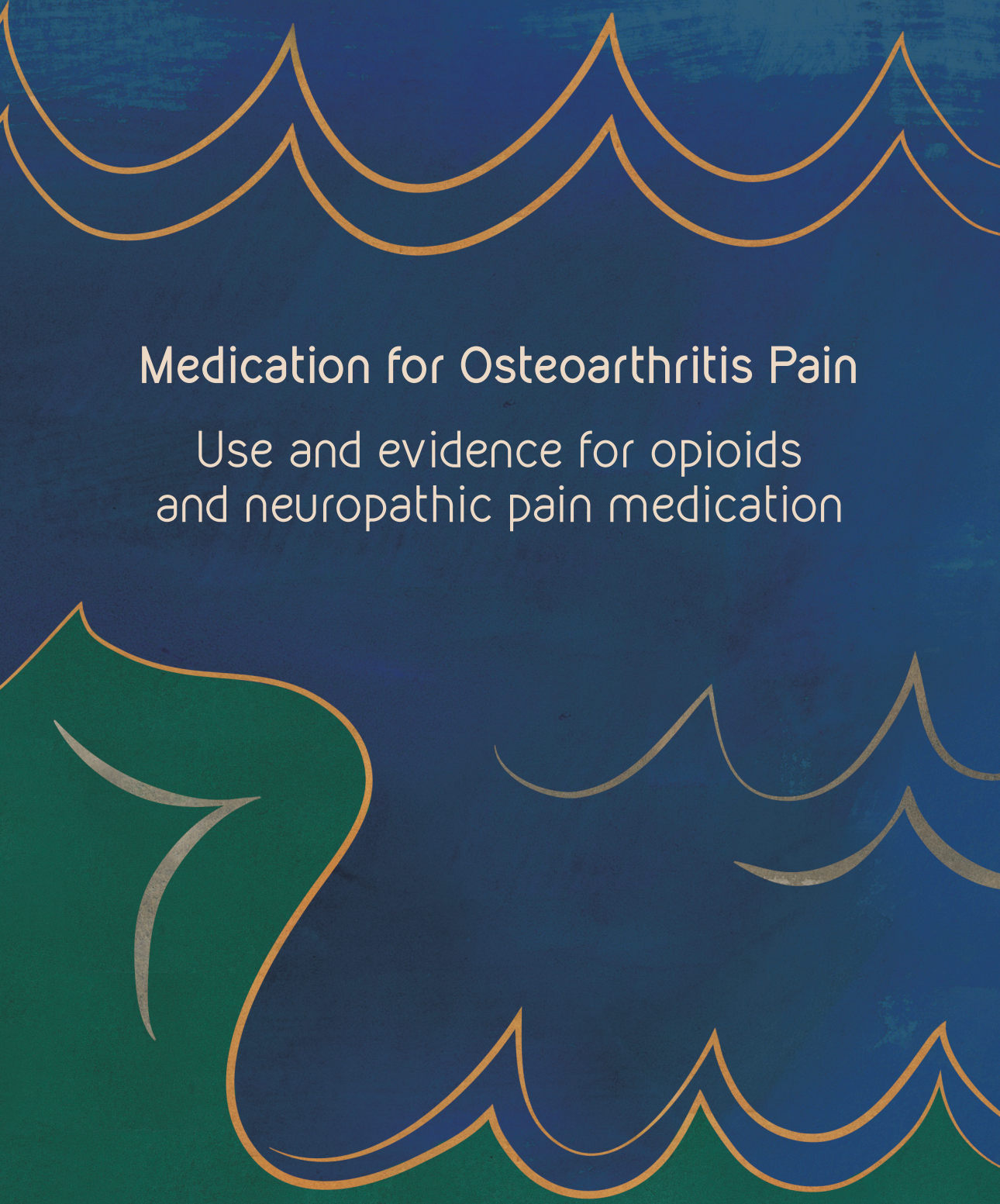
Medication for Osteoarthritis Pain

Use and evidence for opioids and neuropathic pain medication



Jacoline van den Driest

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Jacoline van den Driest

SBOH
voor artsen in opleiding

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Medication for Osteoarthritis Pain

Use and evidence for opioids and neuropathic pain medication

Medicatie voor pijn door artrose

Gebruik van en bewijs voor opioiden en neuropathische pijnmedicatie

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Contents

Chapter 1	General introduction	7
Chapter 2	Analgesic use in Dutch patients with osteoarthritis: frequent but low doses	17
Chapter 3	Opioid prescriptions in patients with osteoarthritis: a population-based cohort study	35
Chapter 4	Antidepressant and anticonvulsant prescription rates in patients with osteoarthritis: a population-based cohort study	57
Chapter 5	Amitriptyline for musculoskeletal complaints: a systematic review	97
Chapter 6	Effectiveness and cost-effectiveness of duloxetine added to usual care for patients with chronic pain due to hip or knee osteo-arthritis: protocol of a pragmatic open-label cluster randomised trial (the DUO trial)	121
Chapter 7	No added value of duloxetine for patients with chronic pain due to hip or knee osteoarthritis: a cluster randomised trial	139
Chapter 8	General discussion	167
Chapter 9	Summary Samenvatting Dankwoord PhD portfolio List of publications	185

CHAPTER 1

General introduction

OSTEOARTHRITIS

Osteoarthritis (OA) is a highly prevalent chronic disease of the musculoskeletal system that causes pain and disability. The knee, hand and hip joints are the most commonly affected joints, with knee OA being most prevalent[1]. Approximately 15% of the population suffers from OA. In the Netherlands, the overall year prevalence of OA in 2018 was 109.9 persons per 1000 person years for women and 60.1 persons per 1000 person years for men[2]. Furthermore, the Global Burden of Disease study ranked OA as the 11th largest contributor to global disability[3]. Since the population is ageing and the prevalence of obesity is increasing, it is expected that the prevalence of OA will increase and that OA will be the most prevalent disease of all diseases in 2040[4].

PAIN

Pain is the most debilitating symptom of OA[5]. Pain in OA was long believed to consist solely of nociceptive pain of the joint, but nowadays it is known that alterations in the peripheral and central nervous system can also occur.

Nociceptive pain of the joint

OA affects the whole joint and the disease process involves mechanical, inflammatory and metabolic factors which lead to damage and remodelling of the joint. The main characteristics are cartilage loss, formation of osteophytes, subchondral bone remodelling and synovitis[6]. Pain from the joint is associated with bone marrow lesions, synovitis and joint effusion. Furthermore, the primary sensory neurons are stimulated by the neovascularization of the cartilage and menisci, which is mediated by hypoxia and the inflamed synovium[7 8].

Peripheral sensitization

Hyperexcitability of the nociceptive system occurs when inflammation is present. The inflammatory mediators lower the excitation threshold in the peripheral neurons, making the neurons more likely to respond to stimuli[7 8]. Peripheral sensitization occurs in the first hours after onset of inflammation and can persist for weeks[9].

Central sensitization

In addition to alterations in pain processing in the peripheral nervous system, alterations in pain processing in the central nervous system can occur. Pain hypersensitivity is caused by increased spontaneous neuronal activity, reduced activation thresholds and an expanded receptive field; i.e. there is enhanced activity of the ascending pathways.

Furthermore, inhibitory descending antinociceptive pathways are less active[7 8]. This process is maintained by peripheral nociceptive input from the joint. Features of pain that are associated with central sensitization are burning pain, paraesthesia, mechanical and thermal hyperalgesia, allodynia, paroxysmal pain and numbness[10]. Patients with symptoms of central sensitization are more likely to report intense pain severity and a decreased quality of life compared to patients without symptoms of central sensitization[11].

A recent meta-analysis found that central sensitization is present in around 23% of patients with OA[12]. No association was found between radiographic severity and central sensitization[13]. Synovitis and joint effusion may be related to central sensitization, while the evidence on whether symptom or disease duration is associated with central sensitization is conflicting[13 14].

TREATMENT OF PAIN

The majority of patients with OA are treated in primary care by the general practitioner (GP). The care provided by the GP consists of education, dietary advice, referral for exercise therapy and prescribing pain medication in a stepwise approach[15].

Analgesics

The first step is paracetamol, which has a small therapeutic effect size (<0.2)[16]. Paracetamol used to be considered relatively safe, but concerns have now been raised regarding the safety of paracetamol (hepatotoxicity, cardiovascular side-effects). The second step is topical non-steroidal anti-inflammatory drugs (NSAIDs), which have an effect size of 0.3 for pain and are relatively safe[17]. Oral NSAIDs are effective for OA pain, but are often contra-indicated for (elderly) patients due to cardiovascular, gastro-intestinal and renal side-effects[18]. The third step, according to the WHO pain ladder, is opioids. However, the current guidelines for treatment of OA have restrictive advice on the use of opioids or do not recommend the use of opioids[19 20], since it is questionable whether they offer benefit for OA pain and side-effects often occur. Common side-effects for opioids are nausea, constipation and somnolence. The elderly in particular are at risk of falls and fractures when using opioids[21 22]. Finally, opioids can be abused and can be addictive[23 24]. Despite this, opioids are increasingly prescribed for OA pain[25-27].

Adherence to analgesics

A factor contributing to the effectiveness of the treatments mentioned above is the adherence of patients to the medication. Many patients do not take their medication as prescribed: they often use their medication at lower doses and take their medica-

tion irregularly[28 29]. The decision by patients on whether to adhere to the medication is complex and can be affected by pain severity, concerns about side-effects, education and understanding of OA, poly-pharmacy and out-of-pocket costs[30-32].

If these conservative treatment options fail, joint replacement can be considered. Joint replacement is costly, does not always lead to satisfactory results and is of limited durability[33 34]. Therefore, better conservative treatment options are necessary.

NEUROPATHIC PAIN MEDICATION

A possible new option for treating OA pain may be the use of neuropathic pain medication (i.e. antidepressants and anticonvulsants), which is hypothesized to have an effect in the central nervous system on the alterations caused by central sensitization. None of these medications are registered in the Netherlands for the treatment of OA pain.

Antidepressants

The antidepressants often prescribed for neuropathic pain conditions are the tricyclic antidepressants amitriptyline and nortriptyline, and the serotonin and noradrenalin reuptake inhibitor (SNRI) duloxetine.

The antidepressant most extensively studied for OA pain is duloxetine. Several short-term, placebo-controlled studies showed a small to moderate effect of duloxetine[35-40]. Based on these trials the Osteoarthritis Research Society International (OARSI) and the American College of Rheumatology (ACR) conditionally recommend duloxetine, but emphasize the occurrence of side-effects[19 20]. The effectiveness of duloxetine is unknown, nor is it known whether the effect is predominantly found in patients with symptoms of central sensitization.

Amitriptyline and nortriptyline are often prescribed for neuropathic pain conditions and musculoskeletal disorders. No evidence exists for the prescription of amitriptyline and nortriptyline for OA pain. Currently, one trial comparing nortriptyline to a placebo for OA pain is ongoing[41].

Anticonvulsants

The other group of neuropathic pain medication consists of the anticonvulsants pregabalin and gabapentin (gabapentinoids). Two small studies have compared pregabalin to a placebo, one in patients with knee OA and one in patients with hand OA[42 43]. Both studies showed small effects of pregabalin. No studies for gabapentin have been carried out. Despite this lack of evidence, the prescription rates of gabapentinoids in patients with OA tripled in the UK between 2005 and 2015[44] and prescription rates were three times higher in OA patients than in matched controls[45].

OUTLINE OF THIS THESIS

The aim of this thesis is to provide insight into the current prescription rates and use of medication for OA, the prescription rates of neuropathic pain medication for OA, and to assess the effectiveness of duloxetine as a third choice for patients with OA.

Chapter 2 provides information on how often patients use their analgesics and in what doses.

Chapter 3 describes the prescription rates of opioids between 2008 and 2017 in patients with OA. Chapter 4 describes the prescription rates of neuropathic pain medication between 2008 and 2017 for patients with OA. In Chapter 5, the evidence is examined for the prescription of amitriptyline for musculoskeletal complaints.

Chapter 6 describes the design of the DUO trial, in which the effectiveness and cost-effectiveness of duloxetine added to usual care was compared to usual care alone. The results of the trial are presented in Chapter 7.

Finally, Chapter 8 summarizes and discusses the main findings and the clinical implications and gives suggestions for further research.

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CHAPTER 2

Analgesic use in Dutch patients with osteoarthritis: frequent but low doses

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ABSTRACT

Objective

To examine which analgesics are used by patients with osteoarthritis (OA)-related pain and how the analgesics are used in the preceding month. In addition, their beliefs about (pain) medication and the rationale of those declining to use analgesics.

Methods

An online cross-sectional survey was sent to 1521 patients participating in the panel of the Dutch Arthritis Foundation. Descriptive analyses and logistic regression were used to analyse data.

Results

Of the 842 (56%) participants with OA that responded, 70% had generalized OA, 26% had concomitant fibromyalgia and 34% had another musculoskeletal morbidity. Of all participants, 71% used analgesics and 34% used more than one type. Analgesics were used for more than 14 days in the preceding month by most participants, with paracetamol being used most frequently (51%). Doses used were predominantly lower than the Daily Defined Dose; 58.2% for paracetamol, 31.2% for NSAIDs/COX-2 inhibitors, and 75.7% for weak opioids. Compared with participants with concomitant fibromyalgia or other musculoskeletal morbidities, participants with OA alone significantly more frequently declined to use analgesics ($p<0.01$) and significantly less frequently used two or three types of analgesics ($p<0.05$).

Conclusion

In this population with generalized OA and musculoskeletal comorbidities, medication use was high and more than one type of analgesic was frequently used. Patients with concomitant fibromyalgia or other musculoskeletal morbidities more frequently used two or three types of analgesics; however, this use was often intermittent and in low doses. Medication use on a daily basis and at higher doses may lead to improved analgesic effect.

INTRODUCTION

Osteoarthritis (OA) is a highly prevalent chronic disease of the musculoskeletal system. OA is present in approximately 15% of the population and is expected to become the fourth leading cause of disability by 2020[1 2]. Pain and loss of function are two important complaints of patients with OA. To reduce OA-related pain, paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs) and opioids are recommended in the guidelines of the Dutch General Practitioners (GP) and in international guidelines[3 4]. However, in many cases, medication is not taken as prescribed[5 6].

This lack of adherence to analgesic prescriptions may lead to a suboptimal reduction of pain. Analgesics are often used irregularly and at a lower dose than that prescribed[6-8]. The decision to adhere to medication is complex and can involve pain severity, level of education, and an understanding of OA and current medication use[7 8]. Studies assessing this topic have frequently used qualitative methods[8], or have excluded patients with concomitant inflammatory arthritis[9] despite the regular co-occurrence of other musculoskeletal disorders[10]. This implies that less is known about analgesic use in patients with OA.

Therefore, this study examines which analgesics are used and how these are used by patients with OA related pain. Also assessed are patients' beliefs about (pain) medication and the rationale of those declining to use analgesics for OA-related pain.

METHOD

Study population

This cross-sectional survey was performed in collaboration with the Dutch Arthritis Foundation (DAF); the DAF primarily serves the interest of patients with rheumatic diseases[11]. Patients, their relatives and healthcare professionals can participate in this panel and can register themselves online[12]; demographic data of participants are collected after registration. Of the 4005 participants in the DAF panel, 1521 participants were registered as having OA. The present survey was sent to patients registered with self-reported OA; participants could also have additional self-reported rheumatic diseases (e.g. auto-immune rheumatic diseases, or gout). Generalized OA was defined as self-reported OA in three or more groups of joints.

Data collection

For the present study, the online questionnaire was mailed to 1521 patients with OA; in case of non-response a reminder was sent two weeks later. Before filling in the questionnaire, all participants were informed about the use of the data by Erasmus University

Medical Center. No ethical approval was required. All data were processed anonymously and the researchers received an anonymized data file.

The questionnaire included multiple-choice questions on: pain related to OA, joints affected by OA, which medication(s) participants had ever used, and which medication(s) was used in the preceding month for OA-related pain. For analgesics used in the preceding month the following details were requested: dose, frequency, perceived effect, side-effects, and whether medication(s) was based on prescription or purchased over-the-counter. If participants did not use medication in the preceding month, they were asked to give their reasons for not using analgesics.

The Beliefs about Medication Questionnaire (BMQ) was filled out to assess participants' ideas about medication. The BMQ has two sections i) beliefs about medication in general (BMQ-General) and ii) beliefs about specific medication, e.g. analgesics for OA (BMQ-Specific)[13]. The BMQ-General consists of two subscales (with four questions each) asking about harm and overuse of medication. The BMQ-Specific has two subscales (with five questions each) asking about the necessity for and concerns about specific medication. Answers are scored on a 5-point Likert scale, ranging from 1 (Strongly disagree) to 5 (Strongly agree). Total scores for subscales range from 4-20 for the BMQ-General and from 5-25 for the BMQ-Specific. High scores on the General-Harm scale indicate low expectations regarding the positive effects of medication. High scores on the General-Overuse scale indicate low confidence in the responsible prescription of medication by physicians. High scores on the Specific-Necessity scale indicate high confidence in the need for prescribed medication, and high scores on the Specific-Concerns scale indicate low expectations for the beneficial effects of the prescribed medication[13].

Dose of analgesics

The daily dose of analgesics taken is expressed as the proportion of the Defined Daily Dose (DDD) taken per day (self-reported daily dose/defined daily dose). DDDs are defined by the WHO and are the assumed average maintenance doses per day[14]. DDDs are often the lower limits of doses of medication as advised by the Dutch (GP) guidelines[3]. For the present study, the DDD of tramadol was changed to 150 mg/day, instead of the 300 mg/day as defined by the WHO, because 300 mg/day is not recommended in the Dutch guidelines[3 15] (Online Resource 1, Table S1 for the DDD and the recommended doses in the Netherlands).

'Intermittent' use of analgesics was defined as use for 14 days or less per month and 'continuous use' was defined as use for 15-31 days.

The dose of medication used was self-reported by the patients. Any patients reporting a daily dose above the upper limit of the daily advised dose, or a non-existent dose, were excluded from the analysis.

Statistical analyses

Descriptive statistics were used to describe demographic and clinical characteristics of the participants. Total numbers of medications used were calculated. Logistic regression analyses were used to assess whether differences in medication use existed between patients with and without additional musculoskeletal comorbidities, and to determine which patient characteristics were associated with current medication use, and continuous or intermittent use of analgesics. Variables were included in the multivariate analysis when the p-value was <0.1 in the univariate analysis. All analyses were performed using SPSS version 21 (SPSS Inc., Chicago, IL, USA).

RESULTS

Study population

In total, 842 (56%) patients filled out the questionnaire. Table 1 presents the characteristics of the study population. Besides OA, the most frequently reported musculoskeletal comorbidities were rheumatic arthritis (20%), gout (4%) and Tietze's syndrome (4%). Baseline characteristics of the present study population are comparable to those of the entire DAF panel. For example, in the DAF panel, 86% was female (compared with 83% in the present sample). In the entire panel, OA was diagnosed ≤1 year ago in 9% of the participants, 1-5 years ago in 32%, 5-10 years ago in 20% and ≥10 years ago in 37% of the participants. These overall percentages are similar to those in the present sample (Table 1); moreover, the level of education and employment status were also similar. Therefore, we believe that this study sample is representative of all participants in the DAF panel. In the present study, most participants reported that they always feel or often feel pain. Always having pain was more frequently reported by participants with concomitant fibromyalgia (46.6%) and with additional musculoskeletal morbidities (39.1%) than by participants with OA alone (32.0%) (Chi-square, p<0.001).

Use of medication

In total, 71% of the participants reported use of analgesics in the preceding month. Half of these participants used paracetamol, whereas tricyclic antidepressants as analgesic were the least often used (5.3%) (Online Resource 2, Table S2).

Different classes of analgesics were frequently combined (Table 2). Compared with participants with concomitant fibromyalgia or other musculoskeletal morbidities, participants with OA alone significantly more frequently declined to use analgesics (p<0.01) and significantly less frequently used two or three types of analgesics (p<0.01). Among all study patients, the two most frequently used combinations of analgesics were i) paracetamol and NSAIDs (14.6%), and ii) paracetamol and opioids (7.4%). Almost 4% of

Table 1. Characteristics of the study population

	N (%)
Age, mean (SD), y	61.7 (8.7)
Women	701 (83.3)
Time since diagnosis	
<12 months	53 (6.3)
1-5 years	221 (26.1)
5-10 years	144 (17.1)
>10 years	278 (33.0)
Employment	227 (27.0)
Pain	
Always	322 (38.2)
Often	388 (46.1)
Sometimes	120 (14.3)
Rare	11 (1.3)
Never	1 (0.1)
Joints involved	
Hand	617 (73.3)
Back/ neck	493 (58.6)
Hip	316 (37.5)
Knee	471 (55.9)
≥ 3 joints involved	592 (70.3)
Income level	
Lower than average/no income	184 (21.9)
Average	220 (26.8)
Higher than average	263 (31.2)
Education level	
Low	219 (26.0)
Middle	305 (36.2)
High	310 (36.8)
Comorbidity	
OA only	334 (39.7)
OA and fibromyalgia*	219 (26.0)
OA and other MSK comorbidities**	289 (34.3)

* 93 have concomitant other musculoskeletal comorbidities, ** 58 have more than 1 musculoskeletal comorbidity, MSK indicates musculoskeletal

the participants combined the use of paracetamol, NSAIDs and opioids in the preceding month.

Most of the participants used analgesics for > 14 days in the preceding month; moreover, often, paracetamol and opioids were not used according to the DDD (Table 3). Continuous use of paracetamol was associated with a reasonable amount of perceived benefit, use on prescription, and on a person's education level. For NSAIDs (including COX-2 inhibitors) continuous use was associated with higher scores on the BMQ-

Table 2. Number of groups of oral analgesics used

	Total, ever used (n=842)	Total, preceding month (n=842)	OA only (n=334)	OA and fibromyalgia (n=219)	OA and other musculoskeletal comorbidity (n=289)
0 drugs	142 (15.7)	242 (28.7)	125 (37.4)	**39 (17.8)***	**78 (27.0)****
1 drug	238 (28.3)	310 (36.8)	124 (37.1)	78 (35.6)	108 (37.3)
Paracetamol	112 (13.3)	165 (19.6)	66 (19.8)	36 (16.4)	63 (21.8)
NSAIDs/COX-2-inhibitors	82 (9.7)	97 (11.5)	44 (13.2)	23 (10.5)	30 (10.4)
Opioids	40 (4.8)	44 (5.2)	12 (3.6)	17 (7.8)	15 (5.2)
TCAs	4 (0.5)	4 (0.5)	2 (0.6)	2 (0.9)	0
2 drugs	320 (38.0)	238 (28.3)	73 (21.9)	**81(37.0)***	**84 (29.1)*****
Paracetamol & NSAIDs	194 (23.0)	123 (14.6)	39 (11.7)	38 (17.4)	46 (15.9)
Paracetamol & opioids	62 (7.4)	62 (7.4)	19 (5.7)	22 (10.0)	21 (7.3)
Paracetamol & TCAs	8 (1.0)	11 (1.3)	1 (0.3)	5 (2.3)	5 (1.7)
NSAIDs & opioids	49 (5.8)	32 (3.8)	11 (3.3)	12 (5.5)	9 (3.1)
NSAIDs & TCAs	4 (0.5)	4 (0.5)	1 (0.3)	3 (1.4)	0
Opioids & TCAs	3 (0.4)	6 (0.7)	2 (0.6)	1 (0.5)	3 (1.0)
3 drugs	132 (15.7)	49 (5.8)	11 (3.3)	**20 (9.1)****	18 (6.3)
Paracetamol, NSAIDs, opioids	98 (11.6)	32 (3.8)	8 (2.4)	10 (4.6)	14 (4.8)
Paracetamol, NSAIDs, TCAs	15 (1.8)	10 (1.2)	3 (0.9)	6 (2.7)	1 (0.3)
Paracetamol, opioids, TCAs	10 (1.2)	3 (0.4)	0	2 (0.9)	1 (0.3)
NSAIDs, opioids, TCAS	9 (1.1)	4 (0.5)	0	2 (0.9)	2 (0.7)
4 drugs	20 (2.4)	3 (0.4)	1 (0.3)	1 (0.5)	1 (0.3)

*p<0.001, **p <0.01 ***p<0.05; TCA indicates tricyclic antidepressants

Table 3. Number of days and dose of analgesic use

	Paracetamol n (%)*	**NSAIDs** n (%)**	**Weak opioids** n (%)***
Days			
0-7	58 (16%)	56 (21%)	32 (23%)
8-14	48 (14%)	34 (13%)	5 (3.6%)
15-21	42 (12%)	31 (12%)	12 (9%)
22-28	20 (6%)	8 (3%)	5 (4%)
29-31	188 (53%)	135 (51%)	83 (61%)
DDD			
DDD<1	181 (58%)	63 (33%)	61 (87%)
DDD ≥ 1	129 (42%)	131 (67%)	9 (13%)

DDD= Defined Daily Dose. Intermittent use: 28 days or less in the past month. Continuous use: 29-31 days in the past month. Participants were excluded from the analysis when doses were unknown or non-existent and/or participants did not report the number of days analgesics were used in the past month. * * 433 participants used paracetamol in the past month; Days n=356 (77 excluded), DDD n=310 (123 excluded); **309 participants used NSAIDs in the past month; Days n= 264 (excluded 45), DDD n=194 (excluded 115); ***145 participants used opioids in the past month; Days n=137 (8 excluded, DDD n=70 (75 excluded).

Specific-Necessity scale, always having pain, a diagnosis of OA ≥ 5 years ago, and use on prescription base (Table 4) (Online Resource 3, Table S3 for univariate analysis).

Characteristics associated with current analgesic use

In the multivariate regression analysis, current use of medication was associated with the score on the BMQ-Specific-Necessity scale [OR 1.168 (1.117-1.221)] (Table 5). Higher scores on this scale increase the odds of using medication, i.e. higher scores indicate greater confidence in prescribed medication. In the multivariate analysis, always/often having pain was also associated with current medication use. In the univariate analysis, the concomitant presence of fibromyalgia and other musculoskeletal morbidities was associated with current medication use; however, this association disappeared when controlling for other variables (pain, score on BMQ-Specific-Necessity scale, level of education, and time since diagnosis).

Beliefs about medication

Participants' general beliefs about medication were assessed by the BMQ-General subscales. The mean score on the BMQ-General-Overuse scale was 11.9 (SD 3.0) and on the BMQ-General-Harm scale it was 10.7 (SD 2.8). Participants' opinions about OA medication was evaluated using the BMQ-Specific scales. For the entire group, the mean score on the Specific-Necessity scale was 15.2 (SD 4.8) and on the Specific-Concern scale it was 13.9 (SD 3.8). For participants using analgesics, the mean score on the Specific-Necessity scale was 16.4 (SD 4.2) and on the Specific-Concern scale it was 14.0 (SD 3.8) indicating

Table 4. Multivariate analysis of continuous versus intermittent use of paracetamol and NSAIDs

	Paracetamol (n=352*)			NSAIDs (n=214**)		
	OR	CI	p-value	OR	CI	p-value
BMQ-Specific-Necessity	1.042	0.969-1.119	0.265	**1.165**	**1.064-1.275**	0.001
BMQ-General-Overuse	0.981	0.892-1.080	0.701			
Other analgesic use (yes)	1.777	0.960-3.288	0.067			
Pain						
Always	2.089	0.729-5.985	0.170	**6.427**	**1.645-25.107**	0.007
Often	2.320	0.839-6.419	0.105	1.823	0.489-6.796	0.371
Sometimes/rare/never	1			1		
Time since diagnosis						
<12 months	1			1		
1-5 years	2.132	0.698-6.519	0.184	3.779	0.997-14.319	0.050
5-10 years	2.091	0.632-6.918	0.227	**7.496**	**1.840-30.538**	0.005
>10 years	2.171	0.719-6.556	0.169	**6.559**	**1.787-24.080**	0.005
Perceived benefit						
Good	2.562	0.914-7.185	0.074			
Reasonable	**3.135**	**1.306-7.528**	0.011			
Bad	1					
Comorbidity						
None	1					
Fibromyalgia	1.474	0.671-3.237	0.333			
Other MSK	1.261	0.630-2.526	0.513			
Prescribed	**3.631**	**1.912-6.896**	<0.001	**5.895**	**1.751-19.846**	0.004
Employed	0.765	0.388-1.505	0.437			
Education level						
Low	1.717	0.808-3.647	0.160			
Middle	**1.958**	**1.011-3.793**	0.046			
High	1					

Participants were excluded from the analysis when they did not report the number of days analgesics were used in the past month. Values in bold font are values that were statistically significant in our analyses. ** *433 participants used paracetamol in the past month;81 were excluded from the analysis; **** 309 participants used NSAIDs in the past month; 95 were excluded from the analysis. CI indicates confidence interval; OR, odds ratio.

that, for participants using analgesics, their beliefs about the necessity of medication outweighed their concerns about medication.

Reasons for not using analgesics

In total, 280 (33.3%) participants did not use medication for OA-related pain in the preceding month, and 12% never used analgesics for OA-related pain. The most frequently mentioned reasons for this were that pain is bearable without the use of analgesics (55%), and reluctance to use analgesics (21%) (Table 6). For these participants, the concerns about medication outweighed the necessity for the medication. The mean score

Table 5. Multivariate analysis for current use of medication

	Univariate			Multivariate		
	OR	CI	p-value	OR	CI	p-value
Age	0.997	0.981-1.013	0.685			
Gender	0.768	0.528-1.117	0.168			
BMQ-Specific-Necessity	**1.201**	**1.159-1.245**	<0.001	**1.168**	**1.117-1.221**	<0.001
BMQ-Specific-Concerns	1.020	0.983-1.059	0.297			
BMQ-General-Overuse	**0.891**	**0.848-0.936**	<0.001	0.934	0.865-1.009	0.082
BMQ-General-Harm	0.950	0.901-1.001	0.053	0.921	0.846-1.003	0.059
Pain						
Always	**10.894**	**6.802-17.448**	<0.001	**7.318**	**4.172-12.838**	<0.001
Often	**4.067**	**2.662-6.216**	<0.001	**3.314**	**2.003-5.481**	<0.001
Sometimes/rare/never	1			1		
Time since diagnosis						
<12 months	1			1		
1-5 years	1.218	0.663-2.235	0.525	0.952	0.456-1.987	0.896
5-10 years	1.398	0.736-2.656	0.306	0.979	0.450-2.129	0.957
>10 years	**1.931**	**1.057-3.528**	0.032	1.141	0.545-2.391	0.726
Comorbidity						
None	1			1		
Fibromyalgia	**2.808**	**1.904-4.140**	<0.001	1.589	0.960-2.630	0.071
Other MSK	**1.744**	**1.252-2.428**	0.001	1.095	0.707-1.697	0.684
Employed	1.127	0.818-1.552	0.466			
Education level						
Low	**1.704**	**1.173-2.474**	0.005	1.267	0.779-2.060	0.340
Middle	**1.492**	**1.069-2.083**	0.019	1.469	0.964-2.240	0.074
High	1			1		
Income level						
Low	1.317	0.878-1.976	0.183			
Middle	1.148	0.786-1.677	0.475			
High	1					

CI indicates confidence interval; MSK, musculoskeletal; OR, odds ratio

on the BMQ-Specific Necessity scale was 12.8 (SD 4.8) and on the BMQ-Specific Concerns scale it was 13.7 (SD 3.9)

DISCUSSION

In the present study, 71% of the participants used analgesics for OA-related pain and 34.5% used more than one type of analgesic. Patients with concomitant fibromyalgia or another musculoskeletal comorbidity used more types of analgesics than patients with

Table 6. Reasons for not using analgesics

	n (%)
Pain bearable without analgesics	153 (55)
Reluctance to use analgesics	58 (21)
Use of other strategies against pain	51 (18)
Enough other medication	40 (14)
Side-effects	35 (13)
Medication is not useful for me	26 (9)
Drug interactions	15 (5)
Fear of addiction	5 (2)
Lack of money	3 (1)
Other reasons	61 (22)

OA alone. In addition, paracetamol and opioids were frequently taken in doses lower than the DDD. Most of the patients used analgesics for more than 14 days in the preceding month. Furthermore, the necessity of analgesics for OA-related pain outweighed the concerns about the use of analgesics. However, for participants not using analgesics, the concerns about analgesics outweighed the necessity. Finally, the most important reason for not using analgesics was that the pain was considered bearable without the use of analgesics.

In this study population, concurrent musculoskeletal comorbidities frequently occurred, i.e. 26% reported concurrent fibromyalgia and 34.3% another musculoskeletal disease; these subgroups of patients are often excluded from OA studies[9]. In a Dutch open population cohort on self-reported musculoskeletal diseases, OA of the knee was reported by 12% and OA of the hip by 7%[10]. Of these latter participants with OA, 20% reported concomitant rheumatoid arthritis, which is comparable with the present OA population. However, the prevalence of fibromyalgia in the present study was 26%, whereas in the open population cohort only 2.5% of those with knee OA and only 4.3% of those with hip OA had coexistent fibromyalgia.

In our participants, paracetamol was the most frequently used analgesic; this is consistent with other Dutch cross-sectional studies in patients with OA[16,17]. However, two studies from the USA (including the OAI progression cohort), and another study including patients from five European countries with self-reported OA, found that NSAIDs were the most frequently used analgesic for OA-related pain[5,9,18]. An explanation for the difference between those studies and ours might be that the Dutch guidelines advise to use these two analgesics (i.e. paracetamol and NSAIDs) consecutively[3], whereas the American College of Rheumatology guidelines recommend both as first choice treatment for OA-related pain[19]. Furthermore, in our population, the use of NSAIDs was relatively low and the use of opioids relatively high[9,17]. Possible explanations for this are that opioids

are more frequently prescribed for a population with generalized OA, and that the use of opioids for OA can vary between countries[18] since the percentage of opioids used in our study was similar to that in another Dutch population with generalized OA[16]. Another explanation could be that increased awareness of the risks and contraindications for NSAIDs resulted in less frequent prescribing of NSAIDs and more frequent prescribing of opioids[9 20]. Finally, the choice of analgesics might also be influenced by comorbidities.

In the present study, participants frequently used more than one analgesic. Both the presence of generalized OA[16] or the involvement of multiple joints in musculoskeletal diseases[21] and the presence of other musculoskeletal comorbidities or fibromyalgia, can lead to higher analgesic use[22]. Particularly patients with fibromyalgia can use multiple analgesics for a longer period of time, which may potentiate adverse events.

Another finding was that most of these participants used analgesics for >14 days in the preceding month. For NSAIDs, daily use was associated with more severe pain. More than 50% of our participants that used an NSAID did so on a continuous basis, whereas the Dutch guidelines recommend use of NSAIDs for a short period of time[3]. Furthermore, often, paracetamol and weak-acting opioids were not used in doses according to the DDD. In the Netherlands, the DDD is often the lower limit of advised doses and prescribed doses are frequently higher than this threshold. Increasing this threshold to this higher dose would in fact lower this number of patients. Participants who perceived good or moderate benefit from paracetamol had higher odds of using paracetamol according to the DDD, whereas for NSAIDs this effect was not found. Perhaps the benefit derived from analgesics may be improved by the use of higher doses, which may reduce or postpone the use of opioids. On the other hand, participants that do not perceive adequate benefit from analgesics will not be inclined to use a higher daily dose.

In the present population, participants with higher scores on the BMQ-Specific-Necessity (higher confidence in prescribed medication) more frequently used medication and more frequently on a continuous basis. Furthermore, beliefs about the necessity of analgesics outweighed the concerns about analgesics. This is consistent with other studies examining the association between BMQ scores and (self-reported) adherence to therapy[23 24].

Finally, we evaluated participants' rationale for not using analgesics; their main reason was for this was that the pain was bearable. As mentioned, multiple factors are involved in medication adherence in OA; one important moderator is the level of pain experienced by patients[8]. Patients with higher levels of pain use analgesics on a continuous basis rather than on demand[6]. Other factors involved are the perceived effectiveness of analgesics and the current use of other medications (poly-pharmacy)[8].

The present study has some limitations. Firstly, all data are self-reported, which can influence the reported prevalence OA of other musculoskeletal diseases. Although the prevalence of self-reported musculoskeletal diseases is higher compared to data from

registrations or controlled examinations, the reliability of self-reported diseases was found to be fair to good[25]. Furthermore, patients are the single best source of information for assessment of musculoskeletal pain; however, recall bias could have influenced questions on medication use in the preceding month. Some participants reported doses above the upper limit of the recommended daily dose, or non-existent doses of analgesics; these patients were excluded from those specific analyses. However, when these participants were included in the analyses the results remained unchanged. Another limitation is that, for these participants of the DAF panel, we had no data on comorbidities other than musculoskeletal diseases. The presence of, for example, cardiovascular diseases or impaired kidney function could have influenced the patient's choice for specific analgesics.

In summary, in the present study, analgesic use was high and participants in this population with generalized OA and concomitant musculoskeletal comorbidities and fibromyalgia often used more types of analgesics on most days in the preceding month. However, these analgesics were often used in low doses. Clinicians should be aware of this when patients present to them with OA-related pain and evaluate whether higher doses or continuous use of analgesics may improve pain in these patients. This might, in turn, reduce or postpone the use of stronger analgesics, such as opioids.

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SUPPLEMENTARY DATA

Table S1. Daily Defined Dose (DDD) and recommended doses in the Netherlands

Analgesic	DDD (mg)	Recommended dose (mg)
Paracetamol	3000	2500-4000
Celecoxib	200	200-400
Diclofenac	100	50-150
Etoricoxib	60	30-120
Ibuprofen	1200	1200-2400
Naproxen	500	375-1000
Tramadol	150*	50-400
Paracetamol/codein	3000**	3000**

*DDD is lowered to 150 mg, instead of 300 mg as recommended by the WHO, ** DDD is set at the daily dose of paracetamol

Table S2. Use of analgesics per type of analgesic

	Ever (n (%))	Preceding month (n (%))
Paracetamol	519 (61.6)	433 (51.4)
NSAIDs	519 (61.6)	233 (27.7)
Diclofenac	208 (24.7)	82 (9.7)
Ibuprofen	165 (19.6)	74 (8.8)
Naproxen	149 (17.7)	69 (8.2)
Meloxicam	30 (3.6)	24 (2.9)
Topical NSAIDs	77 (9.1)	45 (5.3)
COX-2 inhibitors	118 (14.0)	76 (9.0)
Celecoxib	59 (7.0)	30 (3.6)
Etoricoxib	65 (7.7)	46 (5.5)
Weak opioids	250 (29.7)	145 (17.2)
Paracetamol/codein	100 (11.9)	49 (5.8)
Tramadol	130 (15.4)	65 (7.7)
Tramadol/paracetamol	79 (9.4)	44 (5.2)
Strong opioids	84 (10.0)	49 (5.8)
Buprenorphine	9 (1.1)	4 (0.5)
Fentanyl	27 (3.2)	14 (1.7)
Morphine	27 (3.2)	12 (1.4)
Oxycodone	40 (4.8)	20 (2.4)
Tapentadol	1 (0.1)	1 (0.1)
Tricyclic antidepressants	73 (8.7)	45 (5.3)
Amitriptyline	70 (8.3)	44 (5.2)
Nortriptyline	3 (0.4)	1 (0.1)
Corticosteroid injections	102 (12.1)	16 (1.9)
Hyaluronic acid injections	20 (2.4)	2 (0.2)

Table S3. Continuous vs intermittent use of paracetamol and NSAIDs (univariate analysis)

	Paracetamol (n=356)			NSAID (n=264)		
	OR	CI	p-value	OR	CI	p-value
Age	1.006	0.979-1.033	0.683	1.000	0.971-1.030	0.992
Gender	0.706	0.395-1.261	0.239	0.796	0.402-1.577	0.514
BMQ-Specific-Necessity	**1.120**	**1.061-1.182**	<0.001	**1.189**	**1.112-1.272**	<0.001
BMQ-Specific-Concerns	1.019	0.959-1.083	0.538	1.044	0.981-1.110	0.175
BMQ-General-Overuse	0.927	0.856-1.004	0.062	0.972	0.889-1.064	0.540
BMQ-General-Harm	0.985	0.903-1.074	0.732	0.984	0.898-1.079	0.732
Other analgesic use (yes)	**2.253**	**1.418-3.582**	0.001	1.419	0.838-2.405	0.193
Pain						
Always	**4.700**	**2.112-10.460**	<0.001	**7.308**	**2.502-21.341**	<0.001
Often	**2.991**	**1.360-6.578**	0.006	2.032	0.718-5.754	0.182
Sometimes/ rare/ never	1	1		1		
Time since diagnosis						
<12 months	1			1		
1-5 years	1.839	0.713-4.741	0.207	2.904	0.894-9.431	0.076
5-10 years	2.240	0.810-6.190	0.120	**4.537**	**1.348-15.276**	0.015
>10 years	**2.581**	**1.016-6.552**	**0.046**	**6.142**	**1.934-19.501**	0.002
Perceived benefit						
Good	1.789	0.802-3.990	0.155	1.086	0.418-2.823	0.865
Reasonable	**2.424**	**1.215-4.838**	0.020	1.047	0.428-2.563	0.920
Bad	1			1		
Side-effects						
Many	0.816	0.073-9.115	0.816	0.431	0.070-2.640	0.363
Tolerable	0.816	0.199-3.337	0.777	1.098	0.477-2.530	0.826
Few	0.864	0.460-1.622	0.648	1.590	0.783-30.230	0.200
None	1			1		
Comorbidity						
None	1			1		
Fibromyalgia	**1.848**	**1.037-3.292**	0.037	1.025	0.557-1.883	0.938
Other MSK	1.685	0.987-2.879	0.056	1.145	0.627-2.091	0.659
Prescribed	**3.250**	**1.949-5.419**	<0.001	**6.177**	**2.374-16.070**	<0.001
Employed	0.640	0.387-1.057	0.081	0.666	0.395-1.124	0.128
Education level						
Low	**2.110**	**1.155-3.855**	0.015	1.647	0.856-3.170	0.135
Middle	**1.843**	**1.088-3.120**	0.023	1.533	0.862-2.724	0.146
High	1			1		
Income level						
Low	1.332	0.713-2.490	0.369	1.297	0.660-2.552	0.451
Middle	1.070	0.600-1.905	0.819	0.662	0.348-1.258	0.208
High	1			1		

BMQ= Beliefs About Medication Questionnaire, MSK= musculoskeletal

CHAPTER 3

Opioid prescriptions in patients with osteoarthritis: a population-based cohort study

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ABSTRACT

Objectives

To examine the incidence, prevalence and trends for opioid prescriptions in patients with osteoarthritis. Furthermore, types of opioids prescribed and long-term prescription rates were examined. Finally, the patient characteristics associated with the prescription of opioids were assessed.

Methods

A population-based cohort study was conducted using the Integrated Primary Care Information database. Incidence and prevalence of opioid prescriptions were calculated for the period 2008-2017. Logistic regression was used to assess which patient characteristics were associated with opioid prescriptions.

Results

In total, 157,904 OA patients were included. The overall prescription rate remained fairly stable, at around 100 incident and 170 prevalent prescriptions per 1000 person years. However, the incident prescription rate for oxycodone increased from 7.1 to 40.7 per 1000 person years and for fentanyl from 4.2 to 7.4 per 1000 person years. The incident prescription rate for paracetamol/codeine decreased from 63.0 to 13.3 per 1000 person years. Per follow-up year, long-term use was found in 3% of the patients with incident OA. Finally, factors associated with more prescriptions were increasing age, OA in ≥2joint groups (OR 1.56 [95% CI 1.51-1.65]) and the presence of other musculoskeletal disorders (OR 4.91 [95% CI 4.76-5.05]). Men were less likely to be prescribed opioids (OR 0.78 [95% CI 0.76-0.80]).

Conclusion

Prescription rates for opioids remained stable, but types of opioids prescribed changed. Oxycodone and fentanyl were increasingly prescribed, while prescriptions of paracetamol/codeine decreased. Since the benefit of opioids for OA pain is questionable and side effects are common, opioids should be prescribed with caution.

INTRODUCTION

Osteoarthritis (OA) is one of the major chronic pain conditions of the musculoskeletal system. Approximately 15% of the population suffers from OA, and the Global Burden of Disease study ranked OA as the 11th biggest contributor to global disability[1 2]. One of the major complaints of patients with OA is pain. Since the population is ageing and obesity is increasing, it is expected that the disease burden will increase[2].

Treatment options for OA pain consist of exercise therapy, education, weight loss and pain medication, amongst others. Pain medication is often prescribed in a stepwise approach starting with paracetamol, then topical and oral nonsteroidal anti-inflammatory drugs (NSAIDs), followed by opioids if earlier steps do not reduce the pain sufficiently. Nevertheless, the current guidelines for the treatment of OA have a restrictive advice on the use of opioids for OA-related pain[3], or do not recommend the use of opioids[4], since the benefit for OA pain is questionable and treatment is associated with side effects.

Opioids are increasingly being prescribed for chronic non-cancer pain. It has been estimated that around 70% of the prescribed opioids are prescribed for chronic non-cancer pain. Musculoskeletal disorders, including OA, are an important cause of non-cancer pain[5]. The number of opioid prescriptions has risen in the US in particular, more so than in Europe[6]. Opioids do have a potential to cause harm and frequently have side effects, like nausea, constipation and somnolence. In elderly OA patients, the risk of falls and fractures is increased when using opioids[7 8]. Finally, misuse and addiction are a risk when using opioids[9 10].

Despite the questionable benefit and the frequency of side effects, the use of opioids in OA patients is high[11 12] and increasing[13 14]. Earlier research examined the total use of opioids for OA, but did not focus on which types of opioids were used[11 13]. Furthermore, knowledge about the long-term use of opioids in OA is scarce.

Therefore, the aim of the current study is to examine the incidence and prevalence of the different types of opioids prescribed in patients with OA and the trends in opioid prescription over the past decade. We examined the long-term prescription rate of opioids in patients with OA and assessed which patient characteristics are associated with opioid prescription.

METHODS

Setting

This study was conducted using the Integrated Primary Care Information (IPCI) database. The IPCI database contains the electronic patient records of more than 1.5 million patients in the Netherlands. The database contains all journal entries by general practi-

tioners (GPs), diagnoses coded according to the International Classification of Primary Care (ICPC) codes, laboratory findings and drug prescriptions[15 16].

Study cohort

For this study, the use of opioids by patients with OA and aged ≥ 30 years between 1 January 2008 and 31 December 2017 was examined. Patients who were newly diagnosed with OA in this period (incident OA) as well as patients with a diagnosis of OA in their medical history (prevalent OA) were included in the cohort.

Patients with at least 12 months of valid database history prior to the study entry were included in the cohort. The diagnosis of OA was based on the ICPC codes L84 (spinal OA), L89 (hip OA), L90 (knee OA) and L91 (other peripheral joints affected by OA). Patients younger than 30 were excluded from the cohort (<1% of the patients with a diagnosis of OA), because the use of these ICPC codes in such cases was often a coding error by the GP.

Patients were excluded from the cohort if diagnosed with or having a medical history of malignancy, neuropathic pain disorders or fibromyalgia. Patients were excluded 1 year prior to the first diagnosis of these diseases. If follow-up of the patient was until death, they were excluded from the cohort 1 year before their death. The main reason for exclusion of these patient groups is that there was a probability that opioids were prescribed for reasons other than pain related to OA.

Outcomes

All opioid prescriptions are dispensed by GPs or clinicians in the Netherlands. Opioid prescriptions are identified by Anatomical Therapeutic Chemical (ATC) code. Prescriptions for tramadol (N02AX02), tramadol/paracetamol (N02AJ13), paracetamol/codeine (N02AJ06/N02BE51), oxycodone (N02AA05), fentanyl (N02AB03), morphine (N02AA01) and buprenorphine (N02AE01) were examined since these are commonly prescribed opioids. Hydromorphone, tapentadol, nicomorphine and oxycodone/naloxone were examined, but were rarely prescribed for OA pain (< 1.0 prescriptions per 1000 person years) and were therefore not considered in the analyses. Tramadol, tramadol/paracetamol and paracetamol/codeine were classified as weak opioids, and oxycodone, fentanyl, morphine and buprenorphine as strong opioids.

The incidence for opioid prescriptions was determined as the total number of new episodes of opioid prescriptions divided by the total number of person years in the cohort per calendar year. A new opioid prescription episode was defined as no prescription in the preceding six months. The prevalence of opioid prescriptions was calculated as the total number of patients who had at least one prescription of opioids divided by the total number of person years in the cohort in a calendar year. New episodes of opioid prescriptions within six months of a diagnosis of a trauma (e.g. fracture) were

excluded in both calculations since it was less likely that those prescriptions were for OA-related pain. Those patients remained in the cohort.

For the patients with incident OA, the number of different types of opioids that were prescribed and the order in which they were prescribed were examined. If patients switched back to an opioid that had been prescribed previously, we did not count this as a new type of opioid. Furthermore, the percentage of patients with incident OA who were prescribed opioids over a long term was calculated. Long-term prescription of opioids was defined as six or more prescriptions during one follow-up year (i.e. in the first year after diagnosis, in the second year after diagnosis, etc.). The median duration of a prescription for opioids is 15 days in the IPCI database and other databases[17]. Therefore, six prescriptions corresponds to an estimated 90 days of opioid use in a year.

Statistical analyses

Descriptive statistics were performed to give the baseline characteristics of the cohort and to calculate prevalence and incidence rates of opioid prescriptions. Univariate logistic regression analyses were conducted to examine whether baseline characteristics were related to opioid prescription, and odds ratios (ORs) and their 95% confidence intervals (CI) were calculated. Variables were included in the multivariate analysis if $p<0.1$ in the univariate analysis. All analyses were performed using SPSS version 24 (IBM Corp., Armonk, NY, USA).

Study approval

The study was approved by the Board of Directors of the IPCI database.

RESULTS

Study population

In total, 157,904 patients were included in the cohort (Table 1). Of these, 56,713 were newly diagnosed with OA. Of the total patient group, 65.2% were female. Co-morbidities were present in 55.2% of the patient group. The most common type of OA was knee OA (27.8%) and 21.3% of the patients were diagnosed with OA in more than one joint group. At the start of the follow-up period the mean age was 66.6 years (SD ± 12.5). During the follow-up period, 65% of the patients visited the GP with another musculoskeletal complaint besides OA (mean follow-up duration was 3 years and 4 months).

Trends in incident opioid prescription rate

In the past decade, the overall incident prescription rate for opioids remained fairly stable (Figure 1). However, the prescription rate for strong opioids was increasing while

Table 1. Baseline characteristics

Characteristic	Value (n= 157 904)
Age, mean (S.D.) years	66.6 (12.5)
Age category, *n (%)*	
30-39	2 587 (1.6)
40-49	11 593 (7.3)
50-59	31 409 (19.9)
60-69	46 924 (29.7)
70-79	39 172 (24.8)
80-89	22 640 (14.3)
> =90	3 579 (2.3)
Female, *n (%)*	102 988 (65.2)
Joints affected, *n (%)*	
Back	16 409 (10.4)
Hip	27 508 (17.4)
Knee	43 919 (27.8)
Other joints	36 410 (23.1)
2 or more joints	33 658 (21.3)
Diabetes, *n (%)*	22 763 (14.4)
Hypertension, *n (%)*	63 481 (40.2)
Hyperlipidaemia, *n (%)*	27 218 (17.2)
MI/AP, *n (%)*	17 073(10.8)
Stroke/TIA, *n (%)*	5 869 (3.7)
PAD, *n (%)*	5 585 (3.5)
UGI/ulcer, *n (%)*	5 027 (3.2)
Heart failure, *n (%)*	6 306 (4.0)
Inflammatory arthritis, *n (%)*	7 091 (4.5)
Other MSD during cohort time, *n (%)*	
Upper extremity	36 293 (23.0)
Lower extremity	57 131 (36.2)
Back/neck	47 529 (30.1)
Trauma	18 495 (11.7)
Other musculoskeletal	45 941(29.1)
None	54 170 (34.3)
Renal function, *n (%)*	
eGFR>60 ml/min	98 928 (62.7)
eGFR 30-60 ml/min	18 298 (11.6)
eGFR<30 ml/min	1 613 (1.0)
missing	39 065 (24.7)

MSD= musculoskeletal disorders, eGFR= estimated glomerular filtration rate, MI=myocardial infarct, AP=angina pectoris; TIA= transient ischemic attack; PAD= peripheral arterial disease, UGI= upper gastrointestinal

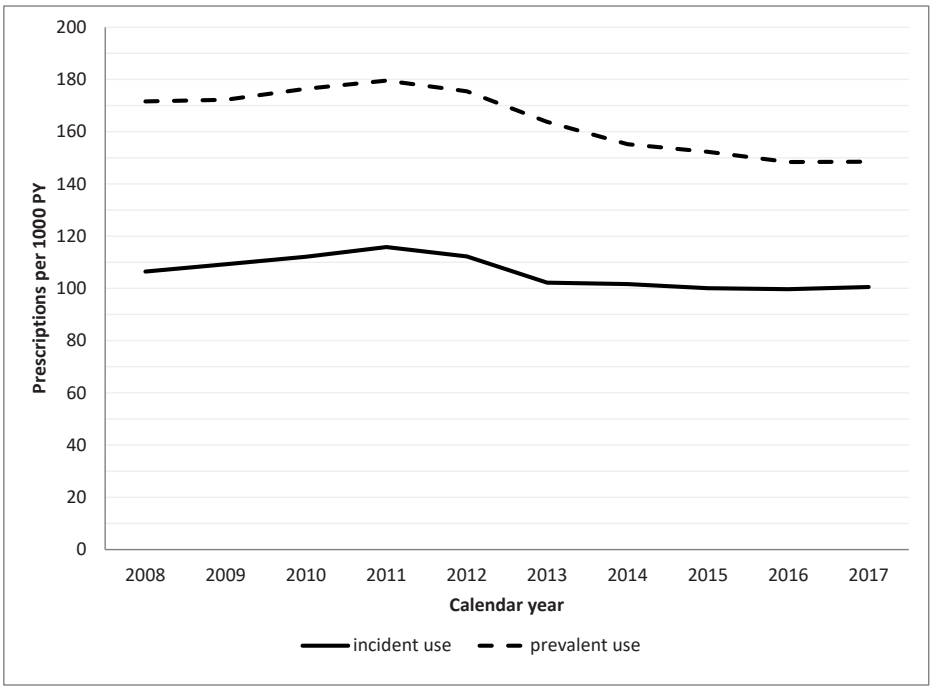


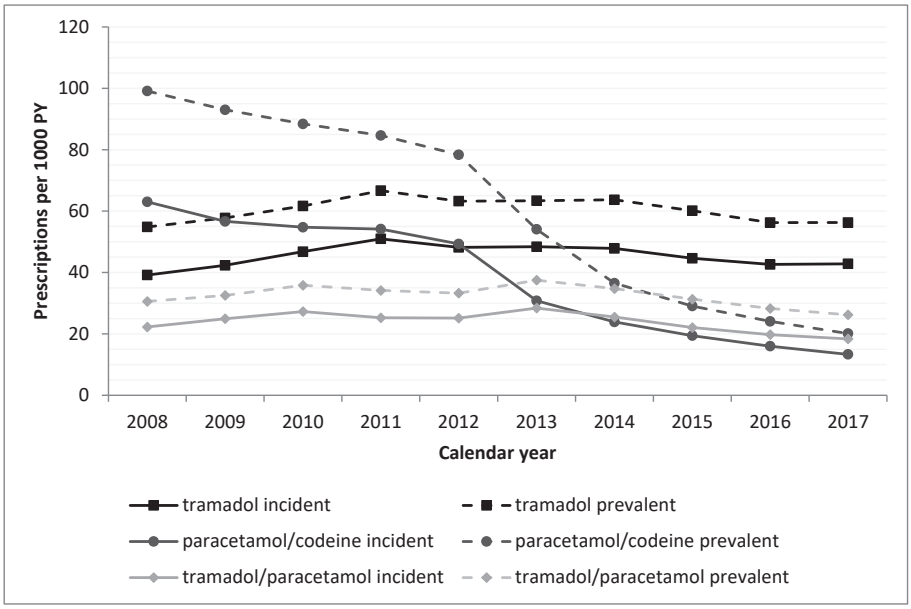
Figure 1. Total opioid prescription rate
PY= person years

the prescription rate for weak opioids was decreasing (Figures 2a and 2b, numbers in Supplemental data Table S1). The incident prescription rate for oxycodone increased from 7.1 per 1000 person years in 2008 to 40.7 per 1000 person years in 2017 and the incident rate for fentanyl increased from 4.2 to 7.4 per 1000 person years. The prescription rate for tramadol/paracetamol decreased from 22.3 to 18.4 per 1000 person years and the prescription rate for paracetamol/codeine decreased between 2008 and 2017 from 63.0 to 13.3 per 1000 person years. In 2013, health insurance companies stopped reimbursing the costs of paracetamol/codeine, which led to the rapid decline since then[18]. The prescription rates for tramadol, morphine and buprenorphine remained stable over the past decade. Buprenorphine was introduced to the market in 2007.

Trends in prevalent opioid prescription rate

The trends in prevalent opioid prescription rates showed similar patterns to the incident prescription rates. The overall rate of prescriptions remained stable, while the prescription rate for strong opioids increased and the prescription rate for weak opioids decreased (Figures 2a and 2b, numbers in Supplemental data Table S1). The major changes were the increase in the prevalent prescription rate for oxycodone from 11.1 to 50.7 per

a. Weak opioids



b. Strong opioids

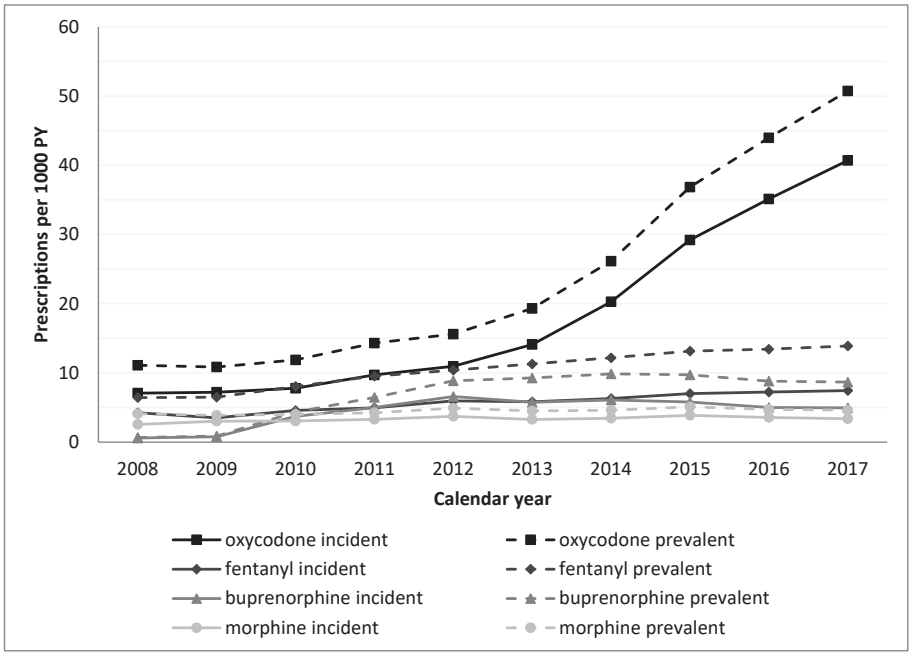


Figure 2. Incidence and prevalence of prescribed opioids
(**A**) Weak opioids, (**B**) strong opioids, PY: person years

1000 person years and the decrease in the rate for paracetamol/codeine from 99.1 to 20.1 per 1000 person years.

Long-term prescriptions

In each follow-up year after the diagnosis of OA, 3% of the patients were prescribed opioids over a long term (≥6 prescriptions), representing around a quarter of the patients prescribed any opioid in a given year (Table 2). When comparing strong opioids to weak opioids, the percentage of patients prescribed opioids over a long term was twice as high for patients prescribed strong opioids than for patients prescribed a weak opioid. Furthermore, these percentages did not change with increasing follow-up years.

Table 2. Chronic users of opioids per follow-up year

Follow-up time (year)	Total	Weak opioids	Strong opioids
	n (% users/ % population)	n (% users/ % population)	n (% users/ % population)
1	1 659 (21.5/3.9)	1 025 (16.4/2.5)	590 (26.4/1.4)
2	996 (22.1/3.2)	601 (16.2/1.9)	366 (30.0/1.2)
3	709 (23.7/3.2)	401 (16.8/1.8)	275 (30.8/1.2)
4	440 (22.8/3.0)	234 (15.5/1.6)	195 (33.0/1.3)
5	276 (23.6/3.1)	142 (15.1/1.6)	130 (35.2/1.5)
6	159 (24.6/3.4)	82 (16.7/1.7)	72 (33.2/1.5)
7	81 (27.5/3.8)	34 (15.7/1.6)	45 (37.8/2.1)
8	38 (31.4/4.1)	20 (21.5/2.1)	18 (37.5/1.9)
9	13 (29.5/4.9)	7 (22.6/2.6)	6 (33.3/2.2)

A chronic user of opioids has ≥6 prescriptions in 1 follow-up year. The number of total chronic users does not equal the sum of the chronic users of weak and strong opioids. Patients can be included in both categories or can be included in the group of total users if the sum of prescriptions for weak and strong opioids ≥6 while the use of weak opioids only or strong opioids only is not classified as chronic use.

Different types of opioids prescribed

Almost 75% of the patients with incident OA were not prescribed an opioid during the follow-up period (Figure 3a). Of the patients with incident OA, 18.4% were prescribed one type of opioid. A switch to another opioid was made in 8.8% of the patients. Two different types of opioids were prescribed for 5.7% of the patients and 2.1% were prescribed ≥ 3 types of opioids. Of all patients, 16.4% were prescribed a weak opioid, 5.1% a strong opioid and 4.6% were prescribed both categories. The most common first opioid prescribed to patients was tramadol (39.7%). Oxycodone was prescribed as the first opioid in 17.2% of cases (Figure 3b and Supplemental data Table S2).

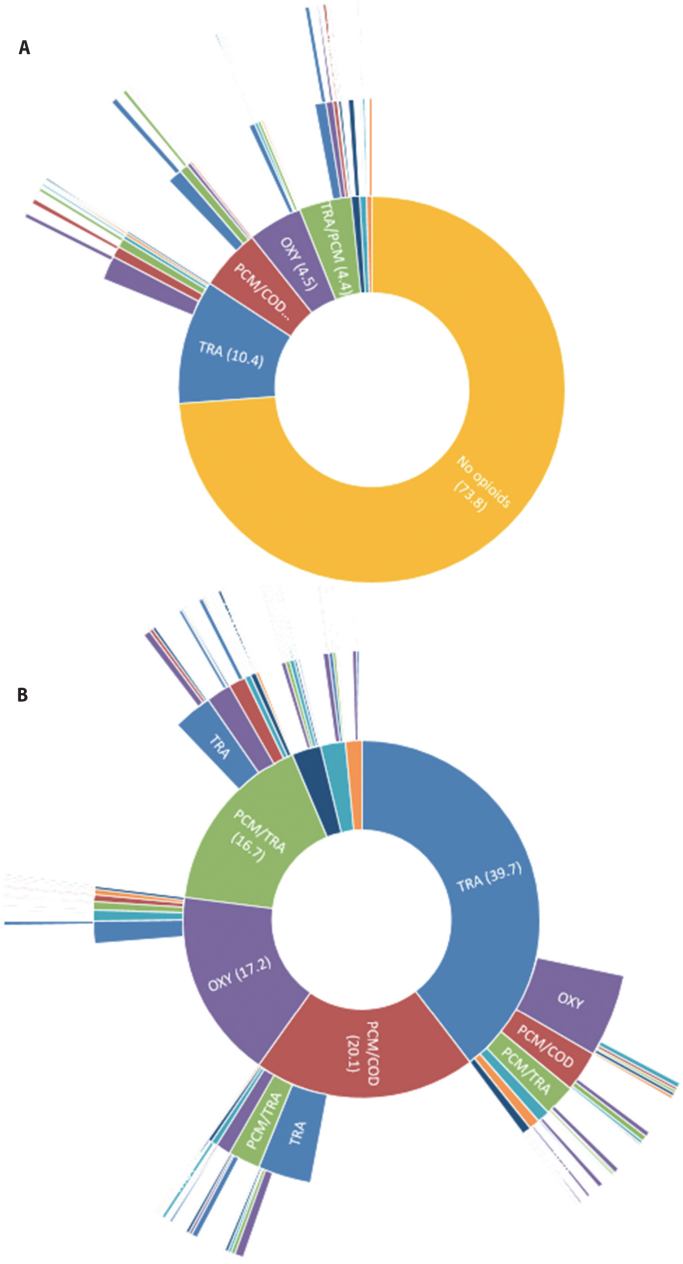


Figure 3. Types of opioids prescribed in patients with incident OA

(**A**) Types of opioids prescribed in patients with incident OA, including patients not prescribed opioids. (**B**) Sequence of types of opioids prescribed in patients with incident OA. n=56713. The inner circle represents the first opioid prescribed, the second circle the second type of opioid prescribed, the outer circle the third type of opioid prescribed. Percentages are shown in parentheses. BUP (dark blue): buprenorphine, FTY (turquoise): fentanyl, MOP (orange): morphine, OXY (purple): oxycodone, PCM/COD (red): paracetamol/codeine, TRA (blue): tramadol, TRA/PCM (green): tramadol/paracetamol.

Characteristics associated with opioid prescription

In both the univariate and the multivariate regression analyses, the prescription of opioids was associated with a more advanced age at the baseline of the cohort and men were less likely to be prescribed opioids than women (OR 0.78 [95%CI 0.76-0.80]) (Table 3). Patients with two or more joint groups involved were more likely to be prescribed opioids (OR 1.97 [95% 1.89-2.05]), while patients with OA in other peripheral joints (ICPC-code L91) were less likely to be prescribed opioids (OR 0.74 [95% CI0.71-0.78]) than patients with back OA. The diagnosis of other musculoskeletal disorders during the follow-up period was associated with the prescription of opioids. Concomitant neck and back problems (OR 3.41 [95% CI3.25-3.57]) and the presence of multiple musculoskeletal disorders (OR 4.91 [95% CI4.76-5.05]) in particular were associated with a greater likelihood of opioid prescriptions.

Table 3. Factors associated with opioid prescription

Factor	Patients prescribed opioid N (%)	Univariate analysis OR (95% CI)	Multivariate analysis OR (95% CI)
Age category			
30-39	495 (19.1)	1	1
40-49	2 902 (25.0)	**1.41 (1.27-1.57)**	**1.30 (1.17-1.46)**
50-59	8 106 (25.8)	**1.47 (1.33-1.63)**	**1.29 (1.16-1.44)**
60-69	12 263 (26.1)	**1.50 (1.35-1.65)**	**1.32 (1.19-1.46)**
70-79	12 036 (30.7)	**1.88 (1.79-2.07)**	**1.57 (1.41-1.74)**
80-89	7 305 (32.3)	**2.01 (1.82-2.23)**	**1.73 (1.55-1.92)**
> 90	1,036 (28.9)	**1.72 (1.52-1.95)**	**1.72 (1.52-1.96)**
Sex			
Female	31 383 (30.5)	1	1
Male	12 760 (23.2)	**0.69 (0.67-0.71)**	**0.78 (0.76-0.80)**
Joint affected			
Spine	4 273 (26.0)	1	1
Hip	7 172 (26.1)	1.00 (0.96-1.05)	1.05 (1.00-1.09)
Knee	11 266 (25.7)	0.98 (0.94-1.02)	1.02 (0.98-1.07)
Other joints	7 641 (21.0)	**0.75 (0.72-0.79)**	**0.75 (0.71-0.78)**
≥2 joints	13 791 (41.0)	**1.97 (1.89-2.05)**	**1.58 (1.51-1.65)**
MSD			
None	7 667 (13.4)	1	1
Upper extremity	1 591 (21.6)	**1.78 (1.67-1.89)**	**1.79 (1.69-1.91)**
Lower extremity	3 916 (23.9)	**2.03 (1.94-2.12)**	**1.94 (1.86-2.02)**
Neck/back	11 451 (34.4)	**3.38 (3.23-3.54)**	**3.41 (3.25-3.57)**
Other MSD	2 542 (24.6)	**2.11 (2.00-2.22)**	**2.09 (1.99-2.20)**
≥2 MSD categories	24 489 (44.3)	**5.14 (4.99-5.29)**	**4.91 (4.76-5.05)**

Values in bold are statistically significant, MSD:musculoskeletal disorder

DISCUSSION

In this study we examined the trends, the long-term prescription and factors associated with the prescription of opioids in patients with OA. The majority of patients with OA were not prescribed an opioid during the follow-up period. The overall prescription rate of opioids remained fairly stable in the period between 2008 and 2017, with on average 100 incident prescriptions per 1000 person years and 170 prevalent prescriptions per 1000 person years. However, there was a change in the types of opioids that were prescribed. Over time, strong opioids were increasingly prescribed, while prescriptions of weak opioids declined. The prescription rate of oxycodone increased rapidly in this decade from 7.1 to 40.7 incident prescriptions per 1000 person years. The prescription rate for fentanyl also increased from 4.2 to 7.4 incident prescriptions per 1000 person years, while the prescription rates for paracetamol/codeine and tramadol/paracetamol decreased. Weak opioids are still most frequently prescribed for OA related pain. Around 3% of the patients with incident OA were prescribed opioids over a long term per follow-up year. Finally, factors associated with a greater likelihood of more opioid prescriptions were female sex, increasing age, OA in two or more joint groups, and the presence of other musculoskeletal disorders besides OA.

Most of the studies examining opioid prescriptions in OA patients found an increase in the prescription rate[12-14 19] while we found a relatively stable prescription rate. One study looking at US insurance data claims also found a relatively stable opioid prescription rate[20]. However, oxycodone is increasingly being prescribed for patients with OA according to the present study. This is in agreement with other studies, which also found increases in the prescription rate of oxycodone for OA[12] and strong opioids for musculoskeletal pain in general[21]. At the same time as the prescription rates for oxycodone and fentanyl increased, the prescription rates for paracetamol/codeine and tramadol/paracetamol decreased. The decline in prescriptions for paracetamol/codeine was caused by the end to reimbursement of the costs by the health insurance companies[18]. This simultaneous increase and decrease could be a coincidence since the increase in strong opioids is also seen in other countries, but it might also be that GPs are prescribing strong opioids instead of weak opioids. Furthermore, the awareness for cardiovascular and gastro-intestinal risks of NSAIDs has increased in the past decade and NSAIDs are prescribed less in patients with musculoskeletal disorders[22 23]. This may also have influenced the prescription rates of (strong) opioids.

The prevalent prescription rate for all opioids was around 170 per 1000 person years in our study. This number is slightly lower than in some other studies[11 24]. Prescriptions rates of opioids in general in the Netherlands are lower or comparable to the prescription rates in the countries covered by these studies (e.g. USA, Sweden and Spain)[6]. Some studies found lower prescription rates for opioids. However, these studies did not in-

clude tramadol[20] or included only the most commonly prescribed opioids (e.g. tramadol and fentanyl)[13] in the analyses.

Most patients with incident OA were prescribed a weak opioid as their first opioid, which is in line with the current guidelines in the Netherlands[25]. Furthermore, a switch in the type of opioid prescribed was made in 8.8% of the patients with incident OA. A recent study in patients with chronic musculoskeletal pain in the UK also found that weak opioids were most frequently prescribed and that a third of the patients used two or more different opioids. This higher percentage of patients using multiple types of opioids may be because the latter study only included patients with chronic pain. In the Dutch GP guidelines, strong opioids are advised after the prescription of weak opioids[25]. However, almost a quarter of the patients with incident OA were directly prescribed a strong opioid.

Around 3% of the patients with incident OA were prescribed opioids over a long term (≥6 prescriptions per follow-up year). No previous data on long-term use specific to OA is available to our knowledge, but this percentage is comparable to long-term use in musculoskeletal disorders in general[26 27]. We did not find an increase in long-term use with increasing follow-up time. Analyses per calendar year showed similar results (data not shown). The available evidence on whether long-term use of opioids for musculoskeletal disorders is increasing gives conflicting results[26 27].

Factors associated with opioid prescription were increasing age, female sex, the presence of other musculoskeletal disorders and multiple joint groups affected by OA. These characteristics are also found in other studies [14 28 29]. The higher prescription rates in older patients is concerning since use of opioids in this group is associated with more severe side effects like falls and fractures[7 8].

The high rates and long-term use of opioids for OA pain are concerning since the absolute number of patients is high. As mentioned earlier, guidelines have a restrictive advice on the use of opioids[3 4]. Furthermore, a recent study showed that treatment with opioids for patients with OA or for patients with low back pain did not result in better pain relief than treatment with non-opioid analgesics (e.g. paracetamol and NSAIDs)[30]. In addition, long-term use is associated with dose-dependent adverse events, like trauma and addiction[7 31], and does not lead to an improved quality of life[32].

A strength of the current study is that it was conducted using a database that is a representative sample of the Dutch population. That is because in the Netherlands, most opioids are prescribed by the GP. Initial data show that around 70% of the first prescriptions and around 90% of the repeat prescriptions of opioids are prescribed by the GP[33].

There are several limitations to this study. Firstly, patients were only included in the cohort if diagnosed with OA. Since GPs vary in how strictly they apply the ICPC codes, this may have led to an overestimation or underestimation of patients with OA. Studies using UK primary healthcare databases showed that the positive predictive value of hip

OA codes is sufficiently high[34], but that OA is probably under-recorded[35]. Furthermore, in the medical records the indication of the opioid prescription could not be directly linked to a diagnosis. We excluded patients with malignancy, neuropathic pain disorders or fibromyalgia and patients in the year before death. Nevertheless we cannot rule out the possibility that some opioid prescriptions will be for reasons other than OA-related pain. We did not exclude all other musculoskeletal comorbidities for which opioids can be prescribed. These are frequently present in OA patients[36] and we found that the presence of musculoskeletal comorbidities was positively associated with opioid prescriptions.

To conclude, the overall prescription rate of opioids remained fairly stable in the past decade. However, the prescription rate for oxycodone increased rapidly and the prescription rate for fentanyl almost doubled, while the prescription rates for paracetamol/codeine and tramadol/paracetamol decreased. Weak opioids are more commonly prescribed for OA pain than strong opioids. The increase in prescriptions of strong opioids is concerning since clinically relevant effectiveness is questionable for OA pain and serious side effects are common. Therefore, opioids should be prescribed with caution, especially for long-term use, and alternative strategies for reducing pain and for reducing long-term opioid use should be considered.

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Table S1. Incident and prevalent prescription rates for opioids (numbers per 1000 person years)

Year	Tramadol		Tramadol/ paracetamol		Paracetamol/ codeine		Oxycodone		Fentanyl		Buprenorphine		Morphine	
	Incident	Prevalent	Incident	prevalent	incident	prevalent	incident	prevalent	incident	prevalent	incident	prevalent	incident	prevalent
2008	39.2	54.9	22.3	30.6	63.0	99.1	7.1	11.1	4.2	6.4	0.6	0.7	2.6	4.1
2009	42.3	57.8	24.9	32.5	56.6	93.0	7.2	10.8	3.5	6.5	0.8	0.9	3.0	3.9
2010	46.8	61.7	27.3	35.8	54.8	88.4	7.8	11.9	4.6	8.0	3.7	4.3	3.0	4.0
2011	51.0	66.7	25.2	34.2	54.1	84.7	9.7	14.3	4.9	9.5	5.0	6.4	3.3	4.2
2012	48.2	63.2	25.1	33.3	49.3	78.4	10.9	15.6	5.9	10.4	6.6	8.8	3.7	4.9
2013	48.4	63.4	28.4	37.5	30.8	54.1	14.1	19.3	5.8	11.3	5.7	9.3	3.3	4.5
2014	47.8	63.7	25.5	34.7	23.9	36.5	20.3	26.1	6.3	12.2	6.1	9.9	3.4	4.6
2015	44.6	60.1	22.1	31.3	19.4	29.1	29.2	36.8	7.0	13.1	5.8	9.7	3.9	5.1
2016	42.6	56.3	19.8	28.3	16.0	24.1	35.1	44.0	7.2	13.4	5.0	8.8	3.6	4.7
2017	42.8	56.3	18.4	26.2	13.3	20.1	40.7	50.7	7.4	13.9	4.9	8.7	3.4	4.6

Table S2. Sequence in types of opioids prescribed in patients with incident OA

FIRST OPIOID (n (%))	**SECOND OPIOID** (n (%))		**THIRD OPIOID**							
			No opioid (n(%))	TRA (n(%))	PCM/COD (n(%))	TRA/PCM (n(%))	OXY (n(%))	FTY (n(%))	MOP (n(%))	BUP (n(%))
No opioids 41496 (73.8)										
TRA 5848 (10.4)	No opioids	4181 (71.5)								
	PCM/COD	364 (6.2)	257 (70.6)			39 (10.7)	41 (11.3)	16 (4.4)	4 (1.1)	7 (1.9)
	TRA/PCM	283 (4.8)	210 (74.2)		13 (4.6)		34 (12.0)	7 (2.5)	6 (2.1)	13 (4.6)
	OXY	737 (12.6)	617 (83.7)		25 (3.4)	24 (3.3)		31 (4.2)	19 (2.6)	21 (2.8)
	FTY	124 (2.1)	73 (58.9)		5 (4.0)	3 (2.4)	30 (24.2)		8 (6.5)	5 (4.0)
	MOP	82 (1.4)	56 (68.3)		2 (2.4)	3 (3.7)	17 (20.7)	3 (3.7)		1 (1.2)
	BUP	77 (1.3)	48 (62.3)		3 (3.9)	3 (3.9)	13 (16.9)	9 (11.7)	1 (1.3)	
PCM/COD 2964 (5.3)	No opioids	1970 (66.5)								
	TRA	479 (16.2)	346 (72.2)			30 (6.3)	59 (12.3)	19 (4.0)	9 (1.9)	16 (3.3)
	TRA/PCM	279 (9.4)	190 (68.1)	49 (17.6)			23 (8.2)	3 (1.1)	2 (0.7)	12 (4.3)
	OXY	140 (4.7)	110 (78.6)	14 (10.0)		7 (5.0)		5 (3.6)	2 (1.4)	2 (1.4)
	FTY	46 (1.6)	26 (56.5)	6 (13.0)		4 (8.7)	7 (15.2)		2 (4.3)	1 (2.2)
	MOP	17 (0.6)	9 (52.9)	4 (23.5)		1 (5.9)	2 (11.8)	1(5.9)		0
	BUP	33 (1.1)	19 (57.6)	0		5 (15.2)	4 (12.1)	4 (12.1)	1 (3.0)	
TRA/PCM 2463 (4.4)	No opioids	1614 (65.5)								
	TRA	347 (14.1)	242 (69.7)		22 (6.3)		53 (15.3)	11 (3.2)	3 (0.9)	16 (4.6)
	PCM/COD	146 (5.9)	94 (64.4)	33 (22.6)			8 (5.5)	3 (2.1)	2 (1.4)	6 (4.1)
	OXY	227 (9.2)	172 (75.8)	24 (10.6)	6 (2.6)			12 (5.3)	5 (2.2)	8 (3.5)

FIRST OPIOID (n (%))	SECOND OPIOID (n (%))		THIRD OPIOID							
			No opioid (n(%))	TRA (n(%))	PCM/COD (n(%))	TRA/PCM (n(%))	OXY (n(%))	FTY (n(%))	MOP (n(%))	BUP (n(%))
	FTY	57 (2.3)	38 (66.7)	8 (14.0)	5 (8.8)		5 (8.8)		1 (1.8)	0
	MOP	21 (0.9)	12 (57.1)	6 (28.6)	1 (4.8)		2 (9.5)	0		0
	BUP	51 (2.1)	32 (62.7)	7 (13.7)	1 (2.0)		7 (13.7)	3 (5.9)	1 (2.0)	
OXY 2537 (4.5)	No opioids	2029 (80.0)								
	TRA	205 (8.1)	176 (85.9)		8 (3.9)	8 (3.9)		7 (3.4)	4 (2.0)	2 (1.0)
	PCM/COD	57 (2.2)	47 (82.5)	6 (10.5)		1 (1.8)		1 (1.8)	1 (1.8)	1 (1.8)
	TRA/PCM	75 (3.0)	59 (78.7)	8 (10.7)	0			6 (8.0)	1 (1.3)	1 (1.3)
	FTY	99 (3.9)	76 (76.8)	6 (6.1)	2 (2.0)	5 (5.1)			10 (10.1)	0
	MOP	42 (1.7)	34 (81.0)	4 (9.5)	0	0		3 (7.1)		1 (2.4)
	BUP	30 (1.2)	20 (66.7)	2 (6.7)	2 (6.7)	2 (6.7)		4 (13.3)	0	
FTY 346 (0.6)	No opioids	211 (61.0)								
	TRA	38 (11.0)	27 (71.1)		1 (2.6)	1 (2.6)	7 (18.4)		2 (5.3)	0
	PCM/COD	10 (2.9)	7 (70.0)	0		0	1 (10.0)		1 (10.0)	1 (10.0)
	TRA/PCM	16 (4.6)	11 (68.8)	0	2 (12.5)		2 (12.5)		0	1 (6.3)
	OXY	59 (17.1)	45 (76.3)	6 (10.2)	3 (5.1)	0			3 (5.1)	2 (3.4)
	MOP	5 (1.4)	3 (60.0)	2 (40.0)	0	0	0			0
	BUP	7 (2.0)	4 (57.1)	1 (14.3)	1 (14.3)	0	1 (14.3)		0	
MOP 208 (0.4)	No opioids	129 (62.0)								
	TRA	24 (11.5)	17 (70.8)		1 (4.2)	0	3 (12.5)	3 (12.5)		0
	PCM/COD	2 (1.0)	2 (100.0)	0		0	0	0		0
	TRA/PCM	8 (3.8)	5 (62.5)	1 (12.5)	1 (12.5)		1 (12.5)	0		0
	OXY	31 (14.9)	19 (61.3)	5 (16.1)	0	0		7 (22.6)		0

FIRST OPIOID (n (%))	**SECOND OPIOID** (n (%))		**THIRD OPIOID**							
			No opioid (n(%))	TRA (n(%))	PCM/COD (n(%))	TRA/PCM (n(%))	OXY (n(%))	FTY (n(%))	MOP (n(%))	BUP (n(%))
	FTY	10 (4.8)	7 (70.0)	1 (10.0)	0	1 (10.0)	1 (10.0)			0
	BUP	4 (1.9)	2 (50.0)	1 (25.0)	0	1 (25.0)	0	0		
BUP 376 (0.7)	No opioids	213 (56.6)								
	TRA	27 (7.2)	16 (59.3)		2 (7.4)	1 (3.7)	5 (18.5)	3 (11.1)	0	
	PCM/COD	18 (4.8)	8 (44.4)	4 (22.2)		2 (11.1)	1 (5.6)	2 (11.1)	1 (5.6)	
	TRA/PCM	35 (9.3)	23 (65.7)	2 (5.7)	1 (2.9)		5 (14.3)	4 (11.4)	0	
	OXY	46 (12.2)	29 (63.0)	2 (4.3)	3 (6.5)	4 (8.7)		6 (13.0)	2 (4.3)	
	FTY	34 (9.0)	19 (55.9)	4 (11.8)	0	4 (11.8)	7 (20.6)		0	
	MOP	3 (0.8)	2 (66.7)	0	0	0	1 (33.3)	0		

N=56.713; TRA= tramadol, PCM/COD =paracetamol/codeine, TRA/PCM=tramadol/paracetamol, OXY=oxycodone, FTY=fentanyl, MOP=morphine, BUP=buprenorphine.

CHAPTER 4

Antidepressant and anticonvulsant prescription rates in patients with osteoarthritis: a population-based cohort study

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ABSTRACT

Objectives

There are signs that antidepressants and anticonvulsants are being prescribed more often for osteoarthritis patients, despite limited evidence. Objectives are to examine prescription rates and time trends for antidepressant and anticonvulsants in OA patients, to assess the percentage of long-term prescriptions, and determine patient characteristics associated with antidepressant or anticonvulsant prescription.

Methods

A population-based cohort study was conducted using the Integrated Primary Care Information database. First, episodic and prevalent prescription rates for antidepressants (amitriptyline, nortriptyline and duloxetine) and anticonvulsants (gabapentinoids) in OA patients were calculated for the period 2008-2017. Logistic regression was used to assess which patient characteristics were associated with prescriptions.

Results

In total, 164,292 OA patients were included. The prescription rates of amitriptyline, gabapentin and pregabalin increased over time. The increase in prescription rates for pregabalin was most pronounced. Episodic prescription rate increased from 7.1 to 13.9 per 1000 person-years between 2008 and 2017. Amitriptyline was prescribed most (15.1 episodic prescriptions per 1000 person-years in 2017). Prescription rates of nortriptyline and duloxetine remained stable at 3.0 and 2.0 episodic prescriptions per 1000 person-years respectively. For ≤3% of patients with incident OA, medication was prescribed long-term (≥3 months). In general, all medication was prescribed more frequently for older patients (except duloxetine), women, patients with OA in ≥2 joints, patients with spinal OA and patients with musculoskeletal disorders.

Conclusion

Prescription rates of amitriptyline, gabapentin and pregabalin increased over time. Since there is little evidence to support prescription in OA, caution is necessary when prescribing.

INTRODUCTION

OA is a highly prevalent chronic pain condition of the musculoskeletal system. Approximately 15% of the population suffers from OA[1 2]. Since the population is ageing and the number of persons with obesity is increasing, it is expected that the disease burden will increase[3]. Pain, joint stiffness and reduced function are important complaints among patients with OA.

Different treatment options are available for OA related pain[4 5]. An important strategy is the use of analgesics in a stepwise approach. Paracetamol leads to a small, not clinically relevant, reduction of pain compared to a placebo (3%) and concerns have been raised about its long-term use[6]. Another treatment option is topical nonsteroidal anti-inflammatory drugs (NSAIDs), with mean effect sizes of 0.30 for pain relief[7]. Oral NSAIDs have a clinically relevant effect for OA pain, but have serious gastro-intestinal and cardiovascular side effects[8 9]. Opioids are prescribed more frequently than in the past[10-12], but they lack a clinically relevant effect and have serious side effects and a risk of addiction[13 14].

Another option may be the use of antidepressants or anticonvulsants, which are hypothesized to have an effect on the central pain processing[15]. Signs of pain sensitization are present in around 40% of the patients with OA[16 17]. Most extensively studied for OA pain is the antidepressant duloxetine[18], a serotonin and noradrenalin reuptake inhibitor (SNRI). The OARSI guideline recommends using duloxetine in polyarticular OA[5], while the NICE guidelines[19] and Dutch General Practitioner (GP) guidelines[20] on OA do not advise using duloxetine because of insufficient evidence. Tricyclic antidepressants (TCAs) are used in the treatment of neuropathic pain and other chronic pain conditions; they inhibit presynaptic uptake of serotonin and noradrenaline[21]. The efficacy of TCAs for OA related pain is unknown[22]. A study on the efficacy of the TCA nortriptyline in patients with knee OA is currently being carried out[23]. Also, the anticonvulsants pregabalin and gabapentin can inhibit centralized pain[24]. Pregabalin has been investigated for OA pain, and may have a positive effect on pain in hand and knee OA[25 26].

Although none of these medications are registered for OA pain in the Netherlands, it might be that general practitioners (GPs) do already prescribe these as off-label medication for OA related pain. A recent retrospective cohort study in the UK found an almost threefold increase in first prescriptions of gabapentin and pregabalin in patients with OA between 2005 and 2015[27]. Earlier studies in US insurance claims databases found 20 to 30% of the OA patients used an antidepressant and around 15% used an anticonvulsant, which was higher than in patients without OA[28-30]. In the Netherlands, the antidepressants amitriptyline, nortriptyline and duloxetine, and the anticonvulsants gabapentin and pregabalin can be prescribed for neuropathic pain conditions[31] but it is unknown whether these medications are prescribed for pain in OA patients. The aim

of the current study is to examine incident and prevalent prescription rates and time trends for prescriptions of antidepressants and anticonvulsants in OA patients. In addition, baseline characteristics associated with prescriptions will be assessed.

METHODS

Setting

This study was conducted using the Integrated Primary Care Information (IPCI) database. The IPCI database is a primary healthcare database that contains the electronic patient records of over 1.5 million patients in the Netherlands. In the Netherlands, the GP acts as a gatekeeper to secondary care. The electronic records contain all relevant medical information: the medical journal recorded by the GP, diagnoses according to the International Classification of Primary Care (ICPC) codes, laboratory results and referrals to secondary care. Furthermore, it contains all drug prescriptions, which are coded according to the Anatomical Therapeutic Chemical (ATC) classification code.

Study cohort

The study cohort consisted of all patients aged ≥ 30 years with a diagnosis of OA in the period between 1 January 2008 and 31 December 2017. Patients with newly diagnosed OA in this period (incident OA) as well as patients with a medical history of OA (prevalent OA) were included in the cohort. The diagnosis of OA was based on the ICPC codes L84 (spinal OA), L89 (hip OA), L90 (knee OA) and L91 (other peripheral joints affected by OA). Earlier research showed that the positive predictive value of these codes for having OA is around 90%[32]. Patients who had a total knee or hip replacement during or before the study period were retained in the cohort. Patients had to have at least 12 months of valid database history prior to the study entry to assure complete medical records. Patients were followed until the GP practice stopped contributing data to the database, until the end of the study period (31 December 2017) or until one year before first diagnosis of a malignancy or until one year before death. Those patients were excluded because there is a high probability that antidepressants and anticonvulsants were prescribed for pain not related to OA. GPs can use different healthcare information systems to record medical information. Healthcare information systems needed to provide at least six years of data so that time trends could be examined. This resulted in the exclusion of one healthcare information system (Webhis), which provided five years of data.

In addition, a subset of patients with OA were selected who did not have comorbidities for which antidepressants and anticonvulsants could be prescribed ("OA without comorbidities"). Comorbidities for which antidepressants and anticonvulsants could be prescribed were selected based on an earlier study using the IPCI database[33]. Frequently

occurring indications for antidepressants were depression (P03 and P76), anxiety (P01 and P74), sleep disorders (P06), psychosis and schizophrenia (P71, P72 and P98) and neuropathic pain disorders (N94). Patients with epilepsy (N88) and fibromyalgia (L18.01) were often prescribed gabapentin and pregabalin. All patients with these comorbidities were excluded from one year prior to the first date of the diagnosis.

The presence of other musculoskeletal disorders during the cohort period was defined as a minimum of one ICPC diagnosis code for other complaints of the musculoskeletal system. This subset of codes includes non-specific diagnoses, for example shoulder or hip complaints. The group of back/neck symptoms also includes the ICPC codes for radiculopathy.

Outcomes

The prescriptions were identified by the ATC code. Prescriptions of amitriptyline (N06AA09), nortriptyline (N06AA10), duloxetine (N06AX21), pregabalin (N03AX16) and gabapentin (N03AX12) were evaluated. The first prescription rate was defined as the total number of patients with a first prescription of the medication divided by the total of person-years per calendar year. Patients were excluded from the denominator for this subanalysis after receiving first prescription. The episodic rate of these prescriptions was defined as the total of new episodes of medication prescriptions divided by the total of person-years per calendar year. A new episode was determined as occurring if there was no prescription in the preceding six months. The prevalent prescription rate was defined as the total number of patients who had at least one prescription of the specific drug divided by the person-years per calendar year. Furthermore, the percentage was determined of the patients with incident OA who were prescribed an antidepressant or anticonvulsant for a period longer than three months in a follow-up year (long-term prescription). In the IPCI database the median prescription duration was 30 days for amitriptyline, 21 days for nortriptyline, 30 days for duloxetine, 30 days for gabapentin and 28 days for pregabalin. Therefore, 4 prescriptions of the medication per follow-up year was defined as long-term prescription.

Statistical analyses

Descriptive statistics were performed to assess baseline characteristics and to calculate first, incidence and prevalence rates with their 95% confidence intervals (CIs) of the medication prescribed. Possible time trends in medication prescriptions were assessed using joinpoint regression analysis. Permutation tests using Monte Carlo methods were used to determine whether a marked change in trend (e.g. joinpoint) occurred. Since trends were examined over 10 years (10 data points) only one joinpoint was allowed. The joinpoint analysis provides information on the trend over the complete 10 years, the average annual percentage change (AAPC). When a marked change in trend is present,

the annual percentage change (APC) is additionally reported to describe the two different trends. Analyses were performed with the Joinpoint Regression Program (Version 4.8.0.1, released 22 April 2020, Available at https://surveillance.cancer.gov/joinpoint/, National Cancer Institute)

To assess the baseline characteristics (age, sex, joints affected and presence of other musculoskeletal disorders) associated with antidepressant and anticonvulsant prescriptions, univariable and multivariable logistic regression analyses were performed and odds ratios (ORs) and their 95% CIs were calculated. Variables were included in the multivariable regression analyses if $p<0.1$ in the univariable analysis for that variable. Analyses were performed using SPSS Statistics version 24 (IBM Corp., Armonk, NY, USA).

Study approval

The study was approved by the Board of Directors of the IPCI database.

RESULTS

Study population

In total, 164,292 patients with OA were included in the cohort, of whom 59,053 were newly diagnosed with OA. The average follow-up time per patient was three years and five months. Two thirds of the patients were female and the mean age was 66.6 years (SD ± 12.4) (Table 1). With regard to the joints affected, the biggest category was patients with knee OA (27.4%). Almost a quarter of patients had a diagnosis in two or more joint groups. It was common for there to be other musculoskeletal disorders during the cohort period (64.9%). The cohort subset of OA patients without comorbidities for which antidepressants and anticonvulsants could be prescribed, consisted of 99,099patients. The baseline characteristics of these patients were very similar. However, these patients were slightly younger (mean age 66.4 as opposed to 66.6), and had also slightly fewer musculoskeletal (61.8% vs 64.9%) and cardiovascular disorders (54.4% vs 58.1%). Furthermore, patients with incident OA were younger (mean age 64.2 vs 67.9) and had fewer musculoskeletal and cardiovascular disorders than patients with prevalent OA (Supplemental Tables S1 and S2).

Time trends for first prescriptions

In the study period the first prescription rates of gabapentin and pregabalin increased from 2.2 to 3.0 prescription per 1000 person years (AAPC 12.0% (95% CI 6.6-17.8)) and 6.0 to 9.4 prescriptions per 1000 person years (AAPC 4.8% (95% CI 0.9-8.8)) respectively (Figure 1 and Table 2). The first prescription rates of amitriptyline and nortriptyline remained stable. The first prescription rate of duloxetine decreased. The trends were similar for the

Table 1. Baseline characteristics

	OA patients (n=164 292)	OA patients without comorbidities[1] (n=99 099)
Age mean (S.D.), years	66.6 (12.4)	66.4 (12.3)
Age category, *n (%)*		
30-39	2 637 (1.6)	1 730 (1.7)
40-49	12 007 (7.3)	7 246 (7.3)
50-59	32 786 (20.0)	19 276 (19.5)
60-69	48 756 (29.7)	30 156 (30.4)
70-79	40 749 (24.8)	25 195 (25.4)
80-89	23 639 (14.4)	13 543 (13.7)
> =90	3 718 (2.3)	1 953 (2.0)
Female, *n (%)*	107 438 (65.2)	60 720 (61.3)
Joints affected, *n (%)*		
Spine	17 243 (10.5)	10 180 (10.3)
Hip	27 762 (16.9)	18 075 (18.2)
Knee	45 064 (27.4)	28 610 (28.9)
Other joints	37 753 (23.0)	22 189 (22.4)
2 or more joints	36 470 (22.2)	20 045 (20.2)
Diabetes, *n (%)*	25 175 (15.3)	13 608 (13.7)
Hypertension, *n (%)*	66 866 (40.7)	38 005 (38.4)
Hyperlipidaemia, *n (%)*	29 224 (17.8)	15 497 (15.6)
MI/AP, *n (%)*	18 868 (11.5)	9 674 (9.8)
Stroke/TIA, *n (%)*	6 352 (3.9)	3 114 (3.1)
PAD, *n (%)*	6 365 (3.9)	3 096 (3.1)
UGI/ulcer, *n (%)*	5 723 (3.5)	2 753 (2.8)
Heartfailure, *n (%)*	6 989 (4.3)	3 374 (3.4)
Inflammatory arhritis, *n (%)*	7 949 (4.8)	4 122 (4.2)
Fibromyalgia, *n (%)*	2 492 (1.5)	NA
Neuropathic pain disorder, *n (%)*	19 202 (11.7)	NA
Depression, *n (%)*	28 714 (17.5)	NA
Anxiety, *n (%)*	27 397 (16.7)	NA
Psychosis, *n (%)*	4 084 (2.5)	NA
Sleeping disorder, *n (%)*	32 278 (19.6)	NA
Epilepsy, *n (%)*	2 404 (1.5)	NA
Other MSD during cohort time, *n (%)*		
Upper extremity	39 061 (23.8)	21 702 (21.9)
Lower extremity	61 076 (37.2)	34 485 (34.8)
Back/neck	51 260 (31.2)	28 105 (28.4)
Other musculoskeletal	50 559 (30.8)	27 486 (27.7)
None	57 609 (35.1)	37 903 (38.2)
Renal function, *n (%)*		
eGFR>60 ml/min	103 952 (63.3)	59 613 (60.2)
eGFR 30-60 ml/min	19 382 (11.8)	10 794 (10.9)
eGFR<30 ml/min	1 614 (1.0)	896 (0.9)
missing	39 344 (23.9)	27 796 (28.0)

[1]Comorbidities are fibromyalgia, neuropathic pain disorders, depression, anxiety, psychosis, sleeping disorder, epilepsy, MI=myocardial infarction, AP=angina pectoris, TIA= transient ischemic attack, PAD=peripheral arterial disease, UGI= upper gastro-intestinal, MSD=musculoskeletal disorder, eGFR= estimated glomerular filtration rate.

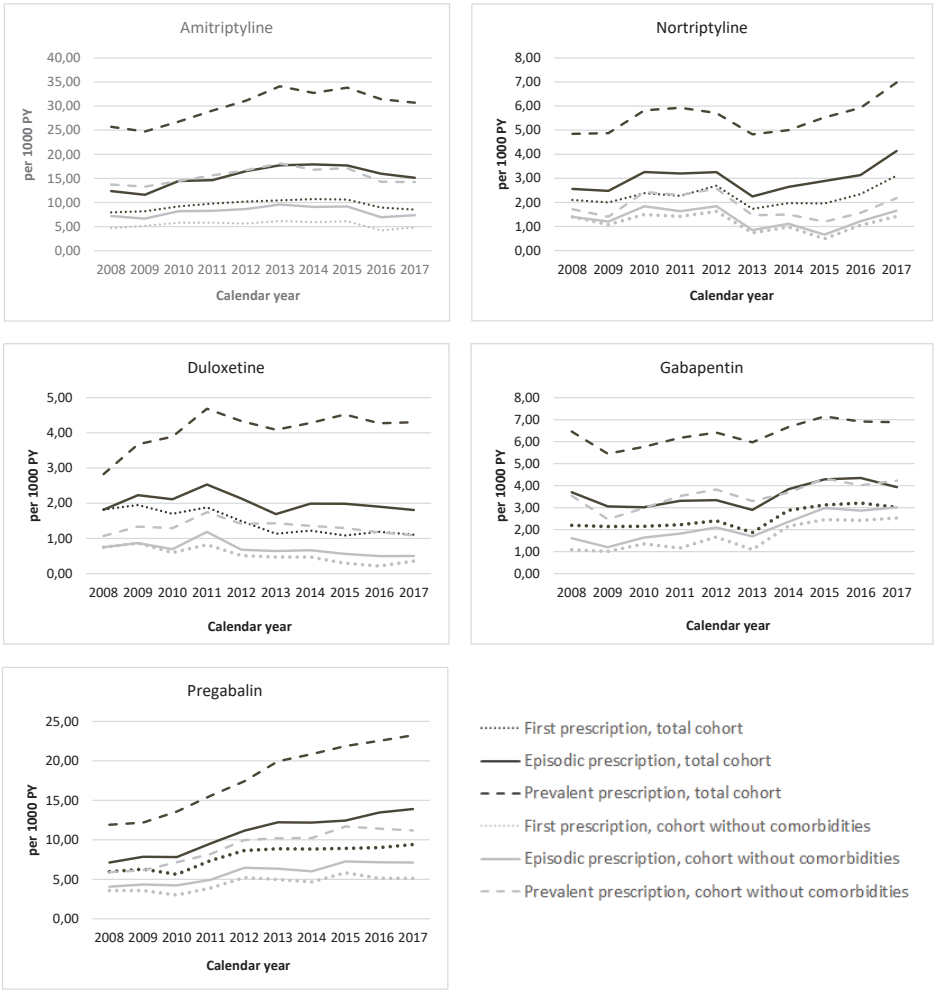

Figure 1. Prescription rates of antidepressants and anticonvulsants

subset of the cohort without comorbidities. The absolute number of prescriptions was lower. The prescription rates were similar for patients with incident and prevalent OA (See supplemental data Figure S1 for prescription rates in incident and prevalent OA and Table S3 and S4 for the absolute numbers.)

Time trends for episodic prescriptions

In the period 2008-2017, amitriptyline was the drug most often prescribed in patients with OA (Figure 1). The incident prescription rate was 15.1 per 1000 person-years in 2017. The episodic prescription rates for amitriptyline, gabapentin and pregabalin increased over the time period. The increase in prescription rates for pregabalin was most

Table 2. Time trends in prescription rates of antidepressants and anticonvulsants

		Overal trend (AAPC (95%CI))	Joinpoint (95% CI)	Trend 1	Trend 2
				APC (95% CI)	APC (95% CI)
TOTAL COHORT					
Amitriptyline	First	0.4 (-1.5;2.3)	2014 (2012-2015)	5.2 (2.3;8.2)	-8.6 (-13.1; -3.9)
	Episodic	2.6 (0.6;4.6)	2014 (2012-2015)	7.6 (4.5;10.8)	-6.7(-11.2; -2.0)
	Prevalent	3.1 (1.2;4.9)	2013 (2012-2015)	7.5 (3.8;11.4)	-2.2 (-5.0; 0.6)
Nortriptyline	First	5.0 (-1.3;11.6)			
	Episodic	3.7 (-1.2;8.9)			
	Prevalent	2.8 (-0.3;6.0)			
Duloxetine	First	-7.0 (-9.7;-4.1)			
	Episodic	-2.4 (-5.1;-0.3)			
	Prevalent	3.8 (0.1;7.7)	2011 (2010-2012)	13.2 (-1.3;29.7)	-0.6 (-2.7;1.6)
Gabapentin	First	5.9 (2.3;9.7)			
	Episodic	4.1 (1.0;7.4)			
	Prevalent	2.4 (0.9;3.8)			
Pregabalin	First	6.6 (2.9;10.4)	2012 (2010-2015)	12.6 (2.4;23.8)	1.9 (-1.5;5.5)
	Episodic	8.2 (5.9;10.5)	2013 (2011-2014)	12.0 (7.2;17.0)	3.5 (0.3;6.8)
	Prevalent	8.8 (7.7;9.9)	2013 (2012-2015)	12.7(10.4;15.0)	4.1 (2.7;5.6)
WITHOUT COMORBIDITIES					
Amitriptyline	First	-1.8 (-5.5; -2.1)			
	Episodic	0.8 (-3.8;5.6)	2013 (2011-2015)	7.5 (-1.6;17.5)	-7.1 (-14.2;0.7)
	Prevalent	1.2 (-1.6;4.0)	2013 (2012-2015)	7.3 (1.8;13.0)	-5.9 (-10.3;-1.3)
Nortriptyline	First	-2.6 (-11.1;6.6)			
	Episodic	-2.2 (-10.5;6.8)			
	Prevalent	-2.4 (-9.6;5.4)			
Duloxetine	First	-12.3 (-17.5;-6.8)			
	Episodic	-7.9 (-13.2;-2.4)			
	Prevalent	0.2 (-3.5;4.0)	2011 (2010-2012)	14.4 (-0.4;31.3)	-6.3 (-8.7; -3.8)
Gabapentin	First	12.0 (6.6;17.8)			
	Episodic	9.9 (6.2;13.8)			
	Prevalent	4.1 (1.5;6.9)			
Pregabalin	First	4.8 (0.9;8.8)			
	Episodic	6.3 (3.4;9.2)			
	Prevalent	8.9 (5.1;12.9)	2012 (2011-2015)	16.5 (5.8;28.3)	3.2 (-0.2;6.8)

AAPC= Average Annual Percentage Change, APC= Annual Percentage Change, CI=Confidence Interval

pronounced, from 7.1 per 1000 person-years in 2008 to 13.8 per 1000 person-years in 2017. This was an average annual percentage change (AAPC) of 8.3% (95% CI 5.9-10.5) (Table 2). The prescription rates for nortriptyline and duloxetine remained stable over this decade. Absolute prescription rates were lower in the subset of patients without

comorbidities than in the total cohort (Figure 1). The prescription rate for pregabalin almost doubled in this subset as well, from 4.1 to 7.1 prescriptions per 1000 person-years. The prescription rates for amitriptyline remained relatively stable in this subset at around 8.0 prescriptions per 1000 person-years, while there was an increase in the total cohort. The increase in prescription rates of gabapentin in this subset was from 1.6 to 3.0 (AAPC 9.9% (95% CI 6.2 -13.8)) and was more pronounced than in the total cohort.

Time trends for prevalent prescriptions

The time trends for the prevalent prescription rates showed similar patterns to the episodic prescription rates (Figures 1). In the total population, prescription rates increased for amitriptyline, gabapentin and pregabalin (Table 2). In addition, the prescription rate of duloxetine increased as well (AAPC 3.8% (95% CI 0.1-7.7)). The prescription rate for pregabalin almost doubled from 11.9 prescriptions per 1000 person-years in 2008 to 23.3 prescriptions per 1000 person-years in 2017. Prescription rates were lower in the subset of patients without comorbidities. The prescription rate for gabapentin and pregabalin increased in this subset, while the prescription rates for the other medications remained stable.

Rates for long-term prescription

Long-term prescription was defined as the prescription of antidepressants or anticonvulsants for more than three months in a follow-up year. In patients with incident OA around 40% of the patients who were prescribed an antidepressant had a long-term prescription for that antidepressant (Table 3). In the patients prescribed an anticonvulsant this figure was 30%.

Table 3. Long term prescription rate of antidepressants and anticonvulsants in patients with incident OA

	Age	**Amitriptyline** N (% users/ % population)	**Nortriptyline** N (% users/ % population)	**Duloxetine** N (% users/ % population)	**Gabapentin** N (% users/ % population)	**Pregabalin** N (% users/ % population)
Female	30-49	98 (44.1/2.9)	10 (41.7/0.3)	20 (64.5/1.9)	11 (33.3/0.3)	41 (38.0/1.2)
	50-69	392 (41.7/2.5)	61 (46.2/0.4)	66 (53.7/0.3)	72 (34.0/0.5)	233 (37.4/1.5)
	70+	246 (40.7/2.4)	67 (49.6/0.7)	24 (36.9/0.4)	52 (34.2/0.5)	142 (36.1/1.4)
Male	30-49	29 (37.6/1.4)	8 (47.1/0.4)	6 (46.2/2.3)	3 (11.1/0.1)	17 (27.4/0.8)
	50-69	140 (40.2/1.5)	25 (38.5/0.3)	19 (45.2/0.5)	31 (28.4/0.3)	111 (40.1/1.2)
	70+	71 (42.3/1.5)	12 (32.4/0.2)	4 (20.0/0.4)	10 (21.3/0.2)	59 (37.6/1.2)

Characteristics associated with antidepressant and anticonvulsant prescriptions

A higher age at baseline was associated with higher episodic prescription rates of amitriptyline, nortriptyline, gabapentin (except for age ≥ 90) and pregabalin (Table 4, multivariable analyses; see Supplemental data Table S5 for univariable analyses). Nortriptyline in particular was prescribed in elderly patients (age ≥ 90: OR 2.23 [1.18-4.20]). Prescription rates for duloxetine declined with increasing age. Men were less likely to be prescribed antidepressants and anticonvulsants than women. Furthermore, patients with ≥2 joint groups affected were more likely to be prescribed duloxetine, gabapentin and pregabalin than patients with spinal OA, while patients with knee, hip or other peripheral OA were less likely to be prescribed amitriptyline, nortriptyline and pregabalin than patients with spinal OA (Table 4 and Supplemental data Figure 2 and Table S6). Finally, patients who visited the GP with other musculoskeletal disorders during the cohort period were more likely to be prescribed antidepressants and anticonvulsants; this was especially marked for patients with ≥2 musculoskeletal disorders.

DISCUSSION

In this study we examined the prescription rates and time trends in prescription rates for antidepressants and anticonvulsants in patients with OA. We found an increase in episodic and prevalent prescription rates for amitriptyline, gabapentin and pregabalin and an increase in first prescription rates for gabapentin and pregabalin between 2008-2017. The increase was most pronounced for pregabalin, where the episodic prescription rate increased from 7.1 to 13.8 per 1000 person-years. The prescription rates for nortriptyline and duloxetine remained stable over time. Amitriptyline was the most prescribed drug in patients with OA. Prescriptions were positively associated with a higher age at baseline (except for duloxetine), the diagnosis of other musculoskeletal disorders during the cohort period, and the diagnosis of OA in two or more joint groups when compared to a diagnosis of spinal OA. The diagnosis of OA in hip, knee or other peripheral joints was associated with lower prescription rates for amitriptyline, nortriptyline and pregabalin compared to spinal OA.

The prevalent prescription rates we found were lower than the rates in other studies. Two US insurance claim studies of OA patients found that around 30% of the population was prescribed an antidepressant in a year[28 29]. Another US insurance claim study, which included patients with at least one opioid prescription in a two-year period, found that 10% of the patients were prescribed an antidepressant and 7% an anticonvulsant which could also be prescribed for pain[30]. These studies were cross-sectional and examined the prescriptions of all antidepressants and anticonvulsants[28-30 34], whereas a specific

Table 4. Multivariable regression analyses characteristics associated with antidepressant or anticonvulsant prescription

	Amitriptyline		Nortriptyline		Duloxetine		Gabapentin		Pregabalin	
	n (%)	OR (95% CI)	n (%)	OR (95% CI)	n (%)	OR (95% CI)	n (%)	OR (95% CI)	n (%)	OR (95% CI)
Age category										
30-39	86 (3.3)	1	13 (0.5)	1	26 (1.0)	1	15 (0.6)	1	67 (2.5)	1
40-49	685 (5.7)	**1.69 (1.34-2.12)**	107 (0.9)	1.73 (0.97-3.07)	126 (1.0)	1.00 (0.65-1.52)	125 (1.0)	1.70 (0.99-2.91)	429 (3.6)	**1.34 (1.03-1.74)**
50-59	1863 (5.7)	**1.62 (1.30-2.03)**	275 (0.8	1.59 (0.91-2.78)	301 (0.9)	0.83 (0.55-1.24)	402 (1.2)	**1.90 (1.13-3.19)**	1234 (3.8)	**1.37 (1.06-1.76)**
60-69	2494 (5.1)	**1.50 (1.20-1.87)**	462 (0.9)	**1.86 (1.07-3.24)**	300 (0.6)	**0.56 (0.37-0.84)**	675 (1.4)	**2.10 (1.26-3.51)**	1905 (3.9)	**1.46 (1.14-1.86)**
70-79	2361 (5.8)	**1.63 (1.31-2.03)**	549 (1.3)	**2.56 (1.47-4.46)**	270 (0.7)	**0.57 (0.37-0.85)**	590 (1.4)	**2.06 (1.23-3.46)**	1794 (4.4)	**1.59 (1.24-2.04)**
80-89	1248 (5.3)	**1.49 (1.19-1.87)**	365 (1.5)	**2.98 (1.71-5.21)**	133 (0.6)	**0.49 (0.32-0.74)**	295 (1.2)	**1.79 (1.06-3.02)**	868 (3.7)	**1.36 (1.05-1.75)**
> 90	126 (3.6)	1.05 (0.80-1.40)	39 (1.0)	**2.23 (1.18-4.20)**	9 (0.2)	**0.72 (0.11-0.50)**	20 (0.5)	**0.86 (0.78-0.95)**	85 (2.3)	0.98 (0.71-1.36)
Gender										
Female	7237 (6.3)	1	1371 (1.3)	1	862 (0.8)	1	1495 (1.4)	1	4570 (4.3)	1
Male	2202 (3.6)	**0.62 (0.59-0.65)**	439 (0.8)	**0.69 (0.63-0.76)**	303 (0.5)	**0.72 (0.63-0.82)**	627 (1.1)	**0.86 (0.78-0.95)**	1812 (3.2)	**0.84 (0.79-0.89)**
Joint affected										
Spine	1138 (6.2)	1	207 (1.2)	1	131 (0.8)	1	196 (1.1)	1	739 (4.3)	1
Hip	1256 (4.2)	**0.70 (0.64-0.76)**	277 (1.0)	**0.82 (0.78-0.98)**	166 (0.6)	0.91 (0.73-1.15)	348 (1.3)	1.14 (0.96-1.37)	868 (3.1)	**0.76 (0.69-0.84)**
Knee	2043 (4.3)	**0.70 (0.65-0.74)**	387 (0.9)	**0.72 (0.61-0.85)**	230 (0.5)	**0.75 (0.60-0.93)**	543 (1.2)	1.09 (0.93-1.29)	1363 (3.0)	**0.73 (0.67-0.80)**

	Amitriptyline		Nortriptyline		Duloxetine		Gabapentin		Pregabalin	
	n (%)	OR (95% CI)	n (%)	OR (95% CI)	n (%)	OR (95% CI)	n (%)	OR (95% CI)	n (%)	OR (95% CI)
Other peripheral joints	1957 (4.8)	**0.73 (0.67-0.79)**	362 (1.0)	**0.81 (0.69-0.97)**	250 (0.7)	0.84 (0.68-1.04)	305 (0.8)	**0.71 (0.60-0.84)**	1238 (3.3)	**0.76 (0.69-0.83)**
Two or more joints	3045 (7.9)	1.04 (0.96-1.11)	577 (1.6)	1.00 (0.85-1.18)	388 (1.1)	**1.34 (1.09-1.64)**	730 (2.0)	**1.48 (1.26-1.74)**	2174 (6.0)	**1.14 (1.04-1.24)**
MSD										
No MSD	1373 (2.3)	1	322 (0.6)	1	198 (0.3)	1	352 (0.6)	1	802 (1.4)	1
Upper extremity	240 (3.0)	**1.28 (1.11-1.48)**	60 (0.8)	**1.44 (1.09-1.90)**	32 (0.4)	1.17 (0.80-1.70)	66 (0.9)	**1.43 (1.10-1.86)**	190 (2.5)	**1.79 (1.53-2.10)**
Lower extremity	718 (4.0)	**1.78 (1.62-1.95)**	135 (0.8)	**1.42 (1.16-1.74)**	73 (0.4)	1.23 (0.94-1.61)	200 (1.2)	**1.87 (1.57-2.22)**	456 (2.7)	**1.93 (1.72-2.17)**
Neck/back	690 (5.5)	**2.43 (2.21-2.68)**	157 (1.3)	**2.39 (1.98-2.90)**	90 (0.8)	**2.12 (1.65-2.72)**	154 (1.3)	**2.12 (1.75-2.57)**	519 (4.5)	**3.19 (2.85-3.65)**
Other MSD	485 (4.2)	**1.76 (1.58-1.96)**	105 (1.0)	**1.72 (1.38-2.15)**	49 (0.5)	1.23 (0.90-1.69)	110 (1.0)	**1.63 (1.31-2.02)**	278 (2.6)	**1.81 (1.57-2.07)**
≥2 MSD	5933 (9.1)	**3.89 (3.65-4.14)**	1031 (1.7)	**2.97 (2.62-3.38)**	723 (1.2)	**3.07 (2.61-3.60)**	1240 (2.1)	**3.15 (2.79-3.56)**	4137 (6.9)	**4.82 (4.46-5.21)**

MSD=musculoskeletal disorders. Values in bold are statistically significant ($p<0.05$). The multivariable regression analyses were adjusted for age, gender, joint affected and musculoskeletal disorders.

selection was made in our study. Moreover, earlier studies of antidepressant prescription rates found that these rates were lower in the Netherlands than in other countries[35]. Furthermore, we included all patients with an incident or prevalent diagnosis of OA in the cohort (including people with total hip or total knee replacements), while other studies included patients with a medication claim or opioid use, which could also be a reason for the lower numbers in our study.

Time trends for prescription rates for antidepressants and anticonvulsants have been examined in the general population in various countries. The prescription rates of tricyclic antidepressants have remained stable or even decreased in the past decade[33 35] and TCAs are prescribed more frequently for indications other than depression and anxiety, e.g. for neuropathic pain disorders, and sleeping disorders and other off-label indications[33]. One study evaluating the prescription rates of antidepressants by British GPs found a stable prescription rate for TCAs, but an increase in prescriptions of low-dose amitriptyline, indicating prescribing for indications other than depression and anxiety[36]. We have found an increase in prescription rates of amitriptyline and nortriptyline in the total cohort of OA patients, in contrast to the stable prescription rate other studies have found. This reflects the increase in the prescription for indications other than depression and anxiety.

The prescription rate of pregabalin almost doubled in our population between 2008 and 2017 and also the prescription rate of gabapentin increased. The rapid increase in prescriptions of gabapentin and pregabalin is also found in the general population[37 38]: up to a tripling of prescription rates in the past decade has been reported in the UK with incident prescription rates of 6.8 per 1000 persons per year for gabapentin and 3.8 per 1000 persons per year for pregabalin[37]. For OA, a retrospective cohort study in the UK found an almost tripled rate of first prescriptions of gabapentinoids between 2005 and 2015 with a prescription rate 27.6 per 1000 person-years in 2015[27]. In this study, we found a less steep increase and lower absolute numbers. In the Netherlands, data from pharmacies show a tripling of prescription rates for pregabalin and relatively stable rates of gabapentin prescriptions[39]. Pregabalin was registered earlier than gabapentin for neuropathic pain disorders in the Netherlands[40], which may have influenced prescription rates. Concerns about this increase have been raised[41 42]. The use is associated with side effects, especially in older patients[43], and gabapentin and pregabalin are often prescribed off-label without enough clinical evidence to support prescription. Only a few studies on anticonvulsants for OA pain have been carried out. In addition, there is some evidence for the misuse and abuse of gabapentin and pregabalin[44 45]. In the UK, gabapentin and pregabalin became controlled class C drugs in April 2019 since the number of deaths related to these medications had increased[46].

We found that increasing age, being female, the presence of other musculoskeletal disorders and the location of OA (spinal OA, and OA in ≥2 joint groups) were positively

associated with prescriptions of antidepressants and anticonvulsants. Increasing age and being female are also found to be associated with higher prescription rates in other studies[34 36 47]. To our knowledge, the effect of the presence of other musculoskeletal disorders and the type of joints involved in OA has not previously been investigated. It might be that GPs see more reason to prescribe these medicines to patients with back complaints and to patients with more generalized pain.

We calculated the time trends of prescription rates for all patients and for patients without comorbidities. The absolute numbers of prescriptions were lower in the OA group without comorbidities. Also, in this subgroup an increase in prescription rates was found for gabapentin and pregabalin but not for the antidepressants. The subgroup is more likely to consist of patients in whom these medications are prescribed for OA-related pain, but even in patients without comorbidities for which these medications are usually prescribed, antidepressants and anticonvulsants may have been prescribed for indications other than OA-related pain. Anxiety, depression and sleep disorders are associated with pain and functional impairment and are more common in OA patients[48-50]. A GP might decide that antidepressants or anticonvulsant could benefit patients with these comorbidities since multiple problems exist.

A strength of the current study is that it was conducted using a large database containing a representative sample of the Dutch population. There are some limitations to the current study. Patients were only included in the cohort when diagnosed with OA. Since GPs may be too rigorous or not rigorous enough in deciding when to use these ICPC codes, this may have led to an underestimation or overestimation of patients with OA. UK primary healthcare database research found that OA is probably under-recorded in patients having total hip or knee replacements[51]. So underestimation of the total number of patients with OA is more likely. Furthermore, as mentioned earlier, the indication for the prescriptions of antidepressants and anticonvulsants is not always clear in the medical records, and prescriptions may relate to another indication than OA related pain.

In conclusion, prescription rates of amitriptyline, gabapentin and pregabalin increased in the past decade in patients with OA. Prescription rates of duloxetine and nortriptyline remained stable. This rise is concerning since these prescriptions are for off-label indications and there is little evidence to support the prescription of these antidepressants and anticonvulsants in patients with OA. Since these medicines have side effects and concerns about the misuse of gabapentin and pregabalin have been raised, these medications should be prescribed with caution for OA related pain.

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SUPPLEMENTARY DATA

Figure S1. Prescription rates for patients with incident OA vs prevalent OA

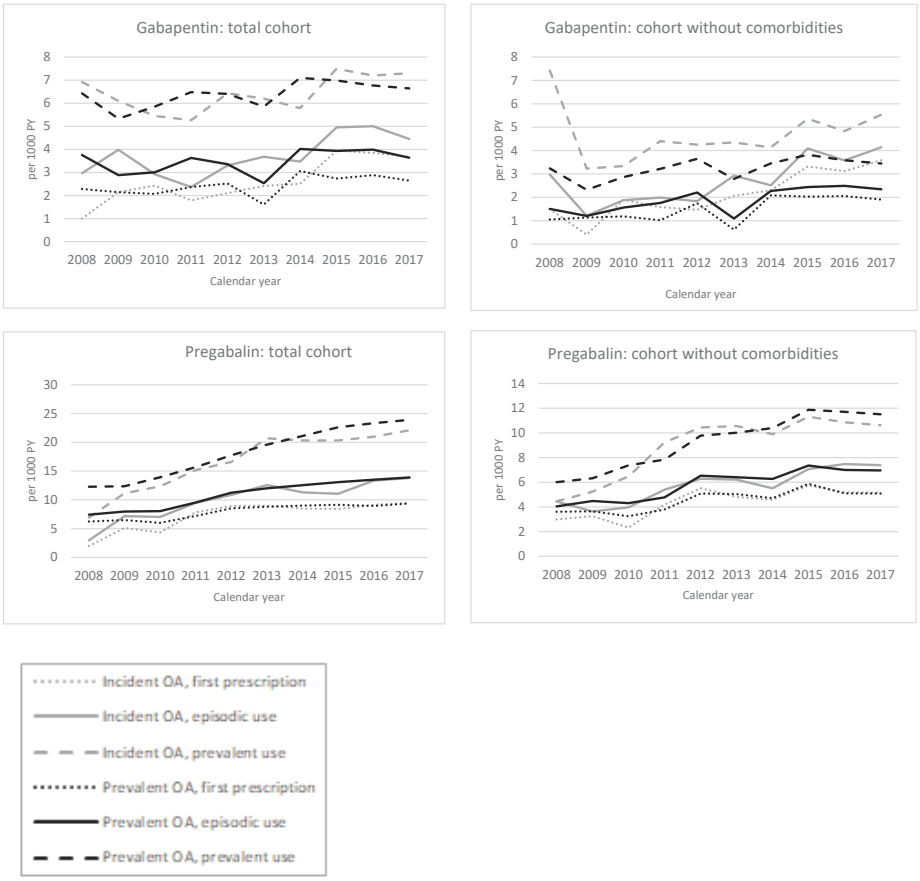
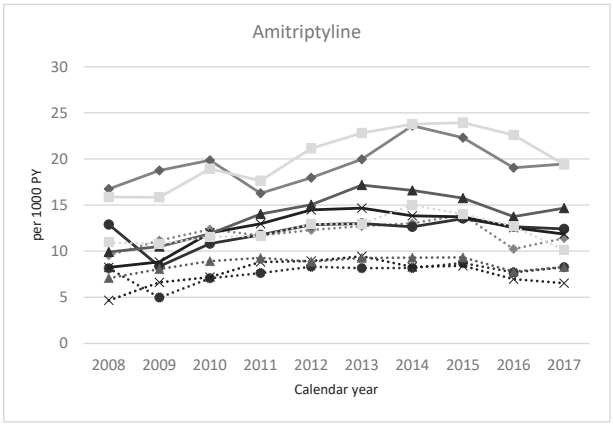
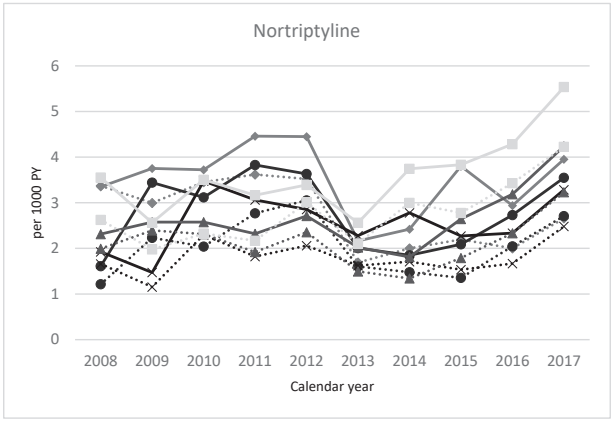


Figure S1. Prescription rates for patients with incident OA vs prevalent OA (continued)





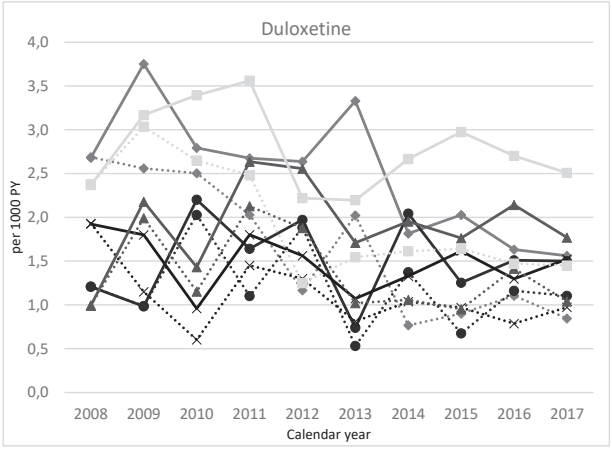
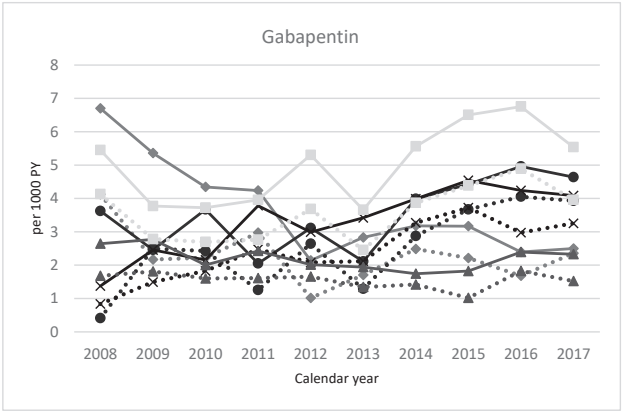
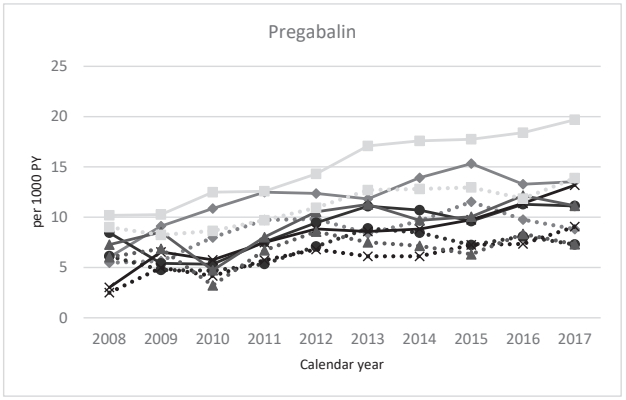


Figure S2. Prescription rates of antidepressants and anticonvulsants per joint groups





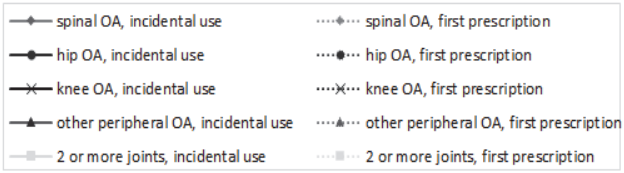


Figure S2. Prescription rates of antidepressants and anticonvulsants per joint groups (continued)

Table S1. Baseline characteristics incident OA vs prevalent OA (total cohort)

	Incident OA (n=59.053)	Prevalent OA (n=105.239)
Age mean (S.D.), years	64.2 (12.1)	67.9 (12.4)
Age category, *n (%)*		
30-39	1 063 (1.8)	1 574 (1.5)
40-49	5 668 (9.6)	6 339 (6.0)
50-59	14 469 (24.5)	18 317 (17.4)
60-69	17 900 (30.3)	30 856 (29.3)
70-79	13 190 (22.3)	27 559 (26.2)
80-89	5 919 (10.0)	17 720 (16.8)
> =90	844 (1.4)	2 874 (2.7)
Female, *n (%)*	37 694 (63.8)	69 744 (66.3)
Joints affected, *n (%)*		
Spine	6 389 (10.8)	10 854 (10.3)
Hip	11 230 (19.0)	16 532 (15.7)
Knee	18 954 (32.1)	26 110 (24.8)
Other joints	16 035 (27.2)	21 718 (20.6)
2 or more joints	6 445 (10.9)	30 025 (28.5)
Diabetes, *n (%)*	8 421 (14.3)	16 754 (15.9)
Hypertension, *n (%)*	22 501 (38.1)	44 365 (42.2)
Hyperlipidaemia, *n (%)*	10 128 (17.2)	19 096 (18.1)
MI/AP, *n (%)*	5 715 (9.7)	13 153 (12.5)
Stroke/TIA, *n (%)*	1 901 (3.2)	4 451 (4.2)
PAD, *n (%)*	2 079 (3.5)	4 286 (4.1)
UGI/ulcer, *n (%)*	1 737 (2.9)	3 986 (3.8)
Heartfailure, *n (%)*	1 721 (2.9)	5 268 (5.0)
Inflammatory arhritis, *n (%)*	2 290 (3.9)	5 659 (5.4)
Fibromyalgia, *n (%)*	1 038 (1.8)	1 454 (1.4)
Neuropathic pain disorder, *n (%)*	6 158 (10.4)	13 044 (12.4)
Depression, *n (%)*	9 930 (16.8)	18 784 (17.8)
Anxiety, *n (%)*	9 514 (16.1)	17 883 (17.0)
Psychosis, *n (%)*	1 075 (1.8)	3 009 (2.9)
Sleeping disorder, *n (%)*	10 934 (18.5)	21 344 (20.3)
Epilepsy, *n (%)*	778 (1.3)	1 626 (1.5)
Other MSD during cohort time, *n (%)*		
Upper extremity	12 934 (21.9)	26 127 (24.8)
Lower extremity	21 067 (35.7)	40 009 (38.0)
Back/neck	16 870 (28.6)	34 390 (32.7)
Other musculoskeletal	16 633 (28.2)	33 926 (32.2)
None	22 216 (37.6)	35 393 (33.6)
Renal function, *n (%)*		
eGFR>60 ml/min	39 027 (66.1)	64 925 (61.7)
eGFR 30-60 ml/min	5 532 (9.4)	13 850 (13.2)
eGFR<30 ml/min	542 (0.9)	1 072 (1.0)
missing	13 952 (23.6)	25 392 (24.1)

Table S2. Baseline characteristics incident OA vs prevalent OA (cohort without comorbidities)

	Incident OA (n=36.147)	**Prevalent OA (n=62.952)**
Age mean (S.D.), years	64.4 (12.1)	67.6 (12.3)
Age category, *n (%)*		
30-39	674 (1.9)	1 056 (1.7)
40-49	3 386 (9.4)	3 860 (6.1)
50-59	8 447 (23.4)	10 829 (17.2)
60-69	11 186 (30.9)	18 970 (30.1)
70-79	8 395 (23.2)	16 800 (26.7)
80-89	3 585 (9.9)	9 958 (15.8)
> =90	474 (1.3)	1 479 (2.3)
Female, *n (%)*	21 676 (60.0)	39 044 (62.0)
Joints affected, *n (%)*		
Spine	3 703 (10.2)	6 477 (10.3)
Hip	7 327 (20.3)	10 748 (17.1)
Knee	11 924 (33.0)	16 686 (26.5)
Other joints	9 420 (26.1)	12 769 (20.3)
2 or more joints	3 773 (10.4)	16 272 (25.8)
Diabetes, *n (%)*	4 658 (12.9)	8 950 (14.2)
Hypertension, *n (%)*	13 078 (36.2)	24 927 (39.6)
Hyperlipidaemia, *n (%)*	5 501 (15.2)	9 996 (15.9)
MI/AP, *n (%)*	3 025 (8.4)	6 649 (10.6)
Stroke/TIA, *n (%)*	965 (4.4)	2 149 (3.4)
PAD, *n (%)*	1 055 (2.9)	2 041 (3.2)
UGI/ulcer, *n (%)*	831 (2.3)	1 922 (3.1)
Heartfailure, *n (%)*	877 (2.4)	2 497 (4.0)
Inflammatory arhritis, *n (%)*	1 233 (3.4)	2 889 (4.6)
Fibromyalgia	NA	NA
Neuropathic pain disorder	NA	NA
Depression	NA	NA
Anxiety	NA	NA
Psychosis	NA	NA
Sleeping disorder	NA	NA
Epilepsy	NA	NA
Other MSD during cohort time, *n (%)*		
Upper extremity	7 270 (20.1)	48 520 (77.1)
Lower extremity	11 978 (33.1)	22 507 (35.8)
Back/neck	9 270 (25.6)	18 835 (29.9)
Other musculoskeletal	9 068 (25.1)	18 418 (29.3)
None	14 812 (41.0)	23 091 (36.7)
Renal function, *n (%)*		
eGFR>60 ml/min	22 610 (62.6)	37 003 (58.8)
eGFR 30-60 ml/min	3 217 (8.9)	7 577 (12.0)
eGFR<30 ml/min	319 (0.9)	577 (0.9)
missing	10 001 (27.7)	17 795 (28.3)

Comorbidities are fibromyalgia, neuropathic pain disorders, depression, anxiety, psychosis, sleeping disorder, epilepsy, MI=myocardial infarction, AP=angina pectoris, TIA= transient ischemic attack, PAD=peripheral arterial disease, UGI= upper gastro-intestinal, MSD=musculoskeletal disorder, eGFR= estimated glomerular filtration rate.

Table S3. Prescription rates (numbers per 1000 person-years)

Amitriptyline

Year	Total cohort			Cohort without comorbidities		
	First (95% CI)	Episodic (95% CI)	Prevalent (95% CI)	First (95% CI)	Episodic (95% CI)	Prevalent (95% CI)
2008	8.0 (6.5-9.6)	12.4 (10.6-14.2)	25.7 (23.2-28.4)	8.0 (6.5-8.6)	7.2 (5.6-9.1)	13.7 (11.5-16.3)
2009	8.2 (7.0-9.4)	11.6 (10.3-13.0)	24.7 (22.8-26.8)	8.2 (7.0-9.4)	6.7 (5.4-8.2)	13.3 (11.5-15.3)
2010	9.2 (8.2-10.4)	14.5 (13.2-15.8)	26.8(24.8-28.3)	9.2 (8.2-10.4)	8.2 (7.0-9.5)	14.5 (12.8-16.2)
2011	9.8 (8.9-10.8)	14.6 (13.5-15.8)	29.1 (27.5-30.6)	9.8 (8.9-10.8)	8.3 (7.3-9.4)	15.6 (14.2-17.2)
2012	10.2 (9.4-11.1)	16.5 (15.5-17.6)	31.1 (29.8-32.6)	10.2 (9.4-11.1)	8.6 (7.7-9.7)	16.7 (15.4-18.1)
2013	10.5 (9.6-11.4)	17.7 (16.7-18.8)	34.1 (32.7-35.6)	10.5 (9.6-11.4)	9.6 (8.6-10.7)	18.1 (16.7-19.6)
2014	10.7 (9.9-11.6)	17.9 (16.9-19.0)	32.7 (31.4-34.1)	10.7 (9.9-11.6)	9.1 (8.1-10.1)	16.8 (15.5-18.2)
2015	10.6 (9.9 (11.4)	17.7 (16.7-18.7)	33.8 (32.6-35.1)	10.6 (9.9-11.6)	9.2 (8.3-10.1)	17.1 (15.9-18.4)
2016	9.0 (7.4-8.7)	16.0 (15.1-16.8)	31.4 (30.3-32.6)	9.0 (7.4-8.7)	7.0 (6.2-7.8)	14.3 (13.2-15.4)
2017	8.5 (7.9-9.2)	15.1 (14.3-16.0)	30.7 (29.6-31.8)	8.5 (7.9-9.2)	7.4 (6.6-8.2)	14.3 (13.2-15.4)

Nortriptyline

Year	Total cohort			Cohort without comorbidities		
	First (95% CI)	Episodic (95% CI)	Prevalent (95% CI)	First (95% CI)	Episodic (95% CI)	Prevalent (95% CI)
2008	2.1 (1.4-3.0)	2.6 (1.8-3.5)	4.8 (3.8-6.1)	1.4 (0.7-2.4)	1.4 (0.7-2.4)	1.7 (0.1-2.8)
2009	2.0 (1.5-2.6)	2.5 (1.9-3.2)	4.9 (4.0-5.8)	1.1 (0.6-1.7)	1.2 (0.7-1.9)	1.4 (0.9-2.1)
2010	2.4 (1.9-3.0)	3.3 (2.7-3.9)	5.8 (5.0-6.7)	1.5 (1.0-2.1)	1.8 (1.3-2.5)	2.4 (1.8-3.2)
2011	2.3 (1.9-2.8)	3.2 (2.7-3.8)	5.9 (5.2-6.7)	1.4 (1.0-1.9)	1.6 (1.2-2.2)	2.3 (1.8-3.0)
2012	2.7 (2.3-3.1)	3.3 (2.8-3.7)	5.7 (5.1-6.4)	1.6 (1.2-2.1)	1.8 (1.4-2.3)	2.6 (2.1-3.2)
2013	1.7 (1.4-2.1)	2.3 (1.9-2.7)	4.8 (4.3-5.4)	0.7 (0.5-1.1)	0.9 (0.6-1.2)	1.5 (1.1-1.9)
2014	2.0 (1.6-2.3)	2.6 (2.3-3.1)	5.0 (4.5-5.6)	1.0 (0.7-1.4)	1.1 (0.8-1.5)	1.5 (1.1-1.9)
2015	2.0 (1.6-2.3)	2.9 (2.5-3.3)	5.5 (5.0-6.1)	0.5 (0.3-0.8)	0.7 (0.4-1.0)	1.2 (0.9-1.6)
2016	2.3 (2.0-2.7)	3.1 (2.8-3.5)	5.9 (5.4-6.5)	1.1 (0.8-1.4)	1.2 (0.9-1.6)	1.6 (1.2-2.0)
2017	3.1 (2.8-3.5)	4.1 (3.7-4.6)	7.0 (6.5-7.5)	1.4 (1.1-1.8)	1.7 (1.3-2.1)	2.2 (1.8-2.6)

Duloxetine

Year	Total cohort			Cohort without comorbidities		
	First (95% CI)	Episodic (95% CI)	Prevalent (95% CI)	First (95% CI)	Episodic (95% CI)	Prevalent (95% CI)
2008	1.8 (1.2-2.7)	1.8 (1.2-2.6)	2.8 (2.0-3.8)	0.8 (0.3-1.5)	0.8 (0.3-1.5)	1.1 (0.5-2.0)
2009	2.0 (1.4-2.6)	2.2 (1.7-2.9)	3.7 (3.0-4.5)	0.9 (0.5-1.5)	0.9 (0.5-1.5)	1.3 (0.8-2.1)
2010	1.7 (1.3-2.2)	2.1 (1.6-2.7)	3.9 (3.3-4.6)	0.6 (0.3-1.0)	0.7 (0.4-1.2)	1.3 (0.8-1.9)
2011	1.9 (1.5-2.3)	2.5 (2.1-3.0)	4.7 (4.1-5.4)	0.8 (0.5-1.2)	1.2 (0.8-1.7)	1.7 (1.3-2.3)
2012	1.5 (1.2-1.8)	2.1 (1.8-2.5)	4.3 (3.8-4.9)	0.5 (0.3-0.8)	0.7 (0.4-1.0)	1.4 (1.1-1.9)
2013	1.1 (0.9-1.4)	1.7 (1.4-2.1)	4.1 (3.6-4.6)	0.5 (0.3-0.8)	0.6 (0.4-1.0)	1.4 (1.1-1.9)
2014	1.2 (1.0-1.5)	2.0 (1.7-2.4)	4.3 (3.8-4.8)	0.5 (0.3-0.8)	0.7 (0.4-1.0)	1.4 (1.0-1.8)
2015	1.1 (0.9-1.3)	2.0 (1.7-2.3)	4.5 (4.1-5.0)	0.3 (0.2-0.5)	0.6 (0.4-0.8)	1.3 (1.0-1.7)
2016	1.2 (1.0-1.4)	1.9 (1.6-2.2)	4.3 (3.9-4.7)	0.2 (0.1-0.4)	0.5 (0.3-0.7)	1.2 (0.9-1.5)
2017	1.1 (0.9-1.3)	1.8 (1.5-2.1)	4.3 (3.9-4.7)	0.4 (0.2-0.6)	0.5 (0.3-0.7)	1.1 (0.8-1.4)

Gabapentin

Year	Total cohort			Cohort without comorbidities		
	First (95% CI)	Episodic (95% CI)	Prevalent (95% CI)	First (95% CI)	Episodic (95% CI)	Prevalent (95% CI)
2008	2.2 (1.5-3.1)	3.7 (2.8-4.8)	6.5 (5.2-7.9)	1.1 (0.5-2.0)	1.6 (0.9-2.7)	3.5 (2.4-5.0)
2009	2.1 (1.6-2.8)	3.1 (2.4-3.8)	5.5 (4.6-6.5)	1.0 (0.6-1.7)	1.2 (0.7-1.9)	2.5 (1.7-3.4)
2010	2.2 (1.8-2.7)	3.0 (2.5-3.7)	5.8 (5.0-6.6)	1.4 (0.9-2.0)	1.6 (1.1-2.3)	3.0 (2.3-3.8)
2011	2.2 (1.8-2.7)	3.3 (2.8-3.9)	6.2 (5.5-6.9)	1.2 (0.8-1.7)	1.8 (1.3-2.4)	3.5 (2.9-4.3)
2012	2.4 (2.0-2.8)	3.3 (2.9-3.8)	6.4 (5.8-7.1)	1.7 (1.3-2.2)	2.1 (1.6-2.6)	3.8 (3.2-4.5)
2013	1.9 (1.5-2.3)	2.9 (2.5-3.4)	6.0 (5.4-6.6)	1.1 (0.8-1.5)	1.7 (1.3-2.2)	3.3 (2.7-4.0)
2014	2.9 (2.5-3.3)	3.8 (3.4-4.3)	6.7 (6.1-7.3)	2.2 (1.7-2.7)	2.4 (1.9-2.9)	3.7 (3.1-4.4)
2015	3.1 (2.7-3.6)	4.3 (3.8-4.8)	7.2 (6.6-7.8)	2.5 (2.0-3.0)	3.0 (2.5-3.6)	4.3 (3.7-5.0)
2016	3.2 (2.8-3.6)	4.4 (3.9-4.8)	6.9 (6.4-7.5)	2.4 (2.0-2.9)	2.9 (2.4-3.4)	4.0 (3.5-4.6)
2017	3.0 (2.7-3.4)	3.9 (3.5-4.4)	6.9 (6.4-7.4)	2.5 (2.1-3.0)	3.0 (2.5-3.5)	4.2 (3.7-4.9)

Pregabalin

Year	Total cohort			Cohort without comorbidities		
	First (95% CI)	Episodic (95% CI)	Prevalent (95% CI)	First (95% CI)	Episodic (95% CI)	Prevalent (95% CI)
2008	6.0 (4.8-7.3)	7.1 (5.8-8.6)	11.9 (10.2-13.8)	3.6 (2.5-5.0)	4.1 (2.9-5.6)	5.9 (4.4-7.7)
2009	6.3 (5.3-7.4)	7.8 (6.8-9.0)	12.2 (10.8-13.6)	3.6 (2.7-4.7)	4.3 (3.4-5.5)	6.2 (5.0-7.5)
2010	5.6 (4.8-6.5)	7.8 (6.9-8.8)	13.6 (12.4-14.9)	3.0 (2.3-3.9)	4.2 (3.4-5.2)	7.2 (6.0-8.4)
2011	7.4 (6.6-8.2)	9.5 (8.6-10.5)	15.6 (14.4-16.8)	3.9 (3.2-4.7)	4.9 (4.1-5.9)	8.2 (7.2-9.4)
2012	8.7 (7.9-9.4)	11.2 (10.3-12.0)	17.4 (16.4-18.5)	5.2 (4.5-6.0)	6.5 (5.6-7.4)	10.0 (9.0-11.1)
2013	8.9 (8.1-9.7)	12.2(11.3-13.1)	20.0 (18.8-21.1)	5.0 (4.2-5.8)	6.3 (5.5-7.2)	10.2 (9.2-11.3)
2014	8.8 (8.1-9.6)	12.2 (11.3-13.1)	20.9 (19.8-22.0)	4.7 (4.0-5.4)	6.0 (5.2-6.9)	10.2 (9.2-11.3)
2015	8.9 (8.2-9.6)	12.4 (11.7-13.3)	21.9 (20.9-22.9)	5.8 (5.1-6.6)	7.3 (6.5-8.1)	11.7 (10.7-12.8)
2016	9.0 (8.4-9.7)	13.5 (12.7-14.2)	22.5 (21.6-23.5)	5.1 (4.5-5.8)	7.2 (6.4-8.0)	11.4 (10.5-12.4)
2017	9.4 (8.8-10.1)	13.9 (13.2-14.7)	23.3 (22.3-24.2)	5.1 (4.5-5.8)	7.1 (6.4-7.9)	11.2 (10.3-12.2)

Table S4. Prescription rates in patients with incident OA and prevalent OA

Amitriptyline (Total cohort)

Year	Incident OA			Prevalent OA		
	First (95% CI)	Episodic (95% CI)	Prevalent (95% CI)	First (95% CI)	Episodic (95% CI)	Prevalent (95% CI)
2008	10.4 (5.2-18.8)	13.8 (7.9-22.7)	32.6 (22.5-45.5)	7.8 (6.3-9.5)	12.1 (10.3-14.1)	25.2 (22.7-27.9)
2009	10.7 (7.6-14.7)	12.2 (9.0-16.2)	25.2 (20.2-30.7)	7.7 (6.5-9.1)	11.4 (10.0-13.0)	24.7 (22.6-26.9)
2010	9.4 (7.3-12.0)	12.6 (10.2-15.4)	24.2 (20.8-27.9)	9.1 (8.0-10.4)	14.9 (13.5-16.5)	27.5 (25.6-29.6)
2011	11.3 (9.4-13.5)	15.2 (13.0-17.6)	27.5 (24.5-30.6)	9.3 (8.2-10.4)	14.4 (13.1-15.7)	29.6 (27.8-31.5)
2012	11.8 (10.1-13.6)	17.2 (15.2-19.2)	31.3 (28.8-34.1)	9.6 (8.6-10.6)	16.2 (15.0-17.4)	31.1 (29.4-32.7)
2013	10.5 (9.0-12.1)	17.7 (15.9-19.8)	34.6 (32.0-37.3)	10.4 (9.4-11.5)	17.7 (16.4-19.0)	33.9 (32.1-35.1)
2014	11.0 (9.6-12.6)	17.8 (16.1-19.7)	32.8 (30.4-35.2)	10.6 (9.6-11.6)	17.9 (16.7-19.2)	32.7 (31.0-34.4)
2015	11.9 (10.5-13.4)	19.3 (17.6-21.1)	35.8 (33.5-38.2)	10.0 (9.1-11.0)	16.9 (15.8-18.0)	32.9 (31.4-34.5)
2016	8.9 (7.8-10.1)	15.5 (14.1-17.0)	32.1 (30.1-34.2)	9.0 (8.2-9.8)	16.1 (15.1-17.2)	31.1 (29.7-32.5)
2017	9.5 (8.4-10.7)	16.2 (14.9-17.6)	32.9 (31.0-34.9)	8.0 (7.2-8.8)	14.5 (13.5-15.5)	29.5 (28.1-30.9)

Amitriptyline (cohort without comorbidities)

Year	Incident OA			Prevalent OA		
	First (95% CI)	Episodic (95% CI)	Prevalent (95% CI)	First (95% CI)	Episodic (95% CI)	Prevalent (95% CI)
2008	9.2 (3.4-20.1)	8.9 (3.0-19.3)	17.8 (9.2-30.9)	4.3 (3.0-6.0)	7.1 (5.4-9.0)	13.4(11.1-16.1)
2009	7.1 (4.2-11.4)	7.7 (4.4-12.1)	15.3 (10.9-21.0)	4.8 (3.6-6.2)	6.5 (5.1-8.1)	12.9 (11.0-15.0)
2010	6.5 (4.4-9.3)	7.9 (5.6-10.9)	13.1 (10.1-16.8)	5.6 (4.5-7.0)	8.3 (6.9-9.9)	14.9 (13.0-16.9)
2011	7.9 (5.9-10.3)	10.7 (8.4-13.4)	16.6 (13.8-19.9)	5.1 (4.1-6.2)	7.4 (6.3-8.7)	15.3 (13.6-17.1)
2012	6.2 (4.7-8.0)	9.3 (7.5-11.3)	16.5 (14.2-19.2)	5.4 (4.5-6.4)	8.4 (7.3-9.6)	16.8 (15.2-18.4)
2013	6.0 (4.6-7.7)	9.1 (7.5-11.3)	17.8 (15.4-20.4)	6.3 (5.3-7.5)	9.8 (8.6-11.2)	18.3 (16.6-20.1)
2014	5.7 (4.4-7.2)	9.2 (7.5-11.0)	16.6 (14.4-19.0)	6.0 (5.1-7.2)	9.0 (7.9-10.4)	16.9 (15.3-18.6)
2015	6.6 (5.2-8.2)	9.8 (8.2-11.6)	17.9 (15.8-20.3)	5.9 (5.0-6.9)	8.9 (7.8-10.1)	16.7 (15.2-18.3)
2016	4.4 (3.4-5.6)	7.1 (5.8-8.5)	14.8 (13.0-16.8)	4.1 (3.4-4.9)	6.9 (6.0-7.9)	14.0 (12.7-15.4)
2017	5.1 (4.1-6.3)	8.0 (6.7-9.4)	15.6 (13.8-17.5)	4.7 (3.9-5.5)	7.0 (6.1-8.0)	13.5 (12.2-14.9)

Nortriptyline (Total cohort)

Year	Incident OA			Prevalent OA		
	First (95% CI)	Episodic (95% CI)	Prevalent (95% CI)	First (95% CI)	Episodic (95% CI)	Prevalent (95% CI)
2008	2.0 (0.2-7.2)	3.0 (0.6-8.7)	4.0 (1.1-10.1)	2.1 (1.4-3.0)	2.5 (1.8-3.5)	4.9 (3.8-6.2)
2009	1.3 (0.4-3.1)	2.1 (0.9-4.2)	4.5 (2.6-7.2)	2.1 (1.5-2.9)	2.5 (1.9-3.3)	4.9 (4.0-6.0)
2010	3.2 (2.1-4.8)	4.3 (2.9-6.0)	7.0 (5.3-9.2)	2.1 (1.6-2.8)	3.0 (2.3-3.7)	5.5 (4.6-6.4)
2011	2.4 (1.6-3.5)	3.3 (2.4-4.6)	6.0 (4.7-7.7)	2.2 (1.8-2.8)	3.2 (2.6-3.8)	5.9 (5.1-6.8)
2012	3.5 (2.7-4.6)	4.0 (3.1-5.0)	6.8 (5.6-8.1)	2.4 (1.9-2.9)	3.0 (2.5-3.5)	5.3 (4.6-6.0)
2013	1.8 (1.2-2.5)	2.4 (1.7-3.2)	4.5 (3.6-5.5)	1.7 (1.3-2.2)	2.2 (1.8-2.7)	5.0 (4.2-5.7)
2014	1.7 (1.2-.2.4)	2.4 (1.8-3.1)	4.7 (3.8-5.7)	2.1 (1.7-2.6)	2.8 (2.3-3.3)	5.1 (4.5-5.9)
2015	1.7 (1.2-2.3)	2.6 (2.0-3.3)	4.9 (4.0-5.8)	2.1 (1.7-2.5)	3.0 (2.6-3.5)	5.8 (5.2-6.5)
2016	1.9 (1.4-2.4)	2.6 (2.0-3.2)	5.0 (4.2-5.9)	2.6 (2.2-3.0)	3.4 (3.0-3.9)	6.4 (5.8-7.1)
2017	2.7 (2.2-3.4)	3.5 (2.9-4.2)	6.0 (5.2-6.9)	3.3 (2.9-3.8)	4.5 (4.0-5.1)	7.5 (6.8-8.2)

Nortriptyline (Cohort without comorbidities)

Year	Incident OA			Prevalent OA		
	First (95% CI)	Episodic (95% CI)	Prevalent (95% CI)	First (95% CI)	Episodic (95% CI)	Prevalent (95% CI)
2008	3.0 (0.4-10.8)	3.0 (0.4-10.7)	4.5 (0.1-1.3)	1.3 (0.6-2.3)	1.3 (0.6-2.3)	1.5 (0.1-2.6)
2009	0.4 (0.0-2.3)	0.4 (0.0-2.2)	2.8 (1.1-5.8)	1.2 (0.7-2.0)	1.4 (0.8-2.2)	1.9 (1.2-2.9)
2010	2.9 (1.6-4.9)	3.8 (2.2-5.9)	4.4 (2.7-6.7)	1.1 (0.6-1.7)	1.2 (0.7-1.9)	1.8 (1.2-2.6)
2011	1.6 (0.8-2.8)	1.7 (0.9-3.0)	2.8 (1.7-4.4)	1.4 (0.9-2.0)	1.6 (1.1-2.3)	2.1 (1.5-2.9)
2012	2.1 (1.3-3.2)	2.2 (1.4-3.3)	3.3 (2.3-4.6)	1.5 (1.1-2.1)	1.7 (1.2-2.3)	2.3 (1.7-3.0)
2013	0.7 (0.3-1.4)	0.8 (0.4-1.5)	1.4 (0.8-2.3)	0.7 (0.4-1.2)	0.9 (0.5-1.3)	1.5 (1.0-2.1)
2014	1.1 (0.6-1.8)	1.1 (0.6-1.8)	1.5 (0.9-2.3)	0.8 (0.5-1.2)	1.1 (0.7-1.7)	1.5 (1.1-2.1)
2015	0.2 (0.0-0.7)	0.3 (0.1-0.8)	1.0 (0.5-1.7)	0.6 (0.3-0.9)	0.8 (0.5-1.3)	1.3 (0.9-1.8)
2016	1.0 (0.6-1.6)	1.2 (0.7-1.9)	1.5 (1.0-2.2)	1.1 (0.7-1.5)	1.2 (0.9-1.7)	1.6 (1.2-2.1)
2017	1.1 (0.6-1.7)	1.2 (0.8-1.9)	1.9 (1.3-2.6)	1.6 (1.2-2.1)	1.9 (1.4-2.5)	2.4 (1.9-3.0)

Duloxetine (Total cohort)

Year	Incident OA			Prevalent OA		
	First (95% CI)	Episodic (95% CI)	Prevalent (95% CI)	First (95% CI)	Episodic (95% CI)	Prevalent (95% CI)
2008	2.0 (0.2-7.2)	2.0 (0.2-7.1)	4.0 (1.1-10.1)	1.8 (1.2-2.7)	1.8 (1.2-2.7)	2.7 (1.9-3.8)
2009	1.9 (0.8-3.8)	1.9 (0.7-3.8)	5.0 (3.0-7.9)	2.0 (1.4-2.7)	2.3 (1.7-3.1)	3.4 (2.7-4.3)
2010	1.9 (1.0-3.1)	2.0 (1.1-3.3)	4.4 (3.0-6.2)	1.7 (1.2-2.2)	2.1 (1.6-2.8)	3.8 (3.0-4.6)
2011	2.0 (1.2-2.9)	2.2 (1.4-3.2)	4.9 (3.7-6.4)	1.9 (1.4-2.4)	2.7 (2.1-3.3)	4.6 (3.9-5.4)
2012	1.4 (0.9-2.1)	1.8 (1.2-2.6)	4.2 (3.3-5.3)	1.5 (1.2-2.0)	2.3 (1.8-2.8)	4.4 (3.8-5.1)
2013	1.3 (0.8-1.9)	1.9 (1.3-2.6)	4.3 (3.4-5.3)	1.1 (0.8-1.4)	1.6 (1.2-2.0)	4.0 (3.4-4.7)
2014	1.0 (0.6-1.6)	1.8 (1.3-2.5)	4.0 (3.2-4.9)	1.3 (1.0-1.7)	2.1 (1.7-2.5)	4.4 (3.8-5.1)
2015	1.1 (0.7-1.6)	1.8 (1.3-2.4)	4.0 (3.4-5.1)	1.1 (0.8-1.4)	2.1 (1.7-2.5)	4.8 (4.2-5.4)
2016	1.5 (1.1-2.0)	2.1 (1.6-2.6)	4.2 (3.5-5.0)	1.1 (0.8-1.3)	1.8 (1.5-2.2)	4.3 (3.8-4.9)
2017	0.8 (0.5-1.2)	1.4 (1.0-1.9)	3.7 (3.1-4.4)	1.3 (1.0-1.6)	2.0 (1.7-2.4)	4.6 (4.1-5.2)

Duloxetine (Cohort without comorbidities)

Year	Incident OA			Prevalent OA		
	First (95% CI)	Episodic (95% CI)	Prevalent (95% CI)	First (95% CI)	Episodic (95% CI)	Prevalent (95% CI)
2008	0.0 (0.0-5.5)	0.0 (0.0-5.5)	0.0 (0.0-5.5)	0.8 (0.3-1.7)	0.8 (0.3-1.7)	1.2 (0.6-2.1)
2009	1.2 (0.3-3.5)	1.2 (0.2-3.5)	2.0 (0.7-4.7)	0.8 (0.4-1.5)	0.8 (0.4-1.5)	1.2 (0.7-2.0)
2010	1.1 (0.3-2.4)	1.0 (0.3-2.4)	1.9 (0.9-3.6)	0.5 (0.2-0.9)	0.6 (0.3-1.1)	1.1 (0.6-1.8)
2011	0.9 (0.3-1.9)	1.0 (0.4-2.0)	1.6 (0.8-2.8)	0.8 (0.5-1.3)	1.3 (0.8-2.0)	1.8 (1.3-2.5)
2012	0.4 (0.1-1.0)	0.4 (0.1-1.0)	0.8 (0.3-1.5)	0.6 (0.3-0.9)	0.8 (0.5-1.2)	1.7 (1.2-2.3)
2013	0.4 (0.1-0.9)	0.5 (0.2-1.2)	1.0 (0.5-1.8)	0.5 (0.3-0.9)	0.7 (0.4-1.1)	1.7 (1.2-2.3)
2014	0.7 (0.3-1.3)	0.7 (0.2-1.4)	1.5 (0.9-2.3)	0.4 (0.2-0.7)	0.6 (0.4-1.0)	1.3 (0.9-1.8)
2015	0.3 (0.1-0.8)	0.4 (0.1-0.9)	1.2 (0.7-1.9)	0.3 (0.1-0.6)	0.7 (0.4-1.0)	1.4 (1.0-1.9)
2016	0.3 (0.1-0.7)	0.6 (0.3-1.1)	1.1 (0.6-1.7)	0.2 (0.1-0.4)	0.5 (0.3-0.8)	1.2 (0.9-1.7)
2017	0.6 (0.3-1.1)	0.6 (0.3-1.1)	1.0 (0.6-1.5)	0.3 (0.1-0.5)	0.4 (0.2-0.7)	1.2 (0.8-1.6)

Gabapentin (Total cohort)

Year	Incident OA			Prevalent OA		
	First (95% CI)	Episodic (95% CI)	Prevalent (95% CI)	First (95% CI)	Episodic (95% CI)	Prevalent (95% CI)
2008	1.0 (0.0-5.6)	3.0 (0.6-8.7)	6.9 (2.8-14.2)	2.3 (1.6-3.2)	3.8 (2.8-4.9)	6.4 (5.2-7.9)
2009	2.2 (0.9-4.2)	4.0 (2.2-6.6)	6.1 (3.9-9.2)	2.1 (1.6-2.9)	2.9 (2.2-3.7)	5.3 (4.4-6.4)
2010	2.4 (1.4-3.8)	2.9 (1.8-4.4)	5.5 (3.9-7.4)	2.1 (1.5-2.7)	3.0 (2.4-3.8)	5.9 (5.0-6.9)
2011	1.8 (1.1-2.8)	2.4 (1.6-3.4)	5.3 (4.0-6.8)	2.4 (1.9-3.0)	3.6 (3.0-4.3)	6.5 (5.7-7.4)
2012	2.1 (1.5-2.9)	3.3 (2.5-4.3)	6.4 (5.3-7.8)	2.5 (2.1-3.1)	3.4 (2.8-4.0)	6.4 (5.7-7.4)
2013	2.4 (1.8-3.2)	3.7 (2.9-4.6)	6.2 (5.1-7.4)	1.6 (1.2-2.1)	2.5 (2.1-3.1)	5.9 (5.1-6.6)
2014	2.5 (1.9-3.3)	3.5 (2.7-4.4)	5.8 (4.8-6.9)	3.1 (2.6-3.6)	4.0 (3.4-4.7)	7.1 (6.3-7.9)
2015	4.0 (3.2-4.8)	5.0 (4.1-5.9)	7.5 (6.5-8.7)	2.7 (2.3-3.2)	3.9 (3.4-4.5)	7.0 (6.3-7-7)
2016	3.9 (3.2-4.6)	5.0 (4.2-5.9)	7.2 (6.3-8.2)	2.9 (2.5-3.4)	4.0 (3.5-4.5)	6.8 (6.1-7.5)
2017	3.7 (3.0-4.4)	4.5 (3.8-5.2)	7.3 (6.4-8.3)	2.6 (2.2-3.1)	3.6 (3.2-4.2)	6.6 (6.0-7.3)

Gabapentin (Cohort without comorbidities)

Year	Incident OA			Prevalent OA		
	First (95% CI)	Episodic (95% CI)	Prevalent (95% CI)	First (95% CI)	Episodic (95% CI)	Prevalent (95% CI)
2008	1.5 (0.0-8.3)	3.0 (0.4-10.7)	7.4 (2.4-17.2)	1.1 (0.5-2.0)	1.5 (0.8-2.6)	3.2 (2.2-4.7)
2009	0.4 (0.0-2.3)	1.2 (0.2-3.5)	3.2 (1.4-6.4)	1.1 (0.6-1.9)	1.2 (0.7-2.0)	2.3 (1.6-3.3)
2010	1.9 (0.9-3.6)	1.9 (0.9-3.6)	3.3 (1.9-5.4)	1.2 (0.7-1.9)	1.6 (1.0-2.3)	2.9 (2.1-3.8)
2011	1.6 (0.8-2.8)	2.0 (1.1-3.3)	4.4 (3.0-6.2)	1.0 (0.6-1.6)	1.8 (1.2-2.4)	3.2 (2.5-4.1)
2012	1.5 (0.8-2.4)	1.8 (1.1-2.9)	4.3 (3.1-5.7)	1.8 (1.3-2.4)	2.2 (1.7-2.9)	3.7 (2.9-4.5)
2013	2.1 (1.3-3.1)	2.9 (2.0-4.1)	4.4 (3.2-5.7)	0.6 (0.3-1.0)	1.1 (0.7-1.6)	2.8 (2.1-3.6)
2014	2.3 (1.5-3.3)	2.5 (1.7-3.6)	4.1 (3.1-5.4)	2.1 (1.5-2.8)	2.3 (1.7-3.0)	3.5 (2.7-4.3)
2015	3.3 (2.4-4.5)	4.1 (3.1-5.3)	5.4 (4.2-6.7)	2.0 (1.5-2.6)	2.4 (1.9-3.1)	3.8 (3.1-4.6)
2016	3.1 (2.3-4.1)	3.6 (2.7-4.6)	4.8 (3.8-6.0)	2.1 (1.6-2.6)	2.5 (2.0-3.1)	3.6 (2.9-4.3)
2017	3.6 (2.8-4.6)	4.1 (3.3-5.2)	5.5 (4.5-6.7)	1.9 (1.4-2.5)	2.3 (1.8-3.0)	3.5 (2.8-4.2)

Pregabalin (Total cohort)

Year	Incident OA			Prevalent OA		
	First (95% CI)	Episodic (95% CI)	Prevalent (95% CI)	First (95% CI)	Episodic (95% CI)	Prevalent (95% CI)
2008	2.0 (0.2-7.2)	3.0 (0.6-8.7)	6.9 (2.8-14.2)	6.3 (5.0-7.7)	7.4 (6.1-9.0)	12.3 (10.5-14.3)
2009	5.1 (3.1-8.0)	7.2 (4.7-10.4)	11.2 (8.0-15.0)	6.5 (5.4-7.7)	8.0 (6.8-9.3)	12.4 (10.9-14.0)
2010	4.4 (3.0-6.1)	7.0 (5.3-9.2)	12.4 (10.1-15.1)	6.0 (5.1-7.1)	8.0 (7.0-9.2)	13.9 (12.5-15.4)
2011	7.9 (6.3-9.7)	9.5 (7.8-11.4)	15.2 (13.0-17.6)	7.2 (6.3-8.2)	9.6 (8.5-10.6)	15.7 (14.4-17.1)
2012	8.9 (7.5-1.0.5)	10.9 (9.3-12.5)	16.6 (14.7-18.6)	8.5 (7.7-9.5)	11.2 (10.3-12.3)	17.7 (16.5-19.0)
2013	9.0 (7.7-10.5)	12.6 (11.0-14.3)	20.7 (18.7-22.8)	8.8 (7.9-9.8)	12.0 (11.0-13.7)	19.6 (18.3-21.0)
2014	8.5 (7.3-9.9)	11.3 (9.9-12.8)	20.3 (18.5-22.3)	9.0 (8.1-10.0)	12.6 (11.5-13.7)	21.1 (19.8-22.5)
2015	8.4 (7.3-9.7)	11.0 (9.8-12.5)	20.3 (18.6-22.2)	9.2 (8.3-10.0)	13.1 (12.1-14.1)	22.6 (21.3-23.9)
2016	9.2 (8.1-10.4)	13.4 (12.1-14.7)	21.0 (19.4-22.7)	8.9 (8.2-9.8)	13.5 (12.6-14.5)	23.3 (22.1-24.6)
2017	9.5 (8.4-10.6)	13.8 (12.6-15.1)	22.1 (20.5-23.7)	9.4 (8.6-10.2)	13.9 (13.0-14.9)	23.9 (22.7-25.2)

Pregabalin (Cohort without comorbidities)

Year	Incident OA			Prevalent OA		
	First (95% CI)	Episodic (95% CI)	Prevalent (95% CI)	First (95% CI)	Episodic (95% CI)	Prevalent (95% CI)
2008	3.0 (0.4-10.8)	4.5 (0.9-13.0)	4.5 (0.9-13.0)	3.6 (2.5-5.1)	4.1 (2.8-5.6)	6.0 (4.5-7.9)
2009	3.3 (1.4-6.4)	3.6 (1.7-6.9)	5.3 (2.8-9.0)	3.6 (2.7-4.9)	4.5 (3.4-5.8)	6.3 (5.0-7.9)
2010	2.3 (1.2-4.2)	4.0 (2.4-6.2)	6.5 (4.4-9.2)	3.2 (2.4-4.3)	4.3 (3.3-5.5)	7.4 (6.1-8.8)
2011	4.2 (2.8-6.0)	5.4 (3.8-7.4)	9.2 (7.1-11.8)	3.8 (3.0-4.8)	4.8 (3.9-5.8)	7.8 (6.7-9.2)
2012	5.5 (4.2-7.2)	6.3 (4.8-8.0)	10.4 (8.6-12.6)	5.1 (4.2-6.1)	6.5 (5.6-7.6)	9.8 (8.6-11.1)
2013	4.8 (3.6-6.3)	6.2 (4.8-7.9)	10.6 (8.8-12.6)	5.0 (4.2-6.1)	6.4 (5.4-7.5)	10.0 (8.8-11.4)
2014	4.6 (3.4-6.0)	5.5 (4.3-7.0)	9.9 (8.2-11.8)	4.7 (3.9-5.7)	6.3 (5.3-7.4)	10.4 (9.1-11.8)
2015	5.7 (4.5-7.2)	7.1 (5.7-8.6)	11.3 (9.6-13.2)	5.9 (5.0-6.9)	7.4 (6.4-8.4)	11.9 (10.6-13.2)
2016	5.2 (4.1-6.5)	7.5 (6.2-8.9)	10.9 (9.3-12.6)	5.1 (4.3-6.0)	7.0 (6.1-8.0)	11.7 (10.5-13.0)
2017	5.2 (4.1-6.4)	7.4 (6.2-8.8)	10.6 (9.2-12.2)	5.1 (4.3-6.0)	7.0 (6.0-8.0)	11.5 (10.3-12.8)

Table S5. Univariable regression analyses to test for characteristics associated with antidepressant or anticonvulsant prescription

	Amitriptyline		Nortriptyline		Duloxetine		Gabapentin		Pregabalin	
	n (%)	OR (95% CI)	n (%)	OR (95% CI)	n (%)	OR (95% CI)	n (%)	OR (95% CI)	n (%)	OR (95% CI)
Age category										
30-39	86 (3.3)	1	13 (0.5)	1	26 (1.0)	1	15 (0.6)	1	67 (2.5)	1
40-49	685 (5.7)	**1.80 (1.43-2.26)**	107 (0.9)	1.82 (1.02-3.23)	126 (1.0)	1.07 (0.70-1.63)	125 (1.0)	**1.84 (1.08-3.15)**	429 (3.6)	**1.42 (1.10-1.85)**
50-59	1863 (5.7)	**1.79 (1.43- 2.23)**	275 (0.8	1.71 (0.98-2.98)	301 (0.9)	0.93 (0.62-1.39)	402 (1.2)	**2.17 (1.29-3.64)**	1234 (3.8)	**1.50 (1.17-1.93)**
60-69	2494 (5.1)	**1.60 (1.29- 1.99)**	462 (0.9)	**1.93 (1.11-3.36)**	300 (0.6)	**0.62 (0.41-0.93)**	675 (1.4)	**2.45 (1.47-4.10)**	1905 (3.9)	**1.56 (1.22-2.00)**
70-79	2361 (5.8)	**1.82 (1.47-2.27)**	549 (1.3)	**2.76 (1.59-4.79)**	270 (0.7)	0.67 (0.45-1.00)	590 (1.4)	**2.57 (1.54-4.29)**	1794 (4.4)	**1.77 (1.38-2.26)**
80-89	1248 (5.3)	**1.65 (1.32-2.07)**	365 (1.5)	**3.17 (1.82-5.51)**	133 (0.6)	**0.57 (0.37-0.87)**	295 (1.2)	**2.21 (1.31-3.72)**	868 (3.7)	**1.46 (1.14-1.88)**
> 90	126 (3.6)	1.04 (0.79-1.38)	39 (1.0)	**2.14 (1.14-4.02)**	9 (0.2)	**0.24 (0.11-0.52)**	20 (0.5)	0.95 (0.48-1.85)	85 (2.3)	0.90 (0.65-1.24)
Sex										
Female	7237 (6.3)	1	1371 (1.3)	1	862 (0.8)	1	1495 (1.4)	1	4570 (4.3)	1
Male	2202 (3.6)	**0.56 (0.53-0.59)**	439 (0.8)	**0.60 (0.54-0.67)**	303 (0.5)	**0.66 (0.58-0.76)**	627 (1.1)	**0.79 (0.72-0.87)**	1812 (3.2)	**0.84 (0.79-0.89)**
Joint affected										
Spine	1138 (6.2)	1	207 (1.2)	1	131 (0.8)	1	196 (1.1)	1	739 (4.3)	1
Hip	1256 (4.2)	**0.65 (0.60-0.71)**	277 (1.0)	**0.83 (0.69-0.99)**	166 (0.6)	**0.79 (0.62-0.99)**	348 (1.3)	1.10 (0.93-1.32)	868 (3.1)	**0.76 (0.69-0.84)**
Knee	2043 (4.3)	**0.66 (0.62-0.72)**	387 (0.9)	**0.71 (0.60-0.85)**	230 (0.5)	**0.67 (0.54-0.83)**	543 (1.2)	1.06 (0.90-1.25)	1363 (3.0)	**0.73 (0.67-0.80)**

	Amitriptyline		Nortriptyline		Duloxetine		Gabapentin		Pregabalin	
	n (%)	OR (95% CI)	n (%)	OR (95% CI)	n (%)	OR (95% CI)	n (%)	OR (95% CI)	n (%)	OR (95% CI)
Other peripheral joints	1957 (4.8)	**0.75 (0.70-0.81)**	362 (1.0)	**0.80 (0.67-0.95)**	250 (0.7)	0.87 (0.70-1.08)	305 (0.8)	**0.71 (0.59-0.85)**	1238 (3.3)	**0.76 (0.69-0.83)**
2 or more joints	3045 (7.9)	1.29 (1.20-1.38)	577 (1.6)	1.32 (1.13-1.55)	388 (1.1)	**1.41 (1.15-1.71)**	730 (2.0)	**1.78 (1.52-2.08)**	2174 (6.0)	**1.42 (1.30-1.54)**
MSD										
No MSD	1373 (2.3)	1	322 (0.6)	1	198 (0.3)	1	352 (0.6)	1	802 (1.4)	1
Upper extremity	240 (3.0)	**1.32 (1.15-1.53)**	60 (0.8)	**1.43 (1.08-1.88)**	32 (0.4)	1.24 (0.85-1.80)	66 (0.9)	**1.44 (1.10-1.87)**	190 (2.5)	**1.83 (1.56-2.15)**
Lower extremity	718 (4.0)	**1.85 (1.69-2.03)**	135 (0.8)	**1.46 (1.19-1.78)**	73 (0.4)	1.28 (0.98-1.68)	200 (1.2)	**1.98 (1.67-2.36)**	456 (2.7)	**2.00 (1.78-2.25)**
Neck/back	690 (5.5)	**2.54 (2.31-2.79)**	157 (1.3)	**2.43 (2.01-2.94)**	90 (0.8)	**2.26 (1.76-2.90)**	154 (1.3)	**2.18 (1.80-2.64)**	519 (4.5)	**3.30 (2.95-2.69)**
Other MSD	485 (4.2)	**1.84 (1.65- 2.05)**	105 (1.0)	**1.74 (1.39-2.17)**	49 (0.5)	1.32 (0.96-1.80)	110 (1.0)	**1.67 (1.34-2.07)**	278 (2.6)	**1.86 (1.62-2.14)**
≥2 MSD	5933 (9.1)	**4.30 (4.05-4.58)**	1031 (1.7)	**3.11 (2.74-3.53)**	723 (1.2)	**3.53 (3.02-4.14)**	1240 (2.1)	**3.43 (3.05-3.86)**	4137 (6.9)	**5.24 (4.85-5.66)**

MSD=musculoskeletal disorders. Values in bold are statistically significant ($p<0.05$).

Table S6. Prescription rates per joint (Total cohort)

Amitriptyline

Year	Spinal OA		Hip OA		Knee OA		Other peripheral OA		≥2 joints	
	First (95% CI)	Episodic (95% CI)	First (95% CI)	Episodic (95% CI)	First (95% CI)	Episodic (95% CI)	First (95% CI)	Episodic (95% CI)	First (95% CI)	Episodic (95% CI)
2008	9.5 (5.1-16.3)	16.8 (10.8-24.7)	8.1 (4.9-12.7)	12.9 (8.8-18.2)	4.7 (2.7-7.6)	8.2 (5.6-11.8)	7.1 (4.3-10.9)	9.9 (6.7-14.2)	10.9 (7.9-14.8)	15.9 (12.3-20.2)
2009	11.2 (7.2-16.6)	18.8 (13.1-26.1)	5.0 (3.0-7.8)	8.4 (5.8-11.7)	6.6 (4.7-9.1)	8.8 (6.6-11.5)	8.1 (5.7-11.1)	10.5 (7.9-13.7)	10.8 (8.3-13.8)	15.8 (13.0-19.2)
2010	12.4 (8.7-17.1)	19.9 (15.3-25.4)	7.1 (5.0-9.8)	10.8 (8.2-14.0)	7.2 (5.4-9.3)	12.0 (9.8-14.6)	8.9 (6.8-11.5)	11.9 (9.5-14.7)	11.6 (9.3-14.1)	18.9 (16.2-22.0)
2011	11.7 (8.6-15.5)	16.3 (12.8-20.5)	7.6 (5.7-10.0)	11.8 (9.4-14.5)	8.8 (7.1-10.8)	13.0 (10.9-15.3)	9.3 (7.4-11.5)	14.0 (11.7-16.6)	11.6 (9.7-13.8)	17.6 (15.4-20.1)
2012	12.3 (9.5-15.7)	18.0 (14.8-21.7)	8.3 (6.5-10.4)	12.9 (10.7-15.3)	8.9 (7.4-10.7)	14.5 (12.6-16.6)	8.9 (7.2-10.7)	15.0 (13.0-17.3)	12.9 (11.1-14.9)	21.1 (19.0-23.5)
2013	12.7 (9.9-16.2)	20.00 (16.6-23.9)	8.2 (6.4-10.3)	13.0 (10.8-15.5)	9.5 (7.9-11.2)	14.7 (12.8-16.8)	9.3 (7.6-11.2)	17.2 (15.0-19.6)	13.0 (11.2-15.0)	22.8 (20.6-25.3)
2014	13.0 (10.3-16.3)	23.6 (20.0-27.6)	8.2 (6.5-10.2)	12.7 (10.6-15.0)	8.3 (6.9-9.9)	13.8 (12.1-15.8)	9.3 (7.7-11.1)	16.6 (14.6-18.8)	15.0 (13.1-17.1)	23.8 (21.6-26.2)
2015	13.9 (11.3-17.0)	22.3 (19.1-25.9)	8.7 (7.1-10.7)	13.5 (11.5-15.8)	8.4 (7.1-9.9)	13.7 (12.1-15.5)	9.3 (7.9-11.0)	15.8 (13.9-17.8)	14.0 (12.3-15.9)	24.0 (21.8-26.2)
2016	10.2 (8.1-12.7)	19.0 (16.3-22.1)	7.7 (6.2-9.4)	12.7 (10.9-14.7)	7.0 (5.9-8.2)	12.5 (11.1-14.1)	7.8 (6.6-9.2)	13.8 (12.2-15.5)	12.7 (11.1-14.5)	22.6 (20.6-24.7)
2017	11.4 (9.2-14.0)	19.5 (16.7-22.5)	8.3 (6.8-10.0)	12.4 (10.7-14.4)	6.5 (5.5-7.7)	11.9 (10.5-13.3)	8.3 (7.0-9.7)	14.7 (13.1-16.4)	10.2 (8.7-11.8)	19.4 (17.6-21.4)

Nortriptyline

Year	Spinal OA		Hip OA		Knee OA		Other peripheral OA		≥2 joints	
	First (95% CI)	Episodic (95% CI)	First (95% CI)	Episodic (95% CI)	First (95% CI)	Episodic (95% CI)	First (95% CI)	Episodic (95% CI)	First (95% CI)	Episodic (95% CI)
2008	3.4 (1.1-7.9)	3.4 (1.1-7.8)	1.2 (0.3-3.6)	1.6 (0.4-4.1)	1.7 (0.6-3.6)	1.9 (0.8-4.0)	2.0 (0.7-4.3)	2.6 (0.9-4.8)	2.6 (1.3-4.7)	3.6 (2.0-5.9)
2009	3.0 (1-2-6.2)	3.8 (1.5-7.7)	2.2 (1.0-4.2)	3.4 (1.9-5.8)	1.2 (0.5-2.4)	1.5 (0.7-2.8)	2.4 (1.2-4.2)	2.6 (1.4-4.4)	2.0 (1.1-3.4)	2.6 (1.5-4.1)
2010	3.5 (1.7-6.2)	3.7 (1.9-6.5)	2.0 (1.0-3.6)	3.1 (1.8-5.0)	2.3 (1.4-3.6)	3.5 (2.3-5.0)	2.3 (1.3-3.8)	2.6 (1.5-4.1)	2.3 (1.4-3.6)	3.5 (2.4-4.9)
2011	3.6 (2.1-5.9)	4.5 (2.7-6.9)	2.8 (1.7-4.3)	3.8 (2.5-5.5)	1.8 (1.1-2.8)	3.1 (2.1-4.3)	1.9 (1.1-3.0)	2.3 (1.5-3.5)	2.2 (1.4-3.2)	3.2 (2.3-4.3)
2012	3.5 (2.2-5.4)	4.5 (2.9-6.5)	3.1 (2.0-4.4)	3.6 (2.5-5.1)	2.1 (1.4-2.9)	2.9 (2.1-3.9)	2.4 (1.6-3.4)	2.7 (1.9-3.8)	3.0 (2.2-4.0)	3.4 (2.6-4.4)
2013	1.7 (0.8-3.1)	2.2 (1.2-3.7)	1.6 (0.9-2.6)	2.0 (1.2-3.1)	1.6 (1.0-2.4)	2.3 (1.6-3.2)	1.5 (0.9-2.3)	2.0 (1.3-3.0)	2.1 (1.5-2.9)	2.6 (1.8-3.5)
2014	2.0 (1.1-3.4)	2.4 (1.4-3.9)	1.5 (0.8-2.4)	1.9 (1.1-2.9)	1.7 (1.1-2.5)	2.8 (2.0-3.7)	1.3 (0.8-2.1)	1.8 (1.2-2.7)	3.0 (2.2-3.9)	3.7 (2.9-4.8)
2015	2.2 (1.3-3.5)	3.8 (2.6-5.4)	1.4 (0.8-2.2)	2.1 (1.4-3.1)	1.5 (1.0-2.2)	2.3 (1.7-3.0)	1.8 (1.2-2.6)	2.6 (1.9-3.5)	2.8 (2.1-3.6)	3.8 (3.0-4.8)
2016	2.0 (1.2-3.2)	2.9 (1.9-4.3)	2.0 (1.4-3.0)	2.7 (1.9-3.7)	1.7 (1.2-2.3)	2.3 (1.8-3.0)	2.3 (1.7-3.1)	3.2 (2.5-4.1)	3.4 (2.7-4.3)	4.3 (3.5-5.3)
2017	2.7 (1.7-3.9)	4.0 (2.8-5.4)	2.7 (1.9-3.7)	3.6 (2.6-4.7)	2.5 (1.9-3.2)	3.3 (2.6-4.1)	3.2 (2.5-4.1)	4.2 (3.4-5.2)	4.2 (3.4-5.2)	5.5 (4.6-6.6)

Duloxetine

Year	Spinal OA		Hip OA		Knee OA		Other peripheral OA		≥2 joints	
	First (95% CI)	Episodic (95% CI)	First (95% CI)	Episodic (95% CI)	First (95% CI)	Episodic (95% CI)	First (95% CI)	Episodic (95% CI)	First (95% CI)	Episodic (95% CI)
2008	2.7 (0.7-6.9)	2.7 (0.7-6.9)	1.2 (0.2-3.5)	1.2 (0.2-3.5)	1.9 (0.8-4.0)	1.9 (0.8-4.0)	1.0 (0.2-2.9)	1.0 (0.2-2.9)	2.4 (1.1-4.4)	2.4 (1.1-4.4)
2009	2.6 (0.9-5.6)	3.8 (1.5-7.7)	1.0 (0.3-2.5)	1.0 (0.3-2.5)	1.2 (0.5-2.4)	1.8 (0.9-3.2)	2.0 (1.0-3.7)	2.2 (1.1-3.9)	3.0 (1.9-4.7)	3.2 (2.0-4.8)
2010	2.5 (1.1-4.9)	2.8 (1.3-5.3)	2.0 (1.0-3.6)	2.2 (1.1-3.8)	0.6 (0.2-1.4)	1.0 (0.4-1.9)	1.2 (0.5-2.3)	1.4 (0.7-2.6)	2.7 (1.7-3.9)	3.4 (2.3-4.8)
2011	2.0 (0.9-3.8)	2.7 (1.4-4.7)	1.1 (0.5-2.2)	1.6 (0.8-2.9)	1.5 (0.8-2.4)	1.8 (1.1-2.8)	2.1 (1.3-3.3)	2.6 (1.7-3.9)	2.5 (1.7-3.5)	3.6 (2.6-4.8)
2012	1.2 (0.5-2.4)	2.6 (1.5-4.3)	1.9 (1.1-3.0)	2.0 (1.2-3.1)	1.3 (0.8-2.0)	1.6 (1.0-2.3)	1.9 (1.2-2.8)	2.6 (1.8-3.6)	1.3 (0.8-1.9)	2.2 (1.6-3.1)
2013	2.0 (1.0-3.5)	3.3 (2.0-5.1)	0.5 (0.2-1.2)	0.7 (0.3-1.5)	0.8 (0.4-1.4)	1.1 (0.6-1.7)	1.0 (0.5-1.7)	1.7 (1.1-2.6)	1.6 (1.0-2.3)	2.2 (1.5-3.0)
2014	0.8 (0.2-1.8)	1.8 (0.9-3.2)	1.4 (0.8-2.3)	2.0 (1.3-3.1)	1.0 (0.6-1.7)	1.3 (0.8-2.0)	1.1 (0.6-1.7)	2.0 (1.3-2.8)	1.6 (1.1-2.3)	2.7 (2.0-3.5)
2015	0.9 (0.4-1.9)	2.0 (1.2-3.3)	0.7 (0.3-1.3)	1.3 (0.7-2.1)	1.0 (0.6-1.5)	1.6 (1.1-2.3)	1.0 (0.5-1.5)	1.8 (1.2-2.5)	1.6 (1.0-2.3)	3.0 (2.3-3.8)
2016	1.1 (0.5-2.0)	1.6 (0.9-2.7)	1.2 (0.7-1.9)	1.5 (0.9-2.3)	0.8 (0.5-1.2)	1.3 (0.9-1.9)	1.4 (0.9-2.0)	2.1 (1.6-2.9)	1.5 (1.0-2.1)	2.7 (2.1-3.5)
2017	0.9 (0.4-1.7)	1.6 (0.9-2.6)	1.1 (0.6-1.8)	1.5 (0.9-2.3)	1.0 (0.6-1.4)	1.5 (1.1-2.1)	1.0 (0.7-1.6)	1.8 (1.3-2.4)	1.5 (1.0-2.1)	2.5 (1.9-3.3)

Gabapentin

Year	Spinal OA		Hip OA		Knee OA		Other peripheral OA		≥2 joints	
	First (95% CI)	Episodic (95% CI)	First (95% CI)	Episodic (95% CI)	First (95% CI)	Episodic (95% CI)	First (95% CI)	Episodic (95% CI)	First (95% CI)	Episodic (95% CI)
2008	4.1 (1.5-9.0)	6.7 (3.2-12.3)	0.4 (0.0-2.3)	3.6 (1.7-6.9)	0.8 (0.2-2.4)	1.4 (0.4-3.2)	1.7 (0.5-3.9)	2.6 (1.1-5.2)	4.1 (2.4-6-6)	5.5 (3.5-8.2)
2009	2.2 (0.7-5.1)	5.4 (2.6-9.9)	2.5 (1.2-4.6)	2.5 (1.2-4.5)	1.5 (0.7-2.8)	2.5 (1.4-4.0)	1.8 (0.8-3.4)	2.8 (1.5-4.7)	2.8 (1.6-4.4)	3.8 (2.4-5.6)
2010	2.2 (0.9-4.6)	4.3 (2.4-7.3)	2.4 (1.3-4.1)	3.7 (2.2-5.7)	1.8 (1.0-3.0)	2.2 (1.3-3.4)	1.6 (0.8-2.9)	2.0 (1.1-3.4)	2.7 (1.7-4.0)	3.7 (2.6-5.2)
2011	3.0 (1.6-5.1)	4.2 (2.6-6.6)	1.3 (0.6-2.4)	2.1 (1.1-3.4)	2.5 (1.6-3.6)	3.8 (2.7-5.1)	1.6 (0.9-2.7)	2.4 (1.5-3.6)	2.8 (1.9-3.9)	4.0 (2.9-5.2)
2012	1.0 (0.4-2.2)	2.1 (1.1-3.7)	2.6 (1.7-3.9)	3.1 (2.1-4.4)	2.1 (1.4-3.0)	3.0 (2.2-4.0)	1.7 (1.0-2.5)	2.0 (1.3-3.0)	3.7 (2.8-4.8)	5.3 (4.2-6.5)
2013	1.7 (0.8-3.1)	2.8 (1.6-4.5)	1.3 (0.7-2.3)	2.1 (1.3-3.3)	2.1 (1.4-3.0)	3.4 (2.5-4.5)	1.3 (0.8-2.2)	1.9 (1.3-2.9)	2.5 (1.7-3.4)	3.7 (2.8-4.7)
2014	2.5 (1.4-4.0)	3.2 (2.0-4.9)	2.9 (1.9-4.1)	4.0 (2.9-5.4)	3.3 (2.4-4.3)	4.0 (3.1-5.1)	1.4 (0.9-2-2)	1.7 (1.1-2.6)	3.9 (3.0-4.9)	5.6 (4.5-6.8)
2015	2.2 (1.3-3.5)	3.2 (2.0-4.7)	3.7 (2.7-4.9)	4.4 (3.3-5.8)	3.7 (2.9-4.7)	4.5 (3.7-5.6)	1.0 (0.6-1.6)	1.8 (1.2-2.6)	4.4 (3.5-5.4)	6.5 (5.4-7.7)
2016	1.7 (0.9-2.8)	2.4 (1.5-3.6)	4.1 (3.1-5.3)	5.0 (3.9-6.3)	3.0 (2.3-3.8)	4.2 (3.4-5.2)	1.8 (1.3-2.5)	2.4 (1.8-3.2)	4.9 (4.0-5.9)	6.8 (5.7-7.9)
2017	2.4 (1.5-3.6)	2.5 (1.6-3.7)	3.9 (3.0-5.1)	4.6 (3.6-5.9)	3.3 (2.6-4.1)	4.1 (3.3-5.0)	1.5 (1.0-2.1)	2.3 (1.7-3.1)	4.0 (3.1-5.0)	5.5 (4.6-6.6)

Pregabalin

Year	Spinal OA		Hip OA		Knee OA		Other peripheral OA		≥2 joints	
	First (95% CI)	Episodic (95% CI)	First (95% CI)	Episodic (95% CI)	First (95% CI)	Episodic (95% CI)	First (95% CI)	Episodic (95% CI)	First (95% CI)	Episodic (95% CI)
2008	5.5 (2.4-10.8)	6.0 (2.8-11.4)	6.1 (3.4-10.1)	8.5 (5.2-12.9)	2.5 (1.1-4.7)	3.0 (1.5-5.4)	6.0 (3.6-9.5)	7.3 (4.6-11.0)	9.0 (6.3-12.4)	10.2 (7.4-13.7)
2009	5.6 (3.0-9.6)	9.1 (5.3-14.6)	4.8 (2.9-7.4)	5.4 (3.4-8.2)	5.0 (3.4-7.1)	6.5 (4.7-8.9)	6.9 (4.8-9.6)	8.5 (6.2-11.5)	8.2 (6.2-10.8)	10.3 (8.0-13.0)
2010	8.0 (5.2-11.8)	10.9 (7.6-15.1)	4.7 (3.0-6.9)	5.3 (3.6-7.6)	4.2 (2.9-5.8)	5.8 (4.2-7.6)	3.2 (2.0-4.9)	4.7 (3.3-6.6)	8.6 (6.8-10.8)	12.5 (10.3-15.0)
2011	9.7 (7.0-13.1)	12.5 (9.4-16.2)	5.4 (3.8-7.3)	7.5 (5.7-9.8)	5.7 (4.4-7.3)	7.5 (6.0-9.3)	6.7 (5.1-8.6)	8.0 (6.3-10.0)	9.7 (8.0-11.6)	12.6 (10.7-14.7)
2012	9.8 (7.4-12.7)	12.4 (9.7-15.5)	7.1 (5.5-9.0)	9.4 (7.6-11.6)	6.8 (5.5-8.3)	8.8 (7.4-10.5)	8.6 (7.0-10.4)	10.5 (8.8-12.5)	10.9 (9.3-12.7)	14.3 (12.5-16.3)
2013	8.4 (6.2-11.1)	11.8 (9.2-14.9)	8.9 (7.1-11.0)	11.1 (9.1-13.4)	6.1 (4.9-7.5)	8.6 (7.2-10.2)	7.5 (6.1-9.2)	11.3 (9.5-13.3)	12.7 (11.0-14.6)	17.1 (15.1-19.2)
2014	9.6 (7.3-12.4)	13.9 (11.2-17.1)	8.5 (6.7-10.5)	10.7 (8.8-12.9)	6.1 (5.0-7.5)	8.8 (7.4-10.4)	7.2 (5.8-8.7)	9.7 (8.1-11.4)	12.8 (11.1-14.7)	17.6 (15.7-19.7)
2015	11.5 (9.2-14.3)	15.3 (12.7-18.3)	7.2 (5.8-9.0)	9.6 (7.9-11.5)	7.2 (6.1-8.6)	9.7 (8.4-11.2)	6.3 (5.1-7.7)	10.1 (8.6-11.7)	13.0 (11.4-14.7)	17.8 (15.9-19.7)
2016	9.8 (7.8-12.1)	13.3 (11.0-15.9)	8.1 (6.6-9.8)	11.3 (9.6-13.2)	7.3 (6.2-8.6)	11.4 (10.0-12.8)	8.3 (7.1-9.7)	12.2 (10.7-13.8)	11.9 (10.4-13.5)	18.4 (16.6-20.3)
2017	8.8 (7.0-11.0)	13.5 (11.3-16.1)	7.3 (5.9-8.9)	11.1 (9.5-13.0)	9.1 (7.9-10.4)	13.2 (11.8-14.7)	7.3 (6.2-8.6)	11.1 (9.8-12.6)	13.9 (12.3-15.7)	19.7 (17.8-21.7)

CHAPTER 5

Amitriptyline for musculoskeletal complaints: a systematic review

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ABSTRACT

Background

The role of amitriptyline in musculoskeletal pain is not as clearly defined as in classical neuropathic pain conditions.

Objective

To assess the efficacy and effectiveness of amitriptyline in the treatment of pain in musculoskeletal complaints.

Methods

An extensive search (including Medline, Embase and Web of Science) was made up to April 2016 for randomised controlled trials on amitriptyline in musculoskeletal complaints compared to placebo, usual care, or other analgesic use. Included studies were assessed for risk of bias. Outcomes of interest were pain reduction and function improvement.

Results

Of the 2066 articles identified, seven were finally included. These studies were performed in patients with low back pain (4), rheumatoid arthritis (2), and patients with arm pain from repetitive use (1). No meta-analysis was performed due to clinical heterogeneity of the studies. Two studies with low risk of bias found positive results. One study found that 50 mg/day of amitriptyline [Visual Analogue Scale (VAS) -3.9 points] resulted in a significantly greater reduction in pain than treatment with pregabalin 600 mg/day (VAS -2.9 points) and improved function (improvement on the Oswestry Disability Index >20%: 65% vs. 49.5%). Amitriptyline improved function in arm pain compared to placebo (Upper Extremity Function Scale: -3.9 vs. 0.8). A similar amount of side-effects occurred in the amitriptyline and the comparison groups.

Conclusion

Few studies have evaluated the use of amitriptyline in musculoskeletal complaints. Although amitriptyline may be effective in musculoskeletal complaints, more studies are required to establish for whom amitriptyline works better than other analgesics.

INTRODUCTION

Chronic musculoskeletal disorders are a common problem among patients visiting a general practitioner (GP). A Dutch database of GP records showed that ≥ 50% of the patients visited their GP with a new musculoskeletal complaint during a 10-year period[1]. In the UK, 1 in 7 of the consultations with a GP concerned musculoskeletal complaints[2]. More importantly, these disorders are the major cause of chronic pain. An European study on the prevalence of chronic pain showed that almost 50% of the patients had back complaints and ≥ 40% of the patients had joint pain[3].

The use of standard analgesics is adequate for most patients with musculoskeletal complaints, but sufficient pain relief is not always obtained. Especially patients with chronic pain may benefit from additional neuropathic pain medication. Although musculoskeletal complaints do not belong to the classic neuropathic syndromes, centrally-acting agents like antidepressants and anticonvulsants ($\alpha_2\delta$-ligands) can be helpful because of the pathophysiological changes in pain processing in the central nervous system (CNS; central sensitization) described in patients with chronic pain[4]. Central sensitization can occur due to prolonged peripheral nociceptive input, which can lead to hyperexcitability of pain circuits in the CNS. A neuropathic pain component is present in 20-35% of the patients with low back pain[5 6] and in 28-45% of patients with osteoarthritis[7-9].

In Finland, antidepressants accounted for 1.9% of the prescriptions for musculoskeletal complaints and for 3% in the USA[10 11]. The NICE guidelines for treatment of neuropathic pain in adults in a non-specialist setting, recommend duloxetine, amitriptyline, gabapentin and pregabalin as first choices[12], while the Dutch GP guidelines recommend amitriptyline as a first-line neuropathic agent[13]. The target points of these analgesics in the CNS differ for antidepressants and anticonvulsants[14]. We chose to focus on antidepressants; moreover, as the use of duloxetine in musculoskeletal pain is reviewed elsewhere[15 16], we focused on amitriptyline.

The role of amitriptyline in musculoskeletal disorders is not as well defined as in classic neuropathic pain syndromes. Therefore, the aim of this review is to assess the efficacy and effectiveness of amitriptyline in the treatment of pain in musculoskeletal complaints.

METHODS

Eligibility criteria

Included in this study were randomised controlled trials (RCTs) on the use of amitriptyline for musculoskeletal disorders. Studies had to compare any dosage of amitriptyline to

placebo, usual care, or standard analgesic use. We defined usual care as physiotherapy, education, other nonsurgical interventions, or 'wait and see'. Analgesics allowed as comparator were paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs), opiates, and other neuropathic pain medication. Moreover, corticosteroid injections were permitted as comparison. No restrictions on the duration of therapy were applied. Articles published in English, German, French, Spanish, Italian, Scandinavian or Dutch were eligible. Outcomes of interest were pain reduction and improvement of function. Studies on fibromyalgia were excluded as these were recently evaluated in a Cochrane review (July 2015)[17]. Also excluded were RCTs evaluating the use of amitriptyline in classic neuropathic pain (e.g. diabetic polyneuropathy, HIV-associated neuropathy, post-herpetic neuralgia, and phantom pain).

Search strategy

An extensive search (including Medline, Embase, Web of Science and Cochrane) up to April 2016 was made with the help of a medical librarian. The main keywords were amitriptyline and musculoskeletal complaints (see Supplementary Data Table S1 for all search terms used). In addition, references of the included articles were screened, and to find unpublished studies the Clinical Trials Search Portal (which includes ClinicalTrials.gov and the EU Clinical Trials Register amongst others) was searched.

Study selection

Two independent reviewers (JD, DS) screened the title and abstract for potentially eligible articles. Then, full articles were retrieved and assessed for eligibility. Any disagreements were resolved during a consensus meeting. If no consensus was reached, a third reviewer (SBZ) made the final decision.

Methodological quality assessment

Two independent reviewers assessed the methodological quality of the selected articles. Any disagreements were discussed in a consensus meeting. The methodological quality of the selected articles was assessed using a checklist based on the Cochrane Collaboration's tool for assessing risk of bias[18]. The following items related to the risk of bias were scored: 1) selection bias (random sequence generation and allocation concealment), 2) performance bias (blinding participants and care providers), 3) detection bias (blinding outcome assessors), 4) attrition bias (drop-out rates, number of participants analysed in the group of allocation), 5) reporting bias (selective reporting), and 6) other bias (comparability of study groups at baseline, co-interventions and compliance to treatment).

Each item on the checklist was rated as *Yes* (indicating low risk of bias), *No* (Indicating high risk of bias) or *Unclear* (indicating unclear, or unknown risk of bias). We defined studies with a low risk of bias on the items *allocation concealment* and *participants ana-*

lysed in the group of allocation, as being studies with a low risk of bias. These two items can affect our outcomes of interest (reducing pain and improvement of function) the most[19]. Blinding of outcome assessors is less important, since in most studies two active treatments are compared.

Data extraction

Data extraction was performed by two reviewers using a standardised form. Disagreements were resolved during a consensus meeting. For each article we extracted data using the PICO approach.

- *Participants*: complaint, duration of the complaint, mean age of the patients, clinical setting and baseline pain intensity.
- *Interventions*: dosage of amitriptyline, duration of the treatment.
- *Comparison*: to placebo, usual care or analgesic use.
- *Outcomes:* pain reduction, improvement of function adverse events and loss to follow-up (when mentioned).

RESULTS

Study selection

The initial search yielded 3816 articles; after removing duplicates, 2066 articles remained. No potentially eligible studies were identified by searching for unpublished literature. After screening the title and abstract, the full-texts of 24 articles were assessed for eligibility. Finally, seven articles were included in this review (Figure 1).

Study characteristics

The characteristics of the included studies (all RCTs) are presented in Table 1. Four studies evaluated amitriptyline in low back pain; three in chronic low back pain (CLBP)[20-22] and one in acute low back pain (ALBP)[23]. One study examined amitriptyline in persistent arm pain due to repetitive use[24]. Another two studies assessed the use of amitriptyline in rheumatoid arthritis (RA)[25 26]. Only one study on CLBP reported whether a neuropathic pain component was present; of the 200 patients, 95 had backache with radiculopathy[22].

Amitriptyline was compared with different interventions. CLBP studies compared amitriptyline with buproprione[20], fluoxetine[21] or pregabalin[22]. For ALBP, amitriptyline was compared with paracetamol[23]. In persistent arm pain[24] and one study on RA[26], amitriptyline was compared with placebo. The second study on RA evaluated the use of amitriptyline in comparison to placebo, desipramine and trazodone; this study had a cross-over design in which patients received all four interventions[25]. Dosage of amitriptyline ranged from 25 mg/day for persistent arm pain to a maximum of 150 mg/day

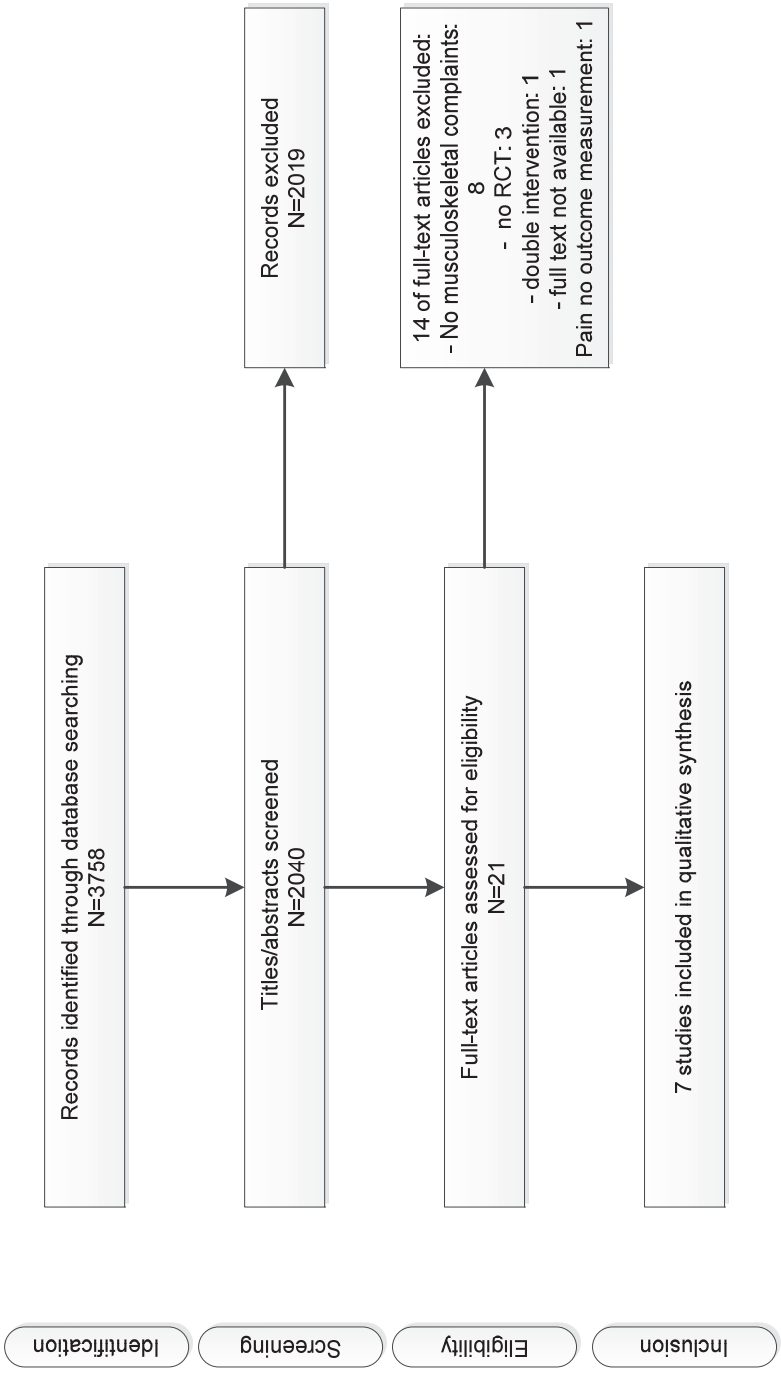

Figure 1. Flowchart inclusion

Table 1. Characteristics of the included studies (n=7)

Study (year)	Complaint	Sample size (n)	Mean age, years (S.D.)	Setting	Duration of disease	Dosage of AMT	Comparator	Duration of treatment (weeks)	Loss to follow-up
Farajirad (2013)[20]	CLBP	60	35.6 (9.5)	Outpatient neurosurgery clinic	NR	Initial 25 mg/ day, added 25 mg/day every 3 days up to 150 mg/day within 2 weeks	Bupropione 150 mg/day in week 1, 300 mgs/day in second week	8	NR
Schreiber (2001)[21]	LBP/ Whiplash	40	52.6	Pain clinic of a large tertiary center	AMT: 8 (4-18) months, FLX 8.5 (3-38) months	Start at 25 mg/ day, increase every other day by 25 mg/day, max 75 mg/day	Fluoxetine: 20 mg/day	6	12.5% (3AMT/ 2 FLX)
Kalita (2014)[22]	CLBP	200	41.5 (11.1)	Department of Neurology	35 (4-360) months	Initial 12.5 mg (2 weeks), 25 mg (4 weeks), 50 mg (8 weeks)	Pregabalin: 150 mg/day for 2 weeks, 300 mg/ day for 4 weeks, 600 mg/day after 6 weeks	14	15% (15 AMT /15 PGB)
Stein (1996)[23]	ALBP	45	36.4 (7.3)	Emergency patients	61.3 (SD 56.3) days	Start at 37.5 mg/ day to 150 mg/ day in 4 days	Paracetamol 2000 mg/ day	5	13.3 % (3 AMT/3 PCM)
Goldman (2010)[24]	Persistent arm pain	118	37.5 (11.2)	Advertisement and referral	27% AMT and 36% PLA had complaints less than 1 year	25 mg	Placebo	6	10.2% (8 AMT/ 4 PLA)

Study (year)	Complaint	Sample size (n)	Mean age, years (S.D.)	Setting	Duration of disease	Dosage of AMT	Comparator	Duration of treatment (weeks)	Loss to follow-up
Frank (1988)[25]	RA	73	58.1 (9.2)	University hospital	NR	First 3 days 1.0 mg/kg/ day, afterwards 1.5 mg/kg/day. Older than 60 years: 1/2 dosage	Placebo; Desipramine :first 3 days 1.0 mg/kg/day, afterwards 1.5 mg/kg/day; Trazodone: first 3 days 1.5 mg/ kg/day 3.0 mg/ kg/day. Older than 60 years: 1/2 dosage	each intervention: 6 weeks, 1 week tapering and 1 week wash-out	36%
Grace (1985)[26]	RA	36	58.05	Urban rheumatic disease clinic, referred by their GP	NR	Start at 25 mg/ day, second week 50 mg/day, third week 75 mg/ week	Placebo	12	22.2 % (4 AMT/ 4 PLA)

ALBP acute low back pain, AMT amitriptyline, BUP bupropione, CI confidence interval, CLBP chronic low back pain, FLX fluoxetine, LBP low back pain, NR not reported, PCM paracetamol, PGB pregabalin, PLA placebo, RA rheumatoid arthritis

for ALBP and CLBP. All studies were conducted in secondary and tertiary care centres. In the study on repetitive arm pain, patients were also recruited through advertisements[24].

In all studies, primary outcome was the reduction of pain. In five studies pain was measured with a 10-point Visual Analogue Scale (VAS) or a 0-10 Numeric Rating Scale (NRS)[21-25]. The trial on RA (comparing amitriptyline with multiple interventions (cross-over design)) also evaluated pain on a 0-5 intensity scale in addition to the VAS[25]. The study on RA (with a placebo as comparator) measured pain on a 5-point scale[26]. The study on CLBP (comparing amitriptyline with bupropione) did not report which method was used to evaluate pain[20].

The secondary outcome, improvement of function, was reported in two studies[22 24]. The study on persistent arm pain evaluated arm function using the Upper Extremity Function Scale (UEFS); the total score ranges from 8-80, with higher scores indicating greater disability[27]. The study on CLBP (comparing amitriptyline with pregabalin) reported on function using the Oswestry Disability Index (ODI); this score ranges from 0-100% with a higher percentage indicating more impairment[28]. Follow-up ranged from 5-32 weeks.

Table 2 shows the risk of bias for each study. Two studies had a low risk of bias[22 24], and 5 studies did not report on the allocation of treatment or intention-to-treat analysis[20 21 23 25 26].

In the present study, the reviewers agreed on 78% of the items scored (Cohen's kappa 0.75)

Effectiveness: improvement of pain

One study with low risk of bias found a significant improvement of pain in the amitriptyline group between baseline and follow-up, and between the treatment groups, in favour of amitriptyline (Table 3)[22]. In this study on CLBP, 50 mg/day of amitriptyline reduced pain by 3.9 points (VAS 0-10), while 600 mg/day of pregabalin reduced pain by 2.9 points (VAS 0-10). Two studies, one on CLBP [20] and one on ALBP[23], found a significant improvement of pain with amitriptyline between baseline and follow-up; however, these studies found no difference between amitriptyline and bupriopione or paracetamol, respectively. In CLBP, treatment with 150 mg/day amitriptyline resulted in a pain score ≤ 2 in 50% of the patients, while at study start only 25% had a pain score ≤ 5[20]. In ALBP, 5 weeks of treatment with 150 mg/day of amitriptyline reduced pain by 4.83 points (VAS)[23].

The trial with the crossover design examining the effect of amitriptyline in comparison to different treatments, found that amitriptyline led to a significantly greater reduction in pain compared with baseline, placebo, trazodone or desipramine (on a 0-5 pain scale); however, no significant differences were found in pain reduction between the treatments when using the VAS[25].

Table 2. Methodological quality of the included studies (n=7)

Study (year)	Sequence generation	Allocation of treatment	Blinding of patients and personnel	Blinding of outcome assessors	Drop-out	Participant analysed in group of allocation	Selective outcome reporting	Similar groups at baseline	Co-inter-ventions	Industry involvement
Farajirad (2013)[20]	Low	Unclear	High	High	Unclear	Unclear	Unclear	Low	Low	Unclear
Schreiber (2001)[21]	Low	Unclear	High	Low	Low	Unclear	Unclear	Low	Low	Unclear
Kalita (2014)[22]	Low	Low	High	High	Low	Low	Unclear	Low	Low	Low
Stein (1996)[23]	Low	Unclear	Low	Unclear	Low	Unclear	Unclear	Low	Low	Unclear
Goldman (2010)[24]	Low	Low	Low	Low	Low	Low	Unclear	Low	Low	Low
Frank (1988)[25]	Low	Unclear	Low	Low	High	High	Unclear	Low	High	Unclear
Grace (1985)[26]	Low	Unclear	Low	Unclear	High	Unclear	Unclear	Low	Low	Unclear

Table 3. Data on outcome of the included studies (n=7)

Study (year)	Severity pain baseline AMT	Severity pain baseline comparator	Pain reduction AMT (CI)	Pain reduction comparator (CI)	Improvement of function
Farajirad (2013)[20]	< 5: 25%, <7.5: 50%, <8: 75%	NR	< 2: 50%*	NR	NR
Schreiber (2001)[21]	NR *(VAS 7.3[2])*	NR *(VAS 7.8[2])*	NR *(VAS -2.3[2])*	NR *(VAS -2.4[2])*	NR
Kalita (2014)[22]	VAS 6.7 (1.6)	VAS 6.7 (1.9)	VAS -3.9*[1]	VAS - 2.9*	ODI improvement >20%: AMT 65% and PGB 49.5%^
Stein (1996)[23]	VAS 7.48 (3.73)	VAS 7.94 (3.42)	VAS -4.83*	VAS -3.46*	NR
Goldman (2010)[24]	NRS 4.7 (1.8)	NRS 4.3 (1.8)	NRS - 0.7 (1.5)	NRS -0.4 (1.8)	UEFS: AMT -3.9, PLA -0.8^
Frank (1988)[25]	VAS 4.3; PP 1.9		VAS -0.5; PP-0.5***	PLA: VAS -0.3; PP -0.1 , TRA: -0.2; PP :0 , DES: VAS -0.3, PP -0.3	NR
Grace (1985)[26]	2.44 ^^	2.45 ^^	-0.94 ^^	-1.07 ^^	NR

AMT amitriptyline, DES desipramine, NR not reported, NRS Numeric Rating Scale for pain, ODI Oswestry Disability Index, PLA placebo, PP Present Pain Intensity (0-5 scale), TRA trazodone, UEFS upper extremity function scale, VAS Visual Analog Scale for pain *significant difference between baseline AMT and follow-up AMT, **significant difference between baseline comparator and follow-up comparator, ***significant difference between present pain baseline and placebo compared to amitriptyline, [1]significant difference between AMT and comparator follow-up, ^significant difference, [2]estimation, only reported in figure, ^^ Pain intensity rating [0 (no pain) to 4 (severe pain)]

Effectiveness: improvement of function

Two studies, both with a low risk of bias, reported on improvement of function[22 24]. Both studies found a significant increase at the end of treatment, but they compared amitriptyline with a different treatment (Table 3). Amitriptyline let to a significant improvement in arm function in patients with persistent arm pain compared with placebo, i.e. the Upper Extremity Function Scale (UEFS (8-80)[27] improved by 3.9 points compared to 0.8 points in the placebo group[24].

In CLBP, 65% of the patients in the amitriptyline group showed an improvement in the Oswestry Disability Index (ODI (by ≥20%; 10 points) compared to 49.5% of the patients in the pregabalin group (p=0.03)[22]. In absolute improvement of function no significant difference was found between the two different treatments.

Side-effects

No serious side-effects were reported in any of the studies. Adverse events occurred in all treatment groups and the prevalence of side-effects was relatively high. In 6 RCTs no significant difference was found between amitriptyline and the comparator. In the study on arm pain due to repetitive use, significantly more side-effects occurred in the amitriptyline group at the midpoint of the treatment period (after 3 weeks); however, this difference had disappeared by the end of the treatment period (after 6 weeks)[24]. In the crossover trial on RA, patients reported significantly more side-effects during treatment with amitriptyline than with a placebo or trazodone. These side-effects did not lead to dose reductions[25]. Frequently occurring side-effects during amitriptyline use were drowsiness, dry mouth and constipation (Table 4).

DISCUSSION

Summary

This systematic review assessed the effectiveness of amitriptyline in musculoskeletal complaints. We found four studies on amitriptyline in LBP, one on amitriptyline in persistent arm pain, and two studies on RA.

Overall, one study on CLBP[22] with low risk of bias found a significant improvement of pain with amitriptyline compared with pregabalin. Two studies with low risk of bias found a significant improvement of function when comparing amitriptyline with pregabalin in CLBP, or placebo in persistent arm pain[22 24]. In CLBP, the effect on function is regarded as clinically relevant since the minimal clinically important difference of the Oswestry Disability Index (ODI) ranges from 6-11 points[28-32]. In absolute improvement of function no significant difference was found between amitriptyline and pregabalin, though the clinically relevant difference occurred significantly more often with treat-

Table 4. Observed side-effects in the included studies (n=7)

Study (year)	Dosage of AMT	Comparator	Adverse events AMT (%)	Adverse events comparator (%)	Side-effect amitriptyline	Side-effects comparator
Farajirad (2013)[20]	150 mg/day	BUP 300 mg/day	AE 43%	30%	dry mouth, somnolence and constipation. 2 DC: 1 orthostatic hypotension, 1 nausea	nausea and insomnia (BUP), DC:0
Schreiber (2001)[21]	75 mg/day	FLX 20 mg/day	7.5% DC	5% DC	DC: 3; blurred vision, dry mouth, constipation and urinary retention	DC 2: nausea, diarrhoea and headache
Kalita (2014)[22]	50 mg/day	PGB 600 mg/day	DC 10.7% and AE 17.5	12.4% DC and 21.6% AE	9.7% drowsiness, 2.9% sedation, 1.9% unsteadiness, 1.9% vertigo	6.2% vertigo, 4.1% sedation, 1% dry mouth, 1% skin rash, 1% restlessness
Stein (1996)[23]	150 mg/day	PCM 2000 mg/day	AE 10%	0%	DC: 1 orthostatic hypotension, 1 urinary retention	DC: 0 due to side-effects
Goldman (2010)[24]	25 mg/day	PLA	AE 31%	22%	41% drowsiness, 2 DC due to side-effects	15% drowsiness
Frank (1988)[25]	1.5 mg/kg/day	PLA, DES, TRA	AE 40%, DC 2.7 %	PLA: AE 20% DC 1,3%, DES AE 51% DC 4.1%, TRA AE 33% DC 5.5%	NR	NR
Grace (1985)[26]	75 mg/day	PLA	DC 22.2%	DC 22.2%	DC: 1 drowsiness, 1 'groggy' feeling. 5 patients reduced dosage AMT to 50 mg/day due to side-effects	DC: 3 nausea and dyspepsia

AE adverse event, AMT amitriptyline, BUP bupropione, DC discontinued, DES desipramine, FLX fluoxetine, NR Not Reported, PCM Paracetamol, PGB pregabalin, PLA placebo, TRA trazodone

ment with amitriptyline compared with pregabalin. This clinically important difference is not as clearly defined for the Upper Extremity Function Scale (UEFS), but the improvement with amitriptyline compared to placebo is small. Overall, a similar amount of side-effects occurred in patients treated with amitriptyline and in patients treated with other analgesics; however, the prevalence of side-effects was relatively high in all studies. In chronic arm pain, patients reported more side-effects (especially drowsiness) after 3 weeks of treatment, which diminished by the end of the study period. This type of pattern is known for amitriptyline[33].

Strengths and limitations

Although we aimed to study the role of amitriptyline in musculoskeletal complaints in general, most of the included studies investigated the role of amitriptyline in LBP. Only one study investigated its use in chronic pain due to repetitive arm use, and two trials in RA. No studies were found for osteoarthritis, another condition in which central sensitization is reported[34 35]. Much research on amitriptyline in musculoskeletal complaints has been performed in patients with fibromyalgia; however, we excluded these studies because a Cochrane review on this topic was recently published[17]. This latter review reported that there is no unbiased evidence for the effect of amitriptyline in fibromyalgia, but there is also no good evidence for a lack of effect of amitriptyline in fibromyalgia[17].

In some of the patients with musculoskeletal pain, central sensitization is thought to be present[5-9] and it may be expected that these patients have a better response to a centrally-acting agent such as amitriptyline[4]. Only one of the included studies in our review investigated whether the presence of a neuropathic pain component modulated the treatment response[22]; the authors found no significant differences in the results.

Another limitation of the present review is the clinical heterogeneity of the included studies. Although all studies investigated the use of amitriptyline in musculoskeletal complaints, different conditions were evaluated. Moreover, amitriptyline was compared with a different treatment in each study, and the dosage of paracetamol was suboptimal at 2000 mg/day[23]. Furthermore, dosages of amitriptyline ranged from 25-150 mg/day. Although, in the studies in which amitriptyline showed a significant improvement of pain and/or function compared with the comparator, the dosage of amitriptyline was 25 mg/day or 50 mg/day. These are the same dosages frequently prescribed in patients with fibromyalgia[17], a condition in which central sensitization is known to occur[14].

Another limitation of the included studies is the relatively short follow-up period. In chronic pain it is advised to evaluate the effect of an analgesic after 12 weeks of treatment. Only one of the included studies treated patients for ≥12 weeks (14 weeks)[22]. A longer treatment period could lead to more robust findings compared with a shorter treatment period.

Moreover, the studies in this review were conducted in relatively young patients; i.e. the mean age was ≤40 years in three studies[20 23 24] and was 41.5 years in one study[22], while the incidence of musculoskeletal increases with age and these conditions are especially troublesome in patients aged ≥50 years[36 37]. Also, pain processing changes with increasing age. In elderly people endogenous pain inhibition (conditioned pain modulation) functions poorly (e.g. the lack of descending analgesia). Furthermore, temporal summation of heat pain may be enhanced in older people[38 39]. Both the lack of endogenous pain inhibition and enhanced temporal summation are known to occur in central sensitization[4 40]. Therefore, amitriptyline might be more effective in older patients. On the other hand, side-effects may be more common in the elderly due to comorbidities, age-related physiological changes, and polypharmacy[41 42].

Comparison with the literature

Multiple systematic reviews have been published on the use of antidepressants in CLBP[43-47]. However, none of the studies included in our review was included in these earlier reviews. These reviews evaluated tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs); they found conflicting results on the use of antidepressants for CLBP, two reviews found no evidence for the use of antidepressants[43 46], while three found some evidence[44 45 47]. Pooled analyses for TCAs showed also contradictory results: Staiger et al. found a significant decrease of pain with TCAs[47] while two other reviews (including a Cochrane review) found no decrease of pain[43 46]. However, the conclusions of these reviews should be interpreted with caution due to the diversity of the included studies and different pooling methods used[48]. Furthermore, different antidepressants with different affinities for receptors were used and these antidepressants may have different analgesic properties[48]. More recent studies with larger samples sizes investigating the use of duloxetine for CLBP show a benefit of treatment with duloxetine, although most of these studies were sponsored by the pharmaceutical industry[49-51].

The use of antidepressants in RA was evaluated in a Cochrane review and concluded that no reliable statement could be made on the use of antidepressants in RA with the current level of evidence[52].

Our review found results similar to the previous reviews; due to the clinical heterogeneity of our included studies it was not possible to perform a meta-analysis; this makes it difficult to draw conclusions about the benefit of amitriptyline. Moreover, we did not include the study by Pheasant et al.[53], a study frequently included in other systematic reviews on CLBP, because it did not report on our primary outcome measurement.

CONCLUSIONS

This systematic review assessed the use of amitriptyline in musculoskeletal complaints. While the rationale for prescribing amitriptyline in chronic musculoskeletal complaints is present in other conditions[34], we only found studies on LBP, persistent arm pain and RA. Despite the few studies, the heterogeneity and the short period of treatment, amitriptyline may improve pain and function in patients with musculoskeletal complaints. However, amitriptyline may not result in a significantly greater improvement of pain compared with other analgesics. More research is needed to establish whether and for which patients amitriptyline may be more effective than other analgesics.

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SUPPLEMENTARY DATA

Search strategy

Embase.com

(Amitriptyline/de OR amitriptylinoxide/exp OR (Amitript* OR Amitrypt*):ab,ti) AND ('musculoskeletal pain'/exp OR 'leg pain'/exp OR 'arm pain'/de OR 'hand pain'/exp OR (('leg'/de OR 'arm'/de OR 'hand'/de OR elbow/de OR 'rheumatic disease'/de OR osteoarthritis/de OR 'shoulder'/de OR 'wrist'/de) AND (pain/de)) OR 'shoulder pain'/de OR 'radicular pain'/exp OR backache/exp OR arthralgia/exp OR 'wrist pain'/exp OR 'neck pain'/de OR (((musculoskelet* OR hip OR knee OR joint* OR shoulder* OR ankle* OR elbow OR neck OR back OR hand OR locomot* OR extremit* OR limb* OR leg OR legs OR arm OR arms OR forearm* OR radicul* OR articular OR wrist* OR rheuma* OR osteoarthrit*) NEAR/3 (pain* OR complaint* OR ache*)) OR radiculalg* OR coxalgi* OR coxodyni* OR gonalgi* OR cervicalgi* OR backache OR dorsalgi* OR backpain* OR arthralgia):ab,ti)

Medline (ovid)

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Cochrane

((Amitript* OR Amitrypt*):ab,ti) AND ((((musculoskelet* OR hip OR knee OR joint* OR shoulder* OR ankle* OR elbow OR neck OR back OR hand OR locomot* OR extremit* OR

limb* OR leg OR legs OR arm OR arms OR forearm* OR radicul* OR articular OR wrist* OR rheuma* OR osteoarthrit*) NEAR/3 (pain* OR complaint* OR ache*)) OR radiculalg* OR coxalgi* OR coxodyni* OR gonalgi* OR cervicalgi* OR backache OR dorsalgi* OR backpain* OR arthralgia):ab,ti)

Web-of-science

TS=(((Amitript* OR Amitrypt*)) AND ((((musculoskelet* OR hip OR knee OR joint* OR shoulder* OR ankle* OR elbow OR neck OR back OR hand OR locomot* OR extremit* OR limb* OR leg OR legs OR arm OR arms OR forearm* OR radicul* OR articular OR wrist* OR rheuma* OR osteoarthrit*) NEAR/2 (pain* OR complaint* OR ache*)) OR radiculalg* OR coxalgi* OR coxodyni* OR gonalgi* OR cervicalgi* OR backache OR dorsalgi* OR backpain* OR arthralgia)))

Scopus

TITLE-ABS-KEY(((Amitript* OR Amitrypt*)) AND ((((musculoskelet* OR hip OR knee OR joint* OR shoulder* OR ankle* OR elbow OR neck OR back OR hand OR locomot* OR extremit* OR limb* OR leg OR legs OR arm OR arms OR forearm* OR radicul* OR articular OR wrist* OR rheuma* OR osteoarthrit*) W/2 (pain* OR complaint* OR ache*)) OR radiculalg* OR coxalgi* OR coxodyni* OR gonalgi* OR cervicalgi* OR backache OR dorsalgi* OR backpain* OR arthralgia)))

PubMed unindexed

(Amitriptyline[mh] OR (Amitript*[tiab] OR Amitrypt*[tiab])) AND ("musculoskeletal pain"[mh] OR (("leg"[mh] OR "arm"[mh] OR "hand"[mh] OR elbow[mh] OR "Rheumatic Diseases"[mh] OR osteoarthritis[mh] OR "shoulder"[mh] OR "wrist"[mh]) AND (pain[mh])) OR "Back Pain"[mh] OR "Neck Pain"[mh] OR arthralgia[mh] OR (((musculoskelet*[tiab] OR hip OR knee OR joint*[tiab] OR shoulder*[tiab] OR ankle*[tiab] OR elbow OR neck OR back OR hand OR locomot*[tiab] OR extremit*[tiab] OR limb*[tiab] OR leg OR legs OR arm OR arms OR forearm*[tiab] OR radicul*[tiab] OR articular OR wrist*[tiab] OR rheuma*[tiab] OR osteoarthrit*[tiab]) AND (pain*[tiab] OR complaint*[tiab] OR ache*[tiab])) OR radiculalg*[tiab] OR coxalgi*[tiab] OR coxodyni*[tiab] OR gonalgi*[tiab] OR cervicalgi*[tiab] OR backache OR dorsalgi*[tiab] OR backpain*[tiab] OR arthralgia)) AND (publisher[sb] OR inprocess [sb])

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Amitriptyline|Amitryptilyne "musculoskeletal|hip|knee|joint|shoulder|ankle|elbow|neck|back|hand|locomotor|extremity|limb| leg|legs|arm|arms|forearm|radicular|articular|wrist|rheumatic|osteoarthritic pain|complaints"|backache|dorsalgia|backpain|arthralgia

Lilacs

Scielo

(Amitriptyline OR Amitriptilyne) AND ("musculoskeletal pain" OR "hip pain" OR "knee pain" OR "joint pain" OR "shoulder pain" OR "ankle pain" OR "elbow pain" OR "neck pain" OR "back pain" OR "hand pain" OR "locomotor pain" OR "extremity pain" OR "limb pain" OR " leg pain" OR "legs pain" OR "arm pain" OR "arms pain" OR "forearm pain" OR "radicular pain" OR "articular pain" OR "wrist pain" OR "rheumatic pain" OR "osteoarthritic pain" OR "musculoskeletal complaints" OR "hip complaints" OR "knee complaints" OR "joint complaints" OR "shoulder complaints" OR "ankle complaints" OR "elbow complaints" OR "neck complaints" OR "back complaints" OR "hand complaints" OR "locomotor complaints" OR "extremity complaints" OR "limb complaints" OR " leg complaints" OR "legs complaints" OR "arm complaints" OR "arms complaints" OR "forearm complaints" OR "radicular complaints" OR "articular complaints" OR "wrist complaints" OR "rheumatic complaints" OR "osteoarthritic complaints" OR backache OR dorsalgia OR backpain OR arthralgia)

Proquest

(ti(Amitriptyline OR Amitriptilyne) OR ab(Amitriptyline OR Amitriptilyne)) AND (ti("musculoskeletal pain" OR "hip pain" OR "knee pain" OR "joint pain" OR "shoulder pain" OR "ankle pain" OR "elbow pain" OR "neck pain" OR "back pain" OR "hand pain" OR "locomotor pain" OR "extremity pain" OR "limb pain" OR " leg pain" OR "legs pain" OR "arm pain" OR "arms pain" OR "forearm pain" OR "radicular pain" OR "articular pain" OR "wrist pain" OR "rheumatic pain" OR "osteoarthritic pain" OR "musculoskeletal complaints" OR "hip complaints" OR "knee complaints" OR "joint complaints" OR "shoulder complaints" OR "ankle complaints" OR "elbow complaints" OR "neck complaints" OR "back complaints" OR "hand complaints" OR "locomotor complaints" OR "extremity complaints" OR "limb complaints" OR " leg complaints" OR "legs complaints" OR "arm complaints" OR "arms complaints" OR "forearm complaints" OR "radicular complaints" OR "articular complaints" OR "wrist complaints" OR "rheumatic complaints" OR "osteoarthritic complaints" OR backache OR dorsalgia OR backpain OR arthralgia) OR ab("musculoskeletal pain" OR "hip pain" OR "knee pain" OR "joint pain" OR "shoulder pain" OR "ankle pain" OR "elbow pain" OR "neck pain" OR "back pain" OR "hand pain" OR "locomotor pain" OR "extremity pain" OR "limb pain" OR " leg pain" OR "legs pain" OR "arm pain" OR "arms pain" OR "forearm pain" OR "radicular pain" OR "articular pain" OR "wrist pain" OR "rheumatic pain" OR "osteoarthritic pain" OR "musculoskeletal complaints" OR "hip complaints" OR "knee complaints" OR "joint complaints" OR "shoulder complaints" OR "ankle complaints" OR "elbow complaints" OR "neck complaints" OR "back complaints" OR "hand complaints" OR "locomotor complaints" OR "extremity complaints" OR "limb complaints" OR " leg complaints" OR "legs complaints" OR "arm complaints" OR "arms complaints" OR "forearm

complaints" OR "radicular complaints" OR "articular complaints" OR "wrist complaints" OR "rheumatic complaints" OR "osteoarthritic complaints" OR backache OR dorsalgia OR backpain OR arthralgia))

CHAPTER 6

Effectiveness and cost-effectiveness of duloxetine added to usual care for patients with chronic pain due to hip or knee osteoarthritis: protocol of a pragmatic open-label cluster randomised trial (the DUO trial)

Jacoline J. van den Driest, Dieuwke Schiphof, Pim A.J. Luijsterburg, Aafke R. Koffeman, Marc A. Koopmanschap, Patrick J.E. Bindels, Sita M.A. Bierma-Zeinstra

BMJ Open. 2017 Sept 11;7(9)

ABSTRACT

Introduction

Osteoarthritis is a highly prevalent painful condition of the musculoskeletal system. The effectiveness of current analgesic options has proven to be limited and improved analgesic treatment is needed. Several randomised placebo-controlled trials have now demonstrated the efficacy of duloxetine, an antidepressant with a centrally acting effect, in the treatment of OA pain. The aim of the current study is to investigate if duloxetine is effective and cost-effective as a third-choice analgesic added to usual care for treating chronic pain compared to usual care alone in general practice.

Methods and analysis

A pragmatic open, cluster randomised trial is conducted. Patients with pain due to hip or knee OA on most days of the past 3 months with insufficient benefit of NSAIDS or contraindications or intolerable side-effects are included. General practices are randomised to either 1) duloxetine and usual care or 2) usual care only. Primary outcome is pain at 3 months measured on the WOMAC pain subscale. Secondary outcomes at 3 months and 1 year are pain (WOMAC, at 1 year), function (WOMAC), adverse reactions, quality of life, and modification of the response to treatment by the presence of centrally sensitized pain (modified PainDETECT). At 1 year medical and productivity costs will be assessed. Analyses will be performed following the intention-to-treat principle taking the cluster design into account.

Ethics and dissemination

The study is approved by the local Medical Ethics Committee (MEC 2015-293). Results will be published in a scientific peer-reviewed journal and will be communicated at conferences.

Trial registration number

This study is registered in the Dutch trial registry http://www.trialregister.nl: trial number ntr4798.

BACKGROUND AND RATIONALE

Osteoarthritis (OA) is a highly prevalent chronic condition of the musculoskeletal system. Approximately 15% of the population suffers from OA. Amongst elderly the lifetime risk for knee OA is 40% in men and 47% in women[1 2] and it is the single-most contributing factor to a decreased physical well-being[3]. It is predicted that OA will become the fourth leading cause of disability worldwide by the year 2020[4]. The majority of patients suffering from OA are treated in primary care[5 6]. The general practitioner (GP) plays a key role in the treatment of symptomatic pain, the most debilitating symptom of this condition. Currently, usual care by the GP consists of education, referral for exercise therapy and prescribing symptomatic pain medication using a step-wise approach. The first step consists of paracetamol. If its analgesic effect proves insufficient, non-steroidal anti-inflammatory drugs (NSAIDs) can be prescribed as a second step, and subsequently tramadol or other opioids[7]. So far, however, the effectiveness of symptomatic pain treatment has proven to be limited[8-10] and the majority of the patients still report pain despite taking pain medication[11 12]. In addition, these analgesics are often contraindicated, especially in elderly patients, and they are associated with the occurrence of serious adverse reactions. Improved analgesic treatment or a new approach to OA pain treatment is therefore needed, especially since there are no treatment options available aimed at delaying or halting the process of OA. Surgical joint-replacement is the exception but is an intervention which is not only costly, does not always lead to a satisfied results for patients and is also of limited durability[4 13]. An effective and relatively safe medicine, when current options fail, could improve the quality of life for these chronic pain patients. In the long term, it could potentially help postpone the need for a joint-replacement and revision surgery, whilst retaining quality of life.

Traditionally, pain in OA was assumed to consist solely of nociceptive pain due to inflammation, degradation and remodelling of joint tissue. However, it has since been demonstrated that in addition to nociceptive pain, peripheral sensitized pain from locally generated inflammatory factors and centrally sensitized pain, can be present in OA[14]. Intense, repeated or prolonged nociceptive input can lead to hyperexcitability of pain circuits in the central nervous system[15]. Normally, descending inhibitory pathways from the brain stem modulate pain processing through the release of noradrenalin and serotonin. These inhibitory pathways can be impaired in patients with OA[15]. This disinhibition of descending pathways further contributes to central sensitization in OA. Centrally sensitized pain is present in a substantial percentage (30-37%)[16 17] of patients with chronic pain due to OA and is thought to respond particularly poorly to currently prescribed analgesics, as it requires medication with a centrally acting agent. Duloxetine is a serotonin norepinephrine reuptake inhibitor (SNRI) and acts centrally by strengthening the inhibition of the descending pathways.

Several randomised placebo-controlled trials have now demonstrated the efficacy of low dose duloxetine versus placebo in the treatment of pain in OA (clinically relevant effect sizes of 0.4 to 0.5 for pain in OA[18 19] and 0.6 for disability in OA[18]) and the most recent guideline of the Osteoarthritis Research Society International (OARSI) now recommend duloxetine for the non-surgical management of knee OA[10]. These trials are short-term randomised placebo-controlled trials in a highly controlled and secondary care setting. The effectiveness of duloxetine as third-choice analgesia in general practice is not known. Neither is clear whether the effectiveness of duloxetine is predominantly found in those patients suffering from pain with characteristics of central sensitization, or whether duloxetine as third-choice analgesia in general practice is cost-effective, if found effective.

METHODS AND DESIGN

Objectives

The primary objective of this study is to investigate whether duloxetine added to usual care is effective as third-choice pain medication (when NSAIDs fail, are contraindicated or have intolerable side-effects) in reducing chronic pain (WOMAC) in primary care patients with osteoarthritis after three months, compared to usual care alone.

Secondary objectives are 1) to assess whether the presence of characteristics of central sensitization (modified painDETECT >12.0) favourably modifies the response to treatment with duloxetine (WOMAC pain at 3 months and WOMAC pain and function at 1 year), and 2) to examine the cost-effectiveness of treatment with duloxetine at 1 year.

Study design

A pragmatic open-label cluster randomised controlled trial with a follow-up of one year is conducted (figure 1). To avoid contamination between the two intervention groups, randomisation takes place on the level of the GP practice. Patients, researchers and GPs are not blinded to the assigned treatment.

Randomisation

GP practices are randomised to the duloxetine or usual care group. Since provided care can differ based on practice characteristics, stratification is performed on: 1) socio-economic status of the practice location (low socio-economic status versus normal and high socio-economic status, based on the registration by The Netherlands Institute for Social Research[20]); 2) the number of GPs working at the practice (one full-time equivalent or smaller versus larger than one full-time equivalent); and 3) the mean age of the GPs per practice (younger than 50 years or 50 years and older[21-23]). The randomisation

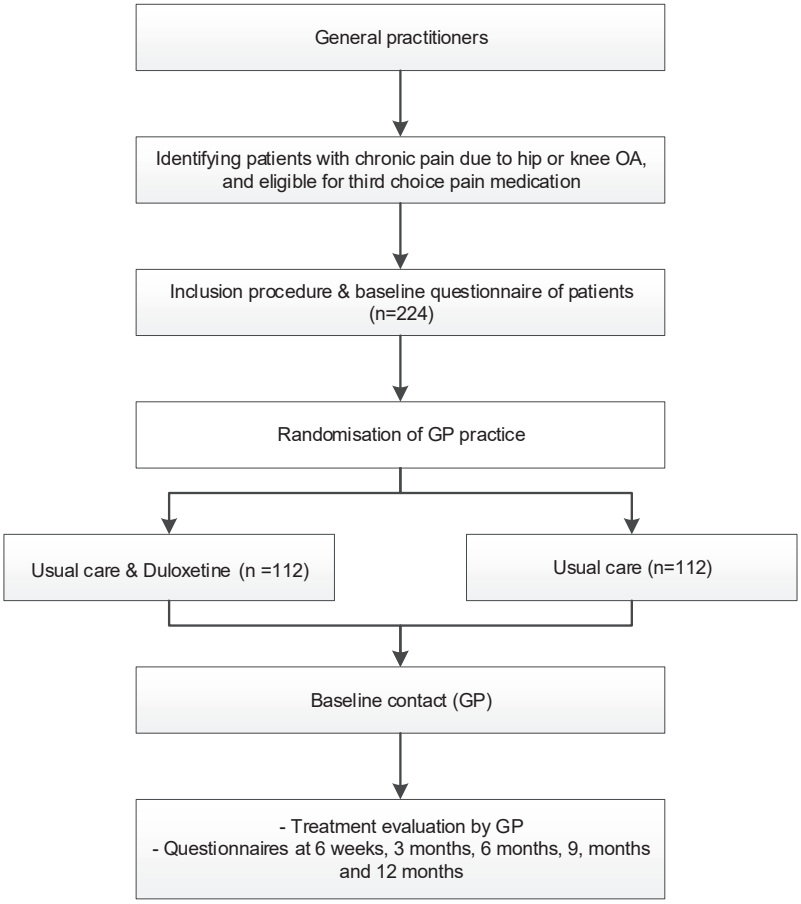

Figure 1. Flowchart of the study

sequence is determined by an independent data manager from the department, with the use of a computer generated randomisation list. A block design with blocks random varying between two and six is used to equally balance the groups. The randomisation procedure is concealed to the involved researchers of the study. Randomisation of the GP practice is performed after eligible patients are identified and the first patient of the GP practice has signed informed consent.

Inclusion criteria

All patients must be aged 18 years or older and have hip and/or knee OA based on the clinical American College of Rheumatology (ACR) criteria[24]. Chronic pain should be present, which is defined as pain on most days during the last three months. In addition, patients must have insufficient benefit of NSAIDs, contraindications for NSAIDs or previous adverse reactions to NSAIDs (i.e. eligible for third-choice pain medication).

Exclusion criteria

Patients who meet one of the following criteria will be excluded from the trial.

- Scheduled for a hip or knee replacement
- Current use of antidepressants
- Current use of neuropathic pain medication
- Rheumatoid arthritis
- Unable to sign informed consent
- Contra-indications for duloxetine (current use of Monoamine Oxidase Inhibitors, uncontrolled narrow-angle glaucoma, the combination with other central nervous acting drugs (e.g. benzodiazepines), hypersensitivity to duloxetine, liver disease resulting in hepatic impairment, severe renal impairment (creatinine clearance < 30 ml/min), current use of strong CYP1A2-inhibitors, current use of CYP2D6- inhibitors and substrates, uncontrolled hypertension, pregnancy or lactation)

Initially, patients who currently used opioids or used these in the past three months were excluded from the trial, because opioids are already third-choice medication in the Netherlands. Though, when patients still feel pain despite the use of opioids it may be that these complaints reflect a centrally sensitized pain, since this type of pain is thought to respond less well to traditional analgesics. Especially these patients can benefit from duloxetine. Therefore, these patients are also eligible.

Intervention

Duloxetine

Patients in the duloxetine arm are prescribed duloxetine 60mg once a day. During the first week of treatment the patient starts with 30mg duloxetine per day to minimize potential adverse events due to duloxetine. If tolerated well, the dose is increased to 60mg/day in the second week. Therapeutic benefit of duloxetine is assessed regularly by the treating GP (after two weeks, 1 month, 3, 6, 9, 12 months and when necessary). If patients experience no effect of duloxetine after three months or patients experience intolerable side-effects, duloxetine can gradually be discontinued. Patients also receive usual care according to the GP guidelines in the Netherlands[7], as described below.

Usual care

Patients are treated according to the current Dutch GP guideline which comprise of education, life style advice, dietary therapy, physiotherapy and analgesics[7]. Analgesics are prescribed according to the opinion and experience of the treating GP. Analgesic choice depends on what the GP and patients decide. Paracetamol and NSAIDs have failed in these patients. A GP can decide to prescribe or continue an opioid, or the treatment can

remain the same. Depending on the comorbidities of the patients, contra-indications and opinion of the GP other interventions are also allowed.

Co-interventions

Patients assigned to the usual care group cannot be prescribed duloxetine. In both groups intra-articular injection with glucocorticoids or a referral for joint replacement is allowed, as these are in accordance with Dutch GP guidelines and appropriate within the pragmatic design of this trial

Study procedures

Patients are recruited from general practices. GPs in the Rotterdam region are invited to participate. If a GP practice is held by more than one GP, all GPs are randomised into the same arm. In this way contamination between the groups is prevented when a patient visits another GP in the same practice. Demographic characteristics of the GP practice are registered. Randomisation of the GP practice is performed after the first patient of the GP practice has signed the informed consent form.

All eligible patients are identified by an electronic search in the participating GPs medical records. The GP decides which patients receive an invitation for the trial. In this way, possible recruitment bias can be monitored. Subsequently, eligible patients are sent information about the current trial. If a patient is interested in participating, the patient is contacted by a member of the research team by telephone. During this contact the study is explained and eligibility of the patient is re-evaluated. If a patient is interested and eligible, the patient receives further written information about the study. After two weeks the patients is contacted a second time by telephone to obtain informed consent. After filling out the baseline questionnaire patients are told to which intervention their GP practice is randomised. In both study arms patients consult their GP for their intervention (figure 1). In the duloxetine arm the GP prescribes duloxetine during the consultation. If at this point the patient decides not to take the duloxetine after all, the patient remains in the study in accordance with the pragmatic approach.

Patients receive follow-up questionnaires at 6 weeks, 3, 6, 9 and 12 months (table 1) after filling out the baseline questionnaire. The questionnaire at 6 weeks is added to the initial protocol to monitor the therapeutic effect of duloxetine more closely in the first weeks.

Safety

All adverse events reported by the subject are recorded. All serious adverse events (SAEs) are reported to the medical ethics committee. All SAEs are monitored until resolution or stabilisation. No Data and Safety Monitoring Board (DSMB) is needed, since adverse events of duloxetine are well known and duloxetine is registered in the Netherlands

Table 1. Overview of questionnaire items

	Baseline	6 weeks	3 months	6 months	9 months	12 months
Outcome measures						
Pain Score (WOMAC)	X	X	X	X	X	X
Function Score (WOMAC)	X	X	X	X	X	X
HOOS/ KOOS	X	X	X	X	X	X
Quality of Life (EuroQol-5D-5L)	X		X	X	X	X
Medical Costs (iMCQ)	X		X	X	X	X
Productivity Cost (iPCQ)	X		X	X	X	X
Co-interventions		X	X	X	X	X
Adverse events		X	X	X	X	X
Compliance	X		X	X	X	X
Patients satisfaction		X	X	X	X	X
Others						
Demographic data	X					
Co-morbidities	X					
Presence of centrally sensitized pain(Modified painDETECT)	X					
Presence of depression or anxiety (HADS)	X		X	X	X	X

BMQ= Beliefs about Medication Questionnaire, HADS= Hospital and Anxiety Depression Scale , HOOS = Hip disability and Osteoarthritis Outcome Score, iMCQ = iMTA Medical Cost Questionnaire, iPCQ = iMTA Productivity Cost Questionnaire, KOOS = Knee disability and Osteoarthritis Outcome Score, WOMAC = Western Ontario and McMaster University Osteoarthritis Index

for the treatment of depressive disorders and diabetic neuropathy. Monitoring of the study is carried out once a year because of the negligible risk profile (Standards of The Netherlands Federation of University Medical Centres)[25].

Outcome measures

Primary outcome

The primary outcome is pain at three months follow-up measured with the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain subscale. During the study period patients complete the Knee injury and Osteoarthritis Outcome Score (KOOS) or the Hip disability and Osteoarthritis Outcome Score (HOOS)[26 27]. The HOOS and KOOS consist of five subscales: pain, other symptoms, ADL function, function in sport and recreation, and knee/ hip related quality of life. The KOOS and HOOS are developed as an extension of the WOMAC score, with the purpose of evaluating both short- and long-term symptoms and function. All WOMAC pain and function questions are included in their full and original form in the KOOS/HOOS questionnaire[26 28].There-

fore, WOMAC scores can be calculated from the KOOS and HOOS scores. The questions apply to the previous week and each indicator is scored on a 5-point Likert scale (0= extreme problems, and 4=no problems). Scores range between 0-100, higher scores indicate less symptoms.

Secondary outcomes

Secondary outcomes are pain at one year (WOMAC pain subscale) and disability at one year (WOMAC function subscale). Adverse reactions and co-interventions for OA pain are systematically recorded in the follow-up questionnaires. Patients' satisfaction with the treatment is measured on an 11-point numerical rating scale (0 = completely dissatisfied, 10= completely satisfied).

Health related quality of life is measured with the EuroQol-5D (EQ-5D-5L) which comprises of a descriptive system with five dimensions and a visual analogue scale[29]. Costs are measured using the iMTA Medical Consumption Questionnaire (iMCQ) and the iMTA Productivity Cost Questionnaire (iPCQ). The iMCQ is a non-disease specific questionnaire to determine the direct medical and patients costs of the previous three months[30]. The iPCQ is focused on the indirect costs of the healthcare system; it measures the productivity losses in the last four weeks[31].

Compliance to the treatment is estimated by questions about medication use (dose, how often each day, number of days). Furthermore the Beliefs about Medication Questionnaire (BMQ) is asked. The BMQ consists of two sections: the BMQ-General and BMQ-Specific section[32] assessing patients thoughts about medicine in general and about OA medication specifically. Each section consists of two subscales. The BMQ-General contains the subscales Harm and Overuse (scores 4-20). The BMQ-Specific encompasses the subscales Necessity and Concerns (scores 5-25). Higher scores on the BMQ-Specific are correlated with self-reported therapy adherence[33 34].

The effect of the intervention will also be evaluated by the OMERACT-OARSI response criteria. These criteria are a uniform core set of outcome measurements for OA. Response is defined as (a) a high improvement in pain (WOMAC pain) or function (WOMAC function) (≥50%) and an absolute change of ≥20 (on an interval scale 0-100) or (b) improvement in at least two of the three following: pain ≥20% (WOMAC pain) and absolute change ≥10; function ≥20% (WOMAC function) and absolute change ≥10; patients global assessment ≥20% and absolute change ≥10[35].

Other study outcomes

At baseline the following patient characteristics are collected: age, gender, height and weight, education, co-morbidities and the duration of complaints. In addition, patients fill out the modified painDETECT questionnaire which is adapted for patients with OA[36]. This questionnaire is validated for identifying 'neuropathic-like' symptoms which

correlate with signs of central sensitization in OA. Higher modified painDETECT scores indicate the presence of central sensitization (scores >12, range -1-35)[16 37]. The modified painDETECT was recently validated in Dutch for both patients with knee OA and for patients with hip OA[38].

Finally, the Hospital Anxiety and Depression Scale (HADS) is assessed to establish the analgesic effect of duloxetine independent of the effects on mood or anxiety[39].

Sample size

To detect a clinically relevant difference in WOMAC pain of 1.9 points (pooled SD 4.8)[18] between the two treatment groups with an effect size of 0.4 (power 80%; alpha 0.05), taking into account the cluster randomization with an assumption of 3 patients per GP and an intra-cluster correlation coefficient (ICC) of 0.01, 102 patients per treatment group are required. As we expect around 10% loss to follow-up[40], we need to include 224 in total (2x112). In order to detect an effect (with an effect size of 0.6) in the patients with centrally sensitized pain we need 44 patients per group (with the same power and cluster assumptions). In the patients that are currently included in the trial, centrally sensitized pain (PainDETECT score >12) is present in 47% of the included patients. This percentage is higher than in the general OA population (37%)[16]. This overrepresentation is probably related to our inclusion and exclusion criteria. When we assume a presence of centrally sensitized pain in 47% of our included patients, 206 patients need to be included to answer the secondary objective. Therefore, no sample size adjustments have to be made.

The current sample size is adjusted due to recruitment problems. In the initial sample size calculation 362 patients needed to be included to detect a clinically relevant difference in WOMAC pain of 1.9 points. In this calculation an ICC of 0.1 and 5 patients per GP were assumed. The inclusion of 5 patients per GP was not feasible and therefore this number was altered to 3. Furthermore, the ICC of 0.1 was a conservative estimate and an ICC tends to be around 0.01 in general practice[41].

Data management

All personal data is handled confidentially and anonymously. Each patient is allocated a unique code, which is used on the questionnaires and in the database. The link between the code and the patient identification is only be accessible to the researcher and the data manager. The software programs Limesurvey and GemsTracker are used for the online questionnaires and patients personal data respectively.

Patient involvement

Within the department of General Practice a patient panel exists (Primeur Patient Panel), with patient representatives who are involved in all phases of research[42]. Patient repre-

sentatives from the Primeur Patient Panel, familiar with OA, have helped to design this study and will be involved in all phases of the study. They read and gave comments on the proposal, all patient information, and procedures.

Statistical analysis

Descriptive statistics will be used to describe patient characteristics, baseline values of the outcome measures and compliance to the intervention. Primary (WOMAC pain at 3 months) and secondary (WOMAC pain and function at 1 year) outcomes will be analysed using generalized linear mixed models with repeated measurements. The stratified cluster randomization will be taken into account when analysing the data (multilevel analysis). When baseline characteristics are statistical significantly different between the two treatment groups, we will perform a confounder analysis. If the effect on the outcome changes 10% or more the baseline characteristic will be considered a confounder and analyses will be adjusted accordingly. All analyses will be performed following the intention- to- treat principle. Additional per protocol analyses will also be carried out; for the primary outcome, WOMAC pain at 3 months, in the intervention arm patients who discontinued duloxetine (within four weeks after start) or did not start at all will not be considered, and patients in the control arm who were prescribed antidepressants will not be considered. Subgroup analyses to assess the effectiveness of treatment in patients with centrally sensitized pain will be completed in patients who score higher than 12 on the modified painDETECT The same analysis as described earlier will be carried out.

To evaluate cost-effectiveness of usual care and duloxetine versus usual care only in patients with chronic pain due to hip or knee OA a cost-effectiveness analysis will be performed using the primary outcome: pain measured with the WOMAC questionnaire. A cost-utility analysis will be performed to compare our study with other studies in OA research using a general accepted outcome: quality adjusted life years (QALY). To calculate QALY's based on the EQ-5D-5L, utility values of the Dutch public for EuroQol health states will be applied[43]. Using non parametric bootstrapping (randomly drawing 2500 observations with replacement from the patient sample), the degree of uncertainty for costs and health effects and the cost-utility ratio will be depicted in a cost-effectiveness plane.

In addition an acceptability curve is drawn, which indicates the probability that the intervention has lower incremental cost per QALY gained than various thresholds for the maximum willingness to pay for an extra QALY.

Social perspective and healthcare perspective will be the basis of the economic analysis in which the direct and productivity costs in the groups will be compared using the medical consumption questionnaire (iMCQ)[30] and the productivity cost questionnaire[31].

SPIRIT guidelines

This protocol meets the SPIRIT guidelines for reporting on study protocols for clinical trials.

DISSEMINATION

Results will be communicated at international and national conferences and will be published in a scientific peer-reviewed journal. Together with the patient representatives of the Primeur Patient Panel the results and ideas for dissemination will be discussed. They will check the validity of the conclusions from a public perspective and highlight findings that are more relevant to the public.

Substantial protocol amendments will be communicated to the medical ethics committee, the competent authority (Centrale Commissie Mensgebonden Onderzoek (CCMO), ZonMw and cooperating GPs.

DISCUSSION

This study assesses the effectiveness and cost-effectiveness of duloxetine added to usual care for patients with chronic pain due to hip and/ or knee OA in a primary care setting. As far as we know this is the first pragmatic trial in which duloxetine is compared directly to usual care in primary care to establish the effectiveness of treatment with duloxetine. Until now only the efficacy has been shown[18 19 44 45]. Long term effects, the comparison with usual care and cost-effectiveness are unknown.

This pragmatic trial evaluates the use of duloxetine in every day practice and has a high external validity due to the relatively unselected patients and flexible conditions. Therefore, the DUO-trial will be helpful in answering the question whether the interventions has additional value in "real-life"[46 47]

We choose the cluster randomised design, because the design has particular utility in effectiveness and implementation studies. This design is particularly appropriate for evaluation of interventions that naturally are applied at cluster level, e.g. general practices that choose a certain stepped approach[47].

Issues that require specific attention in this trial due to the cluster design are the generalizability, recruitment bias and possible baseline imbalances between the randomised groups. We monitored the risk of recruitment bias and maximized the generalizability by inviting all eligible patients from a cluster to participate in this study. Possible baseline imbalances are minimized by the stratification of the clusters.

Finally, it is not known whether the presence of centrally sensitized pain favourably modifies the treatment response to duloxetine. The modified painDETECT is a questionnaire that can be easily used in a primary care setting, in contrast to traditional extensive measurements such as quantitative sensory testing[16]. Patients with knee OA with higher modified painDETECT scores (>12) have higher odds of having signs of central sensitization[16]. If the presence of centrally sensitized pain does modify treatment response to duloxetine, this finding will enable more targeted treatment choices in primary care patients with OA.

In conclusion, the DUO-trial is a cluster randomised trial to assess the effectiveness of duloxetine in patients with hip or knee OA with chronic pain in primary care. The trial will answer the question whether duloxetine can be used as an third-choice pain medication in primary care and may enable more targeted treatment choices.

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6

CHAPTER 7

No added value of duloxetine for patients with chronic pain due to hip or knee osteoarthritis: a cluster randomised trial

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Submitted

ABSTRACT

Objective

To assess the effectiveness of duloxetine added to usual care for patients with chronic osteoarthritis (OA) pain. Secondary objectives were to assess cost-effectiveness and to assess whether the presence of symptoms of centralized pain alters the response to duloxetine.

Design

Multicentre, open label, cluster randomised trial.

Setting

110 general practices in the Netherlands.

Participants

Patients with chronic OA pain of hip or knee in which paracetamol and NSAIDs had insufficient response were included. Patients were excluded when knee or hip replacement was scheduled, when using antidepressants or neuropathic pain medication, if they had rheumatoid arthritis or contra-indications for duloxetine, or were unable to sign informed consent.

Intervention

Patients received duloxetine 60mg/day added to usual care as third choice pain medication or usual care alone. Usual care was provided according to the Dutch GP guidelines.

Main outcome measures

The primary outcome was WOMAC pain (0-20) at 3 months. We aimed to detect a difference between the groups of a clinical relevant effect of 1.9 points (effect size 0.4). Secondary outcomes were WOMAC pain at 12 months, WOMAC function, quality of life, side effects, cost-effectiveness, patient's satisfaction and perceived improvement, and OMERACT-OARSI responder criteria.

Results

In total, 133 patients were included and 132 were randomised. 66 patients (31 practices) were randomised to duloxetine added to usual care and 66 patients (34 practices) to usual care alone. No differences were found for WOMAC pain at 3 months (adjusted difference -0.58 95% confidence interval [-1.80 to 0.63]) or at 12 months (adjusted difference -0.26 95% CI[-1.86 to 1.34]). For the subgroup of patients with symptoms of centralized pain no effect of duloxetine was found either (-0.32 95% CI[-2.32 to 1.67]).

Furthermore, the intervention was not cost-effective; a small positive difference of 0.04 QALY's was found for the duloxetine group.

Conclusions

No effect was found of duloxetine added to usual care compared to usual care alone in patients with chronic OA pain. For patients with symptoms of centralized pain our results need to be confirmed in another trial.

Trial registration

Dutch trial registry NTR4798

INTRODUCTION

Osteoarthritis is one of the major chronic pain conditions of the musculoskeletal system and approximately 15% of the population suffers from OA[1 2]. Persistent pain and loss of function are two important complaints of patients with OA. Treatment is symptomatic and consists of education, exercise, physiotherapy, and analgesics.

Analgesics are prescribed in a stepwise approach to patients with OA. The first step is paracetamol, which has a small therapeutic effect, but is often well tolerated and has few contra-indications[3]. The next step is non-steroidal anti-inflammatory drugs (NSAIDs), which have a moderate effect on OA pain[4]. NSAIDs are often contra-indicated and are associated with side-effects. Finally, opioids can be considered, but effectiveness is often lacking for OA pain and serious side-effects are common[5 6]. Other treatment options are therefore needed.

An option may be duloxetine, a serotonin and norepinephrine reuptake inhibitor (SNRI). Duloxetine is hypothesized to reduce chronic pain by central inhibition of pain and acts by modulation of descending (inhibitory) pain pathways in the central nervous system[7]. Pain in OA can be caused by nociceptive pain of the joint, peripheral sensitized pain from inflammatory factors and centrally sensitized pain[8 9]. This centrally sensitized pain can occur after intense, repeated or prolonged nociceptive input[8 10] and is present in around 23% of the patients with chronic pain due to OA[11].

Several placebo-controlled trials have examined the efficacy of duloxetine for patients with OA and found effect sizes of 0.4-0.5 for pain and 0.6 for disability[12-17]. Based on these trials the Osteoarthritis Research Society International (OARSI) recommends duloxetine for patients with knee OA with depression and/or widespread pain[18] and the American College of Rheumatology (ACR) conditionally recommends duloxetine for OA[19].

The trials investigated the short-term use of duloxetine in placebo-controlled trials in highly controlled secondary care settings[12-17]. The effectiveness in a primary care setting is unknown, while most OA patients are treated in this setting for many years. Neither is known whether the presence of symptoms of centrally sensitized pain alters the response to duloxetine.

Therefore, we conducted a cluster randomised controlled trial with 12-month follow-up to examine the effectiveness and cost-effectiveness of duloxetine for patients with OA in primary care and to assess whether the effect of duloxetine is predominantly found in patients with symptoms of centrally sensitized pain.

METHODS

Study design

A pragmatic open-label cluster randomised trial with two parallel arms was conducted in general practice. A cluster design was chosen, because this type of design is particularly useful for effectiveness and implementation studies, because the cluster design has the advantage of prevention of treatment group contamination and it reflects 'real-life' most closely[20]. The study was approved by the medical ethics committee of the Erasmus MC (MEC 2015-293). Detailed information of the study design is published elsewhere[21].

Setting and participants

GP practices in the South-West of the Netherlands were asked to participate in the study. Participating GPs identified all possible eligible patients in their patient registries and sent these patients an invitation. If patients were interested, patients were screened for eligibility by the research team and gave written informed consent.

Patients were eligible if they were ≥ 18 years, had hip and/or knee OA based on the clinical ACR criteria[22], had chronic pain on most days of the last three months, and had insufficient benefit of NSAIDs, contra-indications for NSAIDs or previous adverse reactions to NSAIDs (e.g. be eligible for third choice pain medication).

Patients were excluded if they were scheduled for total hip replacement (THR) or total knee replacement (TKR), were currently using antidepressants or neuropathic pain medication, had rheumatoid arthritis, were unable to sign informed consent or had contra-indications for the use of duloxetine (current use of monoamine oxidase inhibitors, uncontrolled narrow-angle glaucoma, the combination with other central nervous acting drugs (e.g. benzodiazepines), hypersensitivity to duloxetine, liver disease resulting in hepatic impairment, severe renal impairment (creatinine clearance <30ml/min), current use of CYP1A2 inhibitors, current use of CYP2D6 inhibitors and substrates, uncontrolled hypertension, pregnancy or lactation).

Intervention

GP practices were randomised to treat patients with duloxetine and usual care or usual care alone. In the intervention group, patients were prescribed duloxetine 60mg/day. Patients started with duloxetine 30mg/day in the first week to minimize potential adverse events. When the dose was tolerated well, this was increased to 60mg/day in the second week. The therapeutic effect was assessed regularly by the treating GP (2 weeks and 1,3,6,9 and 12 months). Duloxetine was gradually discontinued after three months when patients experienced no effect and/or when patients had intolerable side-effects.

Usual care was provided according to the Dutch GP guidelines[23] and consists of education, life style advice, diet, physiotherapy and analgesics. Intra-articular injection of glucocorticoids and referral to secondary care were also allowed.

Randomisation

Randomisation was performed at practice level (cluster design). An independent data-manager of the department provided a computer list (allocation ratio 1:1). Block randomisation was used with blocks varying between 2, 4 and 6. Since care provided by the GP can differ based on practice characteristics randomisation was stratified on 1) socio-economic status of the practice location based on the registration by the Netherlands Institute of Social Research (low vs normal and high)[24], 2) the number of GPs working in the practice (≤1fte vs >1 fte), and the mean age of the GPs (<50 years vs ≥50 years)[25 26].

The randomisation procedure was concealed to the researchers. The research team performed randomisation after all eligible patients were identified and the first patient had signed informed consent. Patients were informed about the outcome of randomisation after filling in the baseline questionnaire. The study was open label; patients, GPs and the research team were not blinded for the treatment.

Outcomes

Patients received questionnaires at baseline, at 6 weeks and at 3, 6, 9 and 12 months. Primary outcome was pain at 3 months measured with the Western Ontario Mc Master Universities (WOMAC) Osteoarthritis Index[27]. The WOMAC consists of three domains; pain (0-20), stiffness (0-8) and function (0-68), with higher scores indicating more complaints.

Secondary outcomes were pain and function (WOMAC) at one year, quality of life (EQ-5D-5L), cost-effectiveness, co-interventions, adverse events, patients satisfaction measured on a 11-numeric rating scale (0= completely dissatisfied to 10=completely satisfied) and patient improvement measured on a 7-point Likert scale (from 'totally improved' to 'worse than ever').

The percentage of responders was also evaluated by the OMERACT-OARSI response criteria[28]. Response is defined as 1) a high improvement in pain or function (≥50%) and an absolute change of ≥20 (scale 0–100) or 2) improvement in at least two of the three following: pain ≥20% and absolute change ≥10; function ≥20% and absolute change ≥10; patients' global assessment ≥20% and absolute change ≥10.

Sample size

To detect a clinically relevant difference in WOMAC pain of 1.9 points (pooled SD 4.8)[12] between the two groups with an effect size of 0.4 (power 80%; alpha 0.05), taking into account the cluster randomisation with the assumption of equal cluster sizes with three

patients per practice and an intra-cluster correlation coefficient (ICC) of 0.01, 102 patients per treatment group were required. Around 10% loss to follow-up was expected[29] and we therefore needed to include 224 patients (2x112). In order to detect a larger effect in patients with symptoms of centrally sensitized pain we needed 44 patients per group (effect size 0.6, a difference in WOMAC pain of 2.9 points (pooled SD 4.8), same power and cluster assumptions). In advance we estimated that 37% of the included patients would have symptoms of centrally sensitized pain[30] and 47% of the patients in the trial had symptoms of centrally sensitized pain. Therefore, no sample size adjustments had to be made for this subgroup analysis.

Statistical analysis

Analyses were performed according to the intention to treat principle. Descriptive statistics were used to describe baseline characteristics of GP practices and patients.

A linear mixed model with repeated measurements was used to assess the differences between the two groups. The GP practices were included as a random effect to account for clustering. The change of WOMAC scores over time was non-linear and therefore a natural spline was added at 26 weeks.

Generalised estimating equations (GEE) analysis with an autoregressive correlation structure were performed for dichotomous outcomes. Analyses were adjusted for prognostic factors at baseline when they differed ≥10% between the two groups.

Additional per protocol analyses were carried out. Patients were included in this analysis when using duloxetine for ≥4 weeks or when not using neuropathic pain medication in the usual care group. Furthermore, predefined subgroup analysis for patients with symptoms of centrally sensitized pain was performed. Patients were included in this subgroup analysis when scoring >12 on the modified painDETECT questionnaire. Scores >12 on this questionnaire are associated with the presence of symptoms of centralized pain in OA[30].

A cost-utility analysis was performed. The utility values of the Dutch public for EuroQoL health states were used to calculate quality adjusted life years (QALYs) based on the EQ-5D-5L[31]. The costs were based on the year 2018. Only costs that were related to OA or pain medication were included. The degree of uncertainty for costs was assessed by using non-parametric bootstrapping. From the original sample 2500 observations with replacement were drawn. Two perspectives were assessed, the health care perspective including only health care costs, and the societal perspective, including health care and non-health care costs. The cost-utility was calculated for the follow-up of one year.

The mixed model analyses and GEE analyses were performed with R (version 3.6.3). All other analyses were performed with SPSS version 25 (IBM Corp., Armonk, NY, USA).

Patient and public involvement

The Department of General Practice has a patient panel. Patients with OA were involved in all phases of research. The design of the trial, patient information, study procedures and methods of recruitment were discussed. Once the results of the trial are published, they will be involved in the dissemination of the results of the trial to the patients that participated in the trial and to other patients with OA. They will check the validity of the conclusions from a public perspective and highlight findings that are more relevant to the public.

RESULTS

Participants

Recruitment of patients took place between January 2016 and February 2019 and follow-up was completed in February 2020. 231 GPs in 110 GP practices participated in the study. In total, 4748 patients were registered with knee or hip OA in GP records and 3258 patients could be excluded based on the presence of exclusion criteria in their medical record (Figure 1). 1490 patients were potentially eligible and were invited to participate. 768 patients responded no to the invitation letter, 295 patients were interested but not eligible and 73 patients were interested and eligible, but declined to participate. Most mentioned reason for declining by the eligible patients was fear of side-effects. Finally, 133 patients were included in the study and one patient got lost to follow-up before randomisation; 66 patients (31 GP practices) were randomised to duloxetine and usual care, and 66 patients (35 GP practices) to usual care alone. The 12-month follow-up was completed by 53 patients in each arm (80.3%).

The baseline characteristics of the GP practices and patients are shown in Table 1 (Supplemental data Table S1 for Baseline characteristics of patients with symptoms of centrally sensitized pain). Characteristics of the GP practices were similar in both groups. Some characteristics of the patients differed between the two groups. The duloxetine group consisted of fewer women (59.1% vs 75.8%), patients were slightly younger (63.2 years vs 65.4 years) and had fewer comorbidities (15.2% vs 33.2% had ≥ 2 comorbidities). Most patients included had knee OA (77.3% in duloxetine group and 86.4% in the usual care group) and 40% of the patients had symptoms of centralized pain.

Primary outcome

The primary outcome was WOMAC pain at three months. Patients in the duloxetine group had slightly less pain than patients in the usual care group (adjusted difference -0.49 [95%CI -1.65 to 0.65]), which was not clinically relevant nor statistically significant. The 95% confidence interval even ruled out a clinical relevant effect of 1.9 points. The

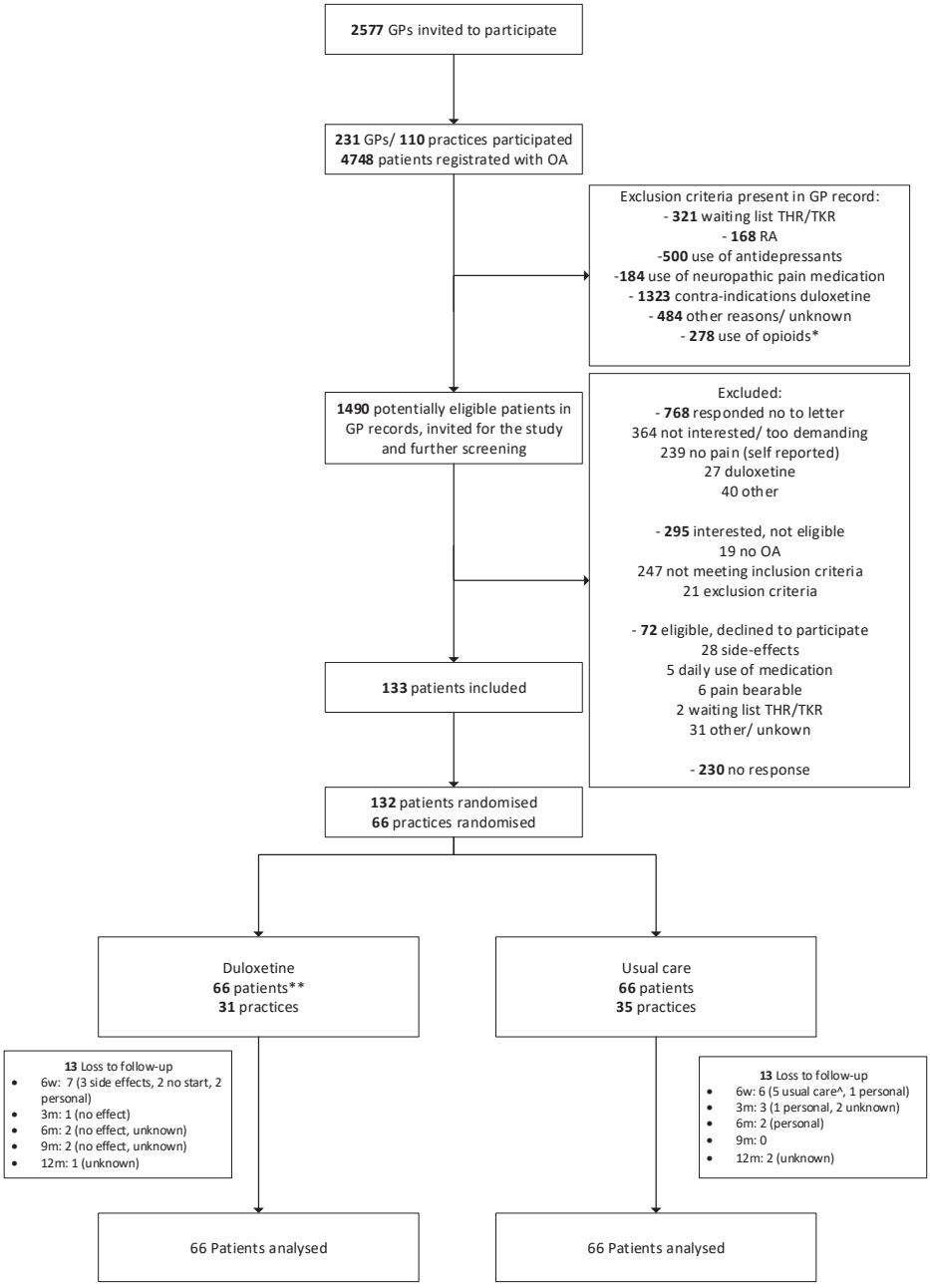

Figure 1. Flowchart of the study

* Initially patients using opioids were excluded from the trial, **One GP practice recruited 4 patients after randomization, ^Patients stopped participating, because they hoped they would receive duloxetine and were randomised to treatment according to usual care

GP=general practitioner, OA=osteoarthritis, THR=total hip replacement, TKR=total knee replacement, RA=rheumatoid arthritis, w=weeks, m=months

Table 1. Baseline characteristics

	Duloxetine (n=66)	Usual care (n=66)
GP Practice		
Number of practices	31	35
Number of GPs, median	2	2
Number of GPs fte	1.7 (1.1)	1.9 (1.0)
High SES (vs low SES)	23 (74.2)	27 (77.1)
Age (years) of GP, mean (SD)	48.7 (8.2)	48.3 (8.8)
Patients included, median (range)	2 (1-6)	2 (1-4)
Patients		
Female, n (%)	39 (59.1)	50 (75.8)
Age, mean (SD)	63.2 (10.5)	65.4 (11.2)
BMI, mean (SD)	30.6 (6.6)	30.9 (6.2)
Comorbidities (self-reported), n (%)		
Cardiovascular diseases	4 (6.1)	9 (13.8)
Lung diseases	4 (6.1)	15 (23.1)
Diabetes mellitus	10 (15.2)	8 (12.3)
Other musculoskeletal disorders	47 (71.2)	50 (75.8)
≥ 2 comorbidities	10 (15.2)	22 (33.8)
Employment, n (%)	31 (47.0)	23 (34.8)
Duration of symptoms (years), mean (SD)	7.8 (6.5)	9.2 (8.2)
Joint affected, n (%)		
Hip	15 (22.7)	9 (13.6)
Knee	51 (77.3)	57 (86.4)
WOMAC, mean (SD)		
Pain (0-20)	9.8 (4.2)	10.5 (3.6)
Stiffness (0-8)	4.5 (1.8)	5.0 (1.5)
Function (0-68)	34.8 (13.3)	36.2 (11.1)
Modified pain detect (0-35), mean (SD)	11.4 (6.8)	13.5 (7.0)
<12, n (%)	39 (59.1)	32 (48.5)
12-18, n (%)	14 (21.2)	13 (21.2)
> 18, n (%)	13 (19.7)	19 (28.8)
Most painful activity (0-10), mean (SD)	7.0 (1.3)	7.4 (1.4)
HADS		
Depression	4.2 (3.5)	3.6 (3.1)
Anxiety	4.5 (3.8)	4.0 (3.3)
EQ5D (-0.446;1), n (%)	0.628 (0.168)	0.613 (0.161)
Treatment, n (%)		
None	18 (27.3)	20 (30.3)
Paracetamol	28 (42.4)	25 (37.9)
NSAIDS	30 (45.5)	28 (42.4)
Opioids	6 (9.1)	10 (15.2)

*Most painful activity as mentioned by the patient, activities are mentioned in Supplemental Table S4.
GP=general practitioner, SES=socio-economic status, SD=standard deviation, BMI=body mass index, WOMAC=Western Ontario and McMaster University Index, HADS=hospital anxiety and depression scale, EQ5D=Euroqol, NSAIDs=non-steroidal anti-inflammatory drugs

analyses were adjusted for age, sex, modified painDETECT score, HADS depression score and the presence of two or more comorbidities. The intra-cluster correlation coefficient for the adjusted analysis for WOMAC pain was 0.18 (Figure 2 and Table 2).

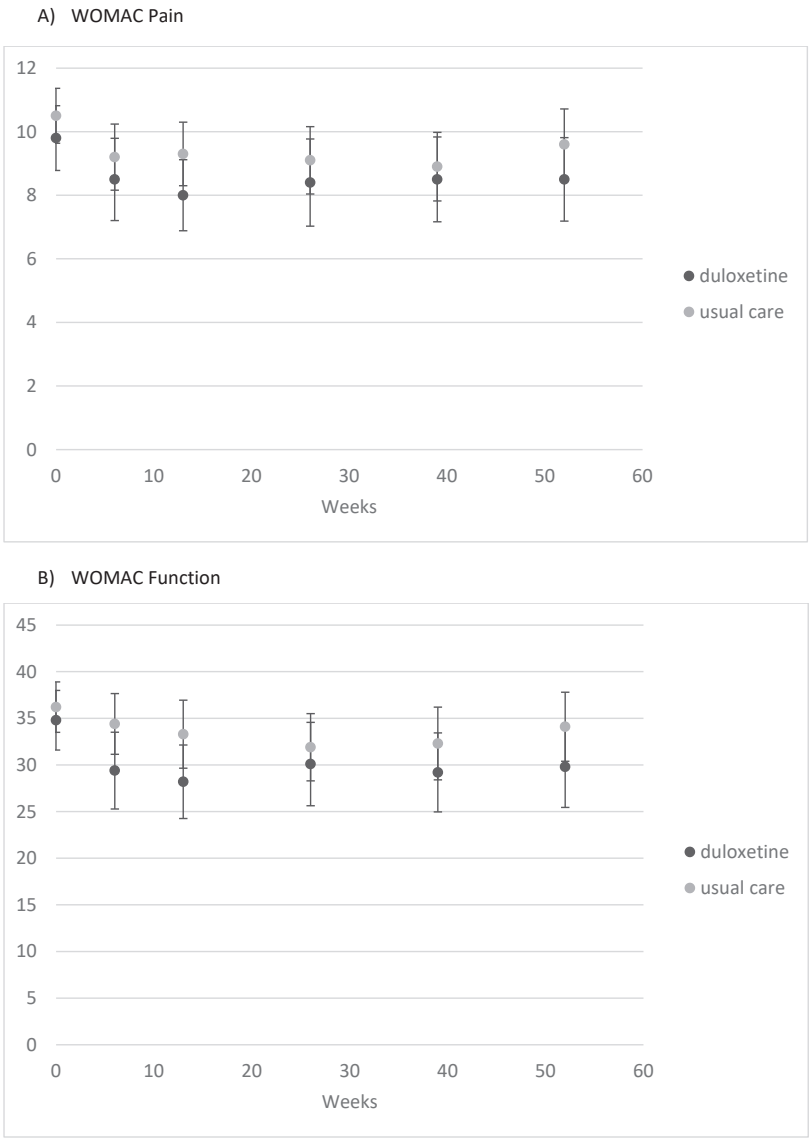

Figure 2. Course of WOMAC Pain and Function
WOMAC=Western Ontario and McMaster University Index

Table 2. Results for primary and secondary outcomes

		Mean (SD)		Unadjusted model		Adjusted model*	
		Duloxetine (n=66)	*Usual care (n=66)*	*Difference (95% CI)*	*Effect size*	*Difference (95% CI)*	*Effect size*
WOMAC pain (0-20)	6w	8.5 (4.9)	9.2 (4.1)	-0.87 (-2.17; 0.42)	0.22	-0.49 (-1.62; 0.65)	0.14
	3m	8.0 (4.3)	9.3 (3.7)	-0.84 (-2.18; 0.49)	0.21	-0.58 (-1.80; 0.63)	0.16
	6m	8.4 (3.9)	9.1 (3.8)	-0.80 (-2.32; 0.70)	0.18	-0.66 (-2.09; 0.78)	0.15
	9m	8.5 (4.6)	8.9 (3.8)	-0.79 (-2.28; 0.71)	0.18	-0.52 (-1.93; 0.89)	0.12
	12m	8.5 (4.8)	9.6 (4.2)	-0.78 (-2.46; 0.91)	0.15	-0.26 (-1.86; 1.34)	0.05
WOMAC function (0-68)	6w	29.4 (15.6)	34.4 (12.6)	-3.95 (-8.03; 0.13)	0.32	-1.42 (-5.31; 2.47)	0.12
	3m	28.2 (15.1)	33.3 (13.4)	-4.19 (-8.61; 0.23)	0.32	-2.10 (-6.39; 2.20)	0.16
	6m	30.1 (16.1)	31.9 (13.2)	-4.49 (-9.70; 0.71)	0.29	-2.84 (-8.00; 2.33)	0.18
	9m	29.2 (14.8)	32.3 (13.8)	-4.52 (-9.57; 0.53)	0.30	-2.61 (-7.52; 2.31)	0.18
	12m	29.8 (16.2)	34.1 (13.8)	-4.38 (-9.84; 1.09)	0.27	-1.79 (-7.22; 3.64)	0.11
WOMAC stiffness (0-8)	6w	4.1 (2.0)	4.5 (1.7)	-0.56 (-1.07; -0.05)	0.37	-0.58 (-1.10; -0.06)	0.37
	3m	4.0 (1.8)	4.7 (1.7)	-0.54 (-1.06; -0.01)	0.34	-0.57 (-1.11; -0.03)	0.35
	6m	4.2 (1.6)	4.5 (1.7)	-0.48 (-1.07; 0.11)	0.27	-0.51 (-1.13; 0.11)	0.27
	9m	4.0 (1.6)	4.4 (1.6)	-0.38 (-0.93; 0.17)	0.23	-0.37 (-0.94; 0.20)	0.22
	12m	4.0 (1.8)	4.3 (1.7)	-0.26 (-0.92; 0.41)	0.13	-0.18 (-0.87; 0.50)	0.09
Most painful activity (0-10)	3m	6.1 (2.3)	6.8 (1.8)	-0.45 (-0.98; 0.06)	0.29	-0.52 (-1.05; 0.02)	0.32
	12m	6.2 (2.6)	6.8 (1.8)	-0.46 (-0.98; 0.05)	0.30	-0.52 (-1.05; 0.01)	0.33
Quality of life (-0,446;1)	3m	0.678 (0.157)	0.641 (0.144)	0.01 (-0.01; 0.03)	0.17	0.02 (-0.04; 0.07)	0.12
	6m	0.642 (0.171)	0.623 (0.180)	0.01 (-0.02; 0.05)	0.10	0.02 (-0.04; 0.09)	0.10
	9m	0.656 (0.172)	0.617 (0.187)	0.01 (-0.03; 0.05)	0.08	0.02 (-0.04; 0.08)	0.11
	12m	0.652 (0.221)	0.638 (0.177)	0.00 (-0.05; 0.05)	0.00	0.01 (-0.06; 0.08)	0.05

		Mean (SD)		Unadjusted model		Adjusted model*	
		Duloxetine (n=66)	*Usual care (n=66)*	*Difference (95% CI)*	*Effect size*	*Difference (95% CI)*	*Effect size*
Patient satisfaction (0-10)	3m	6.0 (2.8)	5.6 (2.7)	0.56 (-0.66; 1.78)	0.15	0.62 (-0.67; 1.91)	0.16
	6m	5.9 (2.7)	5.6 (2.3)	0.56 (-0.66; 1.78)	0.33	0.63 (-0.66; 1.93)	0.16
	9m	5.9 (2.8)	5.7 (2.3)	0.56 (-0.66; 1.77)	0.15	0.63 (-0.66; 1.92)	0.16
	12m	5.8 (2.7)	5.5 (2.5)	0.55 (-0.65; 1.75)	0.15	0.61 (-0.66; 1.88)	0.16
		n(%)	*n (%)*	*OR (95% CI)*		*OR (95% CI)*	
Perceived improvement (yes/no)	3m	16 (28.6)	3 (6.0)	6.38 (1.68-24.21)		17.40 (2.85-106.18)	
	12m	15 (29.4)	4 (7.8)	4.65 (1.39-15.45)		5.33 (1.57-19.29)	
Responder according to OARSI omeract criteria (yes/no)	3m	21 (37.5)	13 (25.0)	1.74 (0.75-4.01)		1.95 (0.78-4.84)	
	12m	17 (32.1)	13 (24.5)	1.69 (0.70-4.04)		1.33 (0.51-3.50)	

*Adjusted for age, gender, modified painDETECT score, HADS depression scale score and the presence of 2 or more co-morbidities, WOMAC=Western Ontario and McMaster University Index, SD=standard deviation, CI=confidence interval, OR=odds ratio, w=weeks, m=months

Secondary outcomes

The WOMAC pain at 12 months also showed a small difference in favour of the duloxetine group (adjusted difference -0.26 [95% CI -1.86 to 1.34]). The WOMAC function scores also showed a small difference at three months (-1.42 [95% CI -5.31 to 2.47]) and at 12 months (-1.79 [95% CI -7.22 to 3.64]). The other secondary outcomes quality of life, patient satisfaction and the OMERACT-OARSI responder criteria also showed small differences. None of the differences between the two groups were clinically relevant or statistically significant. Patient improvement was significantly different between the two groups (OR 17.40 95% CI [2.85 to 106.18]), but numbers were small and confidence intervals were broad. Additional per protocol analysis showed similar results (Supplemental Table S2). In the subgroup analysis for patients with symptoms of central sensitization a small non-significant difference in WOMAC pain was found at 3 and 12 months (adjusted differences -0.32 95% CI [-2.32 to 1.67] and 1.02 95% CI [-1.22 to 3.27] respectively, Supplemental Table S3). Based on the 95% CI a larger effect of duloxetine could be ruled out (difference of 2.9 point in WOMAC pain scale, effect size 0.6), but a smaller effect cannot be excluded based on the 95% CI (1.9 points, effect size 0.4).

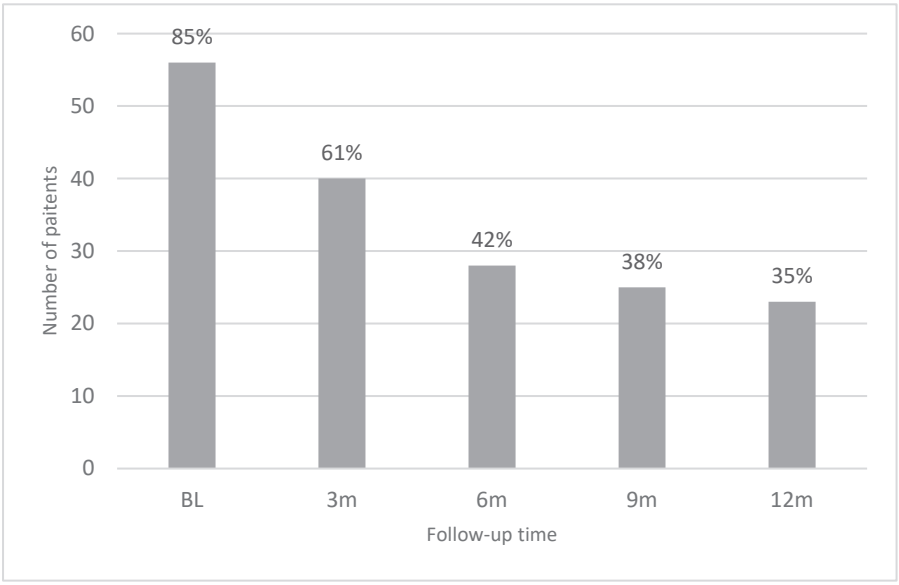

Figure 3. Patients using duloxetine
BL=baseline, m=months

Duloxetine use

Of the 66 patients in the duloxetine group 56 patients (85%) started using duloxetine (Figure 3). The most mentioned reason for not starting with duloxetine was fear of side-effects of duloxetine (7 patients). After three months 61% of the patients and at 1 year 35% of the patients were still using duloxetine. In total, 33 patients (59%) discontinued duloxetine. Patient reported reasons for stopping were no effect (24%), side-effects (49%) and no effect+ side-effects (18%).

Adverse events

At 3 months 89.3% of the patients in the duloxetine group reported at least one side-effect compared to 72.5% in the usual care group (Supplemental Figure S1). Nausea, weight loss, constipation, yawning and hyperhidrosis were reported significantly more frequently by patients in the duloxetine group. These are well known side-effects of duloxetine.

Co-interventions

Patients in the duloxetine group contacted their GP more frequently (51.8% vs 30.8% at 3 months, Table 3) and were more often referred to an orthopaedic surgeon (10.7% vs 3.8% at 3 months). In the total follow-up time, 5 patients in the duloxetine group had a THR or TKR while none of the patients receiving usual care had a THR or TKR. Patients

Table 3. Co-interventions

		Duloxetine, n (%)	Usual care, n (%)
Medication			
Paracetamol	6w	24 (43.6)	29 (50.0)
	3m	31 (55.4)	34 (51.5)
	6m	30 (60.0)	31 (60.8)
	9m	28 (59.6)	27 (56.3)
	12m	30 (56.6)	31 (58.5)
NSAIDs	6w	10 (18.2)	18 (31.0)
	3m	16 (28.6)	25 (48.1)
	6m	25 (50.0)	28 (54.9)
	9m	18 (38.3)	24 (50.0)
	12m	19 (35.8)	29 (54.7)
Opioids	6w	1 (1.8)	3 (5.2)
	3m	2 (3.6)	6 (11.5)
	6m	5 (10.0)	5 (9.8)
	9m	4 (8.5)	4 (8.3)
	12m	5 (9.4)	6 (11.3)
None	6w	25 (45.5)	17 (29.3)
	3m	17 (30.4)	8 (15.4)
	6m	7 (14.0)	4 (7.8)
	9m	11 (23.4)	10 (20.8)
	12m	13 (24.5)	12(22.6)
Co-interventions			
Visit GP	6w	NA	NA
	3m	29 (51.8)	16 (30.8)
	6m	24 (48.0)	5 (9.8)
	9m	16 (34.0)	6 (11.8)
	12m	10 (18.1)	12 (22.6)
Physiotherapy	6w	NA	NA
	3m	11 (19.6)	9 (17.3)
	6m	6 (12.0)	7 (13.8)
	9m	8 (17.0)	5 (10.4)
	12m	7 (13.2)	5 (9.4)
Visit orthopedic surgeon	6w	NA	NA
	3m	6 (10.7)	2 (3.8)
	6m	3 (6.0)	4 (7.8)
	9m	4 (8.5)	2 (4.2)
	12m	1 (1.9)	1 (1.9)
Corticosteroid injections	6w	1 (1.8)	4 (7.0)
	3m	1 (1.8)	3 (6.0)
	6m	3 (6.0)	3 (5.9)
	9m	0	3 (6.3)
	12m	1 (1.9)	4 (7.5)
Joint replacements	6w	1 (1.8)	0
	3m	0	0
	6m	1 (2.5)	0
	9m	1 (2.1)	0
	12m	3 (3.8)	0

NSAIDS=non-steroidal anti-inflammatory drugs, GP=general practitioner, w=weeks, m=months, NA=not applicable

treated according to usual care used more NSAIDs (48.1% vs 28.1% at 3 months) and opioids (11.5% vs 3.6% at 3 months), and were more likely to receive a corticosteroid injection (6.0 vs 1.8% at 3 months).

Cost-effectiveness

A small positive difference of 0.04 QALYs was found for the duloxetine group, a difference of 0.06 is considered clinically relevant [32]. The costs per gained QALY were €13.000,- from a health care perspective. The uncertainty analysis showed 80% probability that these costs were lower than €50.000,- per QALY gained, which is the threshold for moderate disease severity. From a societal perspective, these costs were €54.000,- with a 48% probability of costs being lower than €50.000,-. When leaving out the costs for the THR and TKR the costs per gained QALY were lower. From a health care perspective, the costs were €1.300,- (with 87% probability being lower than €50.000,-) and from societal perspective €42.000,- (58% probability lower than €50.000,-).

DISCUSSION

In this study the effectiveness and cost-effectiveness of duloxetine added to usual care compared to usual care alone was examined for patients with chronic OA pain. Furthermore, it was assessed whether the effect of duloxetine was predominantly found in patients with symptoms of centrally sensitized pain. We did not find a clinically relevant or statistically significant effect of duloxetine for WOMAC pain at 3 months, nor for the other outcomes or at other time points and can rule out the presence of a clinically relevant effect for the total group (1.9 points difference in WOMAC pain). The intervention was also not cost-effective, since the difference in quality of life (EQ-D5-5L) between the duloxetine group and usual care group was too small to be considered clinically relevant. Finally, no effect was found for the subgroup of patients with symptoms of centrally sensitized pain.

A strength of the current trial is the pragmatic cluster design, which is suitable for evaluating an intervention in 'real-life' and provides information on the effectiveness of the intervention [20]. A cluster RCT can be prone to recruitment bias [33 34], but this was minimised by identifying all eligible patients before randomisation of the GP practice. However, one GP practice in the duloxetine group recruited four patients after randomisation. Sensitivity analysis without those four patients did not alter the results (data not shown).

A limitation of the current trial is that we did not recruit the number of patients as calculated in the sample size. However, even with this sample size we can rule out a clinically relevant effect for the complete group since the predefined clinically relevant

difference was not in the 95% confidence interval and a larger study population would have narrowed the 95% CI. For the subgroup analysis of patients with symptoms of centralized pain, we cannot rule out that there may be a clinically relevant effect. We hypothesized that in this subgroup the effect of duloxetine would be larger (difference of 2.9 points on WOMAC pain scale) and this larger effect can be ruled out, but the presence of a smaller difference of 1.9 points on WOMAC pain scale cannot be completely ruled out, though the point estimates of this subgroup analysis were similar to the complete group. Finally, the trial was powered at the primary outcome (WOMAC pain) and not at the cost-effectiveness analysis. Costs usually have greater variability and a much larger sample size would have been necessary for a reliable cost-effectiveness analysis.

We did not find an effect of duloxetine for patients with OA pain, while other studies have found a small to moderate effect of duloxetine [12-17]. The baseline pain scores of the patients in our trial were similar to the pain scores of patients in the other trials [12-17]. This difference can be due to the fact that we studied the effectiveness of duloxetine in primary care, while the other studies examined the efficacy in placebo-controlled trials in secondary care. Furthermore, the patients in our trial were older, had OA complaints for a longer time and had more comorbidities than those in the other studies. It is known that in these more 'real-life' primary care populations and in effectiveness studies smaller effects are found than in highly controlled efficacy trials [20]. We evaluated duloxetine as a third choice analgesic, i.e. when paracetamol and NSAIDs failed. In most other studies this was not a prerequisite to participate in the study. Only in the study of Frakes *et al*. [14], treatment was first optimized with NSAIDs and patients were included in the trial when still in pain despite optimal treatment with NSAIDs.

Finally, we had a follow-up period of one year and found that 35% of the patients were still using duloxetine at one year. The majority of the patients stopped using duloxetine around 3 months because of lack of effect or the presence of side effects. The percentage of patients discontinuing duloxetine is higher in our study than in the two other studies that evaluated the long-term use of duloxetine in OA in an open-label extension phase of the trial. In one study around 80% of the patients continued to use duloxetine up to 26 weeks [35]. In the second study around 85% continued the use of duloxetine up to one year [36]. However, only a quarter of the patients entered the extension phase and reasons for not continuing in the extension phase of the study were not mentioned, which could have led to a selection of patients who benefit and tolerate duloxetine well. In our trial GPs were instructed to discontinue duloxetine after three months when patients did not experience an effect or had intolerable side effects. This may also have contributed to the higher percentage of patients that discontinued duloxetine in our trial.

Interestingly, a THR or TKR was performed more often in patients in the duloxetine group than in patients in the usual care group during the follow-up time. At 3 months, patients were referred to an orthopaedic surgeon more frequently and afterwards more

THR and TKR were performed. We believe this is caused by the fact that patients in the duloxetine group visited their GP more often and when treatment with duloxetine failed, this was the next step. To our knowledge this has not been reported in other pragmatic trials. This higher number of THR and TKR in the duloxetine group influenced the costs of the intervention, the costs from health care perspective were tenfold lower when the THR and TKR were excluded from the analysis.

Furthermore, patients in the duloxetine group reported significantly more often improvement of complaints compared to patients in the usual care group while none of the other outcome measurements differed between the two groups. This may have been caused by the open-label character of the trial. The absolute number of patients reporting improvement was low, which lead to wide 95% CI.

For patients with symptoms of central sensitization also no effect was found. Overall, these patients had more pain at baseline and were slightly younger (but had a similar duration of complaints) compared to the complete group. Higher pain scores are known to be associated with the presence of central sensitization [37]. Since the prognostic differences between the two groups were slightly different a sensitivity analysis was performed with adjustment for these variables (age, sex, joint and comorbidities). Results of this analysis were similar to the original analysis (data not shown).

To conclude, there was no clinically relevant effect of duloxetine added to usual care compared to usual care alone for chronic OA pain and it should not be implemented. For patients with symptoms of centralized pain an effect cannot be ruled out and future research in this subgroup is needed to confirm our results.

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SUPPLEMENTARY DATA

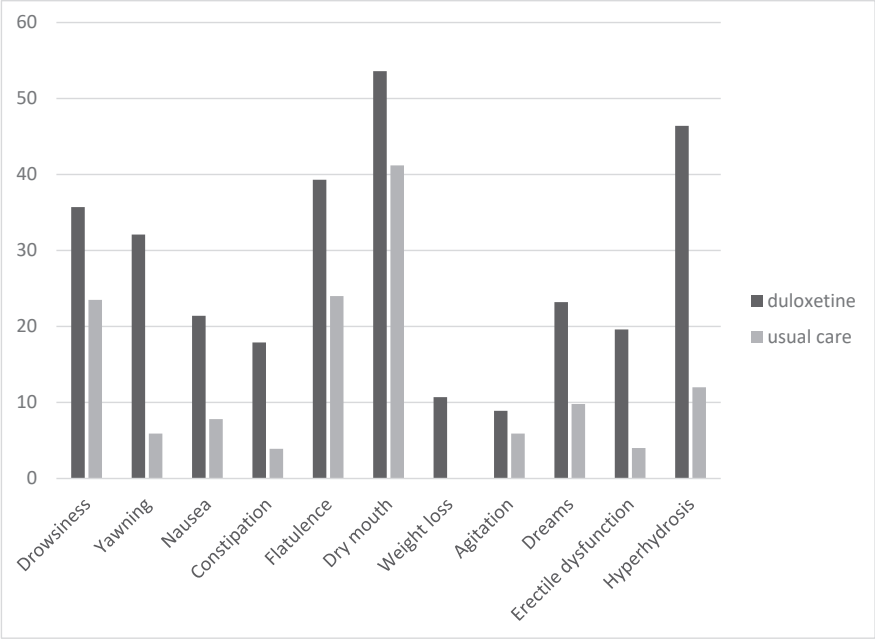

Figure S1. Side-effects at 3 months

Table S1. Baseline characteristics of patients with symptoms of centrally sensitized pain

	Duloxetine (n=27)	Usual care (n=33)
Female, n (%)	17 (63.0)	23 (69.7)
Age, mean (SD)	59.4 (9.6)	63.1 (10.7)
BMI, mean (SD)	30.5 (6.3)	31.2 (6.7)
Comorbidities (self-reported), n (%)		
Cardiovascular diseases	0	3 (9.1)
Lung diseases	1 (3.7)	8 (24.2)
Diabetes mellitus	2 (7.4)	4 (12.1)
Other musculoskeletal disorders	22 (81.5)	24 (72.7)
≥ 2 comorbidities	3 (11.1)	10 (30.3)
Employment, n (%)	17 (37.0)	14 (42.4)
Duration of symptoms (years), mean (SD)	10.0 (8.0)	7.6 (4.8)
Joint affected, n (%)		
Hip	6 (22.2)	3 (9.1)
Knee	21 (77.8)	30 (90.9)
WOMAC, mean (SD)		
Pain (0-20)	12.0 (3.5)	11.7 (3.1)
Stiffness (0-8)	5.0 (1.5)	5.2 (1.6)
Function (0-68)	40.3 (12.0)	39.2 (10.8)
Modified pain detect (0-35), mean (SD)	18.1 (4.1)	19.2 (4.1)
Most painful activity (0-10), mean (SD)	7.1 (1.3)	7.7 (1.2)
HADS		
Depression (0-21)	4.3 (3.5)	4.0 (3.4)
Anxiety (0-21)	4.9 (4.2)	4.1 (3.7)
EQ5D (-0.446;1)	0.626 (0.188)	0.574 (0.185)
Treatment, n (%)		
None	7 (25.9)	8 (24.2)
Paracetamol	10 (37.0)	14 (42.4)
NSAIDS	15 (55.6)	15 (45.5)
Opioids	2 (7.4)	6 (18.2)

*Most painful acitivity as mentioned by the patient, activities are mentioned in Supplemental Table S4.
GP=general practitioner, SES=socio-economic status, SD=standard deviation, BMI=body mass index, WOMAC=Western Ontario and McMaster University Index, HADS=hospital anxiety and depression scale, EQ5D=Euroqol, NSAIDs=non-steroidal anti-inflammatory drugs

Table S2. Per protocol analysis primary and secondary outcomes

		Mean (SD)		Unadjusted model		Adjusted model*	
		Duloxetine (n=45)	*Usual care (n=64)*	*Difference (95% CI)*	*Effect size*	*Difference (95% CI)*	*Effect size*
WOMAC pain (0-20)	6w	8.1 (5.1)	9.2 (4.0)	-0.96 (-2.39; 0.47)	0.25	-0.44 (-1.75; 0.88)	0.12
	3m	7.9 (4.3)	9.1 (3.7)	-0.84 (-2.30; 0.62)	0.21	-0.44 (-1.80; 0.92)	0.12
	6m	8.8 (4.9)	9.1 (3.9)	-0.72 (-2.32; 0.89)	0.17	-0.41 (-1.97; 1.13)	0.10
	9m	8.8 (4.4)	8.9 (3.9)	-0.79 (-2.37; 0.79)	0.19	-0.35 (-1.87; 1.16)	0.09
	12m	8.5 (4.8)	9.8 (4.1)	-0.98 (-2.77; 0.81)	0.20	-0.27 (-2.00; 1.47)	0.06
WOMAC function (0-68)	6w	27.9 (15.6)	34.7 (12.7)	-4.75 (-9.31; -0.19)	0.37	-1.90 (-6.22; 2.43)	0.08
	3m	28.1 (14.9)	33.1 (13.6)	-4.40 (-9.26; 0.46)	0.34	-2.10 (-6.73; 2.54)	0.17
	6m	31.9 (16.0)	31.9 (13.3)	-4.06 (-9.64; 1.52)	0.27	-2.37 (-7.81; 3.07)	0.16
	9m	29.7 (14.5)	32.6 (13.7)	-4.31 (-9.80; 1.17)	0.29	-2.47 (-7.72; 2.78)	0.18
	12m	30.0 (16.3)	34.7 (13.5)	-4.93 (-10.85; 0.99)	0.62	-2.46 (-8.27; 3.34)	0.16
WOMAC stiffness (0-8)	6w	3.9 (2.0)	4.6 (1.6)	-0.65 (-1.20; -0.10)	0.44	-0.62 (-1.21; -0.04)	0.39
	3m	3.9 (1.8)	4.7 (1.7)	-0.59 (-1.16; -0.03)	0.39	-0.60 (-1.18; -0.01)	0.38
	6m	4.3 (1.7)	4.5 (1.8)	-0.48 (-1.10; 0.15)	0.29	-0.50 (-1.16; 0.15)	0.28
	9m	4.1 (1.5)	4.4 (1.6)	-0.35 (-0.92; 0.22)	0.23	-0.33 (-0.93; 0.27)	0.20
	12m	4.2 (1.9)	4.5 (1.6)	-0.22 (-0.92; 0.48)	0.12	-0.11 (-0.84; 0.62)	0.06
Most painful activity (0-10)	3m	6.1 (2.3)	6.8 (1.9)	-0.46 (-1.04;0.11)	0.30	-0.58 (-1.16; 0.01)	0.37
	12m	6.4 (2.3)	6.8 (1.8)	-0.47 (-1.04;0.10)	0.31	-0.58 (-1.16; 0.00)	0.37
Quality of life (-0,446;1)	3m	0.679 (0.166)	0.638 (0.145)	0.05 (-0.02; 0.11)	0.29	0.02 (-0.04; 0.09)	0.11
	6m	0.627 (0.172)	0.620 (0.181)	0.05 (-0.02; 0.13)	0.25	0.03 (-0.04; 0.10)	0.16
	9m	0.646 (0.176)	0.614 (0.188)	0.05 (-0.03; 0.12)	0.25	0.02 (-0.05; 0.09)	0.11
	12m	0.645 (0.239)	0.645 (0.178)	0.03 (-0.06; 0.12)	0.12	0.01 (-0.07; 0.09)	0.05

		Mean (SD)		Unadjusted model		Adjusted model*	
		Duloxetine (n=45)	*Usual care (n=64)*	*Difference (95% CI)*	*Effect size*	*Difference (95% CI)*	*Effect size*
Patient satisfaction (0-10)	3m	6.2 (2.8)	5.6 (2.7)	0.80 (-0.51;2.11)	0.23	0.77 (-0.63; 2.16)	0.21
	6m	6.2 (2.6)	5.6 (2.3)	0.80 (-0.51;2.11)	0.23	0.77 (-0.62; 2.17)	0.21
	9m	6.1 (2.5)	5.6 (2.3)	0.80 (-0.51;2.10)	0.23	0.77 (-0.62; 2.16)	0.21
	12m	6.0 (2.8)	5.5 (2.5)	0.79 (-0.50;2.09)	0.23	0.76 (-0.62; 2.13)	0.21
		n (%)	*n (%)*	*OR (95% CI)*		*OR (95% CI)*	
Perceived improvement (yes/no)	3m	14 (32.6)	3 (6.1)	7.60 (1.95-29.64)		17.27 (3.09-96.37)	
	12m	12 (30.0)	4 (8.0)	4.74 (1.37-16.41)		5.09 (1.40-18.44)	
Responder according to OARSI-omeract criteria (yes/no)	3m	17 (39.5)	13 (26.0)	1.85 (0.76-4.49)		2.24 (0.84-5.95)	
	12m	14 (34.1)	11 (21.6)	2.00 (0.79-5.09)		1.65 (0.59-4.61)	

*Adjusted for baseline score, age, gender, modified painDETECT score, HADS depression scale score and the presence of 2 or more comorbidities, WOMAC=Western Ontario and McMaster University Index, SD=standard deviation, CI=confidence interval, OR=odds ratio, w=weeks, m=months

Table S3. Neuropathic pain subgroup analysis primary and secondary outcomes

		Mean (SD)		Unadjusted model		Adjusted model*	
		Duloxetine (n=27)	*Usual care (n=33)*	*Difference (95% CI)*	*Effect size*	*Difference (95% CI)*	*Effect size*
WOMAC pain (0-20)	6w	10.0 (4.8)	10.8 (4.1)	-0.64 (-2.33; 1.04)	0.19	0.09 (-1.54; 1.72)	0.03
	3m	8.7 (4.5)	9.8 (3.6)	-0.75 (-2.68; 1.17)	0.19	-0.32 (-2.32; 1.67)	0.08
	6m	10.2 (5.5)	10.3 (3.6)	-0.78 (-3.22; 1.67)	0.16	-0.63 (-3.24; 1.98)	0.12
	9m	10.3 (5.3)	9.1 (3.8)	-0.46 (-2.85; 1.93)	0.09	-0.06 (-2.50; 2.37)	0.01
	12m	10.3 (4.4)	10.4 (4.5)	0.07 (-2.33; 2.46)	0.01	1.02 (-1.22; 3.27)	0.22
WOMAC function (0-68)	6w	33.1 (12.0)	36.8 (12.6)	-1.90 (-7.56; 3.76)	0.16	1.82 (-3.55; 7.19)	0.17
	3m	30.4 (15.2)	34.1 (12.6)	-1.85 (-8.36; 4.65)	0.14	1.31 (-5.15; 7.78)	0.10
	6m	35.5 (17.1)	33.3 (14.6)	-1.74 (-10.0; 6.54)	0.10	0.94 (-7.48; 9.36)	0.05
	9m	35.0 (15.1)	33.0 (13.4)	-1.58 (-9.63; 6.46)	0.10	1.66 (-6.03; 9.35)	0.11
	12m	34.0 (14.4)	35.4 (15.7)	-1.40 (-9.34; 6.53)	0.09	3.03 (-4.25; 10.30)	0.20
WOMAC stiffness (0-8)	6w	4.2 (2.1)	5.0 (1.6)	-0.40 (-1.12; 0.32)	0.27	-0.11 (-0.87; 0.64)	0.07
	3m	4.5 (1.3)	4.9 (1.9)	-0.35 (-1.09; 0.40)	0.23	-0.20 (-0.98; 0.59)	0.12
	6m	4.6 (1.6)	4.6 (1.8)	-0.19 (-1.04; 0.65)	0.11	-0.17 (-1.06; 0.73)	0.09
	9m	4.6 (1.6)	4.3 (1.7)	0.06 (-0.72; 0.84)	0.04	0.20 (-0.60; 0.99)	0.12
	12m	4.7 (1.6)	4.4 (1.6)	0.36 (-0.50; 1.23)	0.20	0.76 (-0.09; 1.62)	0.44
Most painful activity (0-10)	3m	6.2 (2.1)	7.1 (1.6)	-0.77 (-1.45; -0.09)	0.55	-0.67 (-1.36; 0.02)	0.48
	12m	6.9 (2.0)	6.9 (1.9)	-0.77 (-1.44; -0.09)	0.56	-0.67 (-1.36; 0.02)	0.48
Quality of life (-0,446;1)	3m	0.646 (0.186)	0.626 (0.134)	-0.03 (-0.07; 0.01)	0.37	-0.01 (-0.09; 0.07)	0.06
	6m	0.596 (0.213)	0.615 (0.173)	-0.05 (-0.11; 0.02)	0.38	-0.03 (-0.13; 0.07)	0.15
	9m	0.633 (0.188)	0.612 (0.183)	-0.05 (-0.11; 0.02)	0.38	-0.03 (-0.13; 0.06)	0.15
	12m	0.627 (0.272)	0.632 (0.169)	-0.03 (-0.11; 0.04)	0.20	-0.04 (-0.15; 0.07)	0.18

		Mean (SD)		Unadjusted model		Adjusted model*	
		Duloxetine (n=27)	*Usual care (n=33)*	*Difference (95% CI)*	*Effect size*	*Difference (95% CI)*	*Effect size*
Patient satisfaction (0-10)	3m	5.2 (2.5)	5.4 (2.5)	0.19 (-1.41; 1.78)	0.06	0.13 (-1.53; 1.79)	0.04
	6m	4.9 (3.0)	5.7 (2.2)	0.18 (-1.41; 1.78)	0.06	0.14 (-1.53; 1.80)	0.04
	9m	5.1 (3.3)	5.7 (2.2)	0.18 (-1.41; 1.77)	0.06	0.13 (-1.53; 1.78)	0.04
	12m	4.5 (2.9)	5.5 (2.7)	0.16 (-1.41; 1.73)	0.05	0.11 (-1.53; 1.74)	0.03
		n (%)	*n (%)*	*OR (95% CI)*		*OR (95% CI)*	
Perceived improvement (yes/no)	3m	4 (18.2)	1 (4.2)	5.43 (0.46-63.74)		14.54 (0.54-393.29)	
	12m	5 (22.7)	3 (11.5)	2.15 (0.45-10.31)		3.34 (0.36-30.94)	
Responder according to OARSI-omeract criteria (yes/no)	3m	9 (40.9)	5 (20.0)	2.70 (0.72-10.12)		3.76 (0.78-18.26)	
	12m	6 (26.1)	6 (22.2)	1.31 (0.36-4.79)		1.32 (0.30-5.79)	

*Adjusted for baseline score, age, gender, modified painDETECT score, HADS depression scale score and the presence of 2 or more comorbidities, WOMAC=Western Ontario and McMaster University Index, SD=standard deviation, CI=confidence interval, OR=odds ratio, w=weeks, m=months

Table S4. Most painful activity

A) Hip (n=23)

	n, (%)
Going up or down stairs	1 (4.2)
Rising from sitting position	6 (25.0)
Sitting	3 (12.5)
Walking	5 (20.8)
Bending hip	6 (25.0)
Bending to the floor	1 (4.2)
Gardening	1 (4.2)
Missing	1 (4.2)

B) Knee (n=103)

	n, (%)
Going up or down stairs	24 (23.3)
Bending to the floor	21 (20.4)
Squatting	1 (1.0)
Rising from sitting	13 (12.6)
Sitting	3 (2.9)
Walking	27 (26.2)
Running	2 (1.9)
Twisting/pivoting knee	2 (1.9)
Standing	9 (8.7)
Straightening knee	1 (1.0)
Missing	5 (4.9)

CHAPTER 8

General discussion

Pain and disability are two important complaints in patients with OA. Non-surgical treatment options for OA are education, dietary advice and weight loss (if necessary), physiotherapy and analgesics. These analgesics are given using a stepwise approach. The first two steps are paracetamol and topical or oral non-steroidal anti-inflammatory drugs (NSAIDs), but these are not always sufficient to reduce pain, and oral NSAIDs can be contra-indicated or can have side-effects[1 2]. As a third step opioids can be prescribed, but the current guidelines do not recommend opioids or give restrictive advice on administering opioids since opioids have not been shown to have a significant effect for OA pain, and side-effects are common[3 4]. An alternative may be the use of neuropathic pain medication, which is hypothesized to have an effect on centrally sensitized pain. The most extensively studied of these options is duloxetine, a serotonin and noradrenalin reuptake inhibitor (SNRI). Several placebo-controlled trials showed a moderate effect of duloxetine[5-10], though the effectiveness in real-life situations is unknown.

The aim of the current thesis was 1) to provide insight into the current prescription rates and use of third-choice pain medication (i.e. opioids and neuropathic pain medication) in patients with OA and 2) to provide evidence for the use of neuropathic pain medication for patients with OA.

In this chapter we discuss the main findings and we consider how the effectiveness of analgesics in patients with OA could be evaluated. Finally, we discuss the implications for general practice and give recommendations for future research.

MAIN FINDINGS

In a cross-sectional survey in patients with OA with a high rate of concomitant musculoskeletal comorbidities, we found that many patients used their analgesics intermittently and in a lower dose than the defined daily dose (DDD). In particular, weak opioids were used in lower doses than the DDD in 76% of the cases (Chapter 2). Furthermore, patients with other concomitant musculoskeletal disorders were more likely to use analgesics than patients without concomitant musculoskeletal comorbidities (Chapters 2 and 3).

We examined the prescription rates for opioids in patients with OA between 2008 and 2017 in a primary healthcare database (the Integrated Primary Care Information (IPCI) database) (Chapter 3). In this period, the overall prescription rates of opioids remained fairly stable. However, there were changes in which opioids were prescribed. Prescription of the strong opioids fentanyl and, especially, oxycodone increased over time, while the prescription rates of paracetamol/codeine declined rapidly after their costs ceased to be reimbursed by health insurances. About 25% of the patients with OA were prescribed an opioid, and 3% of the patients with incident OA were prescribed an opioid for longer than three months.

We also studied the prescription rates of neuropathic pain medication for patients with OA between 2008 and 2017. Amitriptyline was the most commonly prescribed of the neuropathic pain medicines, and prescription rates increased slightly over time (Chapter 4). However, there is no evidence to support the prescription of amitriptyline for OA pain, and the evidence for other musculoskeletal disorders is scarce and of limited quality (Chapter 5). Although we evaluated the prescription rates in patients with OA, we could not determine whether amitriptyline was prescribed specifically for OA pain. It may also have been prescribed for reasons other than pain, even though we excluded patients from the cohort with other diagnoses for which amitriptyline is often prescribed.

In the period 2008-2017, pregabalin and gabapentin (gabapentinoids) were increasingly prescribed for patients with OA. Of these neuropathic pain medications, duloxetine was prescribed least often.

Finally, we studied the effectiveness of duloxetine added to usual care when compared to usual care alone for patients with chronic OA pain. We used a cluster-randomised trial in general practice. Patients were included if paracetamol and NSAIDs did not sufficiently reduce their pain, were contra-indicated or had side-effects. We did not find an effect for duloxetine added to usual care for OA-related pain; we could even rule out a clinically relevant effect. We did not find an effect either for the subgroup of patients with symptoms of central sensitization. We can rule out a large clinical effect of duloxetine for this subgroup, though the presence of a smaller clinically relevant effect cannot completely be excluded (Chapters 6 and 7).

As stated, we found increasing prescription rates for the strong opioids oxycodone and fentanyl. Other studies in other countries have found increasing prescription rates for all opioids[11-14]. This increase in prescriptions of opioids is partly due to an increased awareness of serious adverse events of NSAIDs[15 16], but may also be influenced by pharmaceutical companies' marketing. This increase in prescription rates of opioids seems to reflect a need for (third-choice) analgesics for patients with OA related pain. However, there is growing evidence regarding opioids' lack of effect for musculoskeletal pain[17 18] and regarding their harmful side-effects[19 20]. This increase in the prescription of opioids is therefore concerning. Duloxetine might have been an alternative for patients with OA-related chronic pain. However, in our pragmatic trial we did not find an effect of duloxetine, even in our subgroup of patients with symptoms of centralized pain. Yet efficacy studies did find an effect of duloxetine. Evaluations of the effect of an intervention are often on a continuum from highly controlled clinical trials with placebo to observational data; from proof-of-principle studies to real-life data[21]. Our outcomes could be influenced by different factors. We will discuss the influence of OA subtypes (phenotypes), the context of the treatment and the research design (pragmatic trials and observational research).

PHENOTYPES

OA is considered a heterogeneous disease that is affected by many different risk factors, such as obesity, increasing age, sex, joint shape, trauma, mechanical load and genetic factors. Furthermore, in clinical practice there is considerable variability in symptoms and prognosis[22 23]. Therefore, OA is increasingly seen as a syndrome with different phenotypes instead of a single disease caused by 'wear-and-tear'[24 25].

This heterogeneous nature of the disease may also be one of the reasons why no effect or a small treatment effect is found in OA trials. Different OA phenotypes may respond in different ways to therapy and a certain therapy may therefore be more suitable for one specific phenotype of OA than for another phenotype[22 26 27]. For example, in our trial, we hypothesized that duloxetine would have a larger effect in patients with symptoms of central sensitization.

So far, no specific OA phenotypes have been defined and validated. A recent consensus meeting of experts suggested defining a phenotype as a subtype of OA in which the underlying pathobiological and pain mechanisms, and their structural and functional consequences are similar[28], and which subsequently influence the effectiveness of interventions. Furthermore, the phenotypes are not mutually exclusive and patients can have signs and symptoms of more than one phenotype[28].

Phenotypes are often grouped according to their mechanistic underlying pathobiological processes, the disease prognosis or the response to treatment. Mechanistic phenotypes, also called endotypes, are based on underlying molecular mechanisms[29]. These molecular mechanisms can be a target for the development of drugs (targeted therapy). Phenotypes, sometimes also called subgroups, can also be grouped primarily according to prognosis and how patients respond to therapy. Patients who could benefit from the intervention (or would experience more side-effects) can then be identified in advance. Examples that are often mentioned are disease stage and type of pain.

Phenotypes possibly influencing treatment outcomes should be validated in a randomised clinical trial (RCT) with a subgroup analysis, defined a priori, to examine whether the phenotype really influences treatment outcomes[22]. Furthermore, phenotypes should be easy to recognize in order to make them feasible for use in clinical practice. For example, evaluating OA phenotypes with an MRI will not be feasible in general practice[22 24 25].

In our trial we defined a subgroup analysis a priori for patients with symptoms of central sensitization and hypothesized that these patients would benefit more from duloxetine, because duloxetine is believed to reduce chronic pain through the central inhibition of pain. The gold standard to examine whether signs of central sensitization are present in patients is quantitative sensory testing (QST)[30], for example with pain pressure thresholds. These laboratory tests are time-consuming and expensive and

therefore not feasible in normal daily practice. Instead we used the modified painDETECT questionnaire, which assesses the presence of symptoms of central sensitization and is adapted for patients with knee or hip OA[31 32]. The original painDETECT questionnaire was developed for patients with low back pain to identify patients with a neuropathic pain component[33]. When using a cut-off score of 12, the modified painDETECT questionnaire has sensitivity of 50% and a specificity of 74% to detect symptoms of central sensitization[31]. Small to moderate correlations (r= -0.35 to r=-0.23) have been found between painDETECT scores and pain pressure thresholds[34 35].

Central sensitization can manifest in different forms, ranging from local symptoms of central sensitization to pain in multiple regions of the body — widespread pain[36 37]. Different definitions of widespread pain are used; a common definition of widespread pain is pain above and below the waist on both sides of the body and pain axially[38]. High scores with the modified painDETECT questionnaire (>19) are associated with the presence of widespread pain[39]. The OARSI guidelines on non-surgical management of OA recommend the use of duloxetine in patients with widespread pain[3]. We chose to use the modified painDETECT questionnaire with a cut-off score of 12, which meant that patients with local symptoms of central sensitization or a mixed pain type were included in the sub-analyses of patients with symptoms of central sensitization.

To date, only cross-sectional observational studies have found differences in pain subtypes in patients with OA. No other studies have evaluated whether the presence of symptoms of central sensitization would alter the response to duloxetine. It is only hypothesized that this would alter the response to treatment and that these patients with this type of pain would respond less to treatment with the current analgesics[24 37]. In addition, in the IPCI database we found increased prescription rates over time of amitriptyline, pregabalin and gabapentin for patients with OA, but it is unknown whether this is related to pain phenotypes; and this may also reflect the fact that the patients do not benefit from the current analgesics.

In the DUO trial, 45% of the patients had symptoms of central sensitization. A recent meta-analysis found that 23% of the patients with OA had symptoms of central sensitization based on self-reported neuropathic pain questionnaires (painDETECT or modified painDETECT)[40]. The higher percentage in the trial is probably related to the fact that these patients do not respond well to the current analgesics and represent a group of OA patients with more refractory pain. We did not find a large effect of duloxetine in this subgroup of patients, contrary to our hypothesis. However, we had a limited group of patients due to recruitment problems so we cannot definitively rule out a small effect of duloxetine in this subgroup. Furthermore, the modified painDETECT questionnaire has not been validated extensively and it might be that we did not select the appropriate patients for the subgroup analyses.

CONTEXTUAL FACTORS

Contextual factors, like the beliefs or attitudes of the GPs in our trial, are known to influence the effect of an intervention[41]. In highly controlled, placebo-controlled efficacy studies these factors are a part of the placebo effect; they are considered 'noise' and irrelevant since they do not reflect the specific ('true') effect of a treatment[42], while in pragmatic trials these contextual factors are seen as part of the effect of the treatment. Therefore some interventions have a small effect size in a trial, but a large effect in real life due to these contextual effects[43]. In complex interventions there can be an interaction between the specific treatment effect and the contextual factors, which can make the intervention more effective. An example is exercise therapy delivered by a highly motivating physiotherapist[44]. This difference in the effect of a treatment in an RCT and in clinical practice is called the 'efficacy paradox'[45].

The contextual factors consist of factors associated with the physician, the patient and the type of intervention[42]. A meta-analysis found that the average effect size of the placebo response for OA pain is 0.51 (95% confidence interval 0.46 to 0.55)[46]. The effect size was influenced by the strength of the active treatment, baseline disease severity, type of intervention and sample size of the study[46 47]. Furthermore, up to 75% of the treatment effects found in OA are related to contextual factors[48 49]. The effect of the contextual factors was higher for more invasive therapies (injections, joint lavage), but was also higher for topical NSAIDs than oral NSAIDs.

Factors associated with the treating physician that contributed to contextual effects included warm, attentive consultations and an optimistic attitude about the treatment, reassurance about the prognosis and the possibility of follow-up appointments and a positive or negative belief in the therapy of the physician[42 50].

Finally, some patients are more likely to respond to a placebo than others. One associated factor is optimism about treatment, which is positively associated with the placebo response, while anxiety is negatively associated with the placebo response[42]. Hope can be an important factor as well, especially in patients who experience chronic pain and have tried multiple treatments[51].

Contextual factors do not only have positive effects, but can also negatively influence outcomes — the 'nocebo effect'. The nocebo effect is caused by a negative healthcare context and can aggravate patients' symptoms[52]. Important determinants of the nocebo effects are negative information and prior unsuccessful therapies[53], but as mentioned earlier, patient factors can also play an important role. Especially in the interaction between healthcare professionals and patients, nocebo effects can occur and have an adverse impact on pain[54]. Studies have shown that the clinical response is influenced by how information is given and whether potential adverse reactions are mentioned[55 56]. Knowledge about how these contextual factors influence the therapeutic effect is im-

portant in order to deliver treatment in the best possible way so as to maximize the treatment effect of an intervention[43 50].

But there are ethical considerations to maximizing treatment effects by using contextual factors. A recent qualitative study in British GPs found that the GPs felt the use of contextual factors to be acceptable when using them in a positive manner, with patient-centred communication and empathic relationships. The negative use of contextual factors, like withholding information on side-effects (which leads to fewer reported side-effects[57]), was not deemed ethical and was not in line with the principle of obtaining informed consent for treatment[58].

In the DUO trial, patient-related outcomes were evaluated. Contextual factors played a role at the GP and patient levels. Unfortunately we did not systematically record the attitudes of the GPs and the participating patients to duloxetine to see whether this influenced the effect of duloxetine. However, interviews were held with GPs about their attitudes to duloxetine (unpublished data). About half of the GPs interviewed were also participating in the DUO trial. Some GPs stated that duloxetine may be an option for patients with OA in whom other therapies have failed. It also turned out that they were relatively unfamiliar with duloxetine and were concerned about the occurrence of side-effects. This may have influenced how GPs counselled their patients and consequently the effect of duloxetine.

The patients participating in the trial had tried multiple other treatments before starting the trial, and such patients are prone to experience placebo effects[51]. Patients in the DUO trial often hoped they would be assigned to the duloxetine group, because they would get a new treatment that might benefit them. Being assigned to the preferred treatment group is associated with higher treatment effect sizes[59]. However, we did not find a difference in treatment effect between duloxetine and the usual care group. Patients in the duloxetine group did report an improvement in their complaints more often than patients in the usual care group; this is probably related to the open-label design and to contextual factors. However, the group reporting an improvement in their complaints was small and the point estimate had wide confidence intervals and should be interpreted carefully.

On the other hand, among patients negative expectations about duloxetine were also common. A relatively high percentage (35%) of patients were eligible for the trial but declined to participate after reading the patient information. The reason mentioned most often for declining to participate was fear of experiencing side-effects.

PRAGMATIC TRIALS

The efficacy of duloxetine for patients with OA was assessed in placebo-controlled trials[5-10]. These explanatory trials investigated duloxetine under ideal circumstances with highly selected patients, often relatively young and without comorbidity, to maximize the chance of finding an effect of duloxetine. They tested whether a specific ('true') treatment effect was present.

However, these trials do not show whether the treatment is effective in daily practice and whether the intervention is cost-effective. This information is needed for physicians and policy makers to decide if a treatment is of benefit for a specific patient or group of patients[60]. Pragmatic trials fill this 'efficacy-effectiveness gap' and study the effectiveness in daily practice with relatively unselected patients; they therefore have a relatively high external validity[61]. A benefit of the pragmatic design is that randomization is still performed to allow for potential confounders that could influence the treatment effects.

A pragmatic trial has some specific characteristics: 1) the population included reflects the population that would actually receive the medication or intervention in usual care; 2) the comparator used is preferably an active treatment strategy (e.g. usual care) instead of a placebo; 3) flexibility is allowed in concomitant medication use, complementary care and compliance; and 4) a clinically meaningful outcome (to patients) is used rather than a biological outcome. Most trials contain both explanatory and pragmatic elements; a trial is seldom fully explanatory or fully pragmatic[62 63].

As stated earlier, the benefit of a pragmatic trial is that the complete effect of an intervention is studied, not just the specific effect of an intervention: the effect of the contextual factors is included in the overall effect in addition to how well patients adhere to the medication and if patients accept the intervention[60 64]. Therefore, a treatment can show a lack of effect in a pragmatic trial due to low adherence because of the intervention's side-effects. Furthermore, the population is often less selected patients can be older and/or have more comorbidity, which can also influence treatment effects. A possible disadvantage of a less selected group may be when an intervention benefits a specific OA phenotype rather than all patients with OA[65]. If that subgroup has not been defined a priori, the effect of the intervention may not be found.

The PRECIS-2 (PRagmatic Explanatory Continuum Indicator Summary) tool can be used to assess how pragmatic and generalizable a trial is[66]. This tool contains nine domains scored from 1 (explanatory/ideal situation) to 5 (pragmatic/ usual care). These domains are the eligibility criteria, recruitment, trial setting, organization, flexibility (delivery), flexibility (adherence), follow-up, primary outcome and primary analysis.

Overall, the DUO trial was a pragmatic trial in many respects since the trial was conducted in a primary care setting with many GP practices participating and GPs providing usual care according to the GP guidelines, which allowed for different treatment options.

We had a few relatively explanatory components in some domains. First, our exclusion criteria had some explanatory components. Patients were excluded who were currently using neuropathic pain medication, and at the start of the trial so were patients who were currently using opioids. In clinical practice this medication could be switched to duloxetine, or duloxetine could be added to the therapy. Treatment with neuropathic pain medication would interfere with our intervention and was therefore not allowed. Initially we excluded patients who used opioids, to have a treatment option left in usual care according to our protocol. A few months after the start of the trial this criterion was abandoned after approval by the medical ethics committee, since these patients could benefit from duloxetine and this was also closer to actual clinical practice.

Second, all possible eligible patients in the GP records were identified and these patients were sent an invitation letter. The most pragmatic option would be recruitment by the GP during consultation, but this could introduce recruitment bias in the cluster randomised trial[62] and reduce the validity of our results and this approach was therefore not desirable. Furthermore, recruitment of participants by the GP during consultation is difficult for multiple reasons (e.g. lack of time, forgetting about the trial) and can lead to low numbers of included patients[67-69].

We used a cluster-randomised design to study the effectiveness of duloxetine. Cluster-randomised trials are particularly useful for effectiveness studies and for implementation studies because the GP provided the same intervention to all his/her patients and this therefore closely mimics normal clinical practice[62]. Cluster designs can be used when the intervention is targeted at the cluster level and the design avoids treatment group contamination. The design is particularly appropriate for the evaluation of interventions that aim to change the behaviour of either the professional or the patients. In our trial only a few patients recorded as having OA in each GP practice participated in the trial. We estimated beforehand that more patients per GP practice would participate in the trial and that a GP would get more experience with prescribing duloxetine and would be able to embed this in his/her normal clinical practice.

The pragmatic design of the trial also had some disadvantages. Patients who were randomly assigned to the duloxetine group were seen more often by their GP and this may have introduced bias. A higher proportion of these patients were referred to an orthopaedic surgeon for a hip or knee replacement; GPs and patients may have seen this as the next step if duloxetine did not improve the complaints. Furthermore, the cluster randomization led to baseline differences for prognostic factors between the two groups for which the analyses needed to be adjusted. This suggests that the groups may also have differed with regard to unknown (unmeasured) factors.

OBSERVATIONAL RESEARCH

Observational data is considered the situation closest to the real-life situation. It gives information on use in daily practice for a broad population instead of under ideal circumstances in a placebo-controlled clinical trial. It may also be an attractive option when recruitment is difficult, as in our trial. Sometimes the use of observational data may be an alternative when gathering information on the effect of an intervention.

However, confounding by indication can be a problem in observational research[70]. A physician chooses an intervention for a patient based on specific patient characteristics and these characteristics can influence the outcome. In an RCT this type of confounding is usually corrected by the randomization procedure. In observational data this type of confounding can be addressed by using, for example, propensity score matching to correct statistically for known confounders[70 71]. Propensity scores give each patient a score that estimates the likelihood that a patient would receive an intervention based on patient characteristics. These scores are subsequently used to adjust for confounding when estimating outcome differences between patients who received the intervention and those who did not. However, the analyses can only be adjusted for known confounders, and sometimes residual confounding is still present and differences found may be attributable to (prognostic) factors other than the intervention[70 71].

In a Cochrane review the differences in outcomes between clinical trials and observational data on the same topic were evaluated; overall, similar effect estimates were found[72]. More recent meta-epidemiological studies found that observational studies may overestimate the effect of an intervention despite adjusting for confounding[73 74].

A recent example in OA research showed that residual confounding may still exist after propensity score matching. A cohort study looked at the relationship between all-cause mortality and prescription of tramadol and NSAIDs for OA patients. This study found a higher rate of all-cause mortality for patients who were prescribed tramadol compared to patients prescribed an NSAID after correcting for confounders like sociodemographic factors and comorbidities[75]. However, tramadol is often prescribed to relatively frail patients with more comorbidities and for whom an NSAID is contra-indicated. It is possible that residual confounding is still present after correcting for comorbidities and this accounts for the association that was found.

In our observational research in the IPCI database, we could not study the effect of the different analgesics prescribed to patients registered with OA since no outcome measurements were available. Only the number of prescriptions could be assessed in this registration database. Furthermore, since duloxetine is not registered in the Netherlands for OA-related pain and is currently rarely prescribed by GPs, it would be impossible to assess the effect of duloxetine for OA using the IPCI database.

IMPLICATIONS FOR CLINICAL PRACTICE AND FUTURE RESEARCH

We found that strong opioids were prescribed more frequently to patients with OA pain despite the fact that opioids have not been shown to have an effect for chronic musculoskeletal pain[17 18], including OA, and the fact that side-effects frequently occur when using opioids[19 20]. Clinicians should be aware of this and prescribe opioids with caution. Qualitative studies can be carried out to assess knowledge about opioids and to identify barriers and facilitators for prescribing and stopping the use of opioids. Subsequently, strategies to reduce opioid prescribing can be developed and implemented in clinical practice.

Efficacy studies need to be performed to establish the proof-of-principle for a treatment, but these highly controlled studies show the specific treatment effect in the ideal situation, which can often differ from the effect in clinical practice. OARSI and ACR guidelines conditionally recommend the use of duloxetine for OA patients with widespread pain based on the evidence found in efficacy studies[3 4]. We did not find an effect of duloxetine when added to usual care in our pragmatic trial and we were able to rule out a clinically relevant effect. For the subgroup of patients with symptoms of centralized pain, we could rule out a large effect of duloxetine, but not a smaller clinically relevant effect (effect size 0.4). For this subgroup of patients our results would need to be confirmed in another trial.

Because of this discrepancy in the results between the placebo-controlled and pragmatic trials, more pragmatic OA trials are needed to evaluate the effect in real life. Most trials in OA research are explanatory trials or pragmatic trials that still contain explanatory elements. Pragmatic trials include less selective group of patients and the contextual effects are also incorporated in the overall effect. One advantage of pragmatic trials is that randomization is still performed, which corrects for confounding by indication. Observational studies, which resemble real life most closely, can have residual confounding despite adjusting for known confounders and do not always include the outcomes of interest. Observational data can support findings and can guide research, but the effects of an intervention should preferably be studied in a clinical trial.

Furthermore, more research on OA phenotypes, especially on pain phenotypes, is needed to identify patients who would benefit from the intervention in order to enhance the effectiveness of an intervention. These phenotypes must be easy to identify, for example using a short questionnaire, if they are to be useful in clinical practice.

Finally, contextual factors are important and inevitable aspects of the treatment effect in clinical practice and they can even be used to enhance the treatment effect of an effective intervention. Clinicians should be aware of these effects, both positive and negative, so that they can maximize the treatment impact.

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CHAPTER 9

Summary
Samenvatting
Dankwoord
Curriculum vitae
PhD Portfolio
List of publications

SUMMARY

Osteoarthritis (OA) is a chronic disease of the musculoskeletal system. Pain and disability are two important complaints of patients with OA. The treatment options are education, dietary advice and weight loss, physiotherapy and analgesics. The analgesics that are prescribed (in a stepwise approach) are: paracetamol, (topical) non-steroidal anti-inflammatory drugs (NSAIDs) and opioids. However, these analgesics do not always reduce pain sufficiently, can have side-effects or can be contra-indicated. Therefore, alternatives for treating OA-related pain are necessary. One alternative may be the use of neuropathic pain medication, which is hypothesized to have an effect on centralized pain. This type of pain is present in around 23% of the patients with OA. The alternative that has been studied most extensively for OA pain is duloxetine, a serotonin and noradrenalin reuptake inhibitor (SNRI), and small to moderate effects are found in efficacy studies.

The aim of the current thesis was 1) to provide insight into the current prescription rates and use of third-choice pain medication (i.e. opioids and neuropathic pain medication) in patients with OA and 2) to provide evidence for the use of neuropathic pain medication in patients with OA.

Prescription rates and use of third-choice pain medication

In Chapter 2 we examined which analgesics were used by patients for OA-related pain and how these analgesics were used. We performed a cross-sectional study in patients who were members of the Dutch Arthritis Foundation. Patients filled in a questionnaire on their analgesic use in the past month. In total, 842 (56%) patients completed the questionnaire. Of these patients 70% had generalized OA, 26% also had fibromyalgia and 34% had additional musculoskeletal conditions. 71% of the participants used at least one analgesic; paracetamol was most common (51%). Most patients had used their medication for more than 14 days in the past month (around 70%). Doses were usually lower than the daily defined dose: in 58% of cases for paracetamol, 31% for NSAIDs and 76% for weak opioids. A higher proportion of patients without fibromyalgia or additional musculoskeletal conditions used no analgesics ($p<0.01$) and a smaller proportion used two or three types of analgesics ($p<0.05$).

We examined the opioid prescription rates for patients with OA in the Integrated Primary Care Information (IPCI) database between 2008 and 2017 (Chapter 3). The IPCI database contains the GP records of more than 1.5 million patients in the Netherlands. In total, 157,904 patients with OA were included in the cohort. Patients were excluded from the cohort one year before being diagnosed with a malignancy, a neuropathic pain disorder or fibromyalgia or one year before death. Incident and prevalent prescription rates per 1000 person years were calculated per opioid.

The overall prescription rate of opioids remained stable over time at around 100 incident and 170 prevalent prescriptions per 1000 person years. However, there was a change in which opioids were prescribed to patients. Prescriptions of the strong opioids oxycodone and fentanyl increased over time. Incident prescription rates of oxycodone increased from 7.1 per 1000 person years in 2008 to 40.7 per 1000 person years in 2017. For fentanyl, this rate increased from 4.2 to 7.4 per 1000 person years. The incident prescription rate of the weak opioid paracetamol/codeine decreased from 63.0 per 1000 person years to 13.3. Almost 75% of the patients with incident OA were not prescribed an opioid during the follow-up period and 3% were prescribed an opioid for longer than three months in a follow-up year. Opioids were more likely to be prescribed for patients with concomitant other musculoskeletal disorders (≥2 odds ratio (OR) 4.91 [95% confidence interval (CI) 4.76; 5.05]), with increasing age, and for patients with OA in two or more joint groups (OR 1.58 [95%CI 1.51; 1.65]). Opioids were less likely to be prescribed for men (OR 0.78 [95% CI 0.76; 0.80]).

The aim of Chapter 4 was to examine prescription rates of neuropathic pain medication for patients with OA in the IPCI database between 2008 and 2017. This type of medication may already be prescribed to patients with OA, despite a lack of evidence. Overall, 164,292 patients with OA were included in the cohort. Patients were excluded one year before being diagnosed with a malignancy or one year before death. A subgroup of patients (n=99,099) without comorbidities for which neuropathic pain medication can be prescribed was also selected to evaluate prescription rates in this group to see if they had different rates and trends over time. We examined the first, episodic and prevalent prescription rates of the antidepressants amitriptyline, nortriptyline and duloxetine, and of the anticonvulsants gabapentin and pregabalin (gabapentinoids).

Amitriptyline was the most commonly prescribed medicine; the episodic prescription rate increased to 15.1 per 1000 person years in 2017. The increase in the episodic prescription rate of pregabalin was most pronounced: the rate almost doubled from 7.1 per 1000 person years in 2008 to 13.9 per 1000 person years in 2017 (average annual percentage change 8.3% [95% CI 5.9-10.5]). Furthermore, the episodic prescription rates of gabapentin increased to 3.9 per 1000 person years in 2017. Episodic prescription rates of nortriptyline (3.0 per 1000 person years) and duloxetine (2.0 per 1000 person years) remained stable. Time trends for first, episodic and prevalent prescription rates were similar. For patients without conditions for which neuropathic pain medication could also be prescribed, the absolute prescription rates were lower, but the time trends were similar. In general, all neuropathic pain medication was prescribed more frequently for women, older patients (except duloxetine), patients with OA in ≥ 2 joint groups, patients with spinal OA and patients with other musculoskeletal disorders.

Evidence for the use of neuropathic pain medication

Amitriptyline is the most commonly prescribed neuropathic pain medication in patients with OA. The role of amitriptyline for musculoskeletal disorders is not as clear as for classical neuropathic disorders and therefore a systematic review was conducted to assess the efficacy and effectiveness of amitriptyline for musculoskeletal pain (Chapter 5). Amitriptyline was compared to a placebo, usual care or another analgesic. Only randomised controlled trials (RCT) were included. A database search up to April 2016 identified 2066 articles, of which seven were finally included. Four studies were conducted in patients with low back pain, two in patients with rheumatoid arthritis and one in patients with arm pain from repetitive use. No meta-analysis was performed due to clinical heterogeneity. Two studies with low risk of bias found positive results (low back pain amitriptyline vs pregabalin; and arm pain amitriptyline vs placebo). We concluded that evidence for musculoskeