previous week (NRS): mean ± SD	5.1 ± 2.7	5.6 ± 2.5	5.2 ±2.7
Disability (RDQ): mean ± SD	9.4 ± 5.8	12.1 ± 5.5	9.8 ± 5.8**
Pain location:			
Only thoracic	34 (6)	9 (8)	43 (6)
Only lumbar	382 (67)	68 (62)	450 (67)
Thoracic and lumbar	91 (16)	20 (18)	111 (16)
Perceived cause: accident or trauma	20 (4)	8 (7)	28 (4)
History of back pain	493 (87)	86 (79)	579 (86)
Back surgery in the past	46 (8)	10 (9)	56 (8)
Radiating pain in the leg below the knee	170 (30)	35 (32)	205 (30)
Severity of leg pain (NRS): mean ± SD[a]	4.0 ± 2.8	4.0 ± 2.8	4.0 ± 2.8
Morning stiffness of the back	10 (2)	4 (4)	14 (2)
Medical consumption			
Use of pain medication for back pain	403 (71)	80 (73)	483 (72)
Care from a physical therapist	251 (44)	48 (44)	299 (44)
Psychological factors			
Quality of life (SF-36) physical summary scale: mean ± SD	43.8 ± 8.7	40.0 ± 9.5	43.2 ± 8.9**
Depressive symptomatology (CES-D): mean ± SD	9.7 ± 7.8	11.8 ± 7.6	10.0 ± 7.8*
Kinesiophobia (FABQ) physical activity subscale: mean ± SD	13.2 ± 5.7	14.6 ± 6.1	13.4 ± 5.8*
Pain catastrophizing (PCS): mean ± SD	13.9 ± 10.6	15.5± 10.5	14.1 ± 10.6
Attitude and beliefs about back pain (BBQ): mean ± SD	26.8 ± 7.1	24.5 ± 7.5	26.4 ± 7.2**

* p< 0.05, ** p< 0.01 [a] Means and SD computed only with the patients which reported leg pain (n=375)
IQR: interquartile range (presented as 25-75 IQR), SD: standard deviation, AUDIT-C: Alcohol Use Disorders Identification Test, NRS: numeric rating scale (range 0-10), RDQ: Roland disability questionnaire (range 0-24), SF-36: Short Form-36, physical summary scale (range 0-100), CES-D: Center for Epidemiologic Studies Depression Scale (range 0-60), FABQ: Fear avoidance beliefs questionnaire, physical activity subscale (range 0-28), PCS: Pain Catastrophizing Scale (range 0-52), BBQ: Back beliefs questionnaire (range 9-45)

ference between the two groups. Patients aged ≥75 years reported lower quality of life, more depressive symptoms, more fear and avoidance beliefs, and more negative thoughts about back pain compared with patients aged >55–74 years.

Physical examination

Table 3 presents the results of the physical examination tests. Pain during palpation was more often present with palpation of the paravertebral muscles (34%) than with palpation of the spinous processes and sacroiliac joint (19%). Differences between left and right knee tendon reflex was found in 21% of the back pain patients, and a positive test of Lasegue in 15%. A significant difference was found between the two groups in lateroflexion: 44% of the patients aged ≥75 years had differences between lateroflexion to the left and right compared to 34% in the younger group. The older group took longer to complete the timed up and go test (median 13.0; IQR 10.2–17.1 s) compared with the younger group (median 9.9; IQR 8.5–11.9 s).

Table 3. Results of the physical baseline examination.

	>55-74 years (n=566) n (%)	**≥ 75 years (n=109) n (%)**	**Total (n=675) n (%)**
General examination			
Pain during palpation of the paravertebral muscles	193 (34)	34 (31)	227 (34)
Pain during palpation of the spinous processes and sacroiliac joint	105 (19)	22 (20)	127 (19)
Heberden's or Bouchard's nodules	131 (23)	30 (28)	161 (24)
Range of motion			
Anteflexion (finger-floor distance in cm): mean ± SD	10.6 ± 12.0	12.2 ± 11.4	10.9 ± 11.9
Lateroflexion[a]	194 (34)	48 (44)	242 (36)*
Rotation upper body[a]	133 (24)	23 (21)	156 (23)
Hip external rotation[a]	68 (12)	14 (13)	82 (12)
Hip internal rotation[a]	86 (15)	16 (15)	102 (15)
Additional diagnostic tests			
Knee tendon reflex[a]	117 (21)	25 (23)	142 (21)
Quadriceps strength[a]	67 (11)	11 (10)	78 (12)
Positive Laseque	87 (15)	13 (12)	100 (15)
Sensation of the foot[a]	101 (18)	18 (17)	119 (18)
Timed up and go test, in sec: median (IQR)	9.9 (8.5-11.9)	13.0 (10.2-17.1)	10.2 (8.6-12.6)**
Low bone quality	45 (8)	32 (29)	77 (11)**
CRP level > 10 mg/l	20 (4)	6 (6)	26 (4)

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

SD: standard deviation, IQR: interquartile range (presented as 25-75 IQR), CRP: C-reactive protein

[a] Difference between left and right side of the body

Laboratory test and bone quality test

Only 4% of the patients had an increased CRP level. There was no statistically significant difference between the age groups. The older group more often had low bone quality, indicating a higher risk for fractures: 29% of patients aged ≥75 years compared with 8% of patients aged >55–74 years.

Co-morbidity

Table 4 presents the patients' self-reported comorbidity. The musculoskeletal disorders occurring most frequently were neck/shoulder complaints (52% of all patients), knee complaints (46%) and hip complaints (41%). There were no significant differences between the two age groups for the prevalence of these complaints. Several other disorders were more often present in patients aged ≥75 years than in the younger group: high blood pressure (50% vs. 35%), heart diseases (29% vs. 13%), osteoporosis (21% vs. 13%), kidney disease (9% vs. 3%), and anaemia or other blood disease (6% vs. 1%). There

Table 4. Reported co-morbidity (n=675).

	>55-74 years (n=566) n (%)	**≥ 75 years (n=109) n (%)**	**Total (n=675) n (%)**
Heart disease	72 (13)	32 (29)	104 (15)**
High blood pressure	197 (35)	54 (50)	251 (37)**
Lung disease	55 (10)	14 (13)	69 (10)
Diabetes	62 (11)	18 (17)	80 (12)
Ulcer or stomach disease	50 (9)	12 (11)	62 (9)
Kidney disease	14 (3)	10 (9)	24 (4)**
Liver disease	4 (1)	1 (1)	5 (1)
Anemia or other blood disease	7 (1)	6 (6)	13 (2)**
Cancer	22 (4)	5 (5)	27 (4)
Depression	46 (8)	9 (8)	55(8)
Hip or knee osteoarthritis	161 (28)	40 (37)	201 (30)
Hand osteoarthritis	113 (20)	24 (22)	137 (20)
Rheumatoid arthritis	25 (4)	8 (7)	33 (5)
Neck/shoulder complaints	302 (53)	50 (46)	352 (52)
Hip complaints	236 (42)	40 (37)	276 (41)
Knee complaints	266 (47)	47 (43)	313 (46)
Headache/migraine	89 (16)	16 (15)	105 (16)
Feet problems	155 (27)	37 (34)	192 (28)
Gout	20 (4)	7 (6)	27 (4)
Neurological problems	21 (4)	7 (6)	28 (4)
Osteoporosis	75 (13)	23 (21)	98 (14)*

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

was no significant difference in the prevalence of the following complaints between patients aged >55–74 and ≥75 years: hip/knee osteoarthritis, which was 28% and 37%, respectively; rheumatoid arthritis, which was 4% and 7%, respectively; and depression, which was 8% and 8%, respectively.

DISCUSSION

The present study reports the characteristics of 675 patients aged >55 years visiting their GP for back pain. Back pain severity, level of disability and duration between consultation and baseline measurement were somewhat higher for patients who were invited to join the study directly during the consultation compared with those retrospectively identified and approached within 2 weeks after the consultation. Comparison of patients aged >55–74 and ≥75 years shows a significant difference in disability (RDQ score 9.4 and 12.1, respectively). Patients aged ≥75 years reported significantly higher pain severity at the moment of filling in the questionnaire, but the magnitude of the difference (0.6) was small, and no difference was found between the two groups for average back pain severity in the previous week. Patients aged ≥75 years more often reported other musculoskeletal complaints, as well as high blood pressure, heart diseases, osteoporosis, kidney diseases, and anaemia or other blood diseases. Also, the older group more often had lower bonequality than the younger patients.

The review of Pengel et al.[8] describes the course of acute back pain patients. The baseline pain scores of the studies range from 12 to 65 (on a 100-point scale for pain) and a similar range was found for disability scores, making comparison with our results difficult.[8] Previous research about the difference of pain severity between age groups of other musculoskeletal complaints, such as hip, knee and ankle pain, already indicate that older adults experience higher pain severity than younger adults.[11 28] Although we found a significant difference between our two age groups for back pain severity and disability, the difference is very small. Several studies reported on the minimally clinically important change, ranging from 2 to 8 points for the RDQ and ranging from 2 to 4.5 points on the 11-point NRS scale.[29 30] Proposed consensus for clinically meaningful changes for back pain patients on an 11-point NRS scale and for the RDQ are 2 and 5 points, respectively.[31] The differences between our age groups were smaller, probably indicating no clinically relevant differences, but it is unknown whether these differences will increase in case of a greater age difference between the study groups.

The older patients in our study experience more depressive symptoms and lower quality of life. Other studies indicated that there is an association between pain and depression in older adults, but not in younger adults.[32 33] This association could explain the difference between depressive symptoms between the age groups. In our study

population, the medical consumption of the back pain patients did not differ between the age categories. The percentage of patients who used pain medication and the percentage of patients who received care from a physical therapist were more or less the same. Other research indicated that older back pain patients more frequently received a medication prescription and less often a referral to physical therapy. However, these differences increased when there was a greater difference between the age categories.[34 35]

Our study population has a higher percentage of patients with a history of back pain compared with other back pain study populations.[7 36] The age difference between the various study populations is a likely explanation for this finding. Other studies conducted among the general population comparing different age categories also found some similar differences, e.g., older patients in general, and older patients with musculoskeletal complaints, experienced more disability than younger patients.[12 37 38] Increased age and multi-morbidity were significantly associated with lower quality of life.[39 40] The number of co-morbidities increases with increasing age and patients with co-morbidity used healthcare services more often than patients with one health problem.[9 41] Bone density and bone mass decrease with older age, especially in women.[42 43] Decreased bone quality was associated with pain severity in older patients with hand osteoarthritis.[44] All these differences between age categories might influence the course of back pain and should be taken into account when GPs consider their treatment approach. Prognostic research should examine whether these characteristics are predictors for recovery.

A limitation of the present study is that patient inclusion was accomplished either through invitation directly during consultation or those retrospectively identified and approached within 2 weeks after the consultation. This resulted in small baseline differences between these groups in back pain severity and disability. This is probably due to the difference in the number of days between consultation and baseline measurement. Nevertheless, because mean age is similar in both inclusion groups and the percentage of patients retrospectively identified and approached within two weeks after the consultation was the same (84%) in both age categories, comparison between the age groups within the total population is possible. Using both methods may have decreased the risk of recruiting a more selective sample and increased external validity. Another limitation is that, due to the workload of the participating GPs, not all consecutive eligible patients were referred to the study during consultation. However, when recruiting patients after the consultation, all consecutive eligible back pain patients were invited to participate. This resulted in a higher participation rate when patients were invited directly during consultation. Because there was no information available about the patients who refused to participate, it is unknown if this influenced the results.

In summary, the older patients reported more severe disabilities and co-morbidity. However, the clinical relevance of these differences for the course of the back pain episode in these older patients remains a topic for further research.

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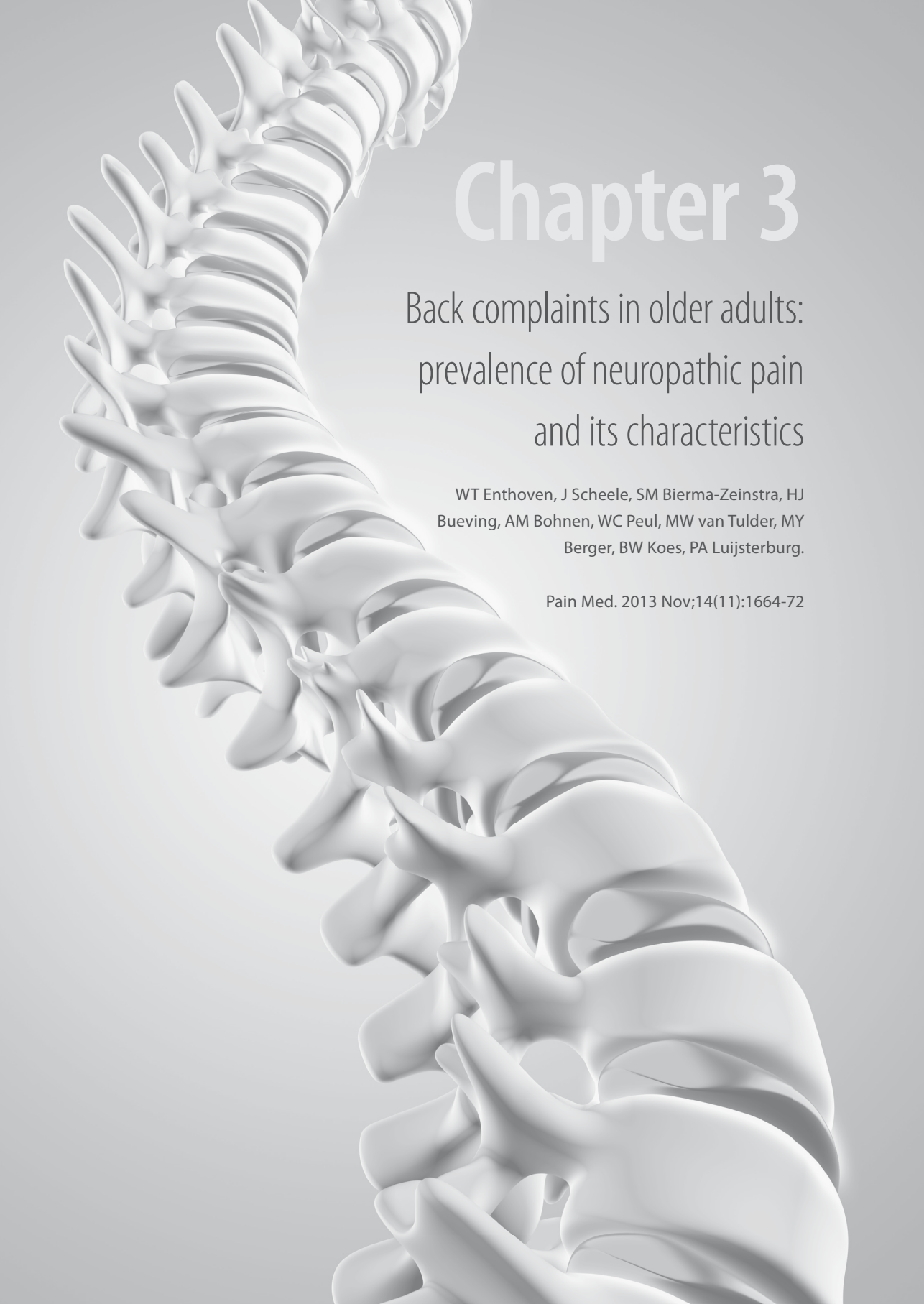

Chapter 3

Back complaints in older adults: prevalence of neuropathic pain and its characteristics

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ABSTRACT

Background

Neuropathic symptoms are reported in 16-55.6% of patients with back pain. Studies were performed in various populations, however, none focused on older adults. The aim of the study was to assess prevalence of neuropathic pain in older adults with back pain.

Methods

Prevalence of neuropathic pain, measured with the Dolour Neuropathique en 4 questions (DN4), was assessed in the BACE study (Netherlands). Patients (>55 years) consulting their general practitioner with a new episode of back complaints were included. Two DN4-versions were used; one based on interview plus physical examination, the other based on interview alone. In the interview plus physical examination version, patients' and complaint characteristics were compared between groups with different scores (0,1,2,3, and ≥4). The DN4 interview-version compared patients with negative and positive scores.

Results

Of the 261 included patients available for analysis were 250 patients (95.8%) with the DN4 interview plus physical examination, and 259 patients (99.2%) with the DN4 interview. *DN4 interview plus physical examination (n=250)*: 5 patients (2%) scored positive (score ≥4). Higher score was associated with pain radiating below the knee ($p<0.001$) and use of paracetamol ($p=0.02$). *DN4 interview (n=259)*: 29 (11.2%) patients scored positive (score ≥3). Positive score was associated with higher body mass index ($p=0.01$), pain radiating below the knee ($p=0.001$) and use of paracetamol ($p=0.002$).

Conclusions

In older adults with back pain presenting with a new episode in primary care prevalence of neuropathic pain is low and seems to be associated with pain radiating below the knee, use of paracetamol and higher body mass index.

INTRODUCTION

Back pain is an important health problem in the community[1-3] with the low back being the most affected area.[4] A recent systematic review estimated the point prevalence of low back pain in the open population to be 11.9%.[3] In older adults, benign or mild back pain seems to be less frequent compared to other age groups, but they experience more episodes with severe or disabling back pain.[5] Pain in older adults is reported to last longer compared to younger patients with back pain.[4] With the aging population it is likely that a greater number of people will suffer from severe back pain in the future. Costs related to back pain are a substantial burden on society.[2 6] As the prevalence of seeking healthcare for back pain increases with age,[2] costs will probably also increase in the coming decades. It is noteworthy that patients with neuropathic pain use more health care compared to patients with nociceptive pain.[7]

Neuropathic pain is defined as pain arising as a direct consequence of a lesion or disease affecting the somatosensory system either at peripheral or central level.[8] In back pain, although the mechanism of neuropathic pain is not fully understood, most likely different mechanisms play a role in the development of neuropathic pain. It is thought that back pain can be a 'mixed' pain consisting of nociceptive and neuropathic components. Neuropathic pain may be caused by lesions of nociceptive sprouts in the degenerated intervertebral discs, by mechanical compression of the nerve root or by action of inflammatory mediators from degenerated intervertebral discs.[9] It is important to identify patients with neuropathic pain and neuropathic components because conventional analgesic treatment may be less effective in this population.[10-12] Thus identification of patients with neuropathic pain may guide the choice of further investigation and/or therapy. Various screening instruments are available to identify neuropathic pain, such as Dolour Neuropathique en 4 questions (DN4),[13] LANSS[14] and painDETECT.[15] These screening instruments have a sensitivity ranging from 66-85% and specificity from 74-90%.[13-18] The DN4 has shown good face validity and interrater reliability in the general population, tested in persons with a mean age of 56 years (SD 17),[13] the validity remained the same whether the patients had neuropathic pain or mixed pain syndromes. The DN4 is also validated in back pain patients aged 22 to 85 years of age.

Neuropathic symptoms are reported in 16-55.6% of patients with low back pain, with and without radiating leg pain.[13 19-24] The range is broad because studies were performed in various populations. However, none of the studies focused on older adults. In this cross-sectional survey we assessed the prevalence of neuropathic pain using the DN4 in older adults who consulted their general practitioner (GP) with a new episode of back complaints. Furthermore we compared two different DN4 versions and evaluated whether differences exist in patients' and back complaint characteristics such as duration of back pain and back pain severity between the groups with and without neuropathic pain.

METHODS

The present study included a subpopulation from the BACE (Back Complaints in the Elders) study in the Netherlands.[25] Patient inclusion in this Dutch BACE study (n=675) took place from March 2009 until September 2011. In BACE, patients aged >55 years were included when they consult a GP with a new episode of back complaints. Back complaints were defined as pain in at least a part or the whole region from the top of the shoulder blades to the first sacral vertebra. If a patient had not visited the GP with the same back complaints in the preceding six months it was considered a new episode. Thus, the sample also included patients with longer durations of back pain who had not visited their GP in the preceding six months for evaluation of this condition. Patients were excluded if they were unable to fill out the questionnaires due to cognitive impairment (e.g. dementia or stroke) or were not able to read and write in Dutch. Patients who were unable to undergo physical examination (e.g. wheelchair-bound patients) were also excluded. For more details see the design article of the BACE study.[25] The subpopulation used in the present study consisted of patients included from January 2011 onwards. From this moment on neuropathic pain was measured in the participating patients during baseline measurement.

The Medical Ethics Committee of Erasmus Medical Center in Rotterdam approved the study protocol.

Measurements

At the entry of this study a baseline questionnaire was completed by the patients and physical examination of the back took place. The questionnaire included socio-demographic characteristics, patients self-reported comorbidity, use of medication, and duration and localization of pain. Severity of pain was measured on an 11-point numerical rating scale (NRS) with 0 as 'no pain' and 10 representing 'worst pain ever'.[26] Disability was measured with the Roland Morris Disability Questionnaire (RDQ).[27] The RDQ scores range from 0 (no disability) to 24 (severe disability). Quality of life was measured with the Short-Form 36 (SF-36), Dutch version.[28] The SF-36 measures eight dimensions: physical function, role-physical function, bodily pain, general health, vitality, social function, role-emotional function and mental health. These eight dimensions can be recoded into two summary scores: a physical component summary score and a mental component summary score. Each dimension and summary score is scored from 0-100 with a higher score representing better health.[29 30] Summary scores were calculated with adapted Z-values, in view of the higher mean age of our study population.[28] Depression was measured with the Center for Epidemiologic Studies Depression Scale (CES-D) (range 0-60). Patients with a higher score are more prone to depression.[31] Pain catastrophizing was measured with the pain catastrophizing scale (PCS) (range 0-52) with a higher score representing a higher risk

for catastrophizing.[32] Back beliefs were investigated with the back beliefs questionnaire (BBQ).[33] Lifestyle factors included smoking and drinking alcohol. Drinking alcohol was measured with the Audit-C.[34 35] Women were defined as possible hazardous drinkers if they scored ≥3 on the scale, men if they scored ≥4. During physical examination, body weight and height were measured and converted to body mass index (BMI).

For this sub-study we included those patients who completed both the DN4 interview plus physical examination. The DN4 consists of a seven-item interview and a three item physical examination with a score range of 0-10. The interview consisted of questions about the pain characteristics (burning, painful cold, electric shocks, tingling, pins and needles sensation, numbness and itchiness), the physical examinations tested sensitivity to touch, pinprick and brush. For a more detailed description of the DN4, see appendix A. In a general population a score of ≥4 indicates neuropathic pain with a sensitivity of 83% and a specificity of 90%.[13] The DN4 is validated in patients with chronic low back pain in the age of 22 to 85 years[36] and linguistically validated in Dutch.[37] The interview (hereafter called the 'DN4 interview') can also be used without the physical examination. In the DN4 interview, the maximum score is 7 and a score of ≥3 indicates neuropathic pain (sensitivity 82% and specificity 86%).[38]

Statistical analysis

Descriptive statistics were used to present patient characteristics in frequencies for all variables with categorical data and to calculate mean and standard deviation (SD) for continuous variables.

The DN4 interview plus physical examination, and the DN4 interview alone, were analyzed separately. For the DN4 interview plus physical examination patients' and complaint characteristics were compared between all groups with different scores (0, 1, 2, 3, and ≥4) with the one-way analysis of variance (ANOVA) for variables with numerical data. Patients with a score of 4 and 5 were analyzed together because of the small number of patients with these scores. There were no patients with a score of 6 or more. Groups were tested for equal variances using Levene's test, and a Kruskal-Wallis test was used if assumptions for normality were not satisfied. Categorical variables were analyzed with the chi-square test linear by linear, in which all groups with different scores were compared. In the DN4 interview analysis, patients' and complaint characteristics were compared between patients with a negative and a positive DN4 score using an independent sample t-test. Levene's test was used to test equal variances; if assumptions for normality were not satisfied a Mann-Whitney U test was performed. Variables with categorical data were analyzed using the chi-square test. If >20% of the cells contained an expected count of <5, the tables were reduced. If the 2x2 table still had an expected count <5, Fisher's exact test was performed. Reported p-values were from 2-sided tests and a $p<0.05$ was defined as statistically significant. All analyses were performed using SPSS software (version 17.0 for Windows, Chicago, IL, USA).

RESULTS

The present study included 261 (38.7%) of the 675 patients from the Dutch BACE study. All patients answered the DN4 questions, but two patients did not answer all the questions in the interview. Nine patients did not have a complete DN4 physical examination. Therefore, 250 patients (95.8%) were available for the DN4 interview plus physical examination analysis, and 259 patients (99.2%) were available for analysis of the DN4 interview.

Table 1. Baseline patient characteristics of the study population.

	All patients (n=261)
Age in years	66.4 ± 7.6
Male, n(%)	103 (39.5)
BMI	27.7 ± 4.7
Low education level, n (%)	106 (40.6)
Smoking, n (%)	43 (16.5)
Hazardous drinking[a], n (%)	122 (46.7)
Severity of back pain[b]	5.0 ± 2.7
Disability[c]	9.8 ± 5.7
Duration of back pain >3 months, n (%)	62 (23.8)
Time in days between consultation with general practitioner and the DN4	29.0 ± 12.8
Pain radiates to below the knee, n (%)	81 (31.0)
Pain location only lumbar, n (%)	188 (72.0)
Use of pain medication for back pain, n (%):	184 (70.5)
Paracetamol, n (%)	100 (38.3)
NSAID, n (%)	97 (37.2)
Opioid, n (%)	22 (8.4)
Benzodiazepine, n (%)	16 (6.1)
Antidepressant or antiepileptic, n (%)	2 (0.8)
Diabetes, n (%)	41 (15.7)
Quality of life physical summary scale[d]	43.7 ± 9.0
Quality of life mental summary scale[d]	49.4 ± 10.2
Depressive symptomatology[e]	9.9 ± 7.8
Pain catastrophizing[f]	14.0 ± 11.0
Attitude and beliefs about back pain[g]	26.4 ± 7.0

All results are presented as mean ±SD unless stated otherwise. [a] Hazardous drinking is measured with Audit-C: range 0-12; ≥3 in woman and ≥4 in men is risk of hazardous drinking; [b] Measured with numerical rating scale; range 0-10; 0 is no pain, 10 is the worst pain imaginable; [c] Measured with the Roland Morris disability questionnaire range 0-24; zero is no disability; [d] Measured with Short Form 36, range 0-100; higher score is higher quality of life; [e] Measured with CED-D, range 0-60; higher score indicates more prone to depression; [f] Measured with pain catastrophizing scale range 0-52; higher score is more risk for catastrophizing; [g] Measured with back beliefs questionnaire range 9-49; higher score is more positive thoughts of recovery

Patients

Table 1 shows the baseline characteristics of the 261 included patients. The mean age of the 261 patients was 66.4 ±7.6 (range 56-87) years. Mean BMI was 27.7 ±4.7. Of these patients, 103 (39.5%) were male, 16.5% (43 patients) smoke, and 122 patients (46.7%) were at risk for hazardous drinking. Chronic back pain (pain lasting more than 3 months) was present in 62 patients (23.8%), and 81 patients (31.0%) had pain radiating below the knee. Mean baseline pain severity measured with the NRS was 5.0 ±2.7. Of all patients, 184 (70.5%) used pain medication. The most frequently used were paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs). Mean time between consulting a GP and DN4 measurement was 29.0 ±12.8 days.

DN4 interview plus physical examination

Table 2 shows a comparison of patients' and complaint characteristics between the different scores of the 250 patients in the DN4 interview plus physical examination analysis. Only 5 patients (2%) scored positive on the DN4 interview plus physical examination (4 patients scored 4; 1 patient scored 5). There was significantly more pain radiation in patients with a higher DN4 score. Patients with a higher DN4 score also used significantly more paracetamol. SF-36 physical summary score tended to be lower in patients with a higher DN4 score but the difference was not significant.

DN4 interview

Table 3 presents data on the comparison between patients with positive and negative scores on the DN4 interview.

In the DN4 interview, 111 patients (42.9%) scored 0 points, 85 patients (32.8%) scored 1 point, and 34 patients (13.1%) scored 2 points. A total of 25 patients (9.7%) scored 3 points, 3 patients (1.2%) scored 4 points and 1 patient (0.4%) scored 5 points. No patients scored higher than 5 (total score range 0-7). Of the 259 patients, 29 (11.2%) had a positive score (≥3 points) on the DN4 interview, which indicated neuropathic pain. Patients having neuropathic pain had a significantly higher BMI compared to patients who did not have neuropathic pain. Patients with neuropathic pain more often had pain radiating below the knee and use paracetamol more frequently. Baseline back pain severity (NRS pain scale) was higher in neuropathic pain patients, but the difference was not significant.

Table 2. Comparison of characteristics between scores of the DN4 interview and physical examination (n=250)

	0 (n=102)	1 (n=82)	2 (n=37)	3 (n=24)	>4 (n=5)	p-value
Age in years	67.0 ± 7.2	67.1 ± 8,5	64.7 ± 7.2	64.8 ± 7.0	62.8 ± 4.4	0.31
Male, n (%)	41 (40.2)	32 (39.0)	18 (48.6)	6 (25.0)	3 (60.0)	0.88
BMI[a]	27.3 ± 4.1	27.4 ± 4.5	28.2 ± 6.0	29.0 ± 4.2	33.2 ± 10.5	0.16
Low education level, n (%)	37 (36.6)	37 (46.3)	15 (40.5)	10 (41.7)	3 (60.0)	0.37
Smoking, n (%)	14 (13.9)	16 (20.0)	7 (18.9)	2 (8.7)	1 (20.0)	0.94
Hazardous drinking[b], n (%)	54 (54.5)	34 (43.6)	17 (45.9)	11 (47.8)	2 (40.0)	0.30
Severity of back pain[c]	4.5 ± 2.7	5.0 ± 2.7	5.5 ± 2.7	5.9 ± 2.2	5.0 ± 3.1	0.15
Disability[d]	8.9 ± 5.6	9.7 ± 5.9	11.1 ± 5.6	11.9 ± 5.1	10.6 ± 5.3	0.10
Duration of back pain >3 months, n (%)	29 (30.9)	14 (19.2)	9 (25.7)	7 (33.3)	1 (20.0)	0.73
Time in days between consultation with general practitioner and the DN4	28.4 ± 13.5	28.2 ± 12.0	28.4 ± 10.5	32.1 ± 16.3	28.0 ± 4.7	0.75
Pain radiates below the knee, n (%)	22 (21.8)	24 (30.0)	15 (40.5)	14 (58.3)	3 (60.0)	**<0.001**
Pain location only lumbar	72 (70.6)	62 (75.6)	28 (75.7)	16 (66.7)	3 (60.0)	0.84
Use of paracetamol, n (%)	35 (34.7)	29 (36.3)	14 (37.8)	17 (70.8)	2 (40.0)	**0.02**
Use of NSAID, n (%)	39 (38.6)	28 (35.0)	17 (45.9)	8 (33.3)	1 (20.0)	0.75
Quality of life physical summary scale[e]	45.2 ± 9.1	43.7 ± 8.7	40.8 ± 8.7	40.9 ± 8.3	42.0 ± 7.8	0.06
Quality of life mental summary scale[e]	50.6 ± 9.9	48.8 ± 10.6	47.7 ± 10.6	48.2 ± 10.4	47.8 ± 9.3	0.54
Depressive symptomatology[f]	8.8 ± 7.9	10.5 ± 7.6	12.3 ± 8.9	9.6 ± 6.6	13.8 ± 8.2	0.15
Pain catastrophizing [g]	13.4 ± 10.7	13.8 ± 11.1	15.4 ± 11.3	15.9 ± 11.7	11.4 ± 12.3	0.48
Attitude and beliefs about back pain[h]	26.8 ± 7.0	26.1 ± 6.7	24.9 ± 7.1	27.0 ± 7.3	22.8 ± 6.5	0.77

All results are presented as mean ±SD unless stated otherwise. Bold values indicate a p-value <0.05.
[a] Analyzed with the Kruskal Wallis test; [b] Hazardous drinking is measured with Audit-C: range 0-12; ≥3 in woman and ≥4 in men is risk of hazardous drinking; [c] Measured with numerical rating scale; range 0-10; 0 is no pain, 10 is the worst pain imaginable; [d] Measured with the Roland Morris disability questionnaire range 0-24; zero is no disability; [e] Measured with Short Form 36, range 0-100; higher score is higher quality of life; [f] Measured with CED-D, range 0-60; higher score indicates more prone to depression; [g] Measured with pain catastrophizing scale range 0-52; higher score is more risk for catastrophizing; [h] Measured with back beliefs questionnaire range 9-49; higher score is more positive thoughts of recovery

DISCUSSION

Prevalence

In older adults with back pain the prevalence of neuropathic pain was 2% using the DN4 interview plus physical examination and was 11.2% using the DN4 interview alone. This is considerably lower than the 16-55.6% reported by others.[13 19-24] There are various possible reasons for this difference. First, most studies were performed in specialist centers (mostly in secondary/tertiary care),[13 19-22 24] whereas the present study was performed in a primary care setting. Beith et al. analyzed primary care patients with back pain who

Table 3. Comparison of patients scoring positive or negative on the DN4 interview

Characteristics	Negative DN4 (n=230, 88.8%)	Positive DN4 (n=29, 11.2%)	Mean difference (95% CI)	p-value
Age in years	66.7 ± 7.7	64.4 ± 6.6	2.3 (-0.6 – 5.2)	0.13
Male, n (%)	93 (40.4)	9 (31.0)		0.33
BMI	27.4 ± 4.5	29.7 ± 5.8	-2.4 (-4.2 – -0.5)	**0.01**
Low education, n (%)	93 (41.0)	13 (44.8)		0.87
Smoking[a]	40 (17.6)	3 (10.7)		0.44
Hazardous drinking[b], n (%)	108 (48.4)	13 (46.4)		0.84
Severity of back pain[c,d]	4.9 ± 2.7	5.7 ± 2.3	-0.9 (-1.9 – 0.17)	0.10
Disability[e]	9.5 ± 5.8	11.7 ± 5.0	-2.1 (-4.4 – 0.1)	0.06
Duration of back pain >3 months n (%)	54 (25.7)	8 (30.8)		0.58
Time in days between consultation with general practitioner and the DN4	28.7 ± 12.5	31.4 ± 15.0	-2.8 (-7.7 – 2.2)	0.28
Pain radiates below the knee, n (%)	63 (27.8)	17 (58.6)		**0.001**
Pain location only lumbar, n (%)	169 (73.5)	19 (65.5)		0.09
Use of paracetamol, n (%)	81 (36.0)	19 (65.5)		**0.002**
Use of NSAID, n (%)	87 (38.7)	9 (31.0)		0.43
Quality of life physical summary scale[f]	44.0 ± 9.1	41.1 ± 8.1	2.9 (-0.6 – 6.4)	0.10
Quality of life mental summary scale[f]	49.5 ± 10.3	48.1 ± 10.1	1.4 (-2.5 – 5.4)	0.48
Depressive symptomatology[g]	9.8 ± 7.9	10.4 ± 7.0	-0.5 (-3.6 – 2.6)	0.73
Pain catastrophizing[h]	13.8 ± 10.9	15.1 ± 11.7	-1.2 (-5.6 – 3.1)	0.57
Attitude and beliefs about back pain[i]	26.3 ± 6.9	26.2 ± 7.2	0.1 (-2.6 – 2.8)	0.94

All results are presented as mean ±SD unless stated otherwise. Bold values indicate a p-value <0.05.
[a] Analyzed using Fisher's exact test; [b] Hazardous drinking is measured with Audit-C: range 0-12; ≥3 in woman and ≥4 in men is risk of hazardous drinking; [c] Analyzed using the Mann-Whitney U test; [d] Measured with numerical rating scale; range 0-10; 0 is no pain, 10 is the worst pain imaginable; [e] Measured with the Roland Morris disability questionnaire range 0-24; zero is no disability; [f] Measured with Short Form 36, range 0-100; higher score is higher quality of life; [g] Measured with CED-D, range 0-60; higher score indicates more prone to depression; [h] Measured with pain catastrophizing scale range 0-52; higher score is more risk for catastrophizing; [i] Measured with back beliefs questionnaire range 9-49; higher score is more positive thoughts of recovery

were referred for physiotherapy, 95% of whom were referred by a GP;[23] they reported a neuropathic pain prevalence of 16% which is more in line with our findings.

The screening tools used to measure neuropathic pain may also explain the different prevalences. Different tools including the DN4, Leeds Assessment of Neuropathic Symptoms and Signs (LANNS),[14] Self-report Leeds Assessment of Neuropathic Symptoms and Signs (S-LANNS)[18] and PainDETECT[15] were used. One study compared S-LANNS and DN4 and obtained a different prevalence for patients with neuropathic pain using these different screening tools.[21] This difference in prevalence might be due to the absence of physical examination in the S-LANSS, resulting in a lower prevalence (33 vs. 42%).

We found a higher prevalence in the DN4 interview group. Physical examination in our study was always performed on the spine. Another research group recently suggested that physical examination as a part of DN4 should also be performed on other painful areas such as the leg.[36] This might also explain the lower prevalence of our patients scoring positive on the DN4 interview plus physical examination. On the other hand, the tests performed in physical examination may not be as sensitive in older adults.

A third difference is the duration of back pain. Most earlier studies included patients if they had suffered back pain for at least 3 months (chronic pain),[13 19 20 22 24] whereas we included all patients with back pain irrespective of the duration. In our population mean duration ±SD of back pain was 8.1 ±31.9 months (median 1.1 month Interquartile range 0.7-3.3 months) (data not shown). In our population, 23.8% of the patients had chronic back complaints. It is possible that the neuropathic component of back pain emerges after a longer period of back pain, which might explain this difference in neuropathic pain prevalence.

Interpretation of findings

Use of paracetamol was more frequent in patients with a positive neuropathic pain score. Torrace et al.[39] reported that patients with neuropathic pain in primary care took stronger painkillers, although they did not report 'over-the-counter' medications these people used. In the present study almost all patients were treated with conventional analgesics rather than with anti-neuropathic drugs; this is in line with the results from a Belgian study.[40] Also, a rat study showed that paracetamol has peripheral antiallodynic and antihyperalgesic effects,[41] mechanism which might contribute to pain relief in patients with neuropathic pain. It is likely that patients with neuropathic pain experience pain relief after taking paracetamol and therefore continue to use them. On the other hand conventional analgesic treatment is also reported to be less effective in neuropathic pain.[10-12] Patients might also use more paracetamol because they did not experience sufficient pain relief.

In the present study, pain radiating below the knee was associated with neuropathic pain, which is in line with other reports[36 38] and with the belief that neuropathic mechanisms play a greater role in leg pain than in non-radiating back pain.[15 24 42]

The physical summary score of the SF-36 tended to be lower in patients with a higher score on the DN4, but the difference was not significant. In the community, neuropathic pain is associated with lower scores on all dimensions of the SF-36 (7, 43). These results were also observed in a study investigating primary care patients.[23] Probably, our study was not sufficiently powered to show significant difference between the groups.

Severity of back pain measured with the NRS tended to be higher in patients with a positive DN4 score, but the difference was not significant. Although some studies reported an association between neuropathic pain and pain severity,[23 38 43-45] only one of

these studies was performed in back pain patients.[23] Another study showed no association between neuropathic pain and back pain severity.[20] It is possible that older adults experience pain differently from younger persons, as demonstrated in back pain.[4 5] Also, our lack of association between pain severity and a positive score on the DN4 might be due to the small number of patients scoring positive on the DN4.

We found no associations between neuropathic pain and age, gender and duration of back pain. Recent literature shows conflicting results concerning these characteristics. Some data are in line with ours,[20 40] whereas others found associations with higher age[19 22 38 44] and gender.[19 22 38 44 45] However, those studies were performed in a general population or in secondary care, while our study was performed in primary care. The studies that found an association with age included a younger group than ours, and their mean age remained under 55 years; in view of the 10-year difference in mean age the effect they found may no longer present at older age (55 years and over). Only Bouhassira et al.[38] reported that neuropathic pain increases with age, peaking at 50-64 years in a general population. It is possible that we found no association with age because our patients were over 55 years of age and the age range of our population was too small.

Some studies reported an association between neuropathic pain and the duration of pain,[38 44] but was not present in a study on patients with back pain.[36] Also, we found no association between neuropathic pain and duration of pain; however, this might be because the studies which found an association were performed in the general population. Also, in the present study, older patients may not precisely recall how long they experienced pain. However, to reduce such recall bias, patients with cognitive problems were excluded.

We also examined depression and disability, because these have also been associated with neuropathic pain.[7 23 46] However, other studies reported no difference in disability and depression between patients with and without neuropathic pain.[21 47] In our patients, although disability tended to be higher in the positive group the difference was not significant and may be due to insufficient power.

Strength and limitations

The present study evaluated neuropathic pain in older adults reporting back pain in general practice. Other studies analyzed neuropathic pain in older adults pooled with patients of all ages. Our study provides additional information about neuropathic pain specific to older adults, which might be important because these patients might experience pain differently.[4 5]

We found a low prevalence of neuropathic pain in older adults with back pain using two versions of the DN4. Due to this low number of patients scoring positive on the DN4, it is difficult to make statements about the differences between patients with and without neuropathic pain. Before we can make any firm statements about the found

associations in this study, similar research should be performed in a larger population of older adults. Statistical power of this study would have increased if all patients of the Dutch BACE cohort had filled in the DN4. However, because we decided to include the DN4 measurement about halfway through the inclusion-period of the BACE-study, less patients could be included. However, because we continued to include consecutive patients for this sub-study it is unlikely that we introduced selection-bias. Furthermore, we analyzed multiple variables in a small population which could have led to findings by chance.

It is thought that neuropathic pain is not just positive or negative, but can be more or less neuropathic.[47-49] This is why we analyzed all scores separately and pooled patients scoring 4 or 5 on the DN4 interview plus physical examination. Still most patients scored low on the DN4. Because specific symptoms were examined in DN4 this does not mean that their pain could not have a neuropathic component, but it makes it less likely.

Conclusions and clinical implications

This study shows a low prevalence of neuropathic pain in older adults with a new episode of back pain (2% on the DN4 interview plus physical examination and 11% on the DN4 interview alone). Neuropathic pain seems to be associated with pain radiating below the knee, increased use of paracetamol and higher BMI. Patients with neuropathic pain could benefit from different treatment options. Although the prevalence is low, it is important that clinicians are aware of the possibility of neuropathic pain in older adults with back pain presenting in general practice.

APPENDIX A

DN4 Questionnaire

Please complete this questionnaire by ticking one answer for each item in the 4 questions below:

INTERVIEW OF THE PATIENT

Question 1: Does the pain have one or more of the following characteristics?

	Yes	No
1 – Burning		
2 – Painful cold		
3 – Electric shocks		

Question 2: Is the pain associated with one or more of the following symptoms in the same area?

	Yes	No
4 – Tingling		
5 – Pins and needles		
6 – Numbness		
7 – Itching		

EXAMINATION OF THE PATIENT

Question 3: Is the pain located in an area where the physical examination may reveal one or more of the following characteristics?

	Yes	No
8 – Hypoesthesia to touch		
9 – Hypoesthesia to prick		

Question 4: In the painful area, can the pain be caused or increased by:

	Yes	No
10 – Brushing		

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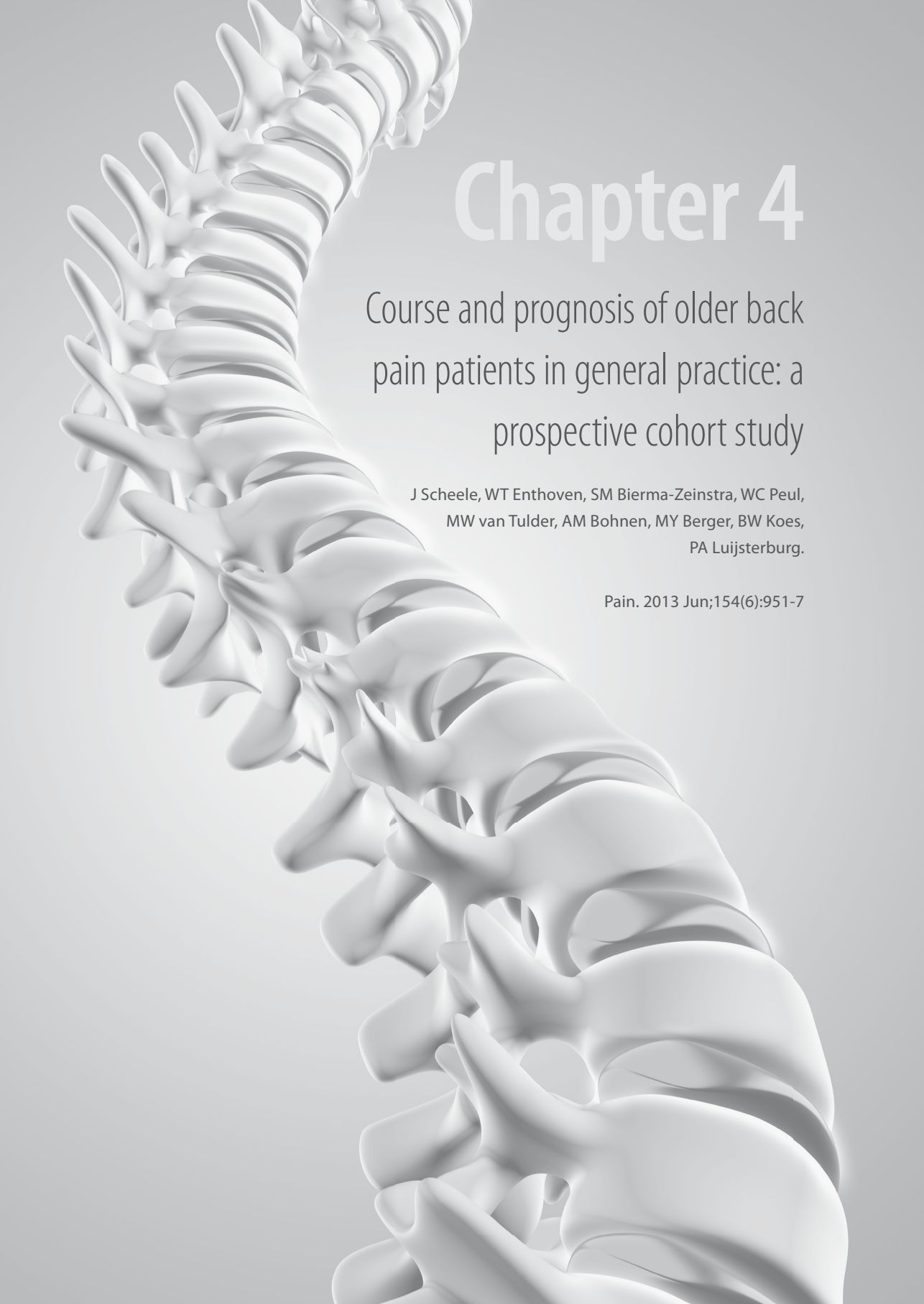

Chapter 4

Course and prognosis of older back pain patients in general practice: a prospective cohort study

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ABSTRACT

Background

The aim of the current study was to determine the course of back pain in older patients and identify prognostic factors for non-recovery at 3 months' follow-up.

Methods

We conducted a prospective cohort study (the BACE study) of patients aged >55 years visiting a general practitioner (GP) with a new episode of back pain in the Netherlands. The course of back pain was described in terms of self-perceived recovery, pain severity, disability, pain medication, and GP visits at 6 weeks' and 3 months' follow-up. Prognostic factors for non-recovery at 3 months' follow-up were derived from the baseline questionnaire and physical examination. Variables with a prognostic value were identified with multivariable logistic regression analysis (method backward), and an area under the receiver operating curve (AUC) was calculated for the prognostic model.

Results

A total of 675 back pain patients (mean age 66.4 (SD 7.6) years) participated in the BACE cohort study. At 6 weeks' follow-up 64% of the patients reported non-recovery from back pain. At 3 months' follow-up 61% still reported non-recovery, but only 26% of these patients had revisited the GP. Longer duration of the back pain, severity of back pain, history of back pain, absence of radiating pain in the leg below the knee, number of comorbidities, patients' expectation of non-recovery, and a longer duration of the timed 'Up and Go' test were significantly associated with non-recovery in a multiple regression model (AUC 0.79).

Conclusion

Longer duration of the back pain, severity of back pain, history of back pain, absence of radiating pain in the leg below the knee, number of comorbidities, patients' expectation of non-recovery, and a longer duration of the timed 'Up and Go' test were significantly associated with non-recovery . This information can help GPs identify older back pain patients at risk for non-recovery.

INTRODUCTION

In clinical guidelines the course of back pain is often described as favorable for most patients, although it is also often emphasized that recurrence of back pain is common.[1-3] Recovery rates vary widely between studies because of different study populations and outcomes.[4 5] The course of back pain may also differ between patients, because individual factors (e.g. age, duration of back pain, or general health) can influence the course.[6 7]

Information on the course and prognostic factors for non-recovery of back pain is helpful for clinicians to better inform their patients. It might also be useful to select (effective) treatment when modifiable prognostic factors for non-recovery are found. Hayden et al. reported that many inconsistent findings exist between reviews on prognostic factors for back pain.[4] Variables consistently reported as prognostic factors for different unfavorable outcomes were older age, poor general health, increased psychological or psychosocial stress, poor relations with colleagues, physically heavy work, worse functional disability at baseline, sciatica, and the presence of work compensation.[4] Although older age is frequently reported as a prognostic factor for non-recovery,[6-8] information on demographic and clinical factors associated with non-recovery during follow-up for older back pain patients is lacking.[9] The course of back pain and factors associated with non-recovery might differ between younger and older adults, because 1) older age is often reported as a prognostic factor for non-recovery, 2) older age is also considered a 'red flag' in patients with back pain, i.e. indicating possible underlying pathology, which could influence the course of back pain,[1 10] and 3) older people have more comorbidities.[11]

Therefore, the aim of the present study is to describe the course of back pain patients aged >55 years recruited in general practice, and to identify prognostic factors for non-recovery of back pain in these patients at 3 months' follow-up.

METHODS

Study design

This is a prospective cohort study including back pain patients aged >55 years consulting their general practitioner (GP) with a new episode of back pain (the BACE study). An episode was defined as 'new' if the patient had not visited a GP during the preceding 6 months for the same back complaint. Back pain was defined as pain in the region from the top of the scapulae to the first sacral vertebra. Exclusion criteria were language problems, cognitive disorders, or being unable to complete the physical examination (e.g. wheelchair-bound patients). Eligible back pain patients were invited to participate

in the BACE study by their GP either directly during consultation, or in writing within 2 weeks after consultation. After inclusion in the BACE study and having signed informed consent, the baseline measurements included a questionnaire and a physical examination of the back. The follow-up period of this study was 3 months, with two follow-up measurements: at 6 weeks and at 3 months. The study protocol was approved by the local Medical Ethics Committee. The BACE study design is described in detail elsewhere.[12]

Measurements

The questionnaires are based on the Multinational Musculoskeletal Inception Cohort Study (MMICS) statement.[13] This is a consensus statement designed to improve the quality of back pain prognosis research by recommending a core set of measurements. The baseline questionnaire and physical examination included measurements of potential prognostic factors for non-recovery. Follow-up questionnaires at 6 weeks and 3 months included the following outcome measurements: 1) self-perceived recovery measured with the Global Perceived Effect (GPE) on a 7-point scale ranging from 'completely recovered' to 'worse than ever',[14] 2) average severity of back pain during the previous week measured on an 11-point numeric rating scale (NRS) ranging from 0 'no pain' to 10 'worst pain ever',[15] 3) disability, measured with the Roland Disability Questionnaire (RDQ), ranging from 0 points (no disabilities) to 24 points,[16] 4) medication used for back pain: a dichotomous variable asking if the patient took pain medication in the 3 months preceding the follow-up questionnaire, and 5) a GP visit in the 3 months preceding the follow-up questionnaire (yes/no).

The potential prognostic factors for non-recovery selected for this study were those factors that had been identified as prognostic factors in the previous literature and/or deemed clinically relevant. These factors were divided into two categories:

(1) History taking: including patients' characteristics and characteristics of the back disorder. The following patient characteristics were included: age, sex, education level, body mass index (BMI), patients' expectation of recovery, quality of life; physical and mental summary scales of the Short Form-36 (SF-36),[17] depressive symptomatology measured with the Center for Epidemiologic Studies Depression Scale (CES-D),[18] kinesiophobia measured with the Fear-Avoidance Beliefs Questionnaire (FABQ) physical activity subscale,[19] pain catastrophizing measured with the Pain Catastrophizing Scale (PCS),[20] comorbidity of musculoskeletal symptoms (neck, shoulder, knee or hip symptoms) and the number of comorbidities measured with the Self-Administered Comorbidity Questionnaire (SCQ).[21] The symptoms measured with the SCQ were heart disease, high blood pressure, lung disease, diabetes, ulcer or stomach disease, kidney disease, liver disease, anemia or other blood disease, cancer, depression, osteoarthritis, rheumatoid arthritis, neck/shoulder complaint, headache, foot problems, and neurological disorder. The following characteristics of the back disorder were included: duration of the back

pain at baseline, severity of back pain at baseline measured on an 11-point NRS, baseline disability measured with the RDQ, history of back pain, the presence of radiating pain in the leg below the knee, and perceived cause of the back pain.

(2) Physical examination: including anteflexion (finger-floor distance in cm), difference in quadriceps strength between the right and left leg, Lasègue test,[22] timed 'Up and Go' test,[23] and bone quality measured using Lunar Achilles InSight (quantitative ultrasound measurement of the heel).[24] Low bone quality is defined as a score of >2.5 standard deviations (SD) lower than the population mean. Information regarding red flags (indicators for possible underlying pathology) were also collected in the BACE study. However, the prognostic value of these factors was not the subject of this study. The prevalence of these factors and their diagnostic value will be described elsewhere.

Statistical analysis

Descriptive analysis was used to report the characteristics of the participants and the course of back pain over the 3-month follow-up period.

To identify prognostic factors, an unfavorable outcome was defined as non-recovery, i.e. a score a score of 'somewhat improved', 'stayed the same', 'somewhat worsened', 'strongly worsened' or 'worse than ever' on the GPE scale. Recovery was defined as a score of 'completely recovered' or 'strongly improved'. Imputation of missing data of the baseline prognostic variables was carried out by multiple imputation, creating five imputed databases.[25] Bivariate logistic regression analysis was performed to gain insight into the association between the baseline variables and outcome. A multivariate logistic regression analysis (method backward, entry $P < 0.05$, removal $P > 0.10$) was first performed with the history-taking variables on all five imputed databases. If a variable was selected in at least three of the five imputed databases in the multivariate analysis, it was included in the final model (method enter). To determine the discriminative ability of the model, the area under the receiver operating curve (AUC) was calculated. An AUC of 0.5–0.7 is considered as moderate discrimination, and an AUC ofP0.7 as good. After selection of these variables, the same analysis of the multivariate (backwards) regression analysis was performed with the variables of the physical examination added to the history-taking model in order to examine the additional value of the physical examination. Sensitivity analysis was performed for the method of patient recruitment in the study.

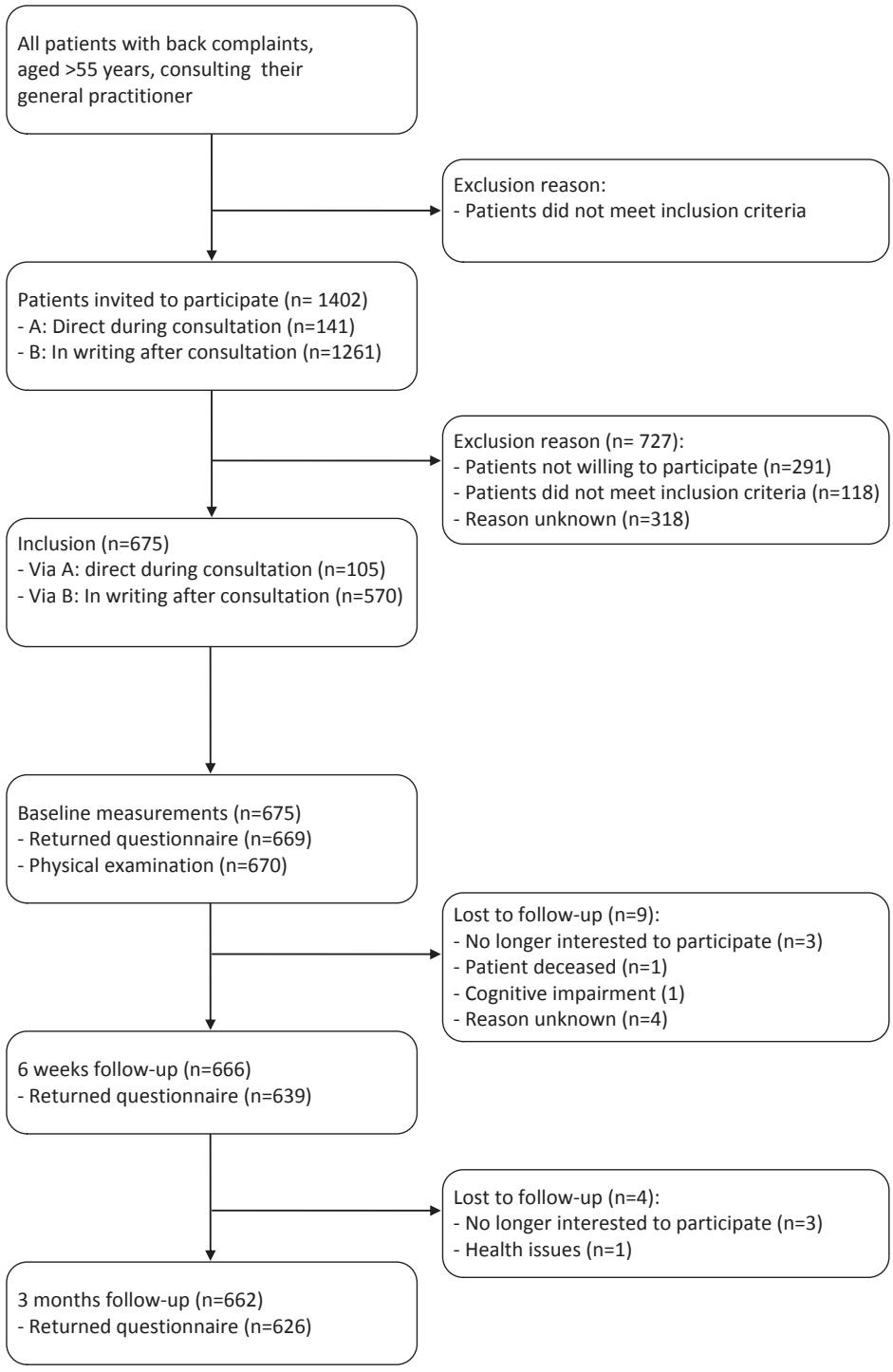

Figure 1. Flow chart of patient recruitment and follow-up

Table 1. Baseline characteristics of the study population.

	Study population n=675
Number of days between consultation and baseline physical examination: median (IQR)	23 (16-31)
History taking	
Age in years: mean ± SD	66.4 ± 7.6
Male: n (%)	274 (41)
body mass index: mean ± SD	27.5 ± 4.7
Education level low: n (%)	279 (41)
Marital status married: n (%)	479 (71)
Employed (paid job): n (%)	177 (26)
Patients' expectation to recover of back pain: n(%)	291 (43)
Quality of life: SF-36 Physical summery scale: mean ± SD	43.2 ± 8.9
Quality of life: SF-36 Mental summery scale: mean ± SD	49.6 ± 10.3
Depressive symptomatology (CES-D): mean ± SD	10.0 ± 7.7
Kinesiophobia (FABQ): mean ± SD	13.4 ± 5.8
Pain catastrophizing (PCS): mean ± SD	14.1 ± 10.6
Co-morbidity musculoskeletal complaints: n (%)	519 (77)
Co-morbidity (number of other complaints): mean ± SD	2.3 ± 1.9
Duration of back pain in days: median (IQR)	35 (20-100)
Duration of back pain > 3 months: n (%)	156 (23)
Severity of back pain (NRS): mean ± SD	5.2 ± 2.7
Pain radiating in the leg below the knee: n (%)	205 (30)
Disability: (RDQ): mean ± SD	9.8 ± 5.8
History of back pain: n (%)	579 (86)
Perceived cause: accident or trauma: n (%)	28 (4)
Physical examination	
Finger-floor distance (in cm): mean ± SD	10.9 ± 11.9
Quadriceps strength difference: n (%)	78 (12)
Positive test of Lasègue: n (%)	100 (15)
Timed 'Up and Go' test (in sec): mean ± SD	11.1 ± 3.9
Low bone quality: n (%)	77 (11)

IQR: interquartile range (presented as 25%-75% IQR), SD: standard deviations, SF-36: Short Form-36 (range 0 'low quality of life' -100 points), CES-D: Center for Epidemiologic Studies Depression Scale (range 0 'no depressive symptomatology ' – 60 points), FABQ: Fear-Avoidance Beliefs Questionnaire (physical act. subscale) (range 0 'no fear and avoidance beliefs'-28 points), PCS: Pain Catastrophizing Scale (range 0 no pain catastrophizing -52 points), NRS: numeric rating scale (range 0 'no pain'-10 'worst pain ever'), RDQ: Roland disability questionnaire (range 0 no disabilities – 24 points).

RESULTS

Population characteristics

The flowchart of the study is presented in figure 1. A total of 675 back pain patients participated in the study. During follow-up, 639 (95%) patients returned the 6-week follow-up questionnaire and 626 (93%) patients returned the 3-month follow-up questionnaire. The baseline characteristics of the study population are presented in table 1. The mean age of the patients was 66.4 years (SD 7.6; range 56–91 years). Forty-one percent of the patients were male. Of all patients, 41% had a low level education, 26% had a paid job and 71% were married. The median duration of the back pain at baseline was 35 days (IQR 20–100 days); 23% of the patients reported back pain lasting ≥3 months. Thirty percent of the patients had pain radiating in the leg below the knee.

Course of back pain

The baseline assessment and outcomes at 6 weeks' and 3 months' follow-up are presented in table 2. At baseline, the mean back pain severity was 5.2 (SD 2.7); at 6 weeks this had decreased to a mean of 3.7 (SD 2.8); and at 3 months' follow-up to a mean of 3.6 (SD 2.8). The average disability score, measured with the RDQ, was 9.8 (SD 5.8) at baseline and was 7.8 (SD 6.2) at 3 months' follow-up. At 6 weeks' and at 3 months' follow-up, non-recovery was reported by 409 patients (64%) and 380 patients (61%) respectively. In total 39% of the back pain patients reported use of pain medication for their back pain in the 3 months after baseline measurement, whereas only 26% of the patients reported that they had revisited their GP in these 3 months.

Table 2. Outcomes at 6 weeks and 3 months follow-up of older back pain patients in general practice.

	Baseline (n=675) n(%)	**6 weeks follow-up (n=639) n(%)**	**3 months follow-up (n=626) n(%)**
Poor recovery (GPE)[a]	-	409 (64)	380 (61)
Severity of back pain (NRS)	5.2 ± 2.7	3.7 ± 2.8	3.6 ± 2.8
Disability (RDQ); mean ±SD	9.8 ± 5.8	-	7.8 ± 6.2
Taking pain medication for back pain	483 (72)	-	246 (39)
Re-visiting GP within 3 months	-	-	161 (26)

GPE: Global Perceived Effect, NRS: numeric rating scale (range 0 'no pain'-10 'worst pain ever'), SD: standard deviations, RDQ: Roland disability questionnaire (range 0 no disabilities – 24 points)

[a] GPE 7-point Likert scale, dichotomized in 1,2: recovered, 3-7: poor recovery,

Table 3. Pooled bivariate association between baseline characteristics and poor recovery at 3-months follow-up (n=619).

	Poor recovery	
	OR (95% CI)	**p value**
History taking		
Age	1.0 (1.0-1.1)	0.02
Male sex	0.6 (0.4-0.8)	<0.01
Low education	1.7 (1.2-2.4)	<0.01
Body mass index	1.1 (1.0-1.1)	<0.01
Patients' expectation to recover	0.3 (0.2-0.4)	<0.01
Quality of life: SF-36 Physical summery scale	0.9 (0.9-1.0)	<0.01
Quality of life: SF-36 Mental summery scale	1.0 (1.0-1.0)	0.06
Depressive symptomatology (CES-D)	1.1 (1.0-1.1)	<0.01
Kinesiophobia (FABQ, physical act. subscale)	1.1 (1.0-1.1)	<0.01
Pain catastrophizing (PCS)	1.0 (1.0-1.0)	<0.01
Co-morbidity musculoskeletal complaints	2.6 (1.8-3.9)	<0.01
Co-morbidity (number of other complaints)	1.4 (1.3-1.5)	<0.01
Duration of the back pain:		
0-6 weeks	Reference cat.	
6-12 weeks	1.7 (1.1-2.6)	0.02
>3 months	5.5 (3.4-9.1)	<0.01
Severity of back pain (NRS)	1.2 (1.2-1.3)	<0.01
Disability (RDQ)	1.1 (1.1-1.1)	<0.01
History of back pain (yes)	1.8 (1.1-2.9)	0.02
Radiating pain in the leg below the knee	1.2 (0.8-1.7)	0.34
Perceived cause: accident or trauma	1.4 (0.6-3.5)	0.43
Physical examination		
Finger-floor distance (in cm)	1.0 (1.0-1.0)	0.42
Quadriceps strength difference	1.8 (1.1-3.1)	0.03
Positive test of Lasègue	1.6 (1.0-2.6)	0.05
Timed 'Up and Go' test (in sec)	1.1 (1.1-1.2)	<0.01
Low bone quality	1.1 (0.7-1.9)	0.64

SF-36: Short Form-36 (range 0 'low quality of life' -100 points), CES-D: Center for Epidemiologic Studies Depression Scale (range 0 'no depressive symptomatology' – 60 points), FABQ: Fear-Avoidance Beliefs Questionnaire (physical act. subscale) (range 0 'no fear and avoidance beliefs'-28 points), PCS: Pain Catastrophizing Scale (range 0 no pain catastrophizing -52 points), NRS: numeric rating scale (range 0 'no pain'-10 'worst pain ever'), RDQ: Roland disability questionnaire (range 0 no disabilities – 24 points).

Prognostic factors for poor recovery

Missing values of the baseline prognostic variables ranged from 0% to 12%. The two variables that missed more than 5% were item rheumatoid arthritis of the SCQ (5.3%)

and 'duration of the back pain' (12% missing). However, for statistical analysis, imputation of missing data was carried out by multiple imputation. Table 3 shows the pooled bivariate associations between baseline characteristics and non-recovery at 3 months' follow-up. The characteristics which were associated with non-recovery in the bivariate regression analysis were older age, male sex, low education, patients' expectation of non-recovery, low quality of life, physical and mental summary score, depressive symptoms, kinesiophobia, pain catastrophizing, the number of comorbidities and musculoskeletal comorbidities, longer duration of the back pain, higher back pain severity, more disabilities, history of back pain, difference in quadriceps strength, a positive test of Lasègue and longer completing duration of the timed 'Up and Go' test.

Table 4. Multivariable association between baseline characteristics and poor recovery at 3 months follow-up (n=619).

	Poor recovery		
	Pooled OR (95% CI)	**p value**	**AUC**
History taking			0.78
Patients' expectation to recover	0.4 (0.3-0.6)	<0.01	
Quality of life: SF-36 Physical summery scale	1.0 (0.9-1.0)	0.03	
Co-morbidity (number of other complaints)	1.2 (1.1-1.4)	<0.01	
Duration of the back pain:			
0-6 weeks	ref. category		
6-12 weeks	1.9 (1.2-3.1)	0.01	
>3 months	4.4 (2.5-7.7)	<0.01	
Severity of back pain (NRS)	1.2 (1.1-1.3)	<0.01	
History of back pain (yes)	1.7 (1.0-3.0)	0.06	
Radiating pain in the leg below the knee	0.6 (0.4-1.0)	0.05	
History taking and physical examination			0.79
Patients' expectation to recover	0.4 (0.3-0.6)	<0.01	
Co-morbidity (number of other complaints)	1.2 (1.1-1.3)	<0.01	
Duration of the back pain:			
0-6 weeks	ref. category		
6-12 weeks	1.8 (1.1-3.0)	0.02	
>3 months	4.3 (2.5-7.5)	<0.01	
Severity of back pain (NRS)	1.2 (1.1-1.3)	<0.01	
History of back pain (yes)	1.8 (1.0-3.2)	0.04	
Radiating pain in the leg below the knee	0.7 (0.4-1.0)	0.06	
Timed 'Up and Go' test (in sec)	1.1 (1.0-1.2)	0.01	

SF-36: Short Form-36 (range 0 'low quality of life' -100 points), NRS: numeric rating scale (range 0 'no pain'-10 'worst pain ever').

Table 4 shows the pooled multivariate associations between baseline characteristics and non-recovery. The history-taking model was calculated with all variables of the categories patients' characteristics and characteristics of the back disorder. The variables remaining in the final history-taking model were patients' expectations of non-recovery, low quality of life, physical summary score of the SF-36, the number of comorbidities, longer duration of back pain (6–12 weeks or >3 months), higher severity of back pain, history of back pain, and absence of radiating pain in the leg below the knee. This model had a discriminative ability of AUC of 0.78.

When the variables of the physical examination were added to this model, the AUC remained quite similar (0.79) and the variables associated with non-recovery were patients' expectation to recover [odds ratio (OR) 0.4; 95% confidence interval (CI): 0.3–0.6], number of comorbidities (OR 1.2; 95% CI: 1.1–1.4), duration of the back pain 6–12 weeks (OR 1.8; 95% CI: 1.1–3.0), duration of the back pain >3 months (OR 4.3; 95% CI: 2.5–7.5) (0–6 weeks as reference category), severity of back pain (OR 1.2; 95% CI: 1.1–1.3), history of back pain (OR 1.8; 95% CI: 1.0–3.2), radiating pain in the leg below the knee (OR 0.7; 95% CI: 0.4–1.0), and duration of the timed 'Up and Go' test (OR 1.1; 95% CI: 1.0–1.2).

We performed an exploratory sensitivity analysis on the method of patient recruitment. We divided the patient population in two groups: the patients who were invited to participate direct during consultation and the patients who were invited in writing. Multiple regression analysis (method enter) for the last model (the history-taking and physical examination model) was performed for both groups. The magnitude of the associations did not change.

DISCUSSION

This study presents the 3-month course of back pain in older patients visiting their GP and identifies factors associated with non-recovery at 3 months' follow-up. The mean age of the population was 66.4 (SD 7.6) years, range 56–91 years. Pain severity of this BACE population decreased from a mean of 5.2 (SD 2.7) at baseline to 3.6 (SD 2.8) at 3 months' follow-up. At 3 months' follow-up 61% of the back pain patients reported non-recovery. Using a multiple backwards regression model, baseline variables associated with non-recovery at 3 months' follow-up were longer duration of the back pain, severity of back pain, history of back pain, absence of radiating pain in the leg below the knee, number of comorbidities, patients' expectation of non-recovery, and a longer duration of the timed 'Up and Go' test (AUC 0.79).

When these results were compared with the review by Pengel, which described the course of back pain in the total adult population, some similarities and differences were found. In their review, Pengel et al. reported that the level of pain decreased rapidly in

the first month and continued to decrease, but more slowly, until 3 months' follow-up.[7] A similar pattern was found in the present study, i.e. pain severity mainly decreased during the first 6 weeks and then only slightly between 6 weeks and 3 months. The studies reviewed by Pengel et al. reported a pain reduction of 12–84% from baseline to 1-month follow-up.[7] In the present study there was a 15% decrease in pain during the first 6 weeks, which is less than the pain reduction reported by most of the studies described in the review. Pengel et al. only reviewed those studies that included patients with back pain lasting less than 3 weeks.[7] Acute back pain patients have a more favorable prognosis than patients with pain of longer duration.[6] However, possible variation in the course of back pain may also be attributed to the fact that our study population consisted of patients aged >55 years, whereas the included study populations of the review were 18 years and over.

To our knowledge, this is the first study that examined prognostic factors for non-recovery of older back pain patients. Most of the variables which were described in the literature to be prognostic factors for non-recovery were also bivariately associated with non-recovery at 3 months in this study (the work-related variables were not relevant for our study population).[4 8] Although age is often reported to be a prognostic factor, and older age was associated with non-recovery in the bivariate regression analysis, it was not a predictor in our multiple regression model. In patients aged >55 years, age might lose its predictive power. Furthermore, the presence of radiating pain in the leg below the knee was not statistically significant associated with non-recovery in the bivariate regression analysis. But in the multiple regression analysis the absence of radiating pain in the leg below the knee was associated with non-recovery. The difference between binary and multiple logistic analysis could be the result of the influence of other variables included in the model. Factors reported as prognostic factors in the literature, but not significantly associated with the outcome in our population, were perceived causes of back pain accident/trauma, and finger–floor distance. Low bone quality was included in the analysis because we hypothesized that this variable could be clinically relevant; however, it was not associated with non-recovery at 3 months' follow-up in our study population. Furthermore the AUC of the multiple regression model remained quite similar when the variables of the physical examination were added to the history-taking multiple regression model. This indicates that the additional value of the physical examination with regard to the discriminative value of the model was small.

A limitation of the study is the missing data in some baseline prognostic variables, but imputation is a valid method to address this issue. The summary scores of questionnaires (e.g. the FABQ and CES-D) and the total number of comorbidities had the highest percentage of missing values (3.0–16.4%), because this value was already missing when one of the items of these questionnaires had not been completed. Therefore, we imputed the separate items of the questionnaire (percentage missing 1.0–5.3%) instead

of the summary scores, in order to obtain most of the patients' information. Besides these summary scores, the only variables with a missing percentage of >5% were 'item rheumatoid arthritis of the SCQ' (5.3%) and 'duration of the back pain (11.9% missing). A second limitation is that patients were either included directly during the GP consultation, or in writing within 2 weeks after the consultation. The time between the consultation and baseline measurement was longer in the group of patients that were invited in writing. Therefore we performed a sensitivity analysis including these latter patients, but no large differences in associations were found.

This present study identified prognostic factors which were associated with non-recovery at 3 months' follow-up in older back pain patients. Validation in another group of older back pain patients is the next step before these results can be implemented in GP practice. Validation is possible in other studies of the BACE consortium; this is a collaboration between different research groups which perform cohort studies with the same methods and design as used in the present study.

In summary, 61% of these older back pain patients reported non-recovery at 3 months' follow-up. Baseline characteristics associated with non-recovery have been identified. This information could serve as a guideline for GPs to better inform back pain patients about their prognosis. However, additional studies are needed to validate our results before implementation in GP practice is possible.

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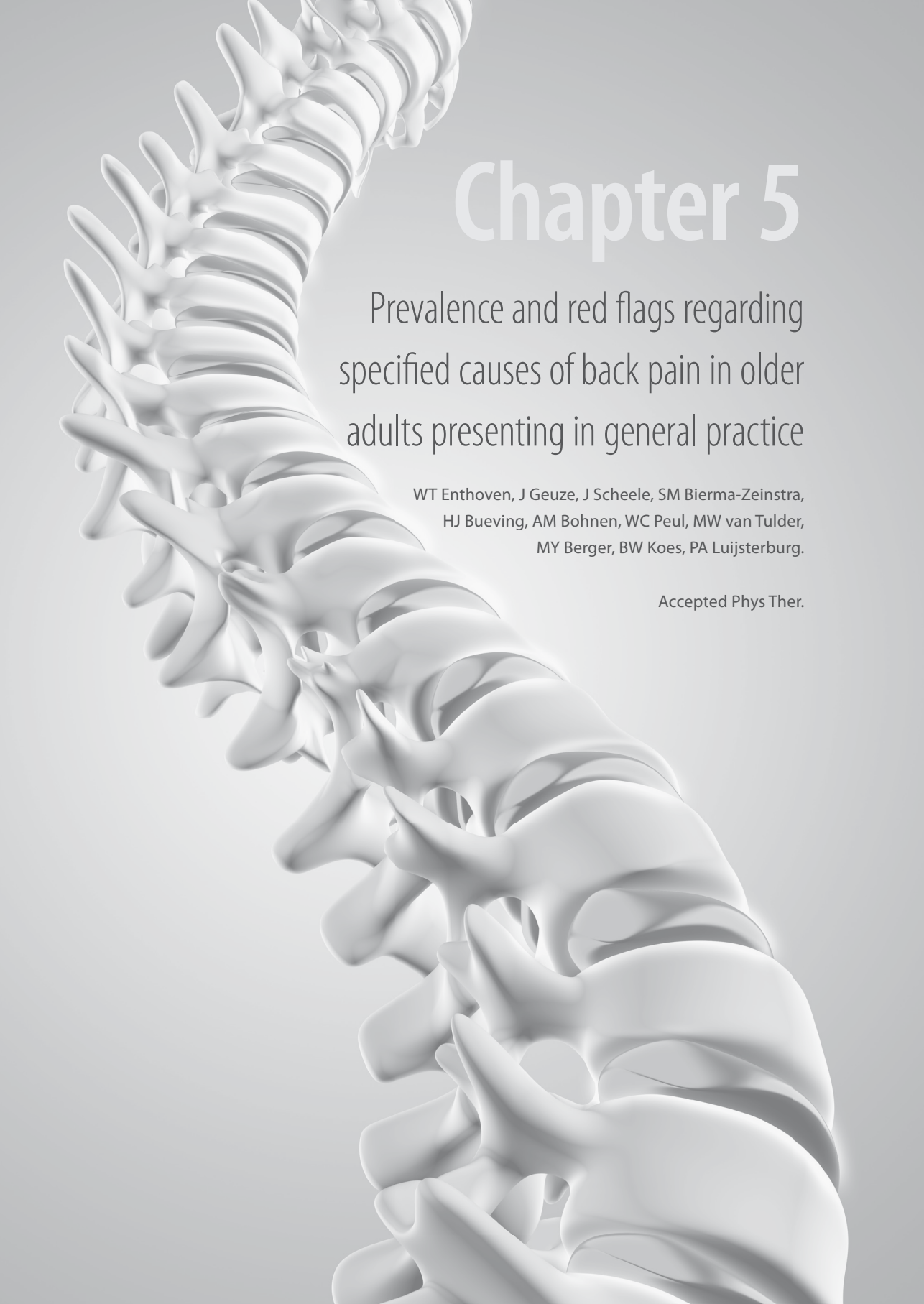

Chapter 5

Prevalence and red flags regarding specified causes of back pain in older adults presenting in general practice

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ABSTRACT

Background

In a small proportion of patients experiencing unspecified back pain, a specified underlying pathology is present. The purposes of this study were: (1) to identify the prevalence of physician-specified causes of back pain and (2) to assess associations between 'red flags' and vertebral fractures, as diagnosed by the patients' general practitioner (GP), in older adults with back pain.

Methods

The Back Complaints in the Elders (BACE) study is a prospective cohort study. Patients (aged >55 years) with back pain were included when consulting their GP. A questionnaire was administered and a physical examination and heel bone densitometry were performed, and the results determined back pain and patient characteristics, including red flags. Participants received a radiograph, and reports were send to their GP. The final diagnoses established at 1 year were collected from the GP's patient registry.

Results

Of the 669 participants included, 6% were diagnosed with a serious underlying pathology during the 1-year follow-up. Most of these participants (n=33, 5%) were diagnosed with a vertebral fracture. Multivariable regression analysis showed that age of ≥75 years, trauma, osteoporosis, a back pain intensity score of ≥7, and thoracic pain were associated with a higher chance of getting the diagnosis of a vertebral fracture. Of these variables, trauma showed the highest positive predictive value for vertebral fracture of 0.25 (95% confidence interval = 0.09, 0.41) and a positive likelihood ratio of 6.2 (95% confidence interval = 2.8, 13.5). A diagnostic prediction model including the 5 red flags did not increase these values. Low prevalence of vertebral fractures could have led to findings by chance.

Conclusions

In these older adults with back pain presenting in general practice, 6% were diagnosed with serious pathology, mainly a vertebral fracture (5%). Four red flags were associated with the presence of vertebral fracture.

INTRODUCTION

Most patients with back pain experience unspecified back pain, although in a minority of the cases, a specified underlying pathology is present.[1-3] Of these specified causes, vertebral fractures, malignancies, infection, cauda equina syndrome, and ankylosing spondylitis are considered serious pathologies and are estimated to account for 1% to 5% of low back pain in primary care.[4 5] Vertebral fractures are the most common underlying serious pathology in patients with back pain.[2] These fractures particularly are more common in older patients.[1] In patients with vertebral fractures, disability is more common than in patients with unspecified back pain.[6] Identifying patients with vertebral fractures is necessary because vertebral fractures can also be an indicator for osteoporosis.[7] In turn, treatment of osteoporosis can prevent future vertebral fractures.[8 9]

To identify specified causes of back pain, most clinical guidelines recommend the use of 'red flags'.[10 11] These alarming symptoms, derived from history taking or physical examination, or both, are suggested to have an association with serious pathology as a cause of back pain. The prevalence of serious pathology as a cause of back pain rises with age, and red flags, consequently, may be more important in patients aged >55 years.[12] Guidelines differ in their recommendations regarding which red flags should be used and what the consequence should be when red flags are present. For example, the Dutch guideline for general practitioners (GPs) makes no statement about the direct consequences if red flags are present, and further diagnostic actions are at the discretion of the patient's GP.[13] The guideline of the American Pain Society advises diagnostic imaging and testing if, based on the presence of red flags, a serious underlying pathology is suspected.[4] A recent systematic review showed that only a limited number of red flags are of diagnostic value. The variables older age, corticosteroid use, and significant trauma are red flags for a vertebral fracture.[14 15] Most individual red flags show poor diagnostic accuracy. There are indications that predictive performance can be improved when combinations of red flags are used. A first step in combining red flags was a diagnostic model for detecting vertebral fractures in primary care, described by Henschke et al.[2] However, this diagnostic model has not yet been evaluated in other populations.

The aims of this study were: 1) to identify the prevalence of physicianspecified causes (eg, vertebral fractures) of back pain, as identified by the patients' GP, in older adults with back pain and 2) to assess the associations between red flags and vertebral fracture in a subgroup of patients diagnosed with vertebral fracture by their GP.

METHODS

Data of the Back Complaints in the Elders (BACE) study, a prospective observational cohort in the Netherlands, was used for this study. Patient inclusion (n=675) took place between March 2009 and September 2011 in a representative sample of 49 general practices in and around Rotterdam. Patients aged >55 years were included when they consulted a GP with a new episode of back pain. *Back pain* was defined as pain in at least a part or the whole region from the top of the shoulder blades to the first sacral vertebra, with or without pain radiation to the leg. If a patient had not visited a GP with the same back pain in the preceding 6 months, this was considered a new episode. Patients were invited to join the study by their GP during the consultation or in writing within 2 weeks after the consultation. Patients were excluded if they were unable to fill out the questionnaires due to cognitive impairment, were not able to read and write in Dutch, or were unable to undergo physical examination (eg, patients using wheelchairs). Details of the BACE study design are described elsewhere.[16]

Data collection

After inclusion in the BACE study and providing written informed consent, baseline measures included a questionnaire, a structured physical examination of the back, a radiograph of the back, and heel bone densitometry. The questionnaire asked about participant characteristics, features of the back pain, and the presence of red flags. Red flags for vertebral fractures were assessed in a questionnaire during the physical examination and were retrieved from the GP's patient registry. The red flags for vertebral fractures were age, sex, trauma, sudden decrease in height, acute onset of pain, osteoporosis, and prolonged corticosteroid use. Red flags were chosen based on those reported in clinical guidelines.[4 11 13 17 18] Corticosteroid use in the year before consulting the GP with back complaints was retrieved from the GP's patient registry because this red flag was not included in the questionnaire. Other determinants that were considered important for diagnosing vertebral fractures were percussion tenderness of the spine,[19] disability, back pain intensity score, osteoarthritis in the hip or knee, and thoracic pain. These variables also were assessed in the questionnaire or during the physical examination.

A radiograph of the lumbar spine was performed. If participants had back pain in the region of the thoracic spine, a thoracic radiograph also was performed. The radiographic findings reported by the radiologist were sent only to the GPs, who could use this information in their final diagnoses. Diagnoses were established by the GPs as they do in regular daily practice using the clinical guidelines for GPs regarding back pain.[13 20]

The final diagnosis regarding the back pain was determined at 1-year follow-up from the GP's patient registry. For each patient included in the cohort, the corresponding diagnosis was retrieved via the associated *International Classification of Primary Care* (ICPC)

code (L03–unspecified low back pain without radiating pain, L86–unspecified low back pain with radiating pain, L76–fracture of the musculoskeletal system, L71–malignancy of the musculoskeletal system, L84–osteoarthritis and spondylosis) and by searching in the free-text field. All GPs checked the collected diagnoses of their participating patients. The final diagnoses were mostly manifest shortly after consulting the GP; however, the 1-year follow-up was decided on for the present study to ensure that all diagnoses would be evident at that time.

Diagnoses collected were categorized as unspecified back pain and specified back pain. Of the specified back pain diagnoses, vertebral fracture, spinal malignancy, ankylosing spondylitis, vertebral infection, and cauda equina syndrome were considered serious pathologies.

Participants' perceived severity of back pain averaged over the previous week was measured on an 11-point numeric rating scale (NRS),[21] with 0 representing 'no pain' and 10 representing 'worst pain ever.' Severe pain was defined as an NRS pain score of ≥7, as it is shown to be a discriminative cutoff value of severe pain in patients with back pain.[22] Disability was measured with the Roland-Morris Disability Questionnaire (RDQ).[23] The RDQ scores range from 0 to 24, and a score of ≥17 was defined as severe disability. Quality of life was measured with the 36-Item Short-Form Health Survey (SF-36), Dutch version.[24] The SF-36 measures 8 dimensions: physical function, role–physical function, bodily pain, general health, vitality, social function, role– emotional function, and mental health. These 8 dimensions can be recoded into 2 summary scores: a physical component summary score and a mental component summary score. Each dimension and summary score is scored from 0 to 100, with a higher score representing better health.[25 26] Summary scores were calculated with adapted *z*-score values, in view of the higher mean age of our study population.[24]

Depression was measured with the Center for Epidemiologic Studies Depression Scale (CES-D) (range: 0–60 points). Patients with a higher score are more prone to depression.[27] Pain catastrophizing was measured with the Pain Catastrophizing Scale (PCS) (range: 0–52 points), with a higher score representing a higher risk for catastrophizing.[28] Back beliefs were investigated with the Back Beliefs Questionnaire (BBQ) (range: 9–49 points), with a higher score representing more positive thoughts on recovery.[29] Lifestyle factors included smoking (yes/no) and drinking alcohol. Alcohol consumption was measured with the Alcohol Use Disorders Identification Test (AUDITC).[30 31] Women were defined as possible hazardous drinkers if they scored ≥3 on the scale, and men were considered possible hazardous drinkers if they scored ≥4. During the physical examination, body weight and height were measured and converted to body mass index (BMI). Low education level was present if the participant had no education or if the highest level of education was primary school or lower vocational education. Trauma, sudden decrease in height, acute onset of pain, and osteoarthritis in the hip or knee were self-reported. Corticosteroid use was de-

fined as oral or inhalation corticosteroid use for more than 90 days. Percussion tenderness of the spine was assessed in the physical examination. Heel bone densitometry was performed using Achilles quantitative ultrasound assessment as a proxy for identification of osteoporosis. In every participant available for the physical examination, both heel bones were measured, a T-score of ≤2.5 on at least one side was considered as osteoporotic.[32]

Data analysis

Descriptive statistics were used to present prevalence of back pain, participant characteristics, back complaint characteristics, psychological factors, and red flags, using frequencies for categorical data and mean and standard deviation for continuous variables. Analyses were performed using complete cases. To assess the associations between red flags and vertebral fractures, red flags and other determinants that were considered important for diagnosing vertebral fractures were separately included in a univariable logistic regression analysis, with diagnosis at 1-year follow-up as outcome. Variables scoring a *P* value of <.05 were examined for correlation using the Pearson test; if variables were correlated (*r*>.6), only one variable (after consensus) was entered in the multivariable logistic regression analysis (backward Wald method, entry .05, removal .10). The multivariable regression analysis was used to find the best fitted model for vertebral fractures in our study population.

For all red flags, the sensitivity, specificity, positive and negative predictive values, and positive and negative likelihood ratios were calculated to establish diagnostic accuracy. Reported *P* values were from 2-sided tests, and a *P* value of <.05 was defined as statistically significant. All analyses were performed using SPSS software (version 20 for Windows, SPSS Inc, Chicago, Illinois).

RESULTS

Participant Characteristics

Of the 1,402 invited patients, 675 were included in the BACE study; 118 patients did not meet the inclusion criteria, 291 patients were not willing to participate, and 318 patients did not respond to the invitation. Six patients (0.9%) were excluded from the analyses because they moved to another city during the 1-year follow-up and, due to a change of GP practice, the diagnosis could not be retrieved.

Table 1 presents the baseline characteristics of the 669 included participants. The age of the included participants ranged from 55 to 91 years (X=66, SD=7.7); 40% of the participants (n=269) were male; mean severity of back pain was 5 (SD=2.7); and 87 participants (13%) reported that they experienced a first episode of back pain. Of all 669 participants, 95% underwent a radiograph of the back.

Table 1. Baseline characteristics of the 669 included patients aged >55 years.

	Patients with diagnosis (n=669)
Patient characteristics	
Age in years, mean (SD)	66 (7.7)
Male	269 (40)
Body mass index, mean (SD)	27 (4.7)
Low education level	278 (42)
Smoking	120 (18)
Hazardous drinking[a]	329 (49)
Back pain characteristics	
Severity of back pain[b], mean (SD)	5 (2.7)
First episode of back pain	87 (13)
Duration of back pain >3 months	154 (23)
Pain radiates below the knee	205 (30)
Use of pain medication for back pain	480 (72)
Psychological factors	
Quality of life physical summary scale[c], mean (SD)	43 (8.9)
Quality of life mental summary scale[c], mean (SD)	50 (10.3)
Depressive symptomatology[d], mean (SD)	10 (7.8)
Pain catastrophizing[e], mean (SD)	14 (10.6)
Attitude and beliefs about back pain[f], mean (SD)	26 (7.2)
Red flags	
Prolonged corticosteroid use[g]	53 (8)
Trauma	28 (4)
Osteoporosis[h]	86 (13)
Sudden decrease in height	23 (3)
Percussion tenderness spine	127 (19)
Severe disability[i]	85 (13)
Acute onset of pain	232 (35)
Back pain intensity score ≥7	255 (38)
Osteoarthritis in hip/knee	199 (30)

All data are presented as numbers (%) unless stated otherwise; Missing values ranged from 0-12%; [a] Hazardous drinking is measured with Audit-C: range 0-12; ≥3 in woman and ≥4 in men is risk of hazardous drinking; [b] Measured with a numerical rating scale as an average of the previous week; range 0-10; 0 indicates no pain, 10 indicates the worst pain imaginable; [c] Measured with the Short Form-36, range 0-100; higher score indicates higher quality of life; [d] Measured with the CED-D, range 0-60; higher score indicates more prone to depression; [e] Measured with pain catastrophizing scale range 0-52; higher score indicates more risk for catastrophizing; [f] Measured with back beliefs questionnaire range 9-49; higher score indicates more positive thoughts of recovery; [g] Oral or inhalation corticosteroid use >90 days; [h] Measured with heel bone densitometry; [i] Measured with the Roland-Morris disability questionnaire; range 0-24; zero indicates no disability, a cut-off value of 17 was used to indicate severe disability.

Prevalence

Of all 669 participants, unspecified back pain with or without radiation below the knee was diagnosed in 384 of them (57%) (table 2). Serious pathology was present in 6% of our study population; vertebral fracture was the most common diagnosis and was seen in 33 participants (5%), of whom 30 were diagnosed with an osteoporotic vertebral fracture. Four participants (1%) were diagnosed with a spinal malignancy, and no spinal infections or cauda equina syndrome were diagnosed. Of the other specified diagnoses that were not defined as serious pathology, vertebral osteoarthritis was the most common (173 patients, 26%); disk herniation was present in 5% of the participants (table 2).

Table 2. GPs diagnosis within one year of follow-up, n=669

	Patients, N (%)
Unspecified back pain without pain radiating below the knee	291 (43)
Unspecified back pain with pain radiating below the knee	93 (14)
Back osteoarthritis	173 (26)
Discopathy	58 (9)
Spondylolisthesis	5 (1)
Disc herniation	35 (5)
Spinal stenosis	21 (3)
Vertebral fracture	33 (5)
Spinal malignancy	4 (1)
Ankylosing spondylitis	1 (0.1)

All data are presented as numbers (%), more than one diagnosis per patient could be reported

Association between red flags and vertebral fracture

In the univariable analyses, age of ≥75 years, prolonged corticosteroid use, trauma, osteoporosis, severe disability, a back pain intensity score of ≥7, and thoracic pain were individually associated with the diagnosis of vertebral fractures (table 3). These variables were included in the multivariable regression analysis. In this model, age of ≥75 years, trauma, osteoporosis, a back pain intensity score of ≥7, and thoracic pain were associated with the diagnosis of vertebral fractures.

Table 4 shows the diagnostic value of the red flags. Age had a positive predictive value of 0.14 (95% confidence interval (CI)=0.07, 0.20) and a positive likelihood ratio of 3.1 (95% CI=2.0, 4.7). Osteoporosis had a similar positive predictive value of 0.14 (95% CI=0.07, 0.21) and likelihood ratio of 3.2 (95% CI=1.9, 5.2). The positive predictive value and the positive likelihood ratio of trauma were 0.25 (95% CI=0.09, 0.41) and 6.2 (95% CI=2.8, 13.5), respectively. These values for trauma were the highest among all variables and raise the probability from .05 to .25 when the test is positive. The negative likelihood ratio for trauma was 0.8 (95% CI=0.5, 1.3), which lowers the probability of a vertebral

Table 3. Univariable and multivariable association of red flags with vertebral fractures in patients aged >55 year with back pain

Red flag	All patients (n=669)	Patients with fracture (n=33)	Univariable OR (95% CI)c	P-value	Multivariable OR (95% CI)	P-value
Age ≥75 years	109	15	4.8 (2.3-9.9)	<0.001	3.5 (1.5-8.6)	0.01
Female gender	400	22	1.4 (0.7-2.9)	0.41		
Prolonged corticosteroid use[a]	53	6	2.8 (1.1-7.1)	0.031	-	-
Trauma	28	7	7.6 (3.0-19.4)	<0.001	7.8 (2.7-22.5)	<0.001
Osteoporosis	86	12	4.5 (2.1-9.5)	<0.001	2.5 (1.0-6.2)	0.05
Sudden decrease in height	23	3	3.1 (0.9-11.2)	0.08		
Percussion tenderness spine	127	7	1.2 (0.5-2.7)	0.74		
Severe disability[b]	85	9	2.9 (1.3-6.5)	0.01	-	-
Acute onset of pain	232	10	0.8 (0.4-1.6)	0.48		
Back pain intensity score ≥7	255	22	3.4 (1.6-7.6)	0.001	3.1 (1.4-7.2)	0.01
Osteoarthritis in hip or knee	199	5	0.4 (0.2-1.1)	0.07		
Thoracic back pain	152	14	2.6 (1.3-5.4)	0.008	2.1 (0.9-4.9)	0.09

All data are presented as numbers unless stated otherwise; Missing values ranged from 0-13%; [a] >90 days use of inhalation or oral corticosteroids; [b] Measured with the Roland-Morris disability questionnaire; range 0-24; >17 was indicated severe disability; [c] variables with a p value <0.05 were included in the multivariable model; OR = Odds ratio, CI = confidence interval. Nagelkerke R^2 20.3

fracture if there was no trauma from .05 to .04. A diagnostic prediction model with 4 red flags combined did not increase these diagnostic values.

DISCUSSION

Summary of results

The present study assessed the prevalence of physician-specified underlying pathologies of back pain, as identified by the participants' GP, in older adults with back pain seen in primary care and the associations of red flags with vertebral fracture. Based on the final diagnoses of back pain retrieved at 1-year follow-up, 57% of the participants were diagnosed with unspecified back pain with or without radiation below the knee, and 6.1% of the participants were diagnosed with serious pathology (vertebral fracture, spinal malignancy, and ankylosing spondylitis). Vertebral fractures were the most common serious pathology (5% of the participants). Red flags associated with vertebral fractures were age of ≥75 years, trauma, osteoporosis, a back pain intensity score of ≥7, and thoracic pain. However, the positive predictive value and positive likelihood ratio of the combined red flags did not increase more than the values for trauma alone.

Table 4. Diagnostic values (and 95% CI) of red flags and other determinants for vertebral fractures (n=33) in patients aged >55 years with back pain (n=669). Prior probability =0.05

Red flag	Sensitivity	Specificity	PV+	PV-	LR+	LR-
Age ≥75 years (n=109)	0.45 (0.28-0.62)	0.85 (0.82-0.88)	0.14 (0.07-0.20)	0.97 (0.95-0.98)	3.1 (2.0-4.7)	0.6 (0.5-0.9)
Female gender (n=400)	0.67 (0.51-0.83)	0.41 (0.37-0.44)	0.06 (0.03-0.08)	0.96 (0.94-0.98)	1.1 (0.9-1.4)	0.8 (0.5-1.3)
Prolonged corticosteroid use[a] (n=53)	0.18 (0.05-0.31)	0.93 (0.91-0.95)	0.11 (0.03-0.20)	0.96 (0.94-0.97)	2.5 (1.1-5.3)	0.9 (0.8-1.0)
Trauma (n=28)	0.21 (0.07-0.35)	0.97 (0.95-0.98)	0.25 (0.09-0.41)	0.96 (0.94-0.97)	6.2 (2.8-13.5)	0.8 (0.5-1.3)
Osteoporosis (n=86)	0.38 (0.21-0.54)	0.88 (0.86-0.91)	0.14 (0.07-0.21)	0.96 (0.95-0.98)	3.2 (1.9-5.2)	0.7 (0.5-0.9)
Sudden decrease in height (n=23)	0.09 (-0.01-0.19)	0.97 (0.95-0.98)	0.13 (-0.01-0.27)	0.95 (0.94-0.97)	2.9 (0.9-9.4)	0.9 (0.8-1.0)
Percussion tenderness of the spine (n=127)	0.21 (0.07-0.35)	0.81 (0.78-0.84)	0.06 (0.02-0.09)	0.95 (0.93-0.97)	1.1 (0.6-2.2)	1.0 (0.8-1.2)
Severe disability[b] (n=85)	0.30 (0.14-0.46)	0.87 (0.84-0.90)	0.11 (0.04-0.17)	0.96 (0.94-0.98)	2.3 (1.3-4.2)	0.8 (0.6-1.0)
Acute onset of pain (n=232)	0.30 (0.15-0.46)	0.64 (0.60-0.68)	0.04 (0.02-0.07)	0.94 (0.92-0.97)	0.8 (0.5-1.4)	1.1 (0.9-1.4)
Back pain intensity score ≥7 (n=255)	0.67 (0.51-0.83)	0.63 (0.59-0.67)	0.09 (0.05-0.12)	0.97 (0.96-0.99)	1.8 (1.4-2.3)	0.5 (0.3-0.9)
Osteoarthritis hip/knee (n=199)	0.16 (0.03-0.28)	0.69 (0.65-0.72)	0.03 (0.00-0.05)	0.94 (0.92-0.96)	0.5 (0.2-1.1)	1.2 (1.0-1.4)
Thoracic back pain (n=152)	0.42 (0.26-0.59)	0.78 (0.75-0.81)	0.09 (0.05-0.14)	0.96 (0.95-0.98)	1.9 (1.3-3.0)	0.7 (0.5-1.0)
Diagnostic prediction model[c]						
≥1 positive features (n=397)	0.88 (0.77-0.99)	0.42 (0.38-0.46)	0.07 (0.05-0.10)	0.99 (0.97-1.00)	1.5 (1.3-1.8)	0.3 (0.1-0.7)
≥2 positive features (n=145)	0.70 (0.54-0.85)	0.81 (0.78-0.84)	0.16 (0.10-0.22)	0.98 (0.97-0.99)	3.6 (2.8-4.8)	0.4 (0.2-0.6)
≥3 positive features (n=43)	0.30 (0.15-0.46)	0.95 (0.93-0.97)	0.23 (0.11-0.36)	0.96 (0.95-0.98)	5.8 (3.2-10.8)	0.7 (0.6-0.9)

Missing values ranged from 0-8%; [a] Oral or inhalation corticosteroids use >90days [b] Measured with the Roland-Morris disability questionnaire; range 0-24; >17 indicated severe disability; [c] Included in the model: osteoporosis, age ≥75 years, trauma, back pain intensity score ≥7 and thoracic pain. AUC = 0.78 (0.69-0.87); PV+ = positive predictive value, PV- = negative predictive value, LR+ = positive likelihood ratio, LR- = negative likelihood ratio.

Interpretation of findings

In our study population, vertebral fractures, malignancies, and ankylosing spondylitis accounted for 6% of the causes of back pain presented to the GP. Vertebral infection and cauda equina syndrome were not identified in our study population. The 6% prevalence in our study is similar to prevalences found in other studies performed in primary care, namely 1% to 5% (1, 2, 4). Most studies on specified causes of back pain describe only serious causes of back pain. Only one study performed in primary care reported all specified diagnosis of back pain.1 Comparing our distribution of specified causesof back pain with the previous findings, it appears that the prevalences of herniated disk, spinal stenosis, vertebral fractures, and spondylolisthesis are about the same in both populations. Only the prevalence of unspecified back pain was somewhat higher in the study by Deyo and Weinstein,[1] and the prevalence of degenerative pathology, such as osteoarthritis, was higher in our study population. These findings were due mainly to our older study population because spine degeneration increases with age.[33] The finding of osteoarthritis might not alter the management of back pain in general practice because there is no specific treatment for this group of patients.

In our multivariable model, age of ≥75 years, trauma, osteoporosis, and a back pain intensity score of ≥7 were associated with vertebral fractures in our population of older patients with back pain. Various cutoff points have been used to determine older age in studies investigating red flags in low back pain. We used the cutoff value of 75 years of age because a recent Cochrane review showed this cutoff value to be the most informative for detecting vertebral fractures in patients with back pain.[15] The finding that patients with older age are more likely to have a vertebral fracture is consistent with other studies.[2 33] Also, the result that trauma, as a red flag, is associated with a vertebral fracture is in line with other studies in primary care.[14 15] However, only 21% of our participants with a fracture reported a trauma.

A back pain intensity score of ≥7 has not been shown in research on red flags to be associated with vertebral fractures. In tertiary care, the presence or absence of pain has been studied,[34-37] although the use of a cutoff value in patients with back pain has not previously been tested. This finding should be further evaluated in other populations with back pain and might be of diagnostic value in patients with back pain seen in primary care.

Prolonged use of corticosteroids appeared to be related with a higher risk of vertebral fractures in older patients with back pain. Oral and inhalation corticosteroids were analyzed because both are associated with an increased risk of vertebral fracture.[38-40] Other topical applications of corticosteroids (injection, dermal, nasal, ocular, and auricular) have not been reported to increase the risk of vertebral fracture.[40 41] In the present study, prolonged use was defined as 3 months of corticosteroid use in the year previous to consulting a GP for back complaints. Two previous studies on corticosteroids as a red flag

in primary care showed likelihood ratios of 4.0[34] and 48.5,[2] whereas the likelihood ratio was only 2.5 in our study. In our study population, corticosteroid use showed an association with vertebral fractures in the binary analysis, but this variable was not included in the final model. Osteoporosis is thought to be a mediator in the relationship between prolonged use of corticosteroids and fractures. It is possible that corticosteroids cause osteoporosis; however, in our population of older adults, it is plausible that osteoporosis also was present without the prolonged use of corticosteroids. The diagnostic prediction model reported by Henschke et al[2] also was assessed in our study population. We used the same red flags (age of >70 years, female sex, trauma, and prolonged use of corticosteroids) but could not reproduce the results as reported. When 2 red flags were present, the positive likelihood ratio in the study by Henschke et al was 15.5 (95% CI=7.2, 24.6), although we found a positive likelihood ratio of only 2.6 (95% CI=1.9, 3.7). Therefore, we used the red flags emerging from the multivariable regression analysis in our study population. The diagnostic values were somewhat better, but the positive likelihood ratios in this new diagnostic model were not as high as the likelihood ratios reported by Henschke et al.[2] The differences between these diagnostic models might be due to the low prevalence of vertebral fractures in both studies or to the somewhat different population of older patients in our study.

Strengths and limitations

To our knowledge, this is the first study assessing the diagnostic value of red flags in older patients with back pain seen in primary care. Older patients may be more prone to a specified cause of back pain, so it is important to evaluate whether red flags are present in this population and predict the most common type of serious pathology (ie, vertebral fractures).

If serious pathology is not identified at the first consultation, disease manifestation may become clearer over time. Also, almost all participants underwent a radiograph of the spine, and these reports were sent to the GPs. We assumed that specified diagnoses, even those not detectable on the radiograph of the spine, became evident within 1 year and were incorporated in the GP registry. Therefore, we identified the final diagnoses regarding specified causes of back pain in the registry of the participants' GP after the 1-year follow-up and assumed that, in this way, we retrieved the most reliable specified diagnoses.

One limitation of the study is the low prevalence of vertebral fractures. Because only 33 participants were diagnosed with a fracture and multiple variables were tested, this limitation could have led to findings by chance. The diagnoses of 6 participants were not available for follow-up, but we expect that they were random missing patients and did not have an important impact on the results of this study. Furthermore, incorporation bias could have occurred. We wanted to know if the red flags are useful to predict

vertebral fractures, but they also could have been used by the GP to determine if a patient had a vertebral fracture. In that case, the strength of the associations could be overestimated. Although almost all of our study participants underwent a radiograph and the findings were sent to their GP, it is more likely that the diagnosis of vertebral fractures was obtained from the radiographic findings rather than from the red flags at baseline.

It is possible that patients with a vertebral fracture were missed, because not all included patients received a radiograph of the back and no standardized imaging protocol was used. The radiographs of the back were made at patients' nearest hospital as usual in normal daily practice. Any additional investigation for the back pain during follow-up was up to the GP; therefore, it is possible that we underestimated the prevalence of vertebral fractures. A final limitation might be that the diagnosis of vertebral fractures was obtained from radiographic findings, and it could have occurred that the fracture found on the radiograph was not linked to this episode of back pain.

Clinical Impact

In older adults with back pain seen in primary care, red flags alone and combined in a diagnostic predication model were not very accurate in predicting vertebral fracture. Also, in this population of older adults, prevalence of vertebral fractures was low. Patients with a traumatic vertebral fracture need to be identified as soon as possible. These patients had a trauma; therefore, if this red flag is present, further diagnostic analysis should be performed. The fractures missed using this red flag alone were all osteoporotic fractures, which do not require immediate treatment, besides pain medication. A wait-and-see policy in the patients without a trauma can be justified, and further diagnostic testing can still be considered if pain lasts longer.

In these older adults with back pain seen in general practice, 43% were diagnosed with specified back pain and 6% with a serious underlying pathology. Most of these patients were diagnosed with a vertebral fracture (5%), and red flags associated with vertebral fracture were age of ≥75 years, trauma, osteoporosis, and a back pain intensity score of ≥7. The red flag of trauma had the highest diagnostic value, and a diagnostic prediction model did not increase this value.

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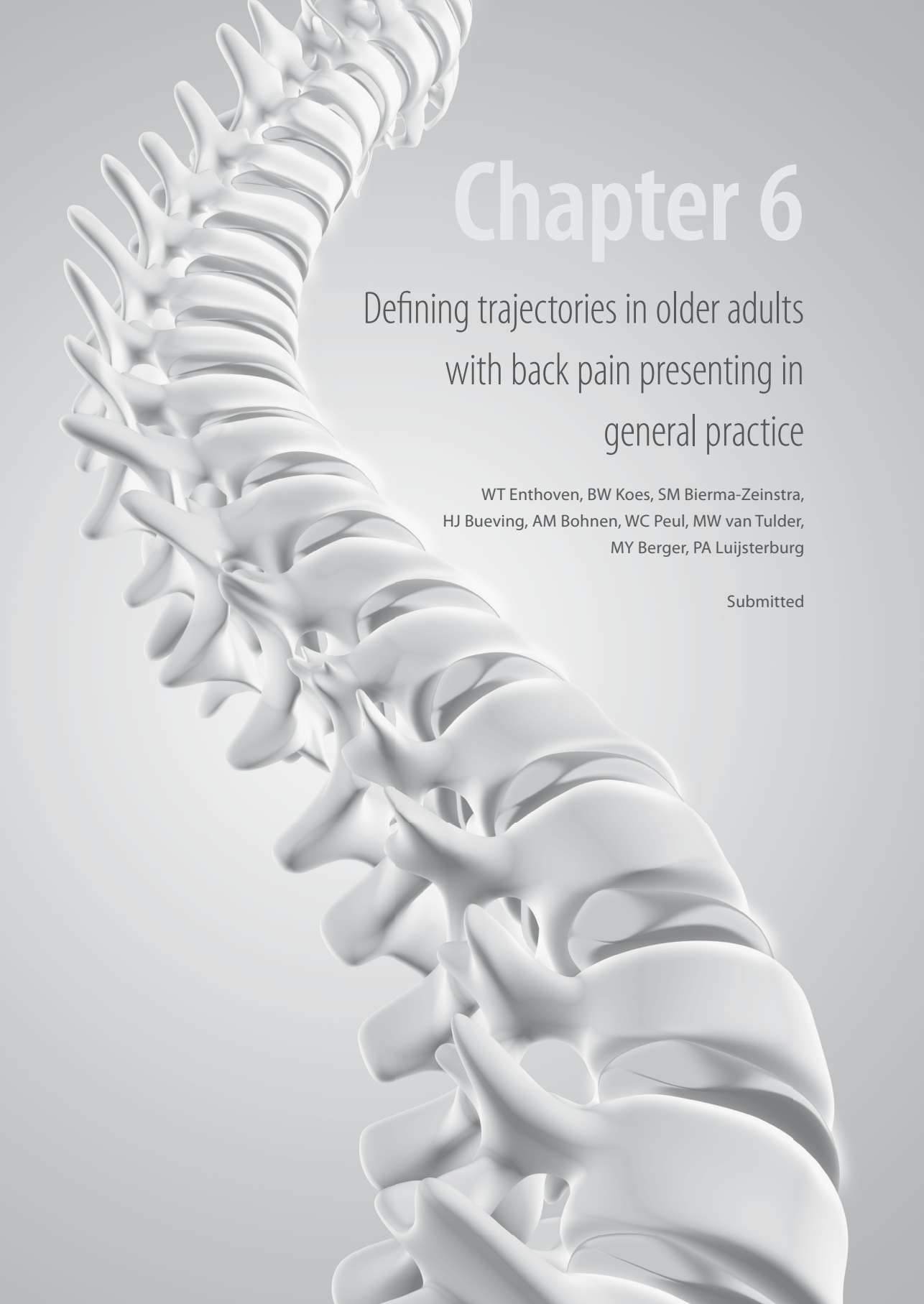

Chapter 6

Defining trajectories in older adults with back pain presenting in general practice

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Submitted

ABSTRACT

Background

Although back pain is a frequently recurring disorder, the course of back pain remains uncertain. Therefore, this study aimed to identify different trajectories in older adults with back pain who presented in general practice and to determine which baseline characteristics are associated with these trajectories.

Methods

The BACE study is a prospective cohort study including 675 patients (aged >55 years) with back pain who consulted a general practitioner; patients were followed for 3 years. Latent class growth analysis was used to identify different trajectories in back pain severity measured at eight different time points. A multinomial regression analysis was used to assess variables associated with membership of an identified trajectory.

Results

Using the different indices of fit and the usefulness of the different trajectories in clinical practice, a 3-class cubic model was determined to be the best model. The three trajectories were defined as 'low pain trajectory', 'high pain trajectory' and 'intermediate pain trajectory'. Baseline variables associated with a higher chance of being in the intermediate or high trajectory were: female gender, higher body mass index, chronic back pain (at baseline), more disability, lower scores on the SF-36 physical summary scale, and negative expectations of recovery.

Conclusions

Three different back pain trajectories were identified in older adults presenting with back pain in general practice. Various baseline characteristics were associated with a higher chance of being in the high or intermediate back pain trajectory. These characteristics might help identify patients at risk for a less favourable outcome.

INTRODUCTION

Back pain is a major problem worldwide; in women and in patients aged 40-80 years the prevalence of back pain is the highest.[1] Due to its high prevalence and the association of back pain with increased disability, it is a leading cause of years lived with disability.[2] With the ageing population it is likely that back pain will become more prevalent and lead to an even higher burden on society and health care.

Most guidelines make a distinction between patients with acute and with chronic nonspecific back pain based on the duration of the episode concerned.[3] However, back pain is often recurrent and many patients do not recover within the first three months of their episode of back pain.[4 5] Since back pain frequently recurs, it is proposed not to focus on a single episode but to consider patterns of back pain on the longer term to better describe the course of back pain.[6] The course of back pain over time can provide additional information and this might be more suitable to identify patients at risk for a non-favourable course. If different groups of patients can be identified, this may help to select the most appropriate interventions for these patients. Understanding the course of back pain also is important to inform both clinicians and patients and, if patients with a less favourable course are identified, to eventually treat these patients different to avoid such a course of back pain.

Studies in various populations have identified different trajectories using diverse statistical methods.[7-13] Most studies created trajectories based on back pain scores of patients and, despite the use of different pain measurements, most found four different trajectories.[7 8 10 13] A recent study using pain as outcome measure identified six trajectories in older adults with back pain;[9] these trajectories consisted of four stable trajectories and two trajectories with substantial improvement over time. Another study had a 7-year follow-up of patients allocated to different trajectories;[14] during follow-up, it appeared that most participants remained in the same trajectory and the allocation of trajectories was stable over time.

Older age is one of the factors associated with a longer time to recovery, or to non-recovery.[15 16] It is possible that these older adults are more often present in the trajectories of non-recovery and that previously defined trajectories for all age groups do not adequately fit this group of older adults with back pain. Therefore, this study aimed to identify different trajectories in older adults with back pain who presented in general practice and to determine which baseline characteristics are associated with membership of a particular trajectory.

METHODS

Study population

Data used in the present study were from the BACE cohort study, a prospective observational cohort.[17] Patient inclusion took place between March 2009 and September 2011 in a representative sample of 49 general practices located around the city of Rotterdam (the Netherlands).

Patients aged >55 years were included when they consulted a general practitioner (GP) with a new episode of back complaints. Back complaints were defined as pain in at least a part or the whole region from the top of the shoulder blades to the first sacral vertebra, with or without pain radiation to the leg. If a patient had not visited a GP with the same back complaints in the preceding 6 months it was considered to be a new episode. Patients were invited to participate in this study by their GP during the consultation, or in writing within 2 weeks after the consultation.

Patients were excluded if they were unable to fill out the questionnaires due to cognitive impairment or were unable to read and write in Dutch. Patients who were unable to undergo physical examination (e.g. wheelchair-bound patients) were also excluded. The Medical Ethics Committee of Erasmus Medical Center (Rotterdam) approved the study protocol. Full details of the BACE study design are described elsewhere.[17]

Data collection

After inclusion in the BACE study and having signed informed consent, patients filled in questionnaires at baseline, 6 weeks, 3, 6 and 9 months, and at 1, 2 and 3 years. The questionnaires asked about patient characteristics and features of the back complaint including patients' perceived severity of back pain averaged over the previous week measured on an 11-point numerical rating scale (NRS)[18] with 0 as 'no pain' and 10 representing 'worst pain ever'. Disability was measured with the Roland Morris Disability Questionnaire (RDQ).[19] The RDQ scores range from 0 (no disability) to 24 (severe disability). Quality of life was measured with the Short-Form 36 (SF-36), Dutch version.[20] The SF-36 measures eight dimensions: physical function, role-physical function, bodily pain, general health, vitality, social function, role-emotional function and mental health. These eight dimensions can be recoded into two summary scores: a physical component summary score and a mental component summary score. Each dimension and summary score is rated on 0-100 scale, with higher scores representing better health.[21 22] In view of the higher mean age of our study population, summary scores were calculated with adapted Z-values (20). Depression was measured with the Center for Epidemiologic Studies-Depression (CES-D; range 0-60); patients with a higher score are more prone to depression.[23] Pain catastrophizing was measured with the Pain Catastrophizing Scale (PCS; range 0-52) with higher scores representing a higher risk for catastrophizing.[24]

Back beliefs were investigated with the back beliefs questionnaire (BBQ; range 9-49) with a higher score representing more positive thoughts on recovery.[25] Lifestyle factors included smoking (yes/no) and drinking alcohol. Drinking alcohol was measured with the Audit-C.[26,27] Women were defined as possible hazardous drinkers if they scored ≥3 on the scale, men if they scored ≥4. Patients were scored as having low education if they had no education or the highest education was middle school or any other education in level 2, according to the International Standard Classification of Education (ISCED) 2011.[28] Expectations about recovery in the coming three months were asked on a 1-5 scale, with 1 representing the most positive and 5 the most negative thoughts about recovery. During the physical examination at baseline, body weight and height were measured and converted to body mass index (BMI).

Statistical analysis

To identify possible trajectories in these older adults with back pain latent class growth analysis (LCGA) was used.[29] The analysis was based on patients' reported severity of back pain averaged over the previous week measured on an 11-point NRS. All questionnaires during the 3-year follow-up were used in the analysis. First, a latent class analysis (LCA) was performed for 2-7 trajectories to get an indication as to how many trajectories would fit the data best, and whether the course of pain would be best described by linear, quadratic or cubic trajectories. Then, the LCGA was performed for 2-5 trajectories and assessed as to whether the course of back pain was best described by quadratic or cubic trajectories.

Model of fit was determined by different indices of fit:[30 31] the Bayesian information criteria (BIC) in which a lower number represents a better model of fit; The Vuong-Lo-Mendell-Rubin likelihood ratio test (LRT), and the bootstrap likelihood ratio test (BLRT), in which a test result of <0.05 indicates that the fit of the model with k groups is better than the model of k-1 groups; and Entropy (a value between 0 and 1) which indicates separation of the trajectories, with values approaching 1 indicating a clear delineation of the trajectories formed.[32]

After determining the number of trajectories and the best fitting trajectory analysis, a multiple imputation was performed and a multinomial regression analysis (3-step approach) used which takes the probability of the membership of the trajectory per patient into account.[33 34]

Description of the baseline characteristics was performed using SPSS software (version 21 for Windows, Chicago, IL, USA). Mplus Version 7.3 (Mutén and Muthén, Los Angeles, CA, USA) was used for the LCGA, for multiple imputation, and for the multinomial regression analysis.

RESULTS

Identification of trajectories

Of the 1402 back pain patients invited by 103 GPs to participate in this cohort study, 675 patients (48%) were included and 727 patients were excluded. Reasons for exclusion were as follows: not willing to participate (*n* = 291), not meeting the inclusion criteria (*n* = 118) or the patient did not respond (*n* = 318). Of these 675 included patients, mean age was 66.4 (standard deviation: SD 7.6) years and 41% were male (table 1). Mean severity of back pain in all patients was 5.2 (SD 2.7).

Using the different indices of fit and the usefulness of the trajectories in practice, the cubic model with three trajectories was determined to best fit this population. The smallest group contained 168 patients, which was 25% of the total number of patients. The entropy of the total model was 0.84, which shows a good discriminative value (32). The Vuong-Lo-Mendell-Rubin LRT showed that a model with four trajectories was no better than the three trajectory model; the BIC and the bootstrap LRT added no information to this model.

The three trajectories were defined as: i) 'low pain trajectory', i.e. patients (n=254) with a mean baseline back pain score of 3.8 (SD 2.9) and a mean back pain score pattern of 0 or 1 from 6 months onwards; ii) 'high pain trajectory', i.e. patients (n=168) with relatively high pain scores during follow-up, these patients had a mean baseline pain score of 7.3 (SD 1.6) and showed a relatively stable mean pain score over time; and iii) 'intermediate pain trajectory', i.e. patients (n=250) with a mean baseline pain score of 5.1 (SD 2.1) and a slight decrease in pain score over time. Three patients failed to report any pain score and were not included in the latent class growth analysis.

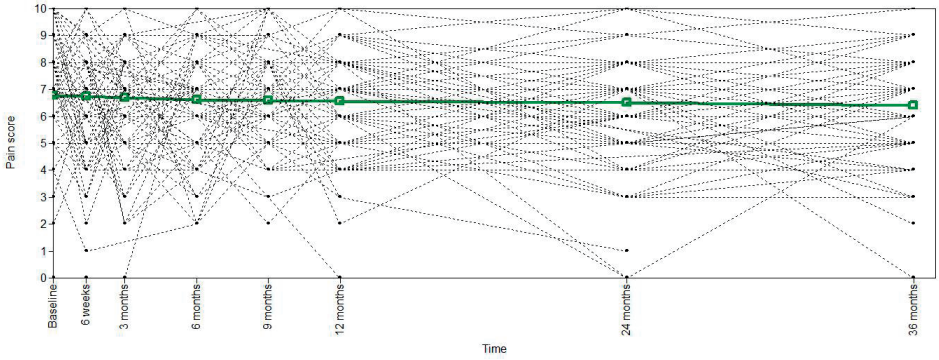
Figure 1 presents estimated means and the individual values of all three trajectories as measured with a NRS at eight time points during the 3-year follow-up. Although there is a stable mean without fluctuation on the group level, individual patterns show a fluctuation in back pain scores. The average SD of the estimated means in the intermediate trajectory was somewhat higher than the SD of mean in the two other trajectories (2.1 vs. 1.7 and 1.6, respectively). Although these differences are small, it is unlikely that the intermediate trajectory included more patients with fluctuating back pain patterns than the other two trajectories. Patients in the high pain class seem to have more or less constant pain over time and patients barely report pain scores under 4. Patients in the intermediate pain class show pain scores over the whole range at all time points. And patients in the low pain class seem to report most pain in the first months and over time the pain gradually decreases.

Table 1. Baseline characteristics of older patients with back pain presenting in general practice.

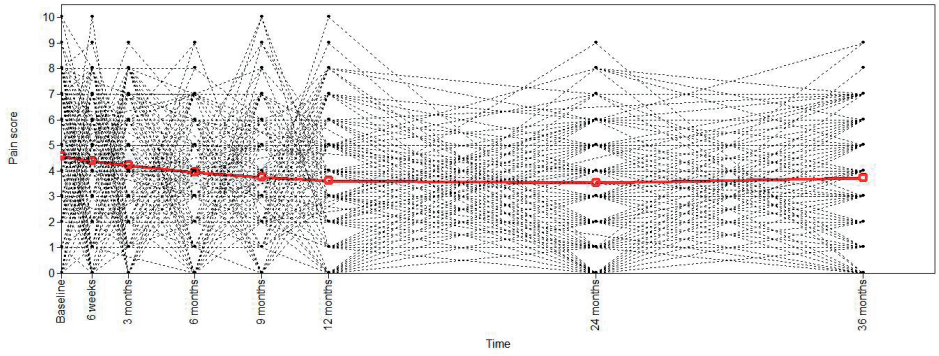
	All patients (n=675)*	Low pain trajectory (n=254)	Intermediate pain trajectory (n=250)	High pain trajectory (n=168)
Age, years	66.4 (7.6)	65.1 (7.1)	66.6 (7.6)	68.1 (8.2)
Male gender, n (%)	274 (41)	130 (51)	87 (35)	55 (33)
Body mass index	27.5 (4.7)	26.8 (4.1)	27.6 (4.4)	28.3 (5.7)
Low education, n (%)	279 (41)	89 (35)	98 (39)	92 (55)
Smoking, n (%)	122 (18)	38 (15)	54 (22)	30 (18)
Hazardous drinking[a], n (%)	333 (49)	142 (56)	121 (48)	70 (42)
Back complaint characteristics				
Severity of back pain[b]	5.2 (2.7)	3.8 (2.9)	5.1 (2.1)	7.3 (1.6)
Duration of back pain > 3months, n (%)	156 (23)	21 (8)	76 (30)	59 (35)
Pain radiating below the knee, n (%)	205 (30)	55 (22)	77 (31)	73 (44)
Medication use, n (%)	483 (72)	176 (69)	170 (68)	137 (82)
History of back pain, n (%)	579 (86)	209 (82)	217 (89)	150 (89)
Disability[c]	9.8 (5.8)	7.0 (5.7)	10.2 (5.1)	13.5 (4.8)
Psychological factors				
Quality of life physical summary scale[d]	43.2 (8.9)	47.3 (8.3)	42.5 (8.2)	38.1 (8.0)
Quality of life mental summary scale[d]	49.6 (10.3)	51.3 (9.1)	49.4 (10.4)	47.1 (11.2)
Depressive symptomatology[e]	10.0 (7.8)	7.7 (6.9)	10.0 (6.8)	13.5 (9.0)
Pain catastrophizing[f]	14.1 (10.6)	11.1 (8.9)	13.4 (10.3)	19.8 (11.2)
Attitude and beliefs about back pain[g]	26.4 (7.2)	29.1 (6.4)	26.3 (7.0)	22.4 (6.8)
Expectations regarding recovery[h], n (%)				
- Completely pain free	113 (17)	83 (33)	23 (9)	7 (4)
- Strong improvement	178 (26)	70 (28)	72 (29)	36 (21)
- The same as now	349 (52)	94 (37)	147 (59)	108 (64)
- Strong worsening	15 (2)	1 (0.4)	2 (0.8)	12 (7)
- More pain than ever	3 (0.4)	0 (0)	0 (0)	3 (2)

*Three patients failed to report any pain score and are not included in this latent class growth analysis. All results are presented as mean (SD) unless stated otherwise. Missing values ranged from 0-22%; [a] Hazardous drinking is measured with Audit-C: range 0-12; ≥3 in women and ≥4 in men is risk of hazardous drinking; [b] Measured with a numerical rating scale as an average of the previous week; range 0-10; 0 indicates no pain, 10 indicates the worst pain imaginable; [c] Measured with the Roland-Morris Disability Questionnaire; range 0-24; zero indicates no disability. [d] Measured with the Short Form-36, range 0-100; higher score indicates higher quality of life; [e] Measured with the CED-D, range 0-60; higher score indicates more prone to depression; [f] Measured with the Pain Catastrophizing scale, range 0-52; higher score indicates more risk for catastrophizing; [g] Measured with the Back Beliefs Questionnaire, range 9-49; higher score indicates more positive thoughts of recovery; [h] Asked on a 1-5 scale, with 1 as the most positive and 5 as the most negative expectations regarding recovery in the coming 3 months.

A: High pain trajectory



B: Intermediate pain trajectory



C: Low pain trajectory

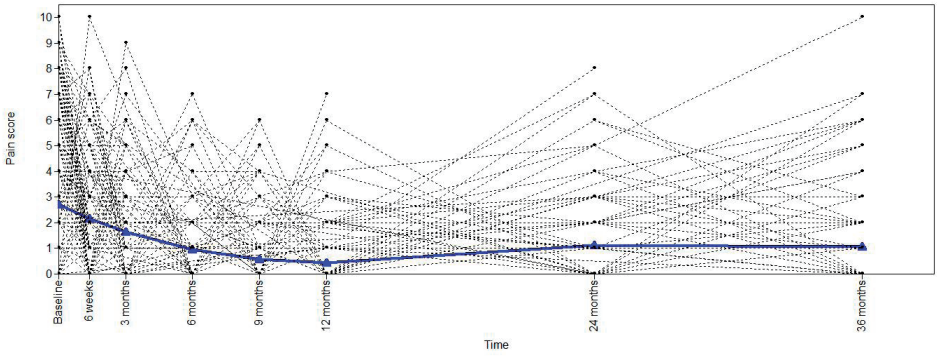


Figure 1. Plot of class means and individual back pain scores at follow-up in the three different trajectories

Multinomial regression analysis

The low pain trajectory was chosen as reference category (table 2). Compared to the low pain trajectory, patients in the intermediate trajectory were more likely to be female (odds ratio: OR 2.04; 95% CI 1.23-3.37), had a higher body mass index (OR 1.07; 95% CI 1.01-1.14), more often had a back pain duration > 3 months at baseline (OR 4.87; 95% CI 2.29-10.37), had lower scores on the SF-36 physical summary scale (OR 0.94; 95% CI 0.90-0.98) and more negative expectations of recovery (OR 2.02; 95% CI 1.40-2.91). Some of these variables were also associated with membership of the trajectory with high pain scores. These associations were even stronger (with higher ORs) in the high pain trajectory: duration of back pain > 3 months at baseline (OR 7.70; 95% CI 3.34-17.74), disability (OR 1.15; 95% CI 1.06-1.25), SF-36 physical summary scale (OR 0.92; 95% CI 0.86-0.97) and negative expectations of back pain (OR 3.48; 95% CI 2.08-5.80).

Table 2. Results of the multinomial regression analysis (reference class is 'low pain trajectory').

	Intermediate pain trajectory			High pain trajectory		
	OR	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**
Age	1.02	0.98-1.06	0.31	1.02	0.97-1.06	0.47
Gender, female	2.04	1.23-3.37	**0.01**	1.55	0.80-3.01	0.19
Body mass index	1.07	1.01-1.14	**0.03**	1.07	0.99-1.15	0.09
Low education	0.73	0.43-1.22	0.22	0.99	0.51-1.90	0.97
Smoking	1.90	0.89-4.05	0.10	1.34	0.52-3.41	0.55
Hazardous drinking[a]	1.10	0.67-1.83	0.70	0.90	0.48-1.70	0.74
Duration of back pain >3 months	4.87	2.29-10.37	**<0.0001**	7.70	3.34-17.74	**<0.0001**
Pain radiating below the knee	1.01	0.58-1.78	0.96	1.18	0.60-2.31	0.63
Medication use	0.79	0.43-1.42	0.43	1.05	0.50-2.22	0.89
History of back pain	1.10	0.57-2.12	0.78	2.05	0.67-6.28	0.21
Disability[b]	1.06	1.00-1.14	0.07	1.15	1.06-1.25	**0.001**
Quality of life physical summary scale[c]	0.94	0.90-0.98	**0.01**	0.92	0.86-0.97	**0.004**
Quality of life mental summary scale[c]	0.98	0.94-1.02	0.30	0.98	0.94-1.02	0.30
Depressive symptomatology[d]	1.00	0.95-1.06	0.97	1.01	0.95-1.07	0.83
Pain catastrophizing[e]	0.99	0.95-1.02	0.52	1.01	0.98-1.05	0.51
Attitude and beliefs about back pain[f]	0.99	0.94-1.03	0.48	0.95	0.90-1.00	0.08
Expectations of recovery[g]	2.02	1.40-2.91	**<0.0001**	3.48	2.08-5.80	**<0.0001**

[a] Hazardous drinking is measured with Audit-C: range 0-12; ≥3 in women and ≥4 in men is risk of hazardous drinking; [b] Measured with the Roland-Morris Disability Questionnaire; range 0-24; zero indicates no disability. [c] Measured with the Short Form-36, range 0-100; higher score indicates higher quality of life; [d] Measured with the CED-D, range 0-60; higher score indicates more prone to depression; [e] Measured with the Pain Catastrophizing scale, range 0-52; higher score indicates more risk for catastrophizing; [f] Measured with the Back Beliefs Questionnaire, range 9-49; higher score indicates more positive thoughts of recovery; [g] Asked on a 1-5 scale, with 1 as the most positive and 5 as the most negative expectations regarding recovery in the coming three months;

DISCUSSION

Summary of results

In older adults presenting in primary care with back pain, LCGA was performed to identify different trajectories regarding the course of back pain. A 3-class cubic model fitted best and low, intermediate and high back pain trajectories were identified. The low trajectory (254 patients; 38%), was the most favourable trajectory with patients recovering over time and with a mean back pain score of 1/10 during follow-up. Patients in the intermediate and the high trajectory did not seem to recover during follow-up.

Baseline characteristics associated with a higher risk of being in the intermediate pain trajectory were female gender, higher body mass index, chronic (>3 months) back pain (measured at baseline), lower scores on the SF-36 physical summary scale, and more negative expectations of recovery. For the high pain trajectory these characteristics were chronic back pain, more disability, lower scores on the SF-36 physical summary scale, and more negative expectations of back pain.

Interpretation of findings

In various populations with back pain, 3-12 trajectories have been reported,[7-13] with most studies describing four trajectories.[7 8 10 13] Most of these studies were performed in a primary care setting, whereas three studies included patients from general practice,[10-12] as in our study. One of these studies in general practice found three trajectories as the model best fitting their population.[12] All other studies found at least four trajectories as best fitting. One study among older adults found six trajectories with pain as outcome.[9] The differences between these studies might be due to differences in study populations, or to the use of varying statistical methods. None of the previous studies used LCGA to incorporate growth over time in the model. Although most of the studies used severity of back pain as outcome measure,[8-13] bothersomeness was also used.[7] In most studies the follow-up was one year,[8 10-13] compared to three years in the present study. Only one study included a trajectory that showed increasing pain over time.[8] Most studies show trajectories with estimated means that were stable over time,[10 13] or had both stable and decreasing trajectories.[7 9 12]

Various characteristics associated with an increased probability of having a less favourable trajectory have also been examined. In the present study, female gender was associated with a higher risk of being in the intermediate pain trajectory, but was not associated with being in the high pain trajectory. In only one other study was female gender also found to be associated with a less favourable trajectory.[9] It is interesting that female gender was not associated with the high pain trajectory. In the present population, chronic back complaints were associated with membership of a less favourable trajectory (intermediate pain trajectory vs. low pain trajectory OR 3.93, and high pain

trajectory vs. low pain trajectory OR 7.18). A longer duration of back pain (at baseline) was previously reported to be associated with an unfavourable course of back pain.[7 9-11] Also, negative patients' expectations about the course of back pain was also reported to be associated with a less favourable course.[9 11] In other studies, only quality of life was not mentioned as a variable associated with a less favourable outcome. In the present study, a lower quality of life on the physical summary scale was associated with membership of the intermediate and high trajectory.

The present study included 168 patients in the high pain trajectory (i.e. 25% of the patients). In studies with younger populations, about 10-20% of the patients were included in the most severe trajectory.[10-13] In only one study was the majority of patients included in the most severe trajectory, despite the younger population in that study.[8] Older patients tend to experience more severe back pain compared to younger patients.[35] Since older age is often associated with a less favourable outcome it is likely that, in the present population of older adults, more patients were included in the highest pain trajectory.

Because of the recurrent character of back pain it is suggested to examine the course of back pain, rather than investigate single episode. Defining different pain trajectories and establishing which characteristics are associated with trajectories with a high pain level, allows to better inform our patients or eventually even treat patients different in each trajectory. Other variables associated with allocation to a high pain trajectory were more disability and lower scores on the SF-36 physical summary scale; however, these latter variables are more likely attributable to the high level of pain on the longer term, rather than being the actual cause of pain. Another possibility is that patients with more disability are less likely to stay active and, therefore, either do not make a good recovery or do not recover at all.

Strengths and limitations

In this study the probability of membership to a class was included in the multinomial analysis which makes the analysis more robust and less likely to be biased. This is not done in previous studies on trajectories. Bias can occur because a patient with a probability of 0.56 of being in the high pain class and a probability of 0.44 of being in the middle pain class, would be accounted fully to the high pain class in the same way as a patient with a probability of 1.00 when this probability is not taken into account.

In previous studies the trajectories of pain were mostly categorized due to non-normality. In contrast, in the present study we measured severity of back pain on a 0-10 scale to obtain the most accurate pain data in the model. Non-normality is not a problem using LCGA, because latent variables can be normal if the predictor variable is not normally distributed. Furthermore, 675 patients were included in the present analysis. A

simulation study showed that non-normality in a maximum likelihood approach is not a problem when a population includes ≥ 500 patients and produces unbiased results.[36]

It is difficult to assess whether our patients in the intermediate trajectory have more fluctuating pain than patients in the low and high pain score trajectories. We assessed the SDs of the estimated mean of the back pain score; this resulted in scores indicating an intermediate trajectory that did not fluctuate more than the other two trajectories, even though these results were indirect evidence for this hypothesis.

A limitation is that the first year of follow-up has six points of measurement compared with only two in the final two years of follow-up. Because these latter measurements may have provided little information, more measurement points during the last two years would have been more informative; e.g. in order not to miss back pain flares, measurements could have been made (at least) every 3 months.

Clinical implications

In our study, different trajectories were identified with different pain patterns. Although the mean of the trajectories remains stable, it is important to note that individual pain patterns do fluctuate over time. Although fluctuation is around the mean of the trajectory, patients seem (overall) to fit well into this three trajectory model. Variables associated with the intermediate and high trajectory were chronic back pain (at baseline), lower scores on the SF-36 physical summary scale, and more negative expectations of recovery in the coming 3 months. These variables might help identify patients at risk for a less favourable outcome; however the models and the variables need to be externally validated and predictive values of variables should be assessed, before being applied in clinical practice.

Conclusion

This study identified three different back pain patterns in older adults with back pain: low, intermediate and high pain groups. Baseline characteristics associated with a greater chance of being in the intermediate trajectory were female gender, higher body mass index, chronic back pain (at baseline), lower scores on the SF-36 physical summary scale, and more negative expectations of recovery in the coming 3 months. Chronic back pain, more disability, lower scores on the SF-36 physical summary scale and more negative expectations of back pain were more frequently present in the high pain trajectory. These characteristics might help to identify patients at risk for a less favourable outcome.

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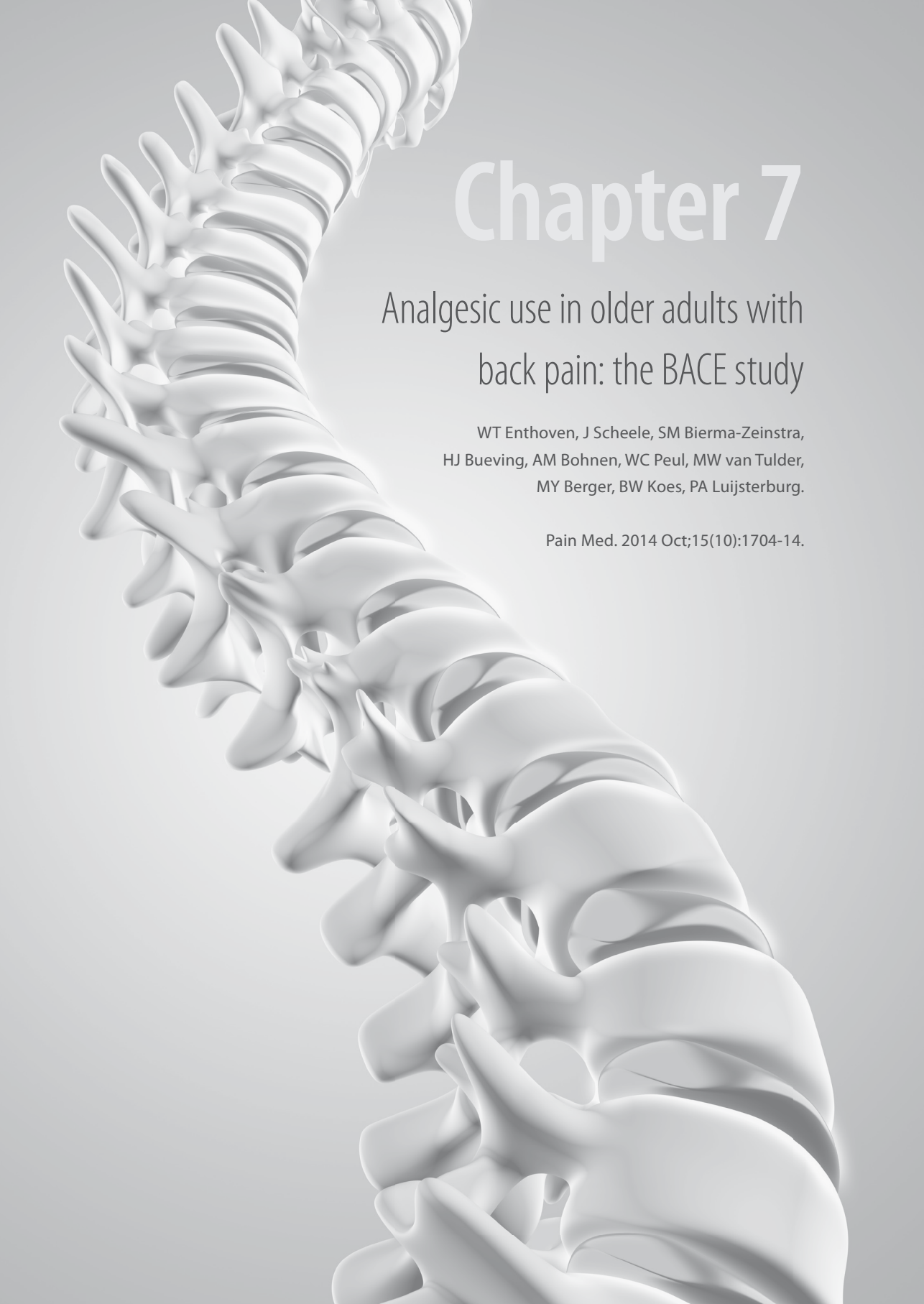

Chapter 7

Analgesic use in older adults with back pain: the BACE study

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ABSTRACT

Background

Older patients with back pain are more likely to visit their general practitioner (GP) and are more likely to be prescribed analgesics. To assess analgesic use in older adults with back pain in general practice.

Methods

The BACE study in the Netherlands is a prospective cohort study. Patients (aged >55 years) with back complaints were recruited when consulting their GP or shortly thereafter. Measurements took place at baseline and at 3- and 6-month follow-up. For medication use, patients were asked if they had used any medication for their back pain in the previous 3 months and, if so, to specify the medication name, dosage used, frequency of usage, and whether the medication was prescribed or purchased over-the-counter.

Results

Of the 1,402 patients who were approached to enter the study, 675 were included. Of these patients, 484 (72%) reported medication use at baseline. Nonsteroidal anti-inflammatory drugs (NSAIDs) (57%) were more often used than paracetamol (49%). Paracetamol was mostly obtained over-the-counter (69%), and NSAIDs were mostly obtained by prescription (85%). At baseline, patients with severe pain (numerical rating scale score ≥7) used more paracetamol, opioids, and muscle relaxants. Patients with chronic pain (back pain >3 months) used more paracetamol, while patients with a shorter duration of pain used more NSAIDs. During follow-up there was an overall decline in medication use; however, at 3- and 6-month follow-up, 36% and 30% of the patients, respectively, still used analgesics.

Conclusions

In these older adults consulting their GP with back pain, 72% used analgesics at baseline. Despite a decrease in medication use during follow-up, at 3 and 6 months a considerable proportion still used analgesics.

INTRODUCTION

Back pain is a major health problem with a reported lifetime prevalence of up to 84%.[1] In the Netherlands, about 30–45% of patients with back pain visit their general practitioner (GP).[2 3] A recent study in the UK showed that older patients (>70 years) with low back pain are more likely to visit their GP and more likely to receive analgesics compared with younger adults with back pain.[4] With regard to analgesic options, international guidelines for low back pain usually recommend paracetamol as first choice, followed by nonsteroidal anti-inflammatory drugs (NSAIDs).[5] Selecting analgesic medication for back pain is important, not only for effective pain relief but also because each class of medication is associated with particular (serious) adverse reactions, especially in older adults.

NSAIDs, for example, are associated with adverse reactions such as gastrointestinal and cardiovascular events.[6 7] An Australian study reported that since NSAIDS such as ibuprofen became available 'over-the-counter,' fewer people were using them appropriately and according to the instructions.[8] Three percent of patients participating in the study used more than the maximum dose of NSAIDs, 7.5% used more than one NSAID, and 13% were at risk of an interaction with another medication that they took.

Adverse reactions from opioids are most commonly dry mouth, nausea, vomiting, dizziness, and constipation.[9 10] Dizziness can cause increased incidence of falls and fractures.[11 12] A frequently used opioid, codeine, can even elevate risk of all-cause mortality after only 30 days' usage.[13]

Most studies on analgesic use only report prescribed medication.[14-16] This can give a wrong impression of medication use, because paracetamol and NSAIDs are often used without prescription. Furthermore, previous studies assessing analgesic use in older adults were mostly performed in settings other than general practice,[4 17 18] and most of these studies were cross-sectional.[4 16 19] In the present study we examine both 'over-the-counter' and prescribed analgesic use in older adults with back pain in general practice. Medication use was assessed over 6 months of follow-up and compared between patients with (1) different ages (55–74 years vs ≥75 years), (2) different durations of pain (<3 months vs ≥3 months), and (3) different pain scores for baseline severity of back pain (<7 vs ≥7; range 0–10).

METHODS

The Back Complaints in the Elders (BACE) study in the Netherlands is a prospective observational cohort study. Patient inclusion (N = 675) took place between March 2009 and September 2011 in a representative sample of 49 general practices around Rotterdam.

Patients aged >55 years were recruited when they consulted a GP with a new episode of back complaints. Back complaints were defined as pain in at least a part of or the whole region from the top of the shoulder blades to the first sacral vertebra, with or without pain radiation to the leg. If a patient had not visited a GP with the same back complaints in the preceding 6 months, it was considered a new episode. Patients were invited to participate in the study by their GP during the consultation or in writing within 2 weeks after the consultation.

Patients were excluded if they were unable to fill out the questionnaires due to cognitive impairment or were not able to read and write in Dutch. Patients who were unable to undergo physical examination (e.g., wheelchair-bound patients) were also excluded.

The Medical Ethics Committee of Erasmus University Medical Center, Rotterdam, approved the study protocol. Details of the BACE study design are described elsewhere.[20]

Data Collection

Baseline measurement included a questionnaire and physical examination of the back. Follow-up measurements took place at 3 and 6 months post-baseline by means of questionnaires. The questionnaires asked about patient characteristics, features of the back complaint, and use of pain medication. Patients' perceived severity of back pain averaged over the previous week was measured on an 11-point numerical rating scale (NRS),[21] with 0 as 'no pain' and 10 representing 'worst pain imaginable.' Disability was measured with the Roland–Morris Disability Questionnaire (RDQ).[22] RDQ scores can range from 0 (no disability) to 24 (severe disability). Quality of life was measured with the Dutch version of the Short Form—36 (SF-36).[23] The SF-36 measures eight dimensions: physical function, physical role function, bodily pain, general health, vitality, social function, emotional role function, and mental health. Scores on these eight dimensions can be summarized by two summary scores: a physical component summary score and a mental component summary score. Each dimension and summary score is scored from 0 to 100, with a higher score representing better health.[24 25] Summary scores were calculated with adapted *Z*-values in view of the higher mean age of our study population.[23] Depression was measured with the Center for Epidemiologic Studies Depression Scale (range 0–60). Patients with a higher score are more prone to depression.[26] Pain catastrophizing was measured with the Pain Catastrophizing Scale (range 0–52), with a higher score representing a higher risk for catastrophizing.[27] Patients' beliefs about their back pain were investigated with the Back Beliefs Questionnaire (range 9–49), with a higher score representing more positive thoughts on recovery.[28] Lifestyle factors assessed included smoking habits (yes/no) and alcohol consumption. Alcohol consumption was measured with the Alcohol Use Disorders Identification Test – Consumption questions.[29 30] Women were defined as possible hazardous drinkers if they scored ≥3 on

the scale, men if they scored ≥4. During physical examination, body weight and height were measured and converted to body mass index (BMI).

For medication use, patients were asked if they had used any medication for their back pain in the previous 3 months and, if so, to specify the medication name, used dosage, frequency of usage, and whether the medication was prescribed or purchased as 'over-the-counter' medication. The exact question asked is shown in the Appendix. The medications reported by the patients were recorded in a database and classified by an MD by group: paracetamol, NSAID, opioid, muscle relaxant, antidepressant, anticonvulsant, and other. Nonpharmacologic treatments were also recorded; patients were asked if they had visited their GP, physiotherapist, or medical specialist in the past 3 months.

Statistical Analysis

Descriptive statistics are used to present patient and back complaint characteristics in patient counts for all variables with categorical data and as mean and standard deviation (SD) for continuous variables. Patients using medication for back pain at baseline were compared with the patients not using any medication for their back pain. For continuous variables, an independent sample *t*-test was used. Variables with categorical data were analyzed using the chi-square test. If >20% of the cells contained an expected count of <5, a Fisher's exact test was performed. Patients using medication for back pain at baseline, 3 months, or 6 months were selected, and medication use was further analyzed. Patient counts were used to describe which medication types were most commonly used and the frequency of medication use.

Patients using medication were divided into groups according to age (>55–74 years vs ≥75 years), to whether pain was acute or chronic (<3 months vs >3 months), and to the severity of back pain at baseline (NRS <7 vs NRS ≥7). Differences were analyzed using the chi-square test. If >20% of the cells contained an expected count of <5, a Fisher's exact test was performed. Reported *P* values were from two-sided tests, and a P value < 0.05 was defined as statistically significant. All analyses were performed using SPSS software (version 20 for Windows, Chicago, IL, USA).

RESULTS

Figure 1 shows that 1,402 patients were invited to participate and that 675 patients were eventually included.

Characteristics of all patients included in the BACE study are presented in table 1. Mean age was 66 ± 7.6 years, and 274 of the patients were male (41%). For all included patients, the mean severity of baseline back pain was 5.2 ± 2.7 (NRS). Pain severity was higher in patients using pain medication at baseline compared with those who did not

use analgesics for their back pain (5.5 ± 2.7 vs 4.4 ± 2.4 respectively). For 87 patients (13%), this episode of back pain was the first in their life. Mean disability measured with the Roland-Morris Disability Questionnaire was 9.8 ± 5.8; disability score was higher in patients using analgesics for their back pain compared with those who did not take analgesics (10.6 ± 5.7 vs 7.7 ± 5.6, respectively). Chronic back complaints (duration >3 months) were reported by 156 patients (23%). Patients who did use pain medication were less likely to have chronic back complaints compared with those who did not use analgesics. Furthermore, patients using pain medication for their back pain had a lower mean quality of life on the SF-36 physical summary scale, scored higher regarding pain catastrophizing, and had less positive thoughts regarding recovery.

Out of all patients, 72% (484 patients) reported using pain medication in the 3 months prior to baseline (table 2). In patients using analgesics, NSAIDs (57%) were more often used than paracetamol (49%). Most patients (69%) using paracetamol purchased it over-the-counter, while NSAIDs were more frequently obtained via a prescription (85%). A relatively large proportion of the patients used opioids (17%), and 8% used muscle relaxant. Used opioids were morphine, codeine, and tramadol. The muscle relaxants were mostly benzodiazepines (92%). Overall, the frequency of taking pain medication

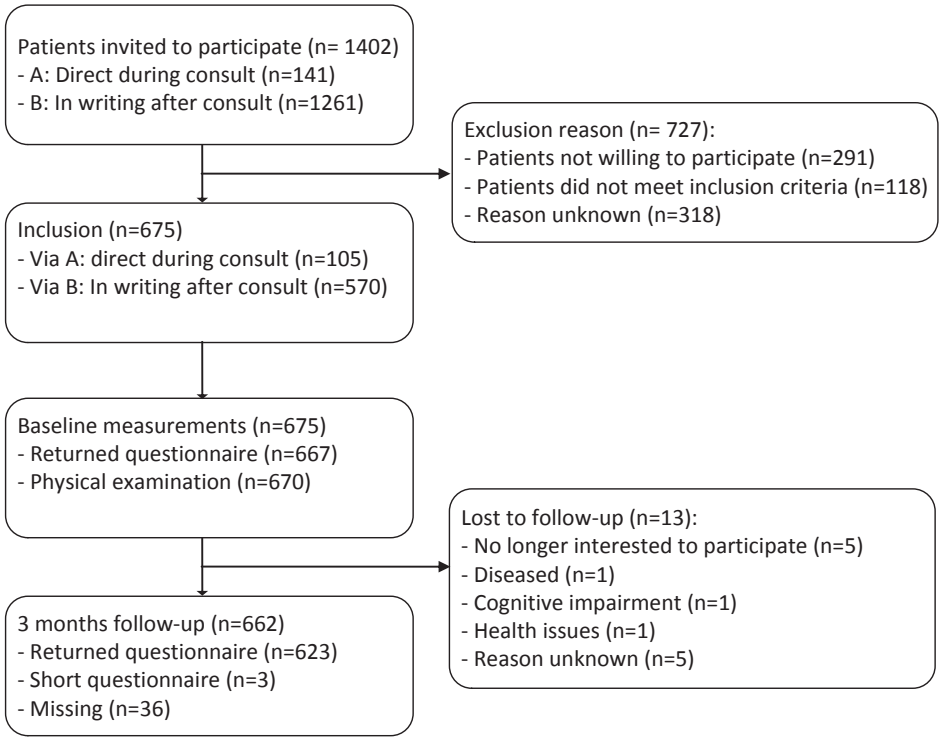

Figure 1. Flow chart of patient inclusion

was mostly daily (67%); only a small proportion (7%) of all medication was used less than once a week. Most patients (49%) used one kind of medication; 120 patients (18%) used two types, and only 35 patients (5%) used three types (figure 2). Medications reported in the 'other' category were hydrocortisone (2 patients), NSAID cream (2 patients), glucosamine (2 patients), homeopathic cream (2 patients), nefopam (1 patient), *Harpagophytum procumbens* (1 patient), and menthol gel (1 patient).

At 3-month follow-up, medication use was lower compared with baseline (table 2). Of the 245 patients (36%) using medication at 3-month follow-up, 214 also used medication at baseline. At 3-month follow-up, paracetamol was used more often than NSAIDs (51% vs 43%). Although most patients still used analgesics on a daily basis, this proportion

Table 1. Baseline characteristics of the patients in the BACE study.

	All patients (n=675)	Patients using pain medication (n=484)	Patients not using pain medication (n=191)	p-value
Age in years, mean ±SD	66 ±7.6	66 ±7.7	66 ±7.6	0.58
Male	274 (41)	188 (39)	86 (45)	0.14
BMI, mean ±SD	27.5 ±4.7	27.3 ±4.7	27.9 ±4.7	0.19
Low education level	279 (41)	205 (42)	74 (39)	0.57
Smoking	122 (18)	87 (18)	35 (18)	0.80
Hazardous drinking[a]	333 (49)	242 (50)	91 (48)	0.88
Severity of back pain[b], mean ±SD	5.2 ±2.7	5.5 ±2.7	4.4 ±2.4	<0.001
Disability[c], mean ±SD	9.8 ±5.8	10.6 ±5.7	7.7 ±5.6	<0.001
First episode of back pain	87 (13)	61 (13)	26 (14)	0.69
Duration of back pain >3 months	156 (23)	104 (21)	52 (27)	0.04
Pain radiates to below the knee	205 (30)	155 (32)	50 (26)	0.20
Pain location only lumbar	450 (67)	313 (65)	137 (72)	0.19
Quality of life physical summary scale[d], mean ±SD	43.2 ±8.9	41.7 ±8.5	47.2 ±8.8	<0.001
Quality of life mental summary scale[d], mean ±SD	49.6 ±10.3	49.8 ±10.4	48.9 ±9.9	0.32
Depressive symptomatology[e], mean ±SD	10.0 ±7.8	10.3 ±7.8	9.2 ±7.7	0.09
Pain catastrophizing[f], mean ±SD	14.1 ±10.6	15.1 ±10.8	11.5 ±9.5	<0.001
Attitude and beliefs about back pain[g], mean ±SD	26.4 ±7.2	25.8 ±7.2	28.0 ±7.1	0.001

All data are presented as numbers (%) unless stated otherwise; Missing values ranged from 0-12%
[a] Hazardous drinking is measured with Audit-C: range 0-12; ≥3 in woman and ≥4 in men is risk of hazardous drinking; [b] Measured with a numerical rating scale as an average of the previous week; range 0-10; 0 indicates no pain, 10 indicates the worst pain imaginable; [c] Measured with the Roland-Morris disability questionnaire; range 0-24; zero indicates no disability; [d] Measured with the Short Form-36, range 0-100; higher score indicates higher quality of life; [e] Measured with the CED-D, range 0-60; higher score indicates more prone to depression; [f] Measured with pain catastrophizing scale range 0-52; higher score indicates more risk for catastrophizing; [g] Measured with back beliefs questionnaire range 9-49; higher score indicates more positive thoughts of recovery

(56%) was smaller compared with baseline (67%). At 3-month follow-up, paracetamol had been obtained over-the-counter by 84 patients (67%), and NSAIDs were obtained by prescription by 82 patients (77%). Nevertheless, among medication users, 178 (73%) reported the use of one type of analgesic (figure 2).

At 3-month follow-up medications reported in the 'other' category were glucosamine (2 patients), prednisone (2 patients), hydroxychloroquine (1 patient), cold cream (2 patients), NSAID cream (1 patient), and menthol cream (1 patient).

At 6-month follow-up there was a further (albeit small) decline in medication use (204 patients; 30%) (table 2). The frequency of medication use at 6-month follow-up was similar to the usage at 3-month follow-up. Other medications reported at 6-month follow-up were glucosamine (2 patients), prednisolone (1 patient), and NSAID cream (4 patients).

Of the 484 patients who reported use of pain medication for their back pain at baseline, 146 patients still reported use of pain medication at 3- and 6-month follow up. Of the 191 patients not using pain medication at baseline, 31 had started using pain medication for their back pain at 3-month follow-up. Of these 31 patients, 11 patients still used pain medication at 6-month follow-up.

Among patients using paracetamol at baseline, 7% also reported use of paracetamol at 3- and 6-month follow-up. A similar percentage was found in patients reporting NSAID

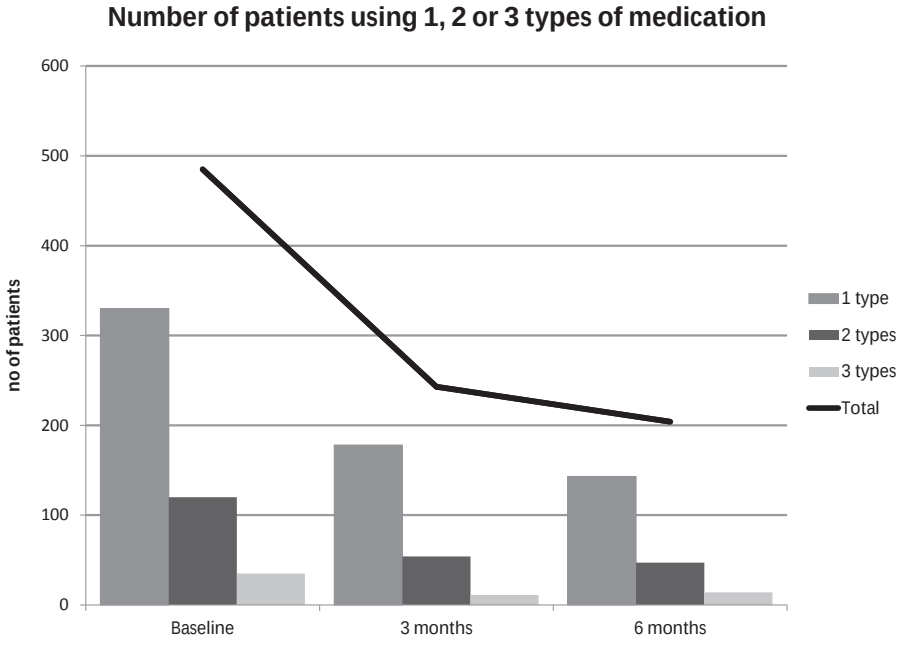

Figure 2. Number of types of medications used by the patients during the study period

Table 2. Frequency of analgesic use in older adults with back pain in general practice

	Baseline				3 months follow-up				6 months follow-up			
	Overall	Less than weekly	Weekly	Daily	Overall	Less than weekly	Weekly	Daily	Overall	Less than weekly	Weekly	Daily
Medication use	**n=484**	**n=32 (7)**	**n=117 (24)**	**n=324 (67)**	**n=245**	**n=16 (7)**	**n=83 (34)**	**n=140 (56)**	**n=204**	**n=18 (9)**	**n=80 (39)**	**n=98 (48)**
Paracetamol	235 (49)	14 (6)	84 (36)	131 (56)	126 (51)	7 (6)	63 (50)	50 (40)	115 (56)	10 (9)	63 (54)	40 (35)
OTC	163 (69)	12 (7)	73 (45)	76 (47)	84 (67)	5 (6)	50 (60)	27 (32)	78 (68)	10 (13)	49 (63)	17 (22)
Prescription	60 (26)	2 (3)	9 (15)	47 (77)	25 (20)	0 (0)	6 (24)	19 (76)	21 (17)	0 (0.0)	5 (24)	15 (71)
Unknown	12 (5)	0 (0)	2 (17)	8 (67)	17 (14)	2 (12)	7 (41)	4 (24)	17 (15)	0 (0.0)	9 (53)	8 (47)
NSAID*	277 (57)	27 (10)	71 (26)	173 (63)	106 (43)	18 (17)	37 (35)	48 (45)	89 (44)	15 (17)	36 (40)	21 (24)
OTC	30 (11)	5 (17)	14 (47)	11 (37)	18 (17)	3 (17)	12 (67)	3 (17)	17 (19)	5 (29)	9 (53)	1 (6)
Prescription	235 (85)	20 (9)	55 (23)	156 (66)	82 (77)	14 (17)	23 (28)	44 (54)	60 (67)	7 (12)	21 (35)	31 (52)
Unknown	12 (4)	2 (17)	2 (17)	6 (50)	6 (6)	1 (17)	1 (17)	2 (33)	12 (14)	2 (17)	5 (42)	2 (17)
Opioid	82 (17)	2 (2)	18 (22)	59 (72)	51 (21)	2 (4)	12 (24)	34 (67)	35 (17)	2 (6)	8 (23)	23 (66)
Muscle relaxant	37 (8)	4 (11)	14 (38)	19 (51)	11 (5)	3 (27)	3 (27)	5 (46)	12 (6)	1 (8)	1 (8)	9 (75)
Antidepressant	5 (1)	1 (20)	0 (0)	4 (80)	7 (3)	0 (0)	0 (0)	7 (100)	4 (2)	0 (0)	0 (0)	4 (100)
Anticonvulsant	4 (1)	0 (0)	0 (0)	4 (100)	4 (2)	0 (0)	0 (0)	1 (25)	5 (3)	0 (0)	0 (0)	4 (80)
Other	10 (2)	0 (0)	0 (0)	10 (100)	10 (4)	0 (0)	3 (30)	7 (70)	7 (3)	0 (0)	3 (43)	3 (43)

OTC: Over-the-counter; All results are presented as numbers (%); Weekly indicates medication use 1-5 times a week; Missing values ranged from 0-75%; * At baseline 5 patients used both OTC and prescribed NSAIDs, compared with 3 patients who did so at 3-months follow-up

use. Of these patients, 14 reported daily use of paracetamol and 9 reported daily use of NSAIDs. Also, 15 patients (2%) reported opioid use at all three measurement points, 7 of whom reported daily use.

Medication use at baseline was compared between the age groups (table 3). Paracetamol was more often used by patients aged ≥75 years (60%) compared with relatively younger patients (46%), while NSAIDs were more often used by patients aged 55–74 years (61% vs 40%). Patients with severe back pain (NRS ≥7) more often used

Table 3. Analgesic use at baseline and at 3 and 6-months follow-up classified by severity of back pain (<7 vs. ≥7), age (55-74 vs. ≥75 years), and duration of back pain (<3 vs. ≥3 months).

		No severe pain	Severe pain	p-value	55-74 years	≥75 years	p-value	<3 months	≥3 months	p-value
Baseline										
	n=484	n=265	n=216		n=404	n=80		n=331	n=104	
Paracetamol	235 (49)	119 (45)	116 (54)	**0.04**	187 (46)	48 (60)	**0.02**	149 (45)	60 (58)	**0.03**
NSAID	277 (57)	157 (59)	117 (54)	0.48	245 (61)	32 (40)	**<0.001**	203 (61)	45 (43)	**<0.01**
Opioid	82 (17)	34 (13)	48 (22)	**<0.01**	67 (17)	15 (19)	0.59	62 (19)	13 (13)	0.13
Muscle relaxant	37 (8)	14 (5)	23 (11)	**0.02**	34 (8)	3 (4)	0.16	31 (9)	4 (4)	0.07
Antidepressant	5 (1)	2 (1)	3 (1)	0.66*	3 (1)	2 (3)	0.19*	2 (1)	2 (2)	0.24*
Anticonvulsant	4 (1)	3 (1)	1 (1)	0.63*	3 (1)	1 (1)	0.51*	1 (1)	2 (2)	0.14*
Other	10 (2)	5 (2)	5 (2)	0.76*	7 (2)	3 (4)	0.21*	9 (3)	1 (1)	0.46*
3-months follow-up										
	n=245	n=119	n=125		n=197	n=48		n=136	n=76	
Paracetamol	126 (51)	58 (49)	68 (54)	0.45	100 (51)	26 (54)	0.64	67 (49)	39 (51)	0.71
NSAID	106 (43)	57 (47)	48 (38)	0.16	87 (44)	19 (40)	0.71	66 (49)	27 (36)	0.06
Opioid	51 (21)	17 (14)	34 (27)	**0.01**	40 (20)	11 (23)	0.69	28 (21)	18 (24)	0.60
Muscle relaxant	11 (5)	2 (2)	9 (7)	**0.04**	8 (4)	3 (6)	0.44*	10 (7)	0 (0)	**0.02***
Antidepressant	7 (3)	4 (3	3 (2)	0.72*	6 (3)	1 (2)	1.00*	4 (3)	3 (4)	0.70*
Anticonvulsant	4 (2)	2 (2)	2 (2)	1.00*	2 (1)	2 (4)	0.17*	1 (1)	3 (4)	0.13*
Other	10 (4)	4 (3)	6 (5)	0.75*	8 (4)	2 (4)	1.00*	4 (3)	3 (4)	0.70*
6-months follow-up										
	n=204	n=99	n=104		n=156	n=48		n=112	n=64	
Paracetamol	115 (56)	54 (55)	60 (58)	0.71	84 (54)	31 (65)	0.20	62 (55)	35 (55)	0.88
NSAID	89 (44)	48 (49)	40 (39)	0.15	71 (46)	18 (38)	0.44	49 (44)	25 (39)	0.57
Opioid	35 (17)	10 (10)	25 (24)	**<0.01**	27 (17)	8 (17)	1.00	19 (17)	13 (20)	0.58
Muscle relaxant	12 (6)	4 (4)	8 (8)	0.28	9 (6)	3 (6)	1.00*	9 (8)	2 (3)	0.33*
Antidepressant	4 (2)	2 (2)	2 (2)	1.00*	4 (3)	0 (0)	0.58*	1 (1)	3 (5)	0.14*
Anticonvulsant	5 (3)	2 (2)	3 (3)	1.00*	3 (2)	2 (4)	0.32*	2 (2)	3 (5)	0.36*
Other	7 (3)	5 (5)	2 (2)	0.27*	6 (4)	1 (2)	1.00*	3 (3)	2 (3)	1.00*

All results are presented as numbers (%); *Fisher's exact test; Missing values ranged from 0-14%; Bold numbers indicate a p-value <0.05

paracetamol, opioids, and muscle relaxants. Patients with chronic pain (≥3 months) more often used paracetamol (58% vs 45%), while patients with acute complaints more often used NSAIDs (61% vs 43%).

At 3-month follow-up, there were no longer any differences between the age groups in analgesic usage. However, patients with severe back pain (NRS ≥7) at baseline still more often used opioids (27% vs 14%) and muscle relaxants (7% vs 2%) at 3-month follow-up compared with patients with less severe back pain.

At 6-month follow-up, no difference in muscle relaxant usage was reported; however, opioids were still used more often by patients with severe back pain at baseline compared with those with less severe back pain at baseline.

Fifty-four percent of all patients also reported at least one (additional) visit to their GP, a physiotherapist, or a medical specialist in the 6 months after baseline. Of the 484 patients reporting medication use at baseline, 33% visited their GP vs 22% of the patients who did not use analgesics at baseline ($P < 0.001$), and 40% of the 484 visited a physiotherapist; in the patients who did not use medication at baseline, the rate was 69% (p 0.74). Medical specialists were visited by 17% of the patients taking medication at baseline and by 8% of those who did not use any medication at baseline ($P < 0.01$).

DISCUSSION

Summary of Results

The present study explores over-the-counter and prescribed analgesic use in older adults with back pain in general practice; ≥70% of these patients reported the use of analgesics. Medication use declined during the 6 months post-baseline. At baseline, NSAIDs were more often used by the relatively younger patients (55–74 years); this may indicate that GPs take into account possible adverse drug reactions related to NSAIDs, especially among older adults. Nevertheless, 40% of those aged ≥75 years used NSAIDs at baseline and at 3- and 6-month follow-up. Patients with severe back pain at baseline more frequently used paracetamol, opioids, and muscle relaxants at baseline and at 3-month follow-up compared with patients with less severe pain at baseline; there was no difference in NSAID use between these groups. All differences in medication use between the age groups and between groups with different durations of complaints had disappeared at 3 months post-baseline.

Interpretation of Findings

Previous studies reported that NSAIDs are the most often prescribed medication for low back pain;[16 31] however, these studies did not take into account over-the-counter medication. We hypothesized that because patients frequently use over-the-counter

paracetamol, it was probably underrepresented in these types of studies. However, the present study showed that (at baseline) NSAIDs were the most frequently used analgesics in older patients (85% obtained by prescription and 11% over-the-counter). During the study period, paracetamol was mostly obtained over-the-counter (69%). The Dutch guidelines for acute low back pain recommend that when medication is prescribed, it should be done on a time contingency basis, with paracetamol as first-choice medication. If there is insufficient pain relief with paracetamol alone, the second step is the use of NSAIDs.[32 33] This is in line with international guidelines.[5] However, patients in the present study most often used NSAIDs, which may not be in line with guideline recommendations. For patients with chronic back pain, the Dutch and European guidelines recommend NSAIDs and (weak) opioids for short-term pain relief.[32-34] The European guideline complements this with the recommendation to consider antidepressants as comedication.[34] In the present study, most patients with chronic pain at baseline used paracetamol, followed by NSAIDs and then by opioids. Antidepressants were used by very few patients (2%) with chronic back pain. In the present study, because details on comorbidity, comedication and other considerations possibly taken into account by the GPs were unknown, it is difficult to draw conclusions about whether analgesic use was in line with current guideline recommendations.

The finding that over 70% of our patients consulting their GP reported use of analgesics is similar to that of Cherkin et al., who reported that about 80% of patients used medication after visiting their GP.[31] Cherkin et al. also reported a similar (but slightly greater) decrease; after 7 weeks, only 13% of their patients used any medication, whereas in our study, after 3 months, 36% of the patients reported analgesic usage. However, patients in the study of Cherkin et al. were younger (mean age 43 years) than our study population.

In a study by Luo et al., older adults (≥65 years) were also less likely to be prescribed traditional NSAIDs compared with younger patients, while there was no prescription difference in cyclooxygenase-2 (COX-2) inhibitors.[15] Federman et al. found that patients aged ≥75 years in an outpatient setting were more likely to use NSAIDs, but mostly used COX-2 inhibitors.[14] However, Federman et al. excluded patients with a contraindication for NSAIDs, which might explain the difference compared with the study of Luo et al. and with the present study. Federman et al. also reported that opioids were less frequently used by older adults,[14] whereas we found no difference in opioid use between our younger and older age categories.

An Australian study in the open population found that analgesics (opioids and combination analgesics) were more often used in those with the highest scores for low back pain.[35]

Another study showed that patients (in primary and secondary care settings) with chronic low back pain who reported increased severity of back pain had increased num-

bers of prescriptions for opioids and decreased numbers of prescriptions for NSAIDs.[18] This is similar to our finding that there was no difference in NSAID use between the subgroups, while there was a difference in opioid use between the subgroups.

Older patients with back pain are more likely to be prescribed analgesics than younger patients.[4 16] This is remarkable, because older patients are more prone to adverse drug reactions, especially in the case of comedication or of comorbidities such as liver or kidney failure. An Australian study found that for over-the-counter medication, 1.9% of paracetamol users and 23.1% of ibuprofen users had contraindications for these analgesics.[36] In another open population, it was shown that 10% of older patients with low back pain used NSAIDs while they were also using a diuretic and an angiotensin-converting enzyme inhibitor or angiotensin II receptor antagonist;[35] such patients are at increased risk of acute renal failure.[37] In our study population, we did not ask about other types of medication use and therefore cannot judge whether our patients were at risk for adverse drug reactions. Also, because we did not ask about the analgesic dose, we could not determine whether the dosage used might potentially cause an adverse drug reaction. We did record that 5 patients at baseline and 3 patients at 3-month follow-up used NSAIDs obtained both by prescription and over-the-counter. However, because we asked about medication use during the previous 3 months, we cannot evaluate whether these medications were used simultaneously. Nevertheless, it should be noted that patients are not always aware of the risks of using over-the-counter medication.[8]

Strengths and Limitations

We used questionnaires to ask patients which analgesics they used for their back pain; this enabled us to report on both prescribed and over-the-counter analgesics. Although this provides more information than data derived from medical records alone, there is a possibility of recall bias. However, it has been reported that patients with chronic disease (including low back pain) generally show good concordance between self-reported medication use and data in the patient's medical record.[38] For ethical reasons, we could not ask patients who did not participate in the study any questions. Therefore, we could not make any comparisons between patients who did and did not participate in the study regarding generalizability.

Conclusions

In this group of patients aged ≥55 years who consulted their GP with back pain, 72% used analgesics at baseline, paracetamol and NSAIDs being the most frequently used. Although a decrease in medication use was seen during follow-up, a substantial proportion of these older adults still used analgesics at 3- and 6-month follow-up (36% and 30%, respectively).

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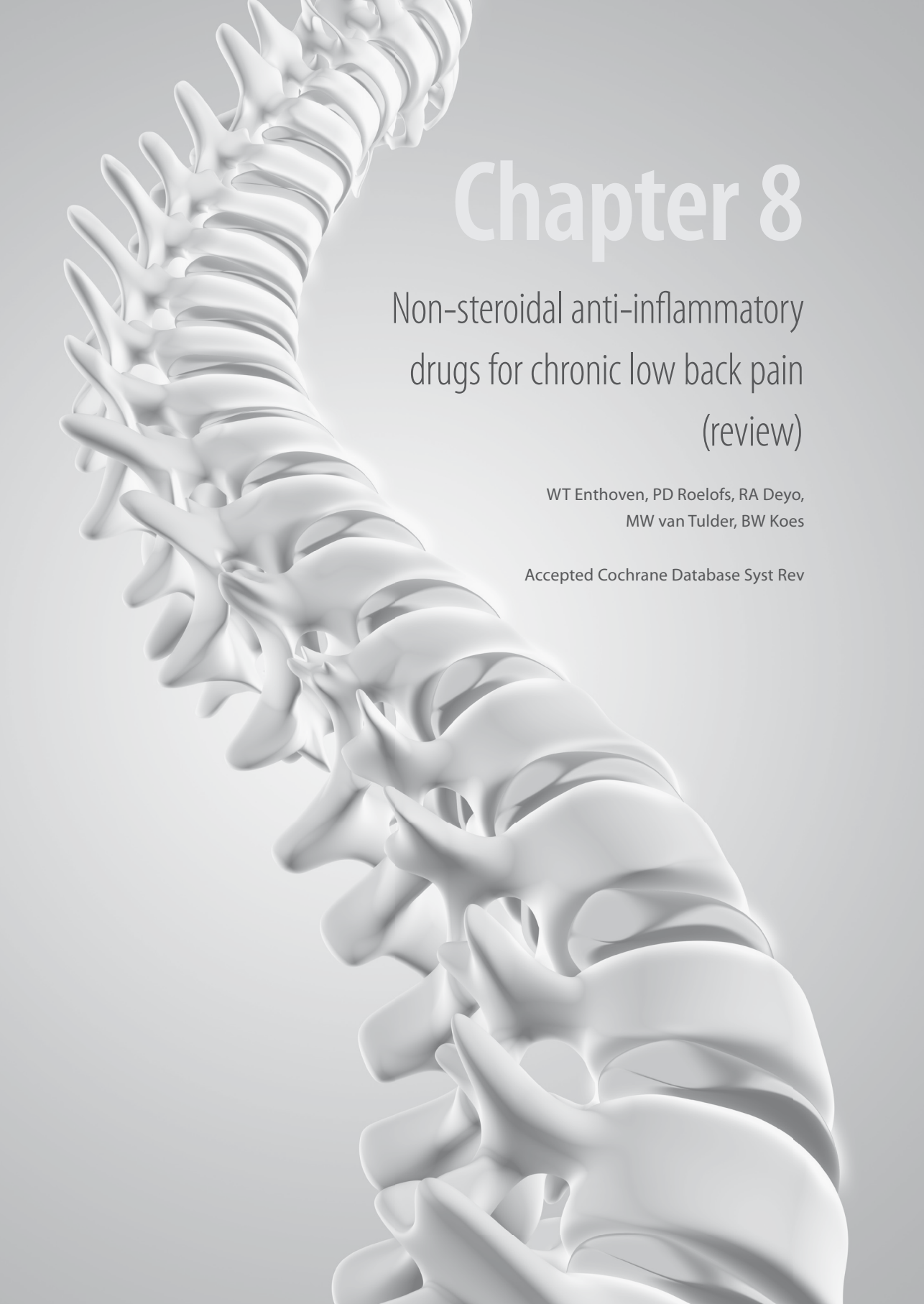

Chapter 8

Non-steroidal anti-inflammatory drugs for chronic low back pain (review)

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Accepted Cochrane Database Syst Rev

ABSTRACT

Background

Chronic back pain is an important health problem. Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used in the treatment of low back pain. Particularly patients with acute back pain can receive NSAIDs for their back pain, but also in chronic back pain patients short term NSAID use is recommended for pain relief. There are two types of NSAIDs available and used in the treatment of back pain: non-selective NSAIDs and selective COX-2 NSAIDs. In 2008 a Cochrane review was performed and identified a small but significant effect from NSAIDs compared to placebo in patients with chronic back pain. This is an update of the Cochrane review published in 2008 focusing on chronic low back pain.

Objectives

The aim of the study was to determine if NSAIDs are more efficacious than various comparison treatments for non-specific chronic low-back pain and if so, which type of NSAID is most efficacious.

Search methods

The MEDLINE, EMBASE, CENTRAL, PubMed and two clinical trials registry databases were searched for randomized controlled trials reported in English, German or Dutch until June 2015. We also screened references given in relevant reviews.

Selection criteria

Randomised controlled trials (double-blind and single-blind) of NSAIDs in the treatment of chronic low back pain were included.

Data collection and analysis

Two review authors independently selected the trials to be included in the systematic review according to the inclusion criteria. One review author extracted the data, and a second review author checked the data. Two authors independently evaluated the risk of bias of all included articles. If data were considered clinically homogeneous, a meta-analysis was performed and quality of evidence was assessed using GRADE.

Results

Thirteen trials were included in this review. Ten of these studies scored 'low risk of bias' and were considered high quality research. Six studies compared NSAIDs with placebo. There is low quality evidence that NSAIDs are more effective than placebo, with a mean difference in pain intensity score from baseline of -3.30 (95% CI -5.33 to -1.27) on a 0-100

visual analogue scale (VAS) with a median follow-up of 56 days (IQR 13-91 days). Disability was measured in three studies with the Roland Morris Disability Questionnaire. There is low quality evidence that NSAIDs are more effective than placebo on disability, with a mean difference from baseline of -0.85 (95% CI -1.30 to -0.40) on a scale from 0 to 24 with a median follow-up of 84 days (IQR 42-105 days). Adverse events were also reported in all six studies, the pooled RR for adverse events was 1.04 (95% CI 0.92 to 1.17), suggesting that adverse events are not statistically significant more frequent in patients using NSAIDs compared to placebo. Due to relatively small sample size and relatively short follow-up in most studies, it is likely that the proportion of patients experiencing an adverse event is underestimated. Therefore it is not possible to make firm statements about the occurrence of adverse events.

There were two studies which compared different types of non-selective NSAIDs, namely ibuprofen compared to diclofenac and piroxicam compared to indomethacin. No differences between these types of NSAIDs were found, but sample size in both studies were small. One study reported no differences on pain intensity between selective and non-selective NSAIDs. One other study compared diflunisal with paracetamol and showed no difference in improvement from baseline on pain intensity score. One study showed a better global improvement in favour of celecoxib compared to tramadol.

NSAIDs were compared in one study with 'home-based exercise'. Disability improved more in patients doing exercises compared to patients receiving NSAIDs, but pain scores were similar.

Authors' conclusions

The evidence of six of the thirteen included studies showed that NSAIDs are more effective than placebo on pain intensity. NSAIDs are slightly more effective than placebo with regard to disability. However, the magnitude of the effects are small, and the quality of evidence is low. When only studies with low risk of bias are included, the differences in effect between NSAIDs and placebo are reduced. We identified no difference in efficacy between different types of NSAIDs, including selective versus non-selective NSAIDs. Due to selection of RCTs, the relatively small sample sizes, and relatively short follow-up in most studies, it is not possible to make firm statements about the occurrence of adverse events or whether NSAIDs are safe for long-term use.

INTRODUCTION

Description of the condition

Back pain is a major health problem with a reported lifetime prevalence of up to 84%.[1 2] More than one quarter of North Americans reported to have experienced low back pain within the previous three months[3] and low back pain is a leading cause of years lived with disability.[4] In the first three months recovery occurs in a substantial part of the patients, but the majority of patients still experience pain after one year.[5] Having chronic back pain is associated with more disability and these patients make a great demand on the health-care system.[6] Also, of patients experiencing any chronic pain, back pain is the most common[7] and patients with chronic back pain have a higher healthcare utilization compared to patients with acute back pain.[8] For treatment, guidelines recommend staying active and exercising, if necessary with the use of analgesics. Non-steroidal anti-inflammatory drugs (NSAIDs) are one of the most frequently used analgesics in the management of back pain.[9 10] Particularly patients with acute back pain can receive NSAIDs for their back pain, but also in chronic back pain patients short term NSAID use is recommended for pain relief.[11]

Description of the intervention

Most guidelines on treatment of back pain recommend using paracetamol as first choice, followed by NSAIDs if paracetamol is not sufficient.[12] NSAIDs are widely available in several types and brands and both over-the-counter and on prescription. The NSAID treatment is based on the analgesic and anti-inflammatory mechanisms of the drug, but is also associated with adverse events, such as gastro-intestinal[13 14] and cardiovascular events.[15]

How the intervention might work

Cyclooxygenase one (COX-1) and two (COX-2) are key enzymes in the synthesis of prostaglandins, which contribute to inflammation, pain, and fever. NSAIDs inhibit the COX enzyme and therefore the production of prostaglandins will be inhibited. Consequently this can reduce the inflammation, pain and fever. COX-1 produces prostaglandins that also support platelets and protect the stomach lining. It also helps to maintain kidney function. Inhibition of COX-1 can raise the risk of renal insufficiency and gastro-intestinal adverse-events such as gastritis or stomach bleeding.

There are two types of NSAIDs: non-selective NSAIDs which inhibit both COX-1 and COX-2 enzymes and selective NSAIDs which inhibit only the COX-2 enzyme. Both selective and non-selective NSAIDs are available for the treatment of pain, and the choice of NSAID is mostly based on the different possible known adverse events, convenience of use, and cost.

Nonselective or traditional NSAIDs have a higher risk compared to the selective NSAIDs on gastro-intestinal adverse events[13] due to the inhibition of both COX enzymes. However, aside from these gastro-intestinal benefits of selective NSAIDs, there is a known cardiovascular risk in these types of NSAIDs. Cardiovascular risks are also present in nonselective NSAIDs and should be taken into account when prescribing any NSAIDs.[16 17]

Why it is important to do this review

This Cochrane review is one of a series of Cochrane reviews of non-steroidal anti-inflammatory drugs for low back pain and is an update of a Cochrane review first published in 2008.[18] The original review consisted of 65 randomized controlled trials on acute back pain, chronic back pain and sciatica. Many articles were available for update, and therefore we decided to make a series of Cochrane reviews regarding NSAID use for acute back pain, chronic back pain and sciatica. Also, efficacy of treatment with NSAIDs can differ among these different types of back pain. This review focusses on NSAIDs for chronic low back pain.

Objectives

The objective of this systematic review was to determine if NSAIDs are more efficacious than various comparison treatments for non-specific chronic low-back pain and if so, which type of NSAID is most efficacious. Comparisons of NSAIDs with reference treatments that were investigated are NSAIDs versus placebo, NSAIDs versus other drugs (e.g. acetaminophen/paracetamol, pregabalin, narcotic analgesics or muscle relaxants), NSAIDs versus NSAIDs (e.g. traditional NSAIDs versus selective COX-2 inhibitors), and NSAIDs versus non-drug treatment.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (double-blind and single-blind) were included. Only English, German and Dutch studies were included in the review, since this was stated in the original protocol.

Types of participants

Subjects age 18 years or older, treated for non-specific chronic low-back pain were included. Chronic back pain was defined as at least twelve weeks. If the duration of back pain was not described, but back pain was labelled as chronic, the study was also

included. If a study included mixed populations (like chronic back pain and subacute or acute back pain), studies were only included if data of chronic back pain was presented separately. Subjects with sciatica and subjects with specific low-back pain caused by pathological entities such as infection, neoplasm, metastasis, osteoporosis, rheumatoid arthritis, or fractures were excluded.

Types of interventions

Studies assessing one or more types of NSAIDs were included. Additional interventions were allowed if there was a contrast for NSAIDs in the study. For example, studies comparing NSAIDs plus muscle relaxants versus muscle relaxants alone were included, while studies comparing NSAIDs plus muscle relaxants versus paracetamol were not.

NSAIDs which were no longer available on the market, like rofecoxib, were excluded from the review.

Types of outcome measures

Primary outcomes

Primary outcome measures were: 1) pain intensity (e.g. Visual Analog Scale or Numerical Rating Scale), 2) global measure (e.g. overall improvement, proportion of patients recovered), 3) back pain-specific functional status (e.g. Roland Disability Questionnaire, Oswestry Scale), 4) return to work (e.g. return to work status, number of days off work), and 5) adverse events (proportion of patients experiencing adverse events).

Secondary outcomes

Secondary outcome measures were physiological outcomes (e.g. range of motion, spinal flexibility, degrees of straight leg raising or muscle strength) and generic functional status (e.g. SF-36, Nottingham Health Profile, Sickness Impact Profile). Other symptoms such as health care consumption were also considered.

Search methods for identification of studies

Electronic searches

RCTs meeting our inclusion criteria were identified by a search of the following databases on June 24th, 2015:

- Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library, Issue 5 of 12, May 2015)
- MEDLINE (OvidSP, 1946 to June Week 2 2015)
- MEDLINE In-Process & Other Non-Indexed Citations (OvidSP, June 23, 2015)
- EMBASE (OvidSP, 1980 to 2015 Week 25)
- ClinicalTrials.gov

- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP)
- PubMed

For this update, the searches were conducted annually between May 2012 and June 2015. The trials registers were added in 2013, MEDLINE In-Process & Other Non-Indexed Citations was added in 2014, and PubMed was added in 2015 to identify studies not in MEDLINE using the strategy recommended by Duffy et al.[19] Search strategies are presented in Appendix 1; Appendix 2; Appendix 3; Appendix 4;and Appendix 5 (online available only).

The searches were devised and run by a research librarian from the Cochrane Back and Neck Review Group according to their guidelines.[20]

Searching other resources

After the electronic search, systematic reviews regarding NSAIDs for chronic low back pain were screened. Articles included in the previous version of this review[18] were also included.

Data collection and analysis

Selection of studies

All search results were screened independently by two authors (BK and PR or PR and WE). Clearly ineligible studies were excluded based on title and abstract. Full text articles were retrieved for all remaining studies and these were again screened independently by two authors for inclusion. Disagreements regarding inclusion were resolved via consensus

Data extraction and management

One review author (WE) extracted the data, a second review author (PR) checked the data. Data were extracted on type and dose of NSAIDs, type of reference treatment, follow-up time, duration of current symptoms, and the outcomes described above. If data were not available for data extraction due to different format, authors of the trial were contacted for further information. Any disagreement was resolved through consensus.

Assessment of risk of bias in included studies

Two authors (WE and PR) independently evaluated the risk of bias of all included articles, using the criteria list recommended by the Cochrane Back Review Group[20] and described in Appendix 6 (online available only). The criteria were scored as 'low risk', 'high risk' or 'unclear'. If the criteria were scored as unclear, authors were not followed up to provide

extra information. Disagreements were resolved by consensus and a third review author was consulted if disagreements persisted.

Measures of treatment effect

The primary outcome pain intensity was measured with the Visual Analogue Scale (VAS) or Numerical Rating Scale (NRS) on a scale from 0 to 100 and 0 to 10 respectively. Global improvement was measured by the proportion of patients recovered. Disability was measured on different disability scales, (e.g. Roland Morris Disability Questionnaire (RDQ) on a 0 to 24 scale). Adverse events were measured by the proportion of patients experiencing any adverse event.

Dealing with missing data

Data that were not reported in the article were not included in the review and were considered missing. If data were not described in the text, but were shown in graphs, data were collected from the graphs.

Assessment of heterogeneity

Clinical heterogeneity was assessed for all included studies that reported similar outcomes. The studies were judged on setting, participants and intervention. If studies were clinically heterogeneous, they were not pooled. Statistical heterogeneity was assessed by chi-square test and I^2. If values of I^2 were higher than 50% substantial heterogeneity could be present[21] and pooling was performed using a random effects model. When no, low or moderate heterogeneity was suspected a fixed effects model was used.

Assessment of reporting biases

Funnel plots were used to investigate reporting bias, when at least four trials were included in a particular comparison.

Data synthesis

Dichotomous outcomes were analysed by calculating the relative risk (RR). Continuous outcomes were analysed by calculating the mean difference (MD) when the same instrument was used to measure outcomes or the standardized mean difference (SMD) when different instruments were used to measure the outcomes. The uncertainty was expressed with 95% confidence intervals (95% CI). The outcome measures from the individual trials were combined through meta-analysis where possible (clinical comparability of population, intervention and outcomes among trials) using a fixed-effect model unless there was significant statistical heterogeneity, in which case a random-effects model was used. A P value of the Chi^2 test that is less than 0.05 indicates a significant

statistical heterogeneity. If a meta-analysis was not possible, the results from clinically comparable trials were described in the text.

We assessed the overall quality of the evidence for each outcome using the GRADE approach, as recommended in The Handbook[21] and adapted in the updated CBRG method guidelines.[20] Factors that may decrease the quality of the evidence were: study design and risk of bias, inconsistency of results, indirectness (not generalizable), imprecision (sparse data) and other factors (e.g. reporting bias). The quality of the evidence for a specific outcome was reduced by a level, according to the performance of the studies against these five factors.

- High quality evidence: there are consistent findings among at least 75% of RCTs with low risk of bias, consistent, direct and precise data and no known or suspected publication biases. Further research is unlikely to change either the estimate or our confidence in the results.
- Moderate quality evidence: one of the domains is not met. Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
- Low quality evidence: two of the domains are not met. Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
- Very low quality evidence: three of the domains are not met. We are very uncertain about the results.
- No evidence: no RCTs were identified that addressed this outcome

Subgroup analysis and investigation of heterogeneity

Subgroup analyses were performed on analysis where both non selective and selective NSAIDs were present. These results were split into results for non-selective and selective NSAIDs.

Sensitivity analysis

A sensitivity analysis was performed on the comparison between NSAIDs and placebo. Studies with high risk of bias (less than six positive items on the risk of bias table) or studies with a 'flare design' were not included in this analysis. A study with a 'flare design' only included patients who previous used NSAIDs and showed an aggravation of the back complaints during a wash out period.

RESULTS

Description of studies

Results of the search

The search update for this review identified a total of 2158 potential articles in the electronic search (figure 1). After screening the titles and abstracts, full texts were assessed and thirteen articles were identified for inclusion in this review. Amongst these were seven of the nine articles on chronic low back pain from the previous review. Two studies reported on rofecoxib which was withdrawn from the market and were excluded from this review.[22 23]

Included studies

The sample size of the thirteen included studies ranged from 28 to 1593 patients, with a total of 4807 included patients in all studies. In six studies NSAIDs were compared with placebo.[24-29] Three studies compared two different types of NSAIDs.[30-32] One study compared NSAIDs versus paracetamol,[33] one study compared NSAIDs versus tramadol,[34] and one study compared NSAIDs versus pregabalin.[35] Exercise therapy was compared to NSAIDs in one study.[36]

Excluded studies

Excluded studies are described in 'Characteristics of excluded studies' (online available only). Most studies were excluded because there was an unclear period of back pain or the study was not an RCT.

Risk of bias in included studies

Risk of bias assessment is presented in figure 2 and 3. Of twelve items on risk of bias, the included studies ranged from four to nine items meeting criteria for low risk of bias. Ten of the thirteen studies scored low risk of bias on at least six items and were considered high quality studies.[25-30 32-34 36]

Allocation (selection bias)

Of the thirteen included studies, six reported a randomization procedure[24 26 27 33 34 36] and of these six studies only four also described concealment of treatment allocation.[26 33 34 36] Most studies did not report the method of randomization or allocation concealment and were scored 'unclear' on these items.

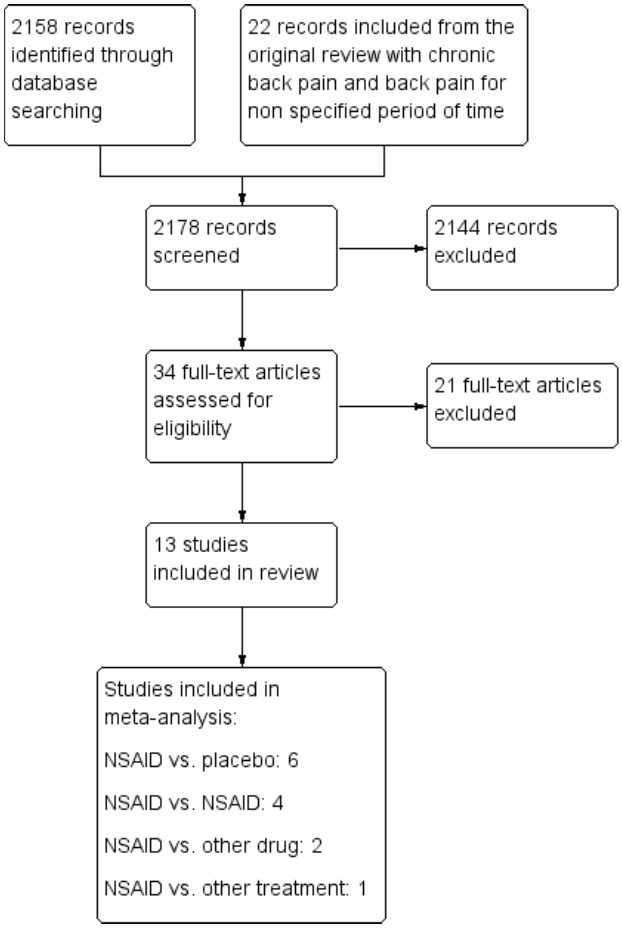

Figure 1. Study flow diagram

Blinding (performance bias and detection bias)

Blinding of patients, care providers and outcome assessors was reported in seven of the thirteen studies.[25 26 30-34] The other studies did not blind patients, and/or care providers, and/or outcome assessors or they did not report on blinding.

Incomplete outcome data (attrition bias)

Six of the studies reported low drop-out rates.[25 31-33 35 36] The seven other studies reported drop-out rates higher than 20%.[24 26-30 34]

An intention to treat analysis was performed in only three studies.[27 28 34]

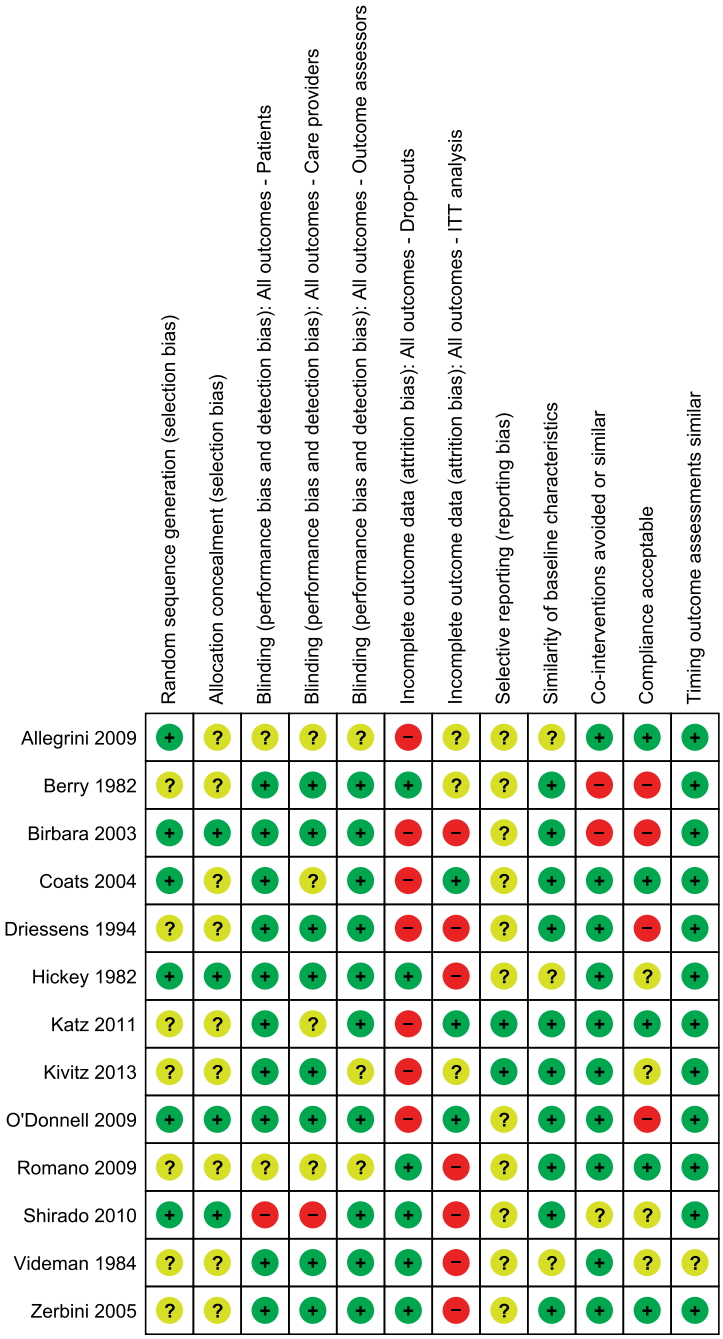

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study

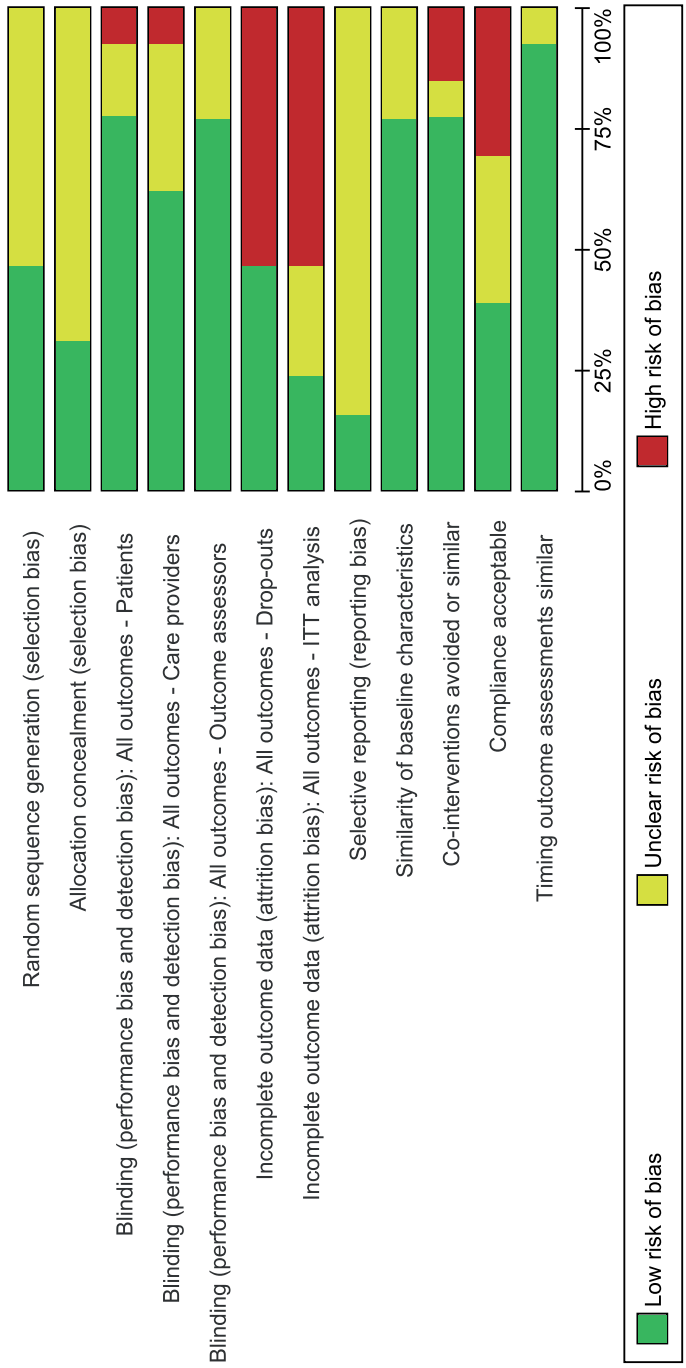

Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies

Selective reporting (reporting bias)

Only two studies were registered in an accessible clinical trial registry[28 29] and were listed as having low risk of reporting bias.

Other potential sources of bias

Most studies showed similarity of baseline characteristics; only three studies did not report this.[24 31 33]

Regarding co-interventions, only paracetamol as rescue medication was allowed; other types of medication were not. All but two studies avoided co-interventions[25 26] and one study did not state anything about co-interventions.[36]

Compliance was reported in nine studies, and in five studies compliance was acceptable.[24 27 28 32 35] In four other studies compliance was not acceptable.[25 26 30 34]

Timing of outcome assessment was similar between the study groups in almost all studies.

Funnel plots were created to assess risk of publication bias and were used for the analysis of NSAIDs versus placebo (figure 4-6). We could not identify publication bias. No funnel plots were created for other comparisons, since there were less than four studies available for this analysis.

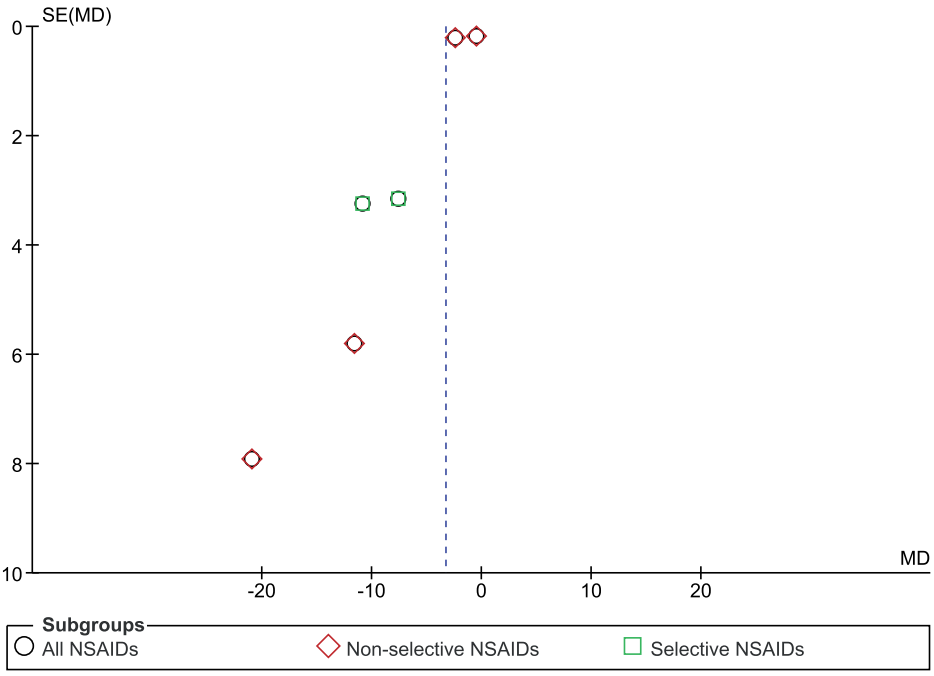

Figure 4. (analysis 1.1) Funnel plot of comparison: 1 NSAIDs versus placebo, outcome: 1.1 Change in Pain Intensity from baseline on 100mm VAS. Follow-up <=12 weeks

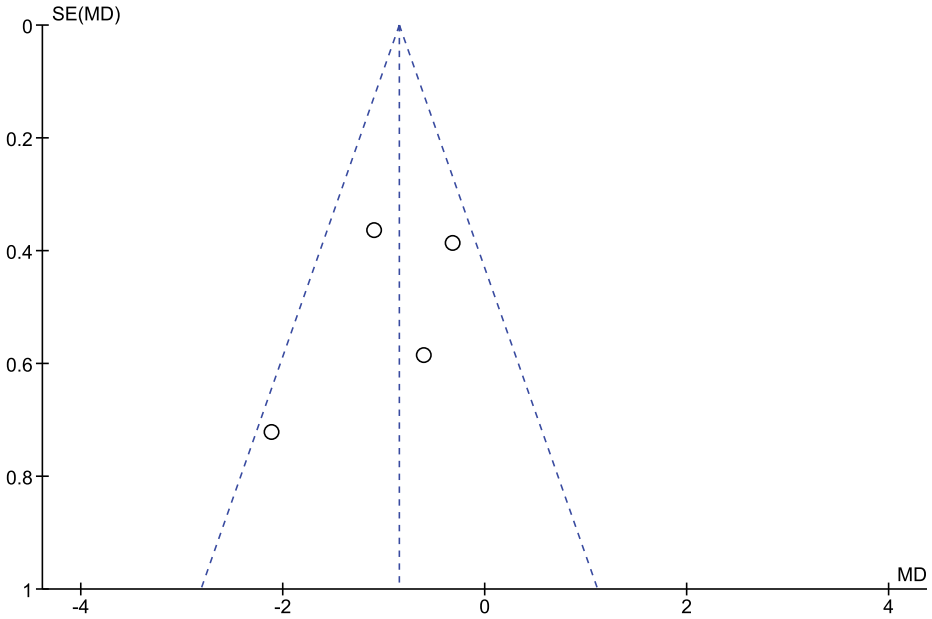

Figure 5. (analysis 1.2) Funnel plot of comparison: 1 NSAIDs versus placebo, outcome: 1.2 Change in Disability from baseline

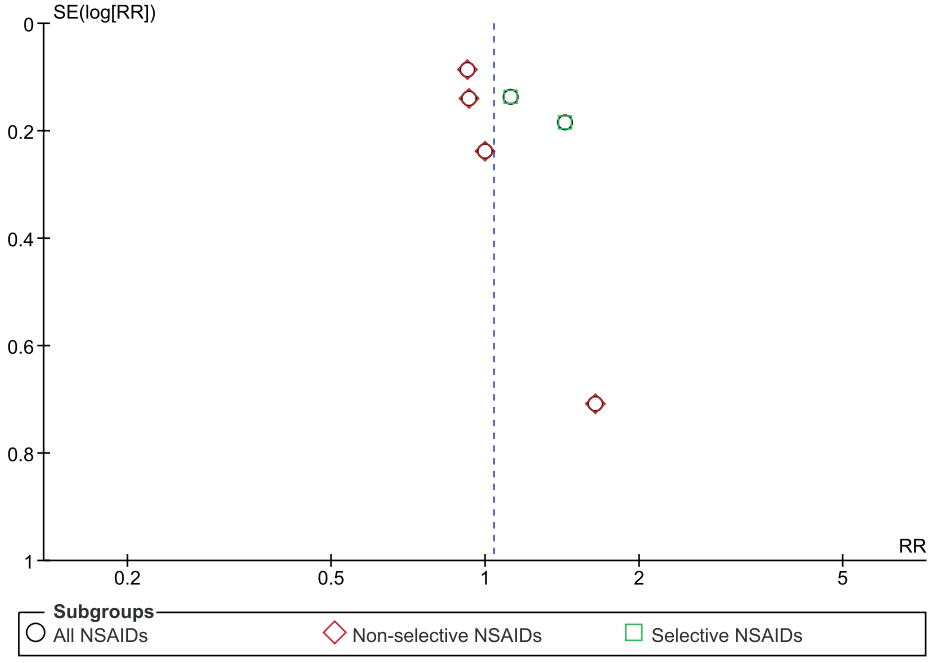

Figure 6. (analysis 1.3) Funnel plot of comparison: 1 NSAIDs versus placebo, outcome: 1.3 Proportion of patients experiencing adverse events. Follow-up <=16 weeks

A potential conflict of interest was reported in half of the studies. Three studies reported support from a pharmaceutical company[26 32 33] and in four studies authors had affiliations with a pharmaceutical company.[27-29 34] The remaining six studies did not report any potential conflict of interest.

Effects of interventions

See: Table 1. Summary of findings

Efficacy of NSAIDs compared to placebo

Six studies[24-29] compared NSAIDs with placebo. Median follow-up was 56 days (IQE 13-91 days). Half of these studies reported short-term outcomes of four weeks or less.[24 25 27] The other three studies had a duration of follow-up of 12 or 16 weeks.[26 28 29] Naproxen was the most common type of NSAID,[25 28 29] but also piroxicam patch, etoricoxib and valdecoxib were compared to placebo.

All studies reported pain intensity on a 100mm VAS or 11-point numerical rating scale (figure 7). The Chi^2 value for homogeneity of the mean difference (MD) was 66.26 (p=<0.0001) and I^2 92%, which could represent substantial statistical heterogeneity. This might be due to different types of NSAIDs used in the studies and a random effects model was used to pool these data. The pooled mean difference in pain intensity score from baseline was -3.30 (95% CI -5.33 to -1.27), indicating a statistically significant ef-

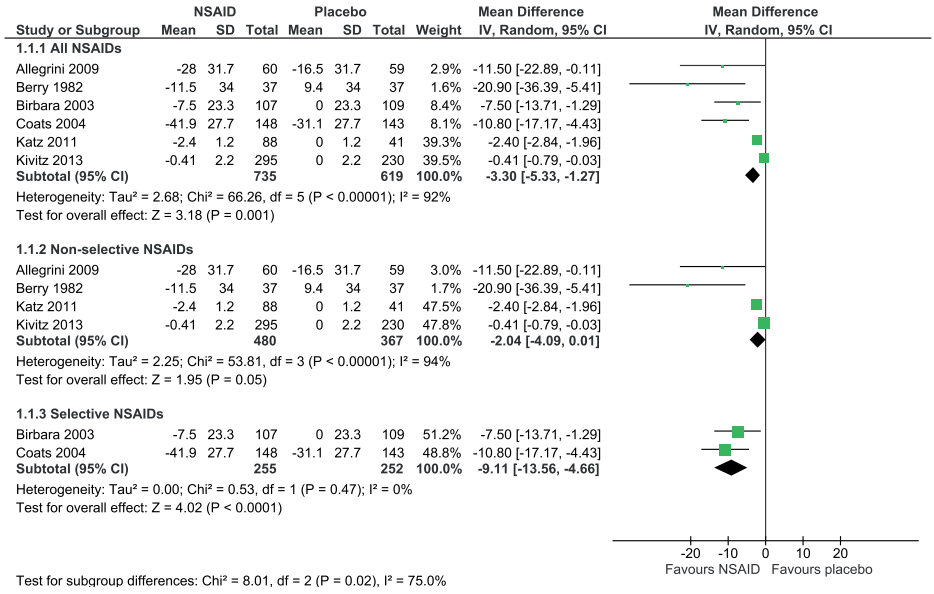

Figure 7. (analysis 1.1) Forest plot of comparison: 1 NSAIDs versus placebo, outcome: 1.1 Change in Pain Intensity from baseline on 100mm VAS. Follow up <=16 weeks

Table 1. Summary of findings

NSAIDs for chronic low back pain compared to placebo					
Patient or population: patients with chronic low back pain Intervention: NSAIDs					
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of Participants (studies)**	**Quality of the evidence (GRADE)**
	Assumed risk	**Corresponding risk**			
	Control	**NSAIDs**			
Change in Pain Intensity from baseline. 100mm VAS Follow-up: 9-112 days	not estimable	The mean change in pain intensity from baseline. in the intervention groups was **3.30 lower** (5.33 to 1.27 lower)		1354 (6 studies)	⊕⊕⊖⊖ **low**[1,2,3]
Change in Disability from baseline Roland Morris Disability Questionnaire 0-24 Follow-up: 4-16 weeks	not estimable	The mean change in disability from baseline in the intervention groups was **0.85 lower** (1.30 to 0.40 lower)		1161 (4 studies)	⊕⊕⊖⊖ **low**[3,4,5]
Proportion of patients experiencing adverse events. Follow-up: 9-112 days	Study population		**RR 1.04** (0.92 to 1.17)	1354 (6 studies)	⊕⊕⊖⊖ **low**[1,2,3]
	410 per 1000	427 per 1000 (378 to 480)			
	Moderate				
	477 per 1000	496 per 1000 (439 to 558)			
Sensitivity analysis Change in Pain Intensity from baseline. 100mm VAS Follow-up: 2-16 weeks	not estimable	The mean sensitivity analysis change in pain intensity from baseline. in the intervention groups was **1.73 lower** (3.77 lower to 0.31 higher)		728 (3 studies)	⊕⊕⊕⊖ **moderate**[6]
Sensitivity analysis Change in Disability from baseline Roland Morris Disability Questionnaire 0-24 Follow-up: 6-16 weeks	not estimable	The mean sensitivity analysis change in disability from baseline in the intervention groups was **0.41 lower** (1.04 lower to 0.23 higher)		654 (2 studies)	⊕⊕⊕⊖ **moderate**[7]
Sensitivity analysis Proportion of patients experiencing adverse events. Follow-up <=16 weeks. Follow-up: 2-16 weeks	Study population		**RR 0.93** (0.81 to 1.07)	728 (3 studies)	⊕⊕⊕⊖ **moderate**[6]
	536 per 1000	498 per 1000 (434 to 573)			
	Moderate				
	522 per 1000	485 per 1000 (423 to 559)			

*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Allocation concealment was uncertain in the majority of studies, and randomization was uncertain in half of the studies, therefore selection bias is likely. High drop-out rates were present in five out of six studies, so attrition bias is likely.
[2] In two out of six studies, cointerventions were allowed. Two studies included a 'flare design'.
[3] See funnel plot, publication bias could not be detected
[4] Allocation concealment was uncertain in the majority of studies. High drop-out rates were present in all four studies, so attrition bias is very likely.
[5] In one study cointerventions were allowed. One study included a 'flare design'.
[6] Allocation concealment and randomization was uncertain in all studies, therefore selection bias is likely. High drop-out rates were present in two out of three studies, so attrition bias is likely.
[7] Allocation concealment and randomization was uncertain in both studies, therefore selection bias is likely. High drop-out rates were present in both studies, so attrition bias is likely.

fect in favour of patients receiving NSAIDs compared to patients receiving placebo. The quality of this evidence defined by GRADE is low (Summary of findings table 1). When results were split into selective and non-selective NSAIDs versus placebo, there was still a substantial statistical heterogeneity among the studies considering non-selective NSAIDs, although three out of four studies used naproxen as study medication. There was statistical homogeneity among the studies on selective NSAIDs. The effect of selective NSAIDs became somewhat larger and the effect of non-selective NSAIDs became smaller and not significant (-2.04, 95% CI -4.09 to 0.01).

Four studies compared NSAIDs with placebo, with disability as outcome measure, measured with the Roland Morris Disability Questionnaire on a 0 to 24 scale (figure 8).[26-29] Median follow-up was 84 days (IQR 42-105 days). The Chi^2 value for homogeneity of the mean difference (MD) was 5.53 (P = 0.14) and I^2 46%, indicating that there could be moderate statistical heterogeneity among these studies. The pooled mean difference in disability from baseline was -0.85 (95% CI -1.30 to -0.40). The quality of this evidence defined by GRADE is low (Summary of findings table 1).

Adverse events were also reported in all studies. The Chi^2 value for homogeneity of the RR for adverse events in all studies was 6.22 (P = 0.28) and I^2 20%, indicating statistical homogeneity among the studies. The pooled RR for adverse events was 1.04 (95% CI 0.92 to 1.17) (figure 9), indicating that adverse events are not statistically significant more present in patients using NSAIDs compared to placebo. Quality of evidence of these studies was low using the GRADE approach (Summary of findings table 1). Results do not change when specified into selective and non-selective NSAIDs, although adverse events in selective NSAIDs show a trend in favour of placebo. However, RCTs have low power in detecting uncommon and delayed adverse events. Sample sizes of most studies were relatively small and duration of follow-up was relatively short. It is possible that not all adverse events have emerged, especially since most important adverse events are rare and can take weeks or months to evolve. Therefore, it is not possible to make firm statements about the difference in occurrence of adverse events between different types of NSAIDs.

Of the studies that compared NSAIDs with placebo, three studies were considered high risk of bias.[24 26 27] The latter two had used of a 'flare design'. A sensitivity analysis was

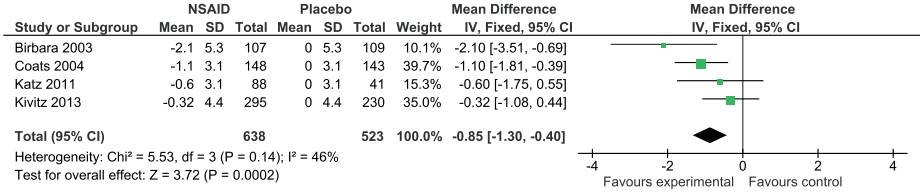

Figure 8. (analysis 1.2) Forest plot of comparison: 1 NSAIDs versus placebo, outcome: 1.2 Change in Disability from baseline

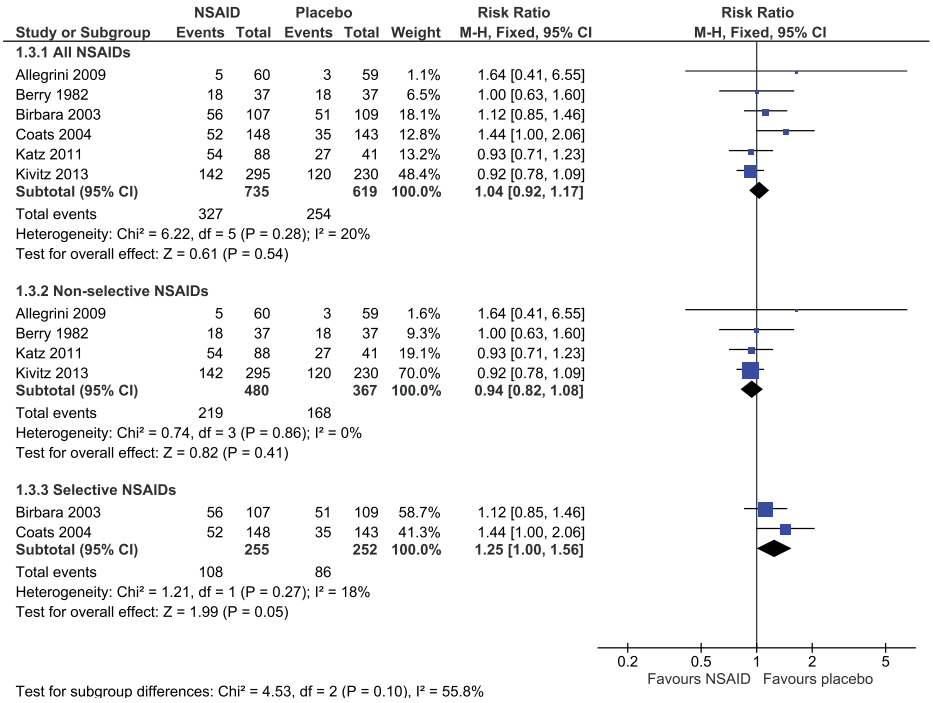

Figure 9. (analysis 1.3) Forest plot of comparison: 1 NSAIDs versus placebo, outcome: 1.3 Proportion of patients experiencing adverse events. Follow up <=16 weeks

performed with the three low risk of bias studies.[25 28 29] The difference between NSAIDs and placebo on pain intensity score on 0-100mm VAS and the disability measured with RDQ 0-24 became smaller and was no longer statistically significant (figure 10-12); difference between NSAIDs and placebo for pain intensity score of -1.73 (95% CI -3.77 to 0.31) and disability of -0.41 (95% CI -1.04 to 0.23). The quality of this evidence defined by GRADE is moderate (Summary of findings table 1).

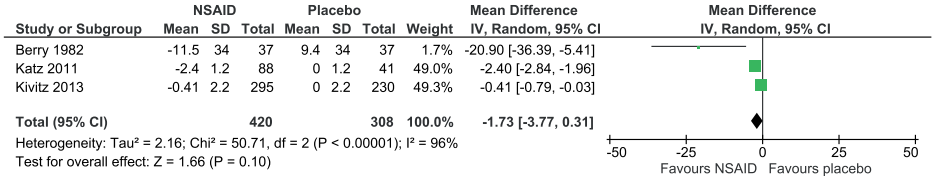

Figure 10. (analysis 1.4) Forest plot of comparison: 1 NSAIDs versus placebo, outcome: 1.4 Sensitivity analysis Change in Pain Intensity from baseline on 100mm VAS. Follow up <=16 weeks

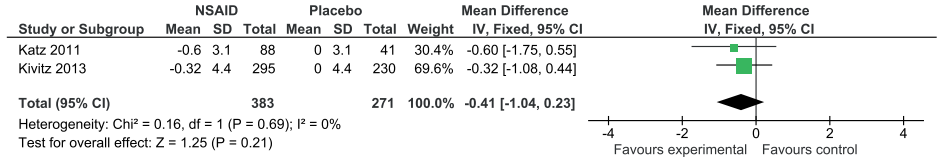

Figure 11. (analysis 1.5) Forest plot of comparison: 1 NSAIDs versus placebo, outcome: 1.5 Sensitivity analysis Change in Disability from baseline

Efficacy of selective versus non-selective NSAIDs and non-selective versus non-selective NSAIDs

Two studies[30 31] compared two types of non-selective NSAIDs. Driessens et al compared ibuprofen 1600mg/day and diclofenac 100mg/day for two weeks,[30] Videman et al compared piroxicam 20mg/day and indomethacin 75mg/day for six weeks.[31] Both studies found no significant difference between the two types of non-selective NSAIDs. It is possible that these studies were underpowered, since the sample size was 62 and 28 patients in both studies, respectively. Adverse events in the study of Driessens et al were statistically significant more present in the diclofenac group. In the study of Videman et al there was no statistically significant difference in experienced adverse events between the two study groups. One other study compared a non-selective NSAID with a COX-2 inhibitor (diclofenac 150mg/day versus etoricoxib 60mg/day for four weeks).[32] In this study 440 patients were included in the analysis and no significant difference in change in pain intensity from baseline between the NSAIDs and COX-2 inhibitors was found. Adverse events in general and specific gastrointestinal adverse events were also examined, but no differences between the two study groups were found.

Efficacy of NSAIDs versus other drugs

NSAIDs compared to other drug types are shown in figure 13 and 14. These studies were not pooled, because different types of medication were used as comparison. One study with 30 included patients compared NSAIDs (diflunisal 1000mg/day) with paracetamol (4000mg/day), in this single study NSAIDs were not significantly better than paracetamol and adverse events were not significantly more present in one study group.[33]

Another study compared NSAIDs (celecoxib 400mg/day) with tramadol (200mg/day) for six weeks in a trial of 1593 patients. Results of global improvement (RR 1.26 (95% CI 1.16 to 1.38) and adverse events (RR 0.83 (95% CI 0.75 to 0.91) after six weeks were both in favour of celecoxib.[34]

The study of Romano et al[35] compared celecoxib with pregabalin and scored change in pain intensity from baseline to four weeks on a VAS score. There was no significant difference found between the two study groups and also adverse events were similar in both celecoxib and pregabalin study groups.

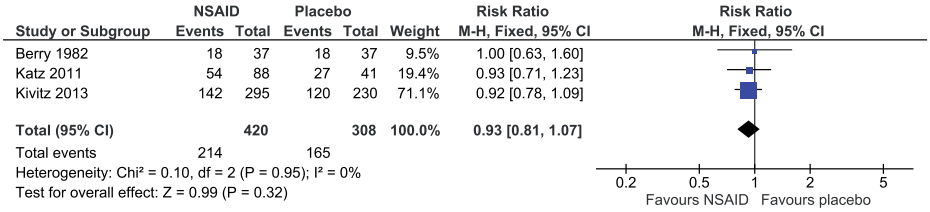

Figure 12. (analysis 1.6) Forest plot of comparison: 1 NSAIDs versus placebo, outcome: 1.6 Sensitivity analysis Proportion of patients experiencing adverse events. Follow up <=16 weeks

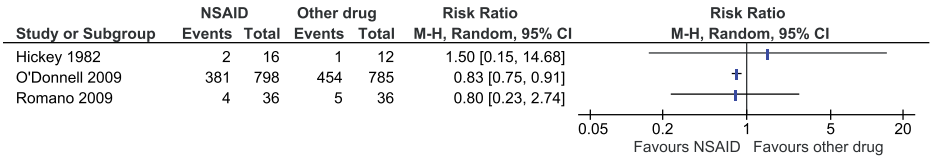

Figure 14. (analysis 2.2) Forest plot of comparison: 2 NSAIDs versus other drug treatment, outcome: 2.1 Proportion of patients experiencing global improvement. Follow-up <=6 weeks

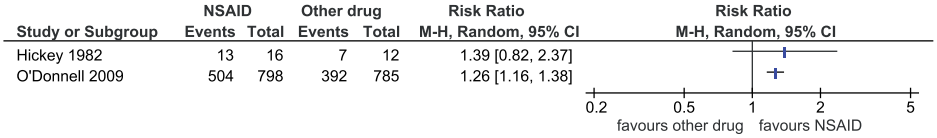

Figure 13. (analysis 2.1) Forest plot of comparison: 2 NSAIDs versus other drug treatment, outcome: 2.2 Proportion of patients experiencing adverse events. Follow-up <=6 weeks

Efficacy of NSAIDs versus non-drug treatment

One study compared NSAIDs with 'home-based exercise'.[36] Improvement of patients between baseline and 8 weeks was significantly better in exercise patients then patients receiving NSAIDs measured with the RDQ. There was no difference in pain measured with a 0-100mm VAS.

DISCUSSION

Summary of main results

In this review we included 13 randomized controlled trials that assessed the efficacy of NSAIDs for the management of chronic low back pain. Studies comparing NSAIDs with placebo showed a pooled effect of NSAIDs that was better than placebo in both outcomes on pain intensity score and disability. When only low risk of bias trials are analysed, the difference between NSAIDs and placebo was no longer significant. Adverse events were not significant more present in the NSAIDs or placebo study group, but this

can be due to the selection of RCTs, a short duration of use and a short follow-up period in most studies.

Studies comparing non-selective versus selective NSAIDs or comparing different types of non-selective NSAIDs were also limited available. All three studies included showed no significant effect between the different types of NSAIDs.

Whether NSAIDs are more effective than other drugs or non-drug therapies for chronic low-back pain still remains unclear. A limited number of studies compared NSAIDs versus other drug treatments and all studies included different kind of drug treatments to compare with NSAIDs. Celecoxib was compared to tramadol in a large study. Results of global improvement and adverse events were both in favour of celecoxib after six weeks.

Overall completeness and applicability of evidence

In two studies a 'flare design' was used. Patients who responded well to NSAIDs were included when they showed a worsening in back pain during a wash-out period. Because these patients already responded well to NSAIDs, these studies are likely to overestimate the effect of NSAIDs. It may also reduce the external validity since this is a select group of patients. When these studies are excluded from the analysis together with one other study with high risk of bias the results changed. The magnitude of effect of NSAIDs became smaller and the difference was not statistically significant anymore.

Outcomes were operationalized differently in some studies and not all studies included disability as outcome. Return to work or other work outcomes were not mentioned in any of the studies, although this might be an important outcome in daily practice.

Adverse events are mentioned in almost all studies. Most studies reported overall number of adverse events, some studies also mentioned specific gastrointestinal adverse events. Cardiovascular adverse events are rarely mentioned. However, these studies were powered to investigate treatment effects of the primary outcomes. As most important adverse events are rare and can take weeks or months to evolve, it is likely that sample sizes were too small and follow-up periods too short to draw clear conclusions from these studies regarding the risks for gastrointestinal and other adverse events of NSAIDs.

Quality of the evidence

Three of the included studies did not reach six positive items in the risk of bias tool. Many other RCTs have other methodological shortcomings such as no clear description of the randomization procedure, high drop-out rates and low or unclear compliance in the study groups. Uncertain or low compliance makes it difficult to interpret the measured effect in the study and can both under- and overestimate the results found.

Follow-up was at least four weeks in most studies, only three studies had follow-up times less than four weeks, ranging from nine days to two weeks.

Included RCTs had different study population sizes, four studies included less than 50 patients and may lack statistical power to detect differences in effects. Pooling may overcome this problem, but due to different comparisons and outcomes in the studies, pooling was not always possible.

The quality of evidence using the GRADE approach was low due to similar issues. Most important reasons for downgrading evidence were 'risk of bias' and 'imprecision'.

A sensitivity analysis with a moderate quality of evidence according the GRADE approach showed that the positive effect of NSAIDs compared to placebo was reduced and no longer statistically significant when only low risk of bias studies were included in the analysis.

Specific outcomes were not always mentioned in text or tables, but only shown in graphs. For the Roland Morris Disability questionnaire, specific results were shown in graphs for three studies.[26-28] Data were extracted from the graphs to calculate mean differences. P-values for differences between the treatment groups were mentioned in the text of these three trials. This was also the case in two other studies where a pain on a VAS scale[25] and pain on a scale of 0 to 31[31] was shown in graphs.

Potential biases in the review process

In this review we used strict inclusion criteria on the duration of back pain, meaning that only studies which reported results on chronic low back pain were included. This has led to less included studies in this review, but makes the results of the review more distinct for patients with non-specific chronic low back pain. We also only included trials published in English, German or Dutch. This could have led to exclusion of trials which could have contribute to the data and conclusions of this review.

Only one reviewer extracted the data and the second reviewer controlled the data. This could have led to a higher risk of wrong data extraction.

NSAIDs come in different types and chemical entities and it makes it difficult to compare different NSAIDs. In the comparison of NSAIDs versus placebo both selective and non-selective NSAIDs were included. An analysis of two separate comparisons showed no differences in directions of the findings when selective and non-selective NSAIDs were compared separately with placebo.

Publication bias may have occurred, but was difficult to assess due to the limited number of studies. Especially in the comparisons of different types of NSAIDs or NSAIDs compared to other types of drugs this could not be examined using a funnel plot. Although half of the studies were supported by or included authors from pharmaceutical companies. Clinical trials sponsored by pharmaceutical companies are less likely to be published and are more likely to have outcomes in favour of the sponsor[37] and could have caused publication bias.

Agreements and disagreements with other studies or reviews

The previous Cochrane review[18] reviewed NSAIDs for sciatica, acute and chronic back pain based on literature from September 1998 to June 2007. They found a change in pain intensity in favour of NSAIDs compared to placebo. In this review we found similar results, but the magnitude of the results in our review was smaller than found in 2008. Adverse events were statistically more present in the NSAID group in the review of 2008, but in our review we did not find a statistical significant difference. This could be due to the included study in this review with mostly a small sample size and/or short-time follow-up. A large meta-analysis on adverse events in RCTs[16] and observational data[38] showed that adverse events are more present in patients using NSAIDs.

After 2008 multiple (systematic) reviews were published regarding NSAID as therapeutic option in the treatment of chronic low back pain. Pain score between NSAIDs and placebo were often reported. In 2013 a review on NSAIDs showed that COX-2 selective NSAIDs were significantly more effective in reducing VAS score and disability measured with RDQ.[39] Four studies were included in these analysis of which two were not included in our review. One study[40] was excluded in the previous version of this review because it is additional information to an earlier reported study that was included in this review.[26] The other study[23] reported on rofecoxib and therefore it was excluded in this review. Kuijpers et al[41] found in a similar systematic review similar results as Chung et al.[39] Regarding VAS scores, they conclude that there is low quality evidence that NSAIDs are more effective than placebo. This is comparable to our findings in this review. Disability was also assessed in the Chung et al review and results were comparable to findings in this review.[39] These reviews use comparable studies in their analysis, only the magnitude of the effect of NSAIDs is larger than found in this review. Some studies were not included in the previous reviews due to timing of publications. Furthermore these reviews did not perform a sensitivity analysis without studies with high risk of bias as was done in this review.

Chung et al also evaluated selective and non-selective NSAIDs and found no differences in efficacy between these two groups.[39] Two studies were analysed in this review, one of those was also examined in this review and found the same results. The other study used in the review of Chung 2013 et al was excluded in this review due to the use of rofecoxib. Adverse events were more present in nonselective NSAIDs according to the two studies, but in our review where only one study compared these two types of NSAIDs, no difference in adverse effects was found.

AUTHORS' CONCLUSIONS

Implications for practice

For patients with chronic low back pain there is low quality evidence that NSAIDs are slightly better in reducing pain and disability than placebo, although when only low risk of bias studies are taken into account no significant difference between NSAIDs and placebo is found. It is questionable if NSAIDs are effective in the treatment of chronic low back pain and if so whether the effects are clinically relevant. It is still unclear if NSAIDs are more effective than other drugs and there is no evidence that one type of NSAID is more effective than other types. When considering NSAIDs it is important to take both these possible small effects as the costs and possible adverse events into account.

Implications for research

Quality of evidence for NSAIDs compared to placebo in patients with chronic low back pain is at best moderate. When studies have higher quality, effects of NSAIDs become smaller or disappear. It is questionable if additional research will change these findings and the estimate of effect. Especially since the observed differences between NSAIDs and placebo are small and possibly not clinically relevant. Since it is seen in studies with flare designs that some patients do respond to NSAIDs, it might be worthwhile looking into subgroups finding patients who are likely to respond well to NSAIDs.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

NSAIDs which were no longer available on the market, like rofecoxib, were excluded from the review. This was not previously stated in the protocol.

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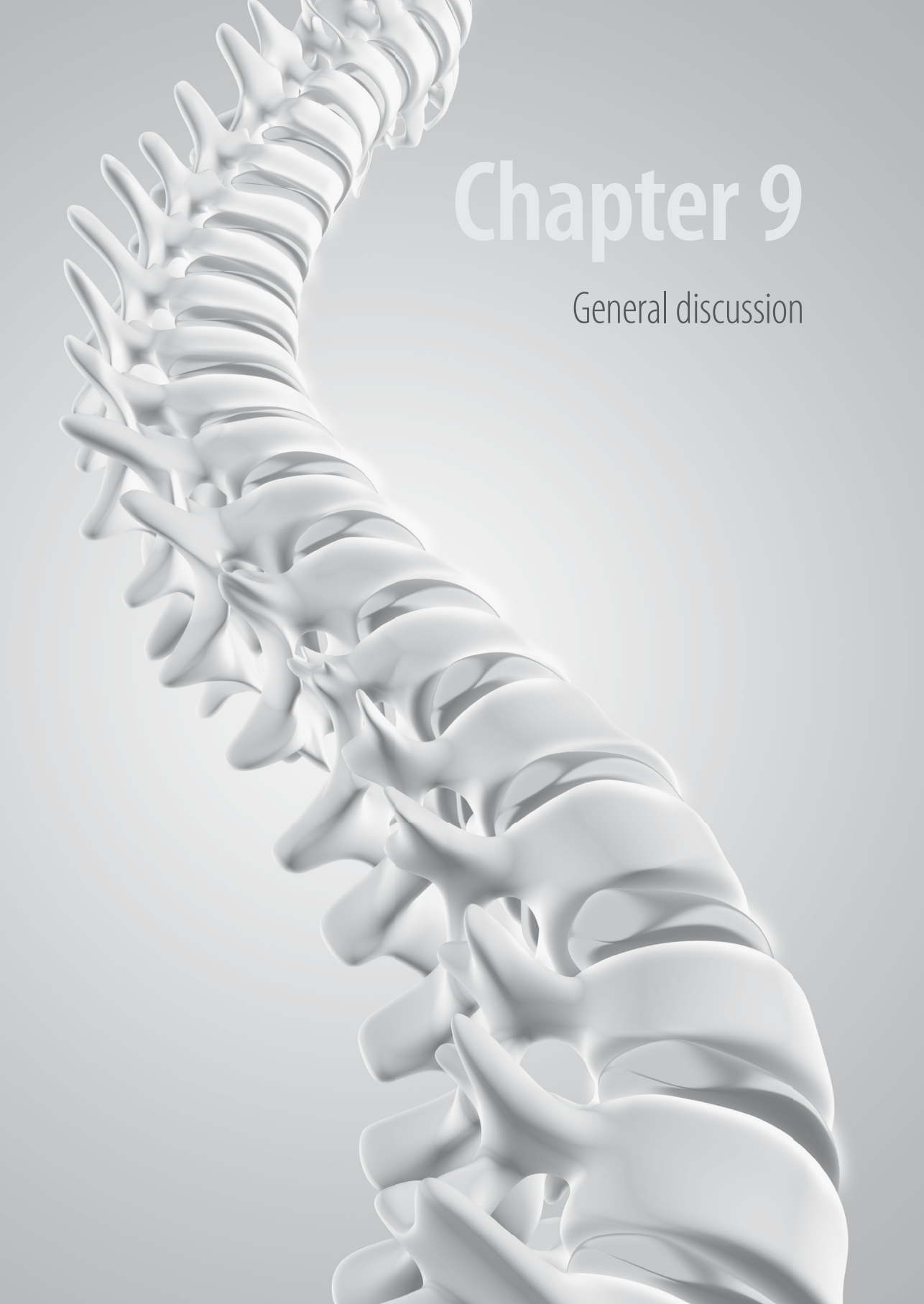

Chapter 9

General discussion

The aim of this thesis was to describe: 1) the characteristics of older adults with back pain; 2) the various ways of identifying different types of patient subgroups, and their course and prognosis of back pain; and 3) healthcare use due to back pain in a population of older adults.

This chapter discusses the findings of the presented studies, including recommendations on how to interpret the results and implications for clinical practice. The strengths and limitations of the studies are also addressed, and some ideas for future research are presented.

MAIN FINDINGS

Older adults with back pain

It is known that older patients with back pain differ from younger patients regarding the severity of their back complaints;[1] furthermore, older patients more often have comorbidities.[2] Although there seem to be differences between older and younger adults with back pain, older adults with back pain are often excluded from randomized controlled trials.[3] Due to the exclusion of these older patients, less is known about back pain in this specific subgroup of patients and the efficacy of the therapy that they receive.

This thesis focuses on older adults with back pain, because we hypothesized that there are important differences in back pain and patients' characteristics as compared to younger patients with back pain.

Within our study population of patients aged over 55 years, several baseline characteristics were shown to differ between the relatively 'younger' and 'older' patients in this group (Chapter 2). For example, disability was significantly higher and quality of life was significantly lower in the older patients. Furthermore, the older patients experienced more kinesiophobia and depressive symptoms, and scored lower on the back beliefs questionnaire. However, the differences between the two groups were relatively small. For disability measured with the Roland Morris Disability Questionnaire (RDQ),[4] the difference was 2.7 points on a scale ranging from 0 to 24; a difference of at least 2 to 5 points is considered to be clinically relevant.[5 6] Furthermore, the difference in disability probably increases when the difference in mean age between the two groups becomes larger. Moreover, when compared to even younger patients (i.e. aged less than 55 years) this difference in disability might be even greater. Other studies report similar results, with more disabling back pain in older patients than in younger patients.[7 8] In an earlier study that also used the RDQ, the authors found small differences between patients aged 65-69 years compared to the oldest age group of patients aged over 85 years.[7] Another study defined disability in a different way, but it is unclear whether the reported differences in disability between the age groups are clinically relevant.[8] Overall, these

earlier studies, and our study presented in Chapter 2, show that in back pain patients older age is associated with more disability. When patients experience more disability they may become less physically active, especially with increasing age.[9] Physical inactivity is also associated with more severe back pain and more disability;[10] this might lead to a negative spiral in which patients become less physically active and experience more back pain and disability. Ultimately this could lead to a sedentary lifestyle in which especially the oldest patients might need extra care or are no longer able to lead an independent life. Therefore, it is important to be aware that back pain is probably even more disabling among the oldest adults.

In the two age groups studied (> 55-74 years vs ≥ 75 years) the differences between the other baseline variables were relatively small. For example, quality of life was measured on a 0-100 scale and, on the physical component summary scale, the difference was only 3.8 points. Co-morbidity was also more frequently present in the older patients. As co-morbidity is known to increase with age, it is not surprising that differences were found between the two age groups for this variable. Furthermore, co-morbidities and back pain are known to be associated with each other.[11] It is questionable whether co-morbidities can be prevented or should receive extra attention in the treatment of back pain. Co-morbidities can complicate treatment, since analgesic usage in patients with co-morbidities such as renal problems, cardiovascular disorders and gastro-intestinal complaints, is associated with a higher risk of adverse drug reactions.[12 13]

Subgroups

Identifying subgroups in the heterogeneous population of back pain patients might add to our understanding of the course and prognosis, and may also help to specify treatment for different subgroups. In our population of older adults with back pain we identified subgroups in different ways and at different time points: 1) patients who were at risk for experiencing neuropathic pain were identified at baseline, 2) patients who might experience back pain due to an underlying serious pathology were also identified, 3) patients reporting non-recovery were compared to those who reported recovery after three months, and 4) different trajectories of back pain were identified based on the course of back pain over a 3-year follow-up period.

Neuropathic pain

In back pain, although the mechanism of neuropathic pain is not fully understood, different mechanisms probably play a role in the development of neuropathic pain. Back pain might be a 'mixed' type of pain, consisting of nociceptive and neuropathic components. Neuropathic pain may be caused by lesions of nociceptive sprouts in the degenerated intervertebral discs, by mechanical compression of the nerve root, or by action of inflammatory mediators from degenerated intervertebral discs.[14] It is impor-

tant to identify this subgroup of patients because they might derive more benefit from a different type of analgesic treatment. Whereas nociceptive pain is generally treated with analgesics such as paracetamol and NSAIDs, neuropathic pain is preferably treated with anti-depressants and anti-epileptic medication.[15 16]

In our study population of older adults, neuropathic pain as measured with the DN4 was barely present. Only 2% of the patients experienced neuropathic components in their back pain (Chapter 3). Different mechanisms may have played a role and may partly explain the differences compared with earlier studies, where the proportion of patients experiencing neuropathic pain was substantially higher.[17-23] Also, the use of different tools to measure neuropathic pain might cause differences in the found prevalence of neuropathic pain, although this may not explain all variation. Furthermore, a study comparing S-LANSS and DN4 as tools to identify neuropathic pain showed that DN4 identified more patients than the S-LANSS.[22] It is unlikely that the pathologic pathway of neuropathic pain differs between younger and older adults and it is unclear whether neuropathic pain is less of a problem in this older population, or whether the tools used are not sensitive enough for this particular group. Since few data are available on neuropathic pain in older adults, it remains unclear how we should interpret these findings. It might be useful to assess whether existing tools for neuropathic pain have the same diagnostic value in both older and younger patients.

Specific underlying pathology

It is likely that the course of back complaints is different when the back pain is caused by an underlying pathology. Furthermore, in most cases of a serious underlying pathology, diagnosis of the underlying pathology is important because a different type of treatment is required. Because serious underlying pathology increases with age, it was surprising that only 6% of our older patients with back pain were diagnosed with a serious underlying pathology during 1-year follow-up (Chapter 4), while in previous studies with an all-age population in primary care 1-5% was found.[24 25] The distribution of the underlying causes in our patients was similar to that reported in a previous study.[24] Of all serious underlying pathology, in our older patients vertebral fractures were the most common.

To help physicians diagnose vertebral fractures, most clinical guidelines recommend the use of red flags.[26 27] In our study, several red flags were positively associated with the diagnosis of vertebral fracture; some of these red flags were associated, but their diagnostic value was relatively low. Other studies on red flags for vertebral fractures in primary care also found a few associated red flags.[28] In our study, age ≥75 years, trauma, osteoporosis and a back pain intensity score ≥7 were all positively associated with underlying pathology. Age and trauma are also mentioned in other studies as being associated with vertebral fractures, whereas osteoporosis and back pain intensity score were

not. In the earlier studies, only prolonged corticosteroid use had good diagnostic value, whereas the other variables showed low diagnostic accuracy for the identification of vertebral fractures in back pain patients.[28] In our study population, use of corticosteroids was not an associated red flag whereas osteoporosis was. Osteoporosis is thought to be a mediator in the relation between prolonged use of corticosteroids and fractures.[29] It is possible that corticosteroids cause osteoporosis; however, in our population of older adults, osteoporosis may well have been present without the prolonged use of corticosteroids.

Other red flags for vertebral fractures have a (very) low diagnostic value and it is questionable whether they should be addressed in the guidelines as red flags. For instance, percussion tenderness of the spine, female gender and a sudden decrease in height, were red flags that were not associated with the diagnosis vertebral fracture. Due to the contradictory results in various studies, it is difficult to decide which red flags should in fact be recommended in the guidelines. In clinical practice, red flags are often used when a patient with back pain consults a physician. However, since the diagnostic value of red flags is low, it is questionable whether they really are valuable for diagnosing the underlying pathology. For example, in clinical practice the situation may arise where a red flag is present but there is no underlying pathology or, vice versa, a pathology may be present but there is no red flag. In this way, an underlying pathology can be missed and the patient may miss out on appropriate treatment. On the other hand, if a red flag cannot rule out or prove an underlying pathology, patients might more frequently be referred for additional tests, e.g. imaging for a suspected underlying pathology. However, both frequent imaging and missing out on treatment are undesirable situations, whereas the use of red flags is supposed to provide support for these decisions. In the presence of back pain, we need to find or develop tests which can make a clearer and more accurate distinction between patients with and without underlying pathology. It appears to be difficult to develop tests which can adequately discriminate between patients with and without these different pathologies. Vertebral fracture as an underlying pathology is the most frequently studied, because it occurs most often. Red flags for other underlying pathologies, such as malignancies or infections, are difficult to assess because they require a very large study population of back pain patients. One possible solution is for institutions to collaborate and share their data; the pooling of different cohorts might add to the knowledge on red flags for rare pathologies. Another possible solution is to use a different type of study design. Also, since our outcome of interest is relatively rare, it might be feasible to perform case-control studies to investigate red flags.

Non-recovery and back pain trajectories

In our study, non-recovery of back pain was determined after the first 3 months of follow-up (Chapter 5). This revealed that the mean pain score of the patients had improved (baseline 5.2 (SD 2.7); 3 months 3.6 (SD 2.8)), despite that after 3 months non-recovery was still reported by 380 patients (61%). Subsequently, the course of back pain in these older patients was assessed over a 3-year period and different trajectories were identified (Chapter 6). These trajectories were based on the pain scores that patients reported at eight time points during the 3-year follow-up period. Three trajectories were identified: 'high pain scores', 'intermediate pain scores' and 'low pain scores'. Because the course of back pain is more informative than back pain status at a single moment in time, the study of trajectories in back pain patients has recently received more attention.[30-36] Trajectories are identifiable courses of back pain in subsets of patients within a larger heterogeneous pool of back pain patients. It is thought that identifying these trajectories might help to identify prognostic factors. Although some studies have already identified trajectories[30-36] most of their analyses did not take growth over time into account. Also, it is important to include the probability of membership in a trajectory when analysing and identifying prognostic factors.

It is probably more meaningful to follow patients over a longer period of time and to employ more time points. In our study, with six time points in the first year and only two time points in both the second and third year, it is questionable whether we identified the potentially recurrent pattern of back pain in these last two years. Had more time points been included during the 3-year follow-up, the recurrent character of back pain (if present) might have been more apparent. In some studies this already takes place using the short messaging service (SMS);[37 38] this will probably add a substantial amount of information about the course of back pain. The use of techniques such as the SMS has the potential to reveal a more precise pattern of back pain per patient.

In Chapter 5 the baseline characteristics of patients reporting non-recovery and recovery at 3 months were compared; in Chapter 6 differences found in baseline characteristics between patients led to the establishment of three trajectories at the 3-year follow-up. Variables associated with both non-recovery after 3 months, and a less favourable outcome in the trajectory study over 3 years, were negative expectations of recovery at baseline and a longer duration of back pain. Another study in older adults also assessed the prognosis of back complaints and found that patients with a longer duration of symptoms had higher pain scores during one year;[39] also, patients with negative expectations for recovery at baseline had more disability at baseline and showed less improvement over one year. Expectations of patients with back pain in primary care are reported to be stable over time.[40] Also, this study could not show that an early change in expectations was associated with a more favourable course of back pain. However, importantly, no specific intervention was performed and it remains unclear

whether influencing a patient's expectations is beneficial in adjusting the course of back pain. A longer duration of pain (at baseline) is also associated with a less favourable outcome. To prevent patients from developing long-lasting back pain, patients at high risk can be identified using the Start Back tool.[41] This promising tool is already used in some clinical settings and the value of this tool is being evaluated in various languages and populations.[42-46] It would also be worthwhile to evaluate this tool in a population of older adults. Although other prognostic factors have also been studied in back pain research, the question as to which factors are true predictive factors for poor recovery still remains unanswered.[47] Reported associations are weak and validation in independent samples is often not performed.[47 48] The importance of identifying patients at high risk for chronic back pain is clear and might lead to specific interventions to prevent chronicity of back pain. However, it might be better to focus more on the validation of earlier prognostic factors and tools, rather than developing new tools. Even in our own study population, two different (statistical) methods and different follow-up times produced different prognostic factors associated with non-recovery. This implies that the prognostic factors found should preferably be validated in independent samples and that the clinical use of these prognostic factors should also be evaluated. Eventually this might help identify patients who are at risk for a less favourable outcome. Patients at high risk for a less favourable outcome may need extra attention or a different type of treatment. However, because this has not yet been studied, it is unknown whether an additional or other type of therapy can prevent this unfavourable course of back pain.

Healthcare utilization

Guidelines for back pain recommend that patients stay active and, if necessary, are also supported by the prescription of analgesics.[49] However, because of the high rate of co-morbidity in older adults, we need to consider the possible adverse reactions of these analgesics. According to the WHO pain ladder paracetamol is the first choice, mainly because it has fewer side-effects. Although paracetamol is widely used for different types of pain (including musculoskeletal pain), evidence for its effectiveness is scarce. A recent study on paracetamol even reported that paracetamol in patients with acute low back pain is not more effective than placebo.[50] However, this result has not been replicated in another population of back pain patients and has not yet been compared with patient reassurance and the advice to stay active. A second step in the pain ladder is the use of NSAIDs, which are known to have (possible) serious adverse reactions such as renal failure, cardiovascular risks and gastro-intestinal problems.[12 13] Therefore, the use of NSAIDs in older patient requires special consideration, since the risk of gastro-intestinal events is higher in these patients. The choice for an NSAID in older patients should preferably be for a short period only and, if necessary, together with the prescription of a gastro-protective drug. Nevertheless, despite this importance, it is reported

that only 41% of patients at high risk of a gastro-intestinal event using NSAIDs were also prescribed a gastro-protective drug.[51]

Furthermore, it remains questionable how effective these NSAIDs are in patients with back pain. In all-age populations, for chronic low back pain the effect of NSAIDs was found to be significant, but very small (Chapter 8). For example, when NSAIDS were compared with placebo, there was a significant difference in the pain score of only -3.30 (95% CI -5.33 to -1.27) on a pain scale ranging from 0 to 100. Although this might imply some effect of NSAIDs, since the differences between patients using NSAIDs compared to placebo are very small, it remains questionable whether this is a relevant difference for clinical practice. Similar very small differences were also found in patients with acute back pain.[52] Although these latter studies were not specifically performed in older adults, they show that the magnitude of the effect of NSAIDs is generally not large.

Despite that analgesics do not seem particularly effective compared to placebo, a considerable proportion of patients with back pain use these medications, either prescribed or over-the-counter (Chapter 7). We hypothesized that, since paracetamol in the Netherlands is mostly obtained over-the-counter, that more use of paracetamol would be apparent. However, although paracetamol was indeed mostly obtained over-the-counter, overall the NSAIDs were more frequently used. Especially in an older population it is important that patients are aware of the risks of analgesic medications. In many cases paracetamol and NSAIDs obtained over-the-counter are not used according to the established guidelines, often exceeding the recommended daily maximum dose or used by patients with contra-indications for such treatment.[53 54] Our study also revealed that some patients used different types of NSAIDs, both over-the-counter and via prescription; however, we could not evaluate whether these medications were taken simultaneously.

Because the efficacy of analgesics (e.g. paracetamol and NSAIDs) are rarely studied in older adults, it is difficult to assess the benefit/harm ratio. Since the harms might be greater in these older patients than in a younger population, knowledge on the efficacy of these analgesics becomes even more important. Furthermore, it would be interesting to examine other forms of treatment without these potential adverse events, such as exercise therapy. Although staying active is advised in guidelines on back pain,[49] it is useful to establish whether exercise therapy or walking therapy is indeed effective for low back pain in older adults.

METHODOLOGICAL ISSUES

BACE is a cohort study which allows to evaluate the course of back pain after visiting their GP, without interfering with usual care. However, this method may have some dis-

advantages. For example, we can identify associations between baseline characteristics and, for instance, different courses of back pain over time, but are unable to determine causality.

We aimed to include all consecutive patients aged over 55 years with back pain who were presenting with a new episode to their GP. However, when compared to incidence per age category in primary care, it appeared that relatively more younger patients were included.[55] This can cause some issues regarding generalizability, and some findings might be altered due to the underrepresentation of the oldest patients in our study. However, because the differences found between our relatively younger and older patients were small and probably not clinically relevant, the selected population probably had only a minor impact on the results. On the other hand, it is possible that, for example, the proportion of patients with an identified specific underlying pathology as a cause of back pain in our population could have been an underestimation.

CLINICAL IMPLICATIONS

The presented findings suggest that back pain in older adults is an important problem. A considerable proportion of the included patients had back pain over a prolonged period of time and, particularly for the older adults, disability is an important problem. Disability can lead to inactivity and, in turn, inactivity can lead to more back pain and disability. This negative spiral should be prevented in older adults, since both mobility and independence are susceptible to negative influences.

Some variables were associated with a less favourable course of back pain in this population of older adults. Although variables such as a longer duration of back pain (at baseline) are known to be associated with a higher risk for a less favourable course, other variables (like patients' expectations of recovery) have not been well studied. These latter variables should be further investigated and tested to establish whether intervention on these variables can alter the course of back pain.

Red flags are also discussed in relation to the diagnosis of vertebral fracture in these older adults. In most studies the red flags seem to have no or only limited diagnostic value. In addition, contradictory results from various studies make it difficult to decide which red flags should be recommended in the guidelines and which should not. One important red flag with the relatively highest diagnostic value is 'trauma', which should be taken into account when older patients with back pain present to their GP.

In our study population the use of analgesics was widespread. Since older adults are prone for adverse events and, especially since the efficacy of analgesics seems low, it is important to establish whether these analgesics are in fact effective in these older adults. Therefore, healthcare professionals should consider both the benefits and harms

of these analgesics. Also, patients should be informed about the potential benefits and harms of the analgesics that they buy over-the-counter themselves, or have been prescribed. It is not yet known whether reassurance and the advice to stay active might be as effective as prescribing analgesics; this is worth investigating, especially because related adverse events are generally minor.

RECOMMENDATIONS FOR FUTURE RESEARCH

The aim of the BACE cohort study is to gain knowledge on older patients with back pain. Although this thesis offers additional valid information about different subgroups and the healthcare use of these patients, it also raises some questions.

Identifying patients with underlying pathology, or ruling out underlying pathology as a cause of back pain, remains a challenge and the use of red flags should be further investigated. Because of the low prevalence of underlying pathologies as a cause of back pain, it might advantageous to address questions about the associations of red flags via case-control studies. At the same time, some red flags have been analyzed in other cohorts and it might be worthwhile to combine these cohorts to further analyze the usefulness of red flags for different underlying pathologies.

The course of back pain has recently been studied in several populations of back pain patients. Although this provides additional information, the statistical analyses and the study designs differ considerably; this can lead to differences in findings and also makes it difficult to compare these studies. For future studies on back pain, it would be beneficial to reach consensus on the use of similar statistical methods and study designs. Furthermore, it would be interesting to not only create subgroups based on pain scores but also on disability, since functioning in daily life is an important factor of independence. Another important item to be evaluated is the use of physical activity and its relationship with the course of back pain.

Regarding analgesics, since the effects of various analgesic options in older adults are unknown and levels of harm might be higher in this specific population, the efficacy of these analgesics needs further evaluation. Also, we need to assess whether physical activity and/or exercise therapy is beneficial in this group of patients. Although guidelines already advise to stay active, it remains unclear exactly how one should stay active and whether certain exercises are more beneficial than others. In younger chronic back pain patients (mean age 41 years) there is some evidence that exercise is slightly more effective in decreasing pain and improving disability than no exercise at all. However, in acute back pain patients such physical activity was not more effective than no exercise.[56] Also, we need to further investigate whether older patients benefit from physical activity, especially since physical activity has shown beneficial effects in older adults with

other musculoskeletal complaints.[57-59] If this proves positive for back pain this would not only benefit their condition, but may also be beneficial for other co-morbidities such as obesity, osteoporosis and osteoarthritis.[60]

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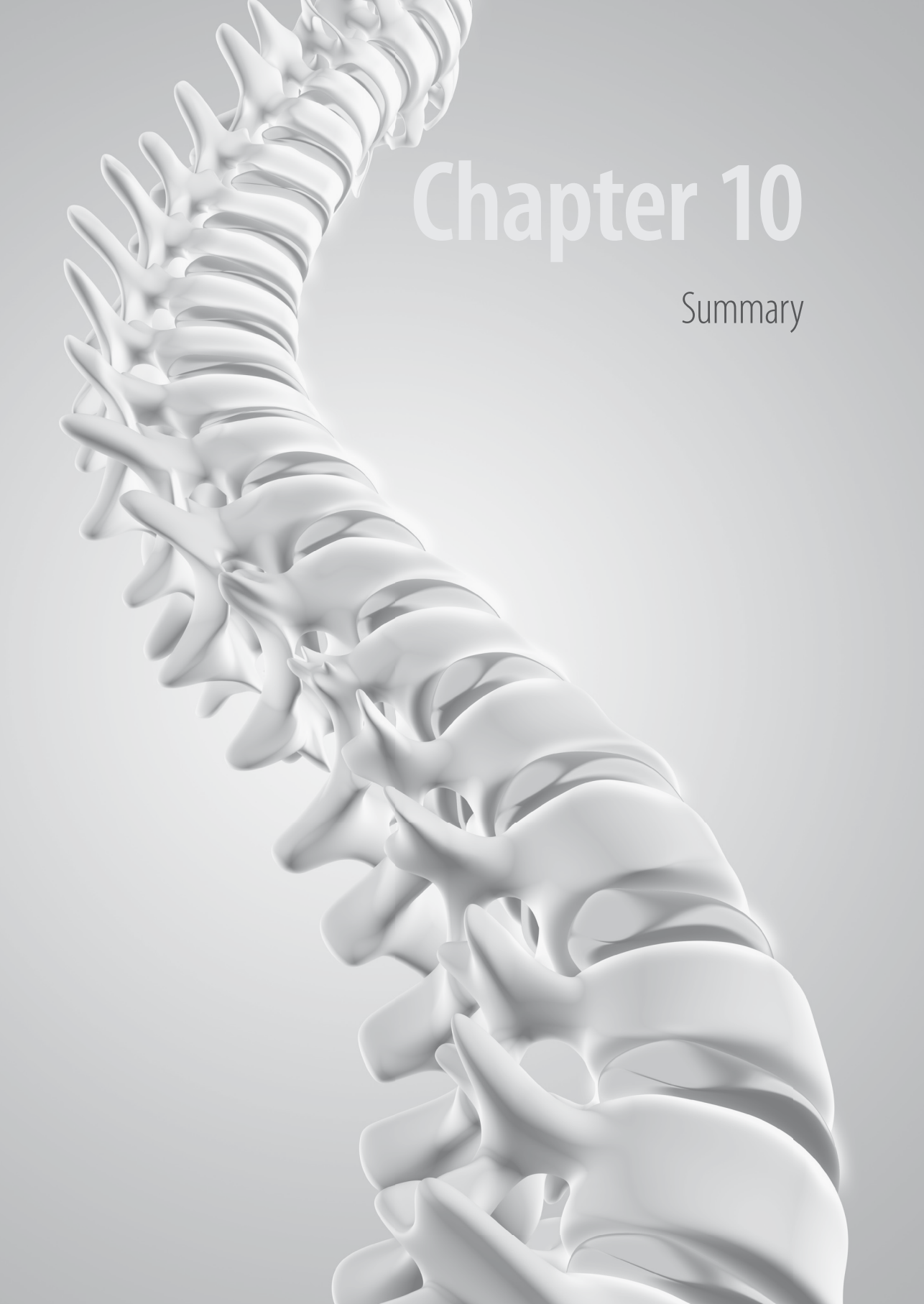

Chapter 10

Summary

SUMMARY

The aim of this thesis was to describe: 1) the characteristics of older adults with back pain; 2) the various ways of identifying different types of patient subgroups and their course and prognosis of back pain; and 3) healthcare use due to back pain in a population of older adults.

Most of the results described in this thesis are based on the BACE study population. The characteristics of these older adults with back pain are described in **chapter 2**. A total of 675 back pain patients were included in the BACE study, with a median age of 65 years (interquartile range 60–71 years). Patients aged >55–74 years had a mean disability score of 9.4 (SD 5.8) on the 0-24 Roland Morris Disability Scale. Compared with patients aged ≥75 years who had a mean score of 12.1 (SD 5.5) ($p \leq 0.01$). Although this difference was statistically significant, the absolute difference between the groups was 2.7 points; a difference of at least 2 to 5 points is considered to be clinically relevant. The older patients also reported more additional musculoskeletal disorders and more often had low bone quality than patients aged >55–74 years.

Different ways of identifying subgroups of patients were used in this thesis. Results on prevalence of neuropathic pain and associations of neuropathic pain with baseline characteristics in this cohort of older adults is presented and discussed in **chapter 3.** Of the 261 included patients available for this analysis were 250 patients (96%) with the DN4 interview plus physical examination, and 259 patients (99%) with the DN4 interview. In the DN4 interview plus physical examination 5 patients (2%) scored positive for the presence of neuropathic pain. A higher score was associated with pain radiating below the knee ($p<0.001$) and use of paracetamol ($p=0.02$). For the DN4 interview alone 29 patients (11%) scored positive and this was associated with a higher body mass index (BMI) ($p=0.01$), pain radiating below the knee ($p=0.001$) and use of paracetamol ($p=0.002$). The found prevalence of neuropathic pain in this study was remarkably lower than reported in other studies including back pain patients.

Chapter 4 presents the assessment of underlying pathology as a cause for the back pain in this population of older adults. Of all included patients 6% were diagnosed during 1 year follow-up with a serious underlying pathology. Most of these patients (n=33; 5%) were diagnosed with a vertebral fracture. Multivariable regression analysis showed that age ≥75 years (OR 3.5; 95% CI 1.5 to 6.8), trauma (OR 7.8; 95% CI 2.7 to 22.5), osteoporosis (OR 2.5; 95% CI 1.0 to 6.2), a back pain intensity score ≥7 at baseline (OR 3.1; 95% CI 1.4 to 7.2), and presence of thoracic pain (OR 2.1; 95% CI 0.9 to 4.9) were associated with a higher chance of getting the diagnosis vertebral fracture. Of these variables, trauma showed the highest positive predictive value for vertebral fracture of 0.25 (95%CI 0.09 to 0.41) and a positive likelihood ratio of 6.2 (95% CI 2.8 to 13.5). A diagnostic prediction model including all five red flags did not increase these values. In clinical practice red

flags are often used when a patients consults the physician with back pain. Since the diagnostic value of the red flags was low, it is questionable if these red flags do really add to the diagnosis of vertebral fractures.

The course and prognosis of their back pain until three months after baseline, was assessed and reported in **chapter 5**. The course of back pain was described in terms of self-perceived recovery, back pain severity, disability, pain medication, and GP visits during 6 weeks and 3 months follow-up. At 6 weeks follow-up 64% of the patients reported no recovery from their back pain. At 3 months follow-up 61% still reported no recovery, but only 26% of these patients had revisited their GP. Longer duration of the back pain (OR 4.4; 95% CI 2.5 to 7.7), severity of back pain at baseline (OR 1.2 95% CI 1.1 to 1.3), history of back pain (OR 1.7; 95% CI 1.0 to 3.0), absence of radiating pain in the leg below the knee (OR 0.7; 95% CI 0.4 to 1.0), number of comorbidities (OR 1.2; 95% CI 1.1 to 1.3), patients' expectation of non-recovery (OR 0.4; 95% CI 0.3 to 0.6), and a longer duration of the timed 'Up and Go' test (OR 1.1; 95% CI 1.0 to 1.2) were associated with non-recovery in a multivariable regression model (AUC 0.79).

Also, after a follow up of 3 years different trajectories of back pain severity were defined in this population. Characteristics of patients in these trajectories were identified and described in **chapter 6**. Using the different indices of fit and the usefulness of the classes in clinical practice, a 3-class cubic model was determined as the best model. The three trajectories were defined as 'low pain trajectory', 'high pain trajectory' and 'intermediate pain trajectory'. Compared to the low pain trajectory, patients in the intermediate trajectory were more likely to be female (OR 2.04; 95% CI 1.23 to 3.37), had a higher BMI (OR 1.07; 95% CI 1.01 to 1.14), more often had a back pain duration > 3 months at baseline (OR 4.87; 95% CI 2.29 to 10.37), had lower scores on the SF-36 physical summary scale (OR 0.94; 95% CI 0.90 to 0.98) and more negative expectations of recovery (OR 2.02; 95% CI 1.40 to 2.91). Some of these variables were also associated with membership of the trajectory with high pain scores. These associations were even stronger (with higher ORs) in the high pain trajectory: duration of back pain > 3 months at baseline (OR 7.70; 95% CI 3.34 to 17.74), disability (OR 1.15; 95% CI 1.06 to 1.25), SF-36 physical summary scale (OR 0.92; 95% CI 0.86 to 0.97) and negative expectations of back pain (OR 3.48; 95% CI 2.08 to 5.80). These characteristics might help to identify patients at risk for a less favourable outcome.

Pain medication is often prescribed for patients with back pain. The use of these analgesics, both prescribed and over-the-counter was described in **chapter 7**. Of all 675 patients, 484 (72%) reported pain medication use at baseline. Non-steroidal anti-inflammatory drugs (NSAIDs) (57%) were more often used than paracetamol (49%). Paracetamol was mostly obtained over-the-counter (69%) and NSAIDs were mostly obtained by prescription (85%). At baseline, patients with severe pain (NRS ≥7) used more paracetamol (p=0.04), opioids (p<0.01) and muscle relaxants (p=0.02). Patients

reporting chronic pain (back pain >3 months) at baseline reported more often the use of paracetamol (p=0.03), while patients with a shorter duration of pain more often reported NSAID use (p<0.01). During follow-up there was an overall decline in pain medication use; however, at 3 and 6-months follow-up 36% and 30% of the patients, respectively, still used analgesics.

To determine the efficacy of NSAIDs for patients with chronic low back pain, a Cochrane systematic review was performed and the results are reported in **chapter 8**. NSAIDs reduced pain and disability in patients with chronic low back pain compared to placebo. However the differences were small: 3.3 points on a 100 point scale for pain intensity. Regarding disability, patients receiving NSAIDs scored 0.9 points better on a 0-24 disability scale also indicating a significant, but small difference between NSAIDs and placebo. The number of adverse events was not significantly different between the patients receiving NSAIDs and patients receiving placebo, but large cohort studies with long duration would be needed to identify rare or delayed adverse events, or important drug interactions. Different types of NSAIDs seem not to show significantly different efficacy. NSAIDs were also compared to other drug types: paracetamol, tramadol and pregabalin. There were no differences found between NSAIDs and paracetamol and pregabalin in either effectiveness or adverse events. A single study comparing celecoxib with tramadol showed a better global improvement than in patients using only celecoxib. One study compared NSAIDs with 'home-based exercise'. Exercise patients improved more than patients receiving NSAIDs with regard to disability, but pain scores were not statistically different. The efficacy of analgesics like paracetamol and NSAIDs are rarely studied in older adults, and therefore it is difficult to assess the benefit/harm ratio. Since the harms might be greater in these older population than in younger populations, knowing the efficacy of these analgesics in this population is even more important.

Chapter 9 summarizes the main findings of the studies presented in this thesis, discusses the results and the clinical implications. Finally, ideas for further research are described.

Samenvatting

Het doel van dit proefschrift was om 1) kenmerken te beschrijven van ouderen met rugklachten; 2) verschillende manieren te beschrijven voor het identificeren van subgroepen van patiënten; en 3) het gebruik van zorg in het kader van rugklachten in een populatie ouderen in kaart te brengen.

De meeste resultaten beschreven in dit proefschrift zijn gebaseerd op de BACE studie populatie. De kenmerken van deze ouderen met rugklachten zijn beschreven in **hoofdstuk 2.** In totaal zijn 675 patiënten geïncludeerd in de BACE studie, met een mediane leeftijd van 65 jaar (interkwartielbereik 60-71 jaar). Patiënten met een leeftijd >55-74 jaar hadden een gemiddelde fysieke beperking score van 9.4 (SD 5.8) op de 0-24 Roland Morris Disability schaal. Zij werden vergeleken met patiënten met een leeftijd ≥75 jaar, die een gemiddelde score hadden van 12.1 (SD 5.5) ($p \leq 0.01$). Dit verschil was statistisch significant, echter het absolute verschil tussen de groepen was 2.7 punten; een verschil van minimaal 2 tot 5 punten wordt beschouwd als klinisch relevant. De oudere groep patiënten rapporteerden ook vaker andere klachten van het bewegingsapparaat en zij hadden vaker een lagere botdichtheid dan patiënten in de leeftijd >55–74 jaar.

Verschillende manieren om subgroepen te identificeren zijn gebruikt in dit proefschrift. De prevalentie van neuropathische pijn en associaties tussen neuropathische pijn en baseline karakteristieken in dit cohort van ouderen met rugklachten is beschreven in **hoofdstuk 3.** Van de 261 geïncludeerde patiënten in deze analyse, waren 250 patiënten (96%) beschikbaar voor de DN4 interview met lichamelijk onderzoek en 259 patiënten (99%) voor de DN4 interview alleen. In de DN4 interview met lichamelijk onderzoek scoorden 5 patiënten (2%) positief op de aanwezigheid van neuropathische pijn. Een hogere score was geassocieerd met uitstralende pijn onder de knie ($p<0.001$) en het gebruik van paracetamol ($p=0.02$). Voor de DN4 interview alleen scoorden 29 patiënten (11%) positief en dit was geassocieerd met een hogere body mass index (BMI) ($p=0.01$), uitstralende pijn onder de knie ($p=0.001$) en het gebruik van paracetamol ($p=0.002$). De prevalentie van neuropathische pijn in deze studie was beduidend lager dan gerapporteerd in andere studies met rugpijn patiënten.

Hoofdstuk 4 laat de onderliggende pathologie zien als oorzaak voor rugklachten in deze populatie van ouderen met rugklachten. Van alle geïncludeerde patiënten werd 6% gediagnosticeerd met een ernstige onderliggende pathologie gedurende 1 jaar follow-up. De meeste patiënten (n=33; 5%) werden gediagnosticeerd met een wervelfractuur. Mutivariabele regressie analyse liet zien dat leeftijd ≥75 jaar (OR 3.5; 95% CI 1.5 tot 6.8), trauma (OR 7.8; 95% CI 2.7 tot 22.5), osteoporose (OR 2.5; 95% CI 1.0 tot 6.2), een rugpijnscore ≥7 op baseline (OR 3.1; 95% CI 1.4 tot 7.2), en aanwezigheid van thoracale pijn (OR 2.1; 95% CI 0.9 tot 4.9) waren geassocieerd met een hogere kans op het krijgen van de diagnose wervelfractuur. Van deze variabelen had trauma de hoogste positief voorspellende waarde voor het krijgen van de diagnose wervelfractuur van 0.25 (95%CI 0.09 tot 0.41) en een positieve likelihood ratio test van 6.2 (95% CI 2.8 tot 13.5). Een

diagnostisch model met alle vijf de rode vlaggen gecombineerd kon deze waarden niet verder verhogen. In de klinische praktijk worden rode vlaggen vaak gebruikt wanneer een patiënt de arts bezoekt met rugklachten. Omdat de diagnostische waarde van de rode vlaggen laag is, is het de vraag of deze rode vlaggen bijdragend zijn voor het stellen van de diagnose wervelfracturen.

Het beloop en de prognose van rugklachten tot drie maanden na baseline, is onderzocht en beschreven in **hoofdstuk 5**. Het beloop van de rugklachten is beschreven op basis van het ervaren herstel, ernst van de rugklachten, fysieke beperking, pijn medicatie en bezoek aan de huisarts gedurende 6 weken en 3 maanden. Na 6 weken follow-up rapporteerde 64% van de patiënten geen herstel te ervaren van hun rugklachten. Na 3 maanden follow-up rapporteerde 61% geen herstel, maar slechts 26% van deze patiënten heeft hun huisarts opnieuw bezocht. Langere duur van de rugklachten (OR 4.4; 95% CI 2.5 tot 7.7), ernst van de rugklachten op baseline (OR 1.2 95% CI 1.1 tot 1.3), rugklachten in de voorgeschiedenis (OR 1.7; 95% CI 1.0 tot 3.0), afwezigheid van uitstralende pijn onder de knie (OR 0.7; 95% CI 0.4 tot 1.0), aantal comorbiditeiten (OR 1.2; 95% CI 1.1 tot 1.3), negatieve patiënt verwachtingen van het herstel (OR 0.4; 95% CI 0.3 tot 0.6), en een langere duur van de 'Up en Go' test (OR 1.1; 95% CI 1.0 tot 1.2) waren geassocieerd met geen herstel in een multivariabel regressie model (AUC 0.79).

Na 3 jaar follow-up werden er verschillende rugpijntrajecten vastgesteld op basis van de ernst van de rugklachten. Patiëntkenmerken in deze verschillende trajecten zijn beschreven in **hoofdstuk 6.** Met verschillende indicatoren om de juistheid en de bruikbaarheid in de klinische praktijk te beoordelen, werd een 3 klassen kubisch model vastgesteld als beste model. De drie trajecten waren gedefinieerd als 'lage pijn traject', 'hoge pijn traject' en 'middel pijn traject'. Vergeleken met het lage pijn traject, waren patiënten in het middel pijn traject vaker vrouw (OR 2.04; 95% CI 1.23 tot 3.37), hadden een hogere BMI (OR 1.07; 95% CI 1.01 tot 1.14), hadden vaker rugklachten met een duur > 3 maanden op baseline (OR 4.87; 95% CI 2.29 tot 10.37), hadden lagere scores op de SF-36 fysieke schaal (OR 0.94; 95% CI 0.90 tot 0.98) en hebben meer negatieve verwachtingen van herstel (OR 2.02; 95% CI 1.40 tot 2.91). Sommige van deze variabelen waren ook geassocieerd met het hoge pijn traject. Deze associaties waren nog sterker (met hogere ORs): duur van de rugklachten > 3 maanden op baseline (OR 7.70; 95% CI 3.34 tot 17.74), fysieke beperking (OR 1.15; 95% CI 1.06 tot 1.25), SF-36 fysieke schaal (OR 0.92; 95% CI 0.86 tot 0.97) en negatieve verwachtingen van het herstel (OR 3.48; 95% CI 2.08 tot 5.80). Deze karakteristieken zouden kunnen helpen in het identificeren van patiënten met een risico op een minder gunstig beloop van de rugklachten.

Pijnmedicatie wordt veel voorgeschreven voor patiënten met rugklachten. Het gebruik van deze medicatie, zowel voorgeschreven door een arts als vrij verkrijgbaar door de patient zelf is beschreven in **hoofdstuk 7.** Van alle 675 patiënten, 484 (72%) rapporteerde het gebruik van pijnmedicatie op baseline. Non-steroidal anti-inflammatory

drugs (NSAIDs) (57%) werden meer gebruikt dan paracetamol (49%). Paracetamol was meest zelf verkregen (69%) en NSAIDs werden het meeste voorgeschreven (85%). Op baseline gebruikte patiënten met erge pijn (NRS ≥7) meer paracetamol (p=0.04), opioïden (p<0.01) en spierontspanners (p=0.02). Patiënten die chronische pijn rapporteerden (rugpijn >3 maanden) op baseline rapporteerden vaker paracetamol gebruik (p=0.03), terwijl patiënten met een kortere duur van de klachten vaker NSAID gebruik rapporteerden (p<0.01). Gedurende follow-up was er een algehele daling in het gebruik van pijnmedicatie; maar op 3 en 6 maanden follow-up gebruikte respectievelijk 36% en 30% van de patiënten nog pijnmedicatie.

Om de effectiviteit van NSAIds te bepalen voor patiënten met chronisch lage rugklachten, is een Cochrane systematische review uitgevoerd en de resultaten hiervan staan in **hoofdstuk 8.** NSAIDs reduceerden pijn en fysieke beperkingen in patiënten met chronisch lage rugklachten in vergelijking met placebo. Echter de verschillen waren klein: 3.3 punten op een 100 punt schaal voor pijnintensiteit. Met betrekking tot fysieke beperkingen scoorde patiënten die NSAIDs kregen 0.9 punten beter op een 0-24 schaal, wat een significant, maar klein verschil betekent tussen NSAIDs en placebo. Het aantal bijwerkingen was niet significant verschillend tussen patiënten die NSAIDs kregen en patiënten die placebo kregen, maar grote cohort studies met langere duur zijn nodig om zeldzame of uitgestelde bijwerkingen of medicatie-interacties te identificeren. Verschillende typen NSAIDs lijken geen significant verschillend effect te laten zien. NSAIDs zijn ook vergleken met andere medicatie: paracetamol, tramadol en pregabaline. Er werden geen verschillen gevonden tussen NSAIDs en paracetamol en pregabaline in effectiviteit of bijwerkingen. Een studie vergeleek celecoxib met tramadol en liet een betere algehele verbetering zien in patiënten die celecoxib gebruikten. Een studie vergeleek NSAIDs met het doen van oefeningen thuis. Patiënten die thuis oefenden verbeterden meer dan patiënten die NSAIDs kregen in fysieke functie, maar de pijnscores waren niet significant verschillend. De effectiviteit van pijnmedicatie als paracetamol en NSAIDs zijn zelden bestudeerd in ouderen en daarom is het moeilijk om de verhouding tussen de baten en de schadelijkheid te beoordelen. Het is mogelijk dat de schadelijkheid in een populatie ouderen groter is dan in een jongere populatie en daarom is het extra belangrijk om de effectiviteit van deze pijnmedicatie te weten in deze populatie.

Hoofdstuk 9 vat de belangrijkste bevindingen samen van de studies beschreven in dit proefschrift, bediscussieert de resultaten en de klinische implicaties. Tenslotte zijn ideeën voor verder onderzoek beschreven.

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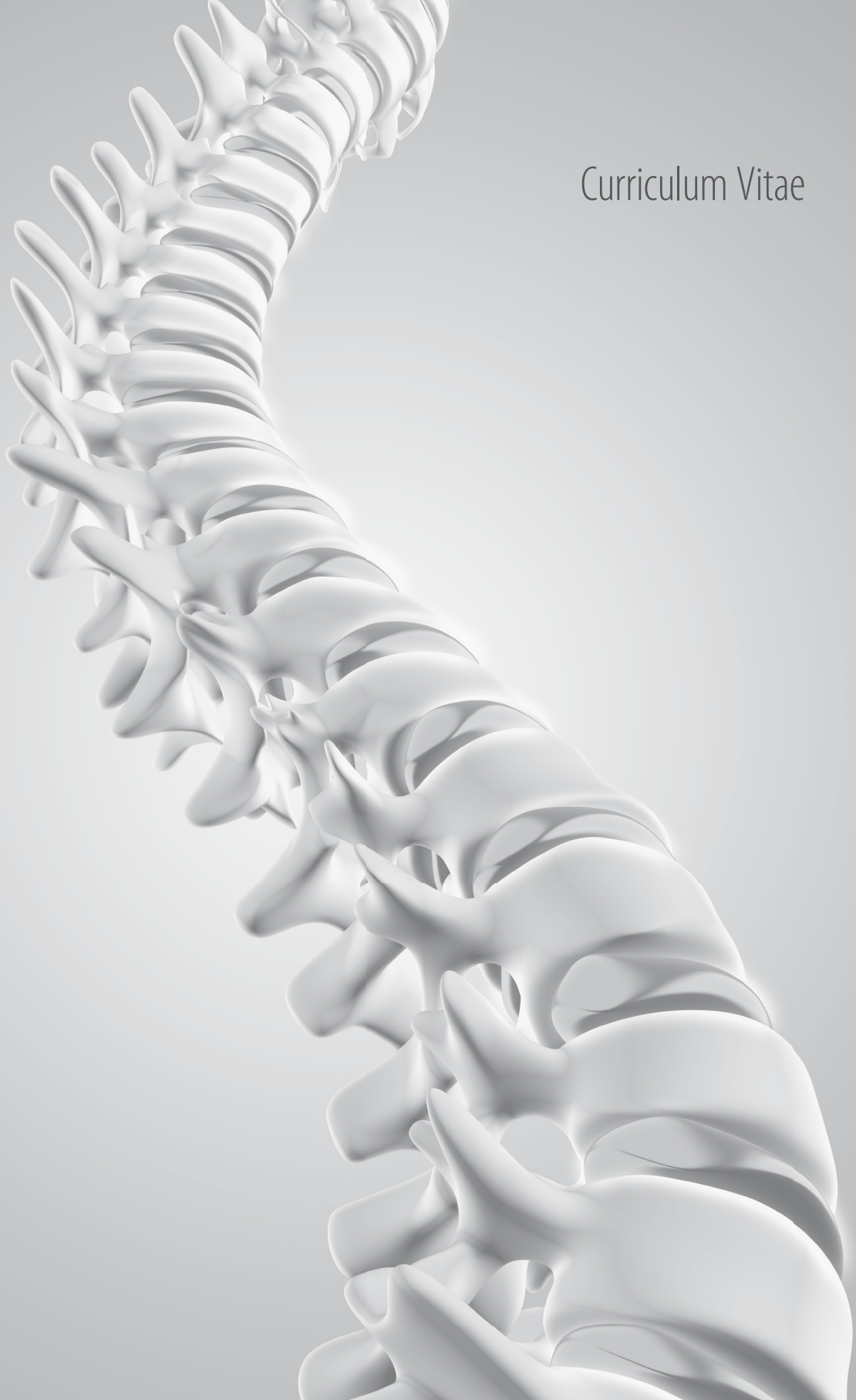
Curriculum Vitae



Wendy Enthoven is op 17 februari 1986 geboren in 's-Gravenzande. Na het behalen van haar VWO diploma in 2004 aan de Interconfessionele Scholengroep Westland (ISW) te Naaldwijk, is zij geneeskunde gaan studeren aan de Erasmus Universiteit in Rotterdam. Naast haar studie is Wendy een jaar voorzitter geweest bij Stichting Stages in Ontwikkelingslanden (STOLA). Na het behalen van haar artsexamen in 2011 heeft zij een jaar als arts-assistent op de spoedeisende hulp gewerkt in het Van Weel Bethesda ziekenhuis te Dirksland.

In maart 2012 startte zij als AIOTHO (arts in opleiding tot huisarts en onderzoeker). Daarbij is zij zowel in opleiding tot huisarts als promotieonderzoeker op de afdeling huisartsgeneeskunde van het Erasmus Medisch Centrum in Rotterdam. Voor haar promotieonderzoek werkt ze aan het onderzoek 'Back complaints in older adults'. Dit is een cohortonderzoek waarin ouderen met rugklachten vijf jaar lang worden gevolgd. Hieruit volgden de artikelen die in dit proefschrift zijn opgenomen.

In 2013 startte Wendy met het eerste jaar van de huisartsopleiding, die ze volgde in een praktijk in Vlaardingen. In 2015 behaalde zij haar Master of Science in Clinical Epidemiology aan het Netherlands Institute for Helath Sciences (NIHES). Daarnaast nam zij zitting in diverse commissies (werkgroep onderwijs, selectiecommissie van de huisartsopleiding Rotterdam en de geschillen- en adviescommissie van de Koninklijke Nederlandsche Maatschappij ter bevordering der Geneeskunst (KNMG)). Tevens geeft zij sinds 2012, in wisselende frequentie, les bij 'De Ruyter training en consultancy' te Vlissingen en geeft zij onderwijs aan geneeskundestudenten in de bachelor en masterfase sinds 2015.

PhD portfolio

	Year	ECTS
Courses / training		
Master of Science in Clinical Epidemiology, NIHES, Rotterdam	2012-2015	70
BROK ('Basiscursus Regelgeving Klinisch Onderzoek')	2014	1
Didactic skills	2013	0.5
BKO (Basiskwalificatie Onderwijs) – onderwijs aan kleine groepen	2015	0.5
Vocational training		
GP training, Department of General practice, Erasmus MC, Rotterdam	2012 - present	
Oral presentations		
Congress on low back and pelvic pain, Dubai	2013	1
Rehabilitation specialists, Working group Pain, the Netherlands	2014	1
Low back pain forum, Brazil	2014	1
Symposium lage rugpijn, Utrecht	2015	1
NHG wetenschapsdag, Rotterdam	2015	1
Poster presentations		
Low back pain forum, Denmark	2012	1
Congress on low back and pelvic pain, Dubai	2013	1
Low back pain forum, Brazil	2014	1
NAPCRG, annual meeting, New York, USA	2014	1
(Inter)national conferences		
NHG wetenschapsdag, Maasstricht	2012	1
Teaching		
GP trainees, scientific meeting, Erasmus MC, Rotterdam	2012, 2015	1
Supervising student master's thesis	2013	1
Clinical reasoning for bachelor and master students	2015	1

List of publications

This thesis

Enthoven WT, Geuze J, Scheele J, Bierma-Zeinstra SM, Bueving HJ, Bohnen AM, Peul WC, van Tulder MW, Berger MY, Koes BW, Luijsterburg PA. *Prevalence and Red Flags Regarding Specified Causes of Back Pain in Older Adults Presenting in General Practice.* Phys Ther. 2015 Jul 16.

Enthoven WT, Scheele J, Bierma-Zeinstra SM, Bueving HJ, Bohnen AM, Peul WC, van Tulder MW, Berger MY, Koes BW, Luijsterburg PA. *Analgesic use in older adults with back pain: the BACE study.* Pain Med. 2014 Oct;15(10):1704-14.

Enthoven WT, Scheele J, Bierma-Zeinstra SM, Bueving HJ, Bohnen AM, Peul WC, van Tulder MW, Berger MY, Koes BW, Luijsterburg PA. *Back complaints in older adults: prevalence of neuropathic pain and its characteristics.* Pain Med. 2013 Nov;14(11):1664-72.

Scheele J, **Enthoven WT**, Bierma-Zeinstra SM, Peul WC, van Tulder MW, Bohnen AM, Berger MY, Koes BW, Luijsterburg PA. *Characteristics of older patients with back pain in general practice: BACE cohort study.* Eur J Pain. 2014 Feb;18(2):279-87.

Scheele J, **Enthoven WT**, Bierma-Zeinstra SM, Peul WC, van Tulder MW, Bohnen AM, Berger MY, Koes BW, Luijsterburg PA. *Course and prognosis of older back pain patients in general practice: a prospective cohort study.* Pain. 2013 Jun;154(6):951-7.

Other publications

Koes BW, **Enthoven WT**. *Do patients with acute low-back pain need paracetamol?* Lancet. 2014 Nov 1;384(9954):1556-7.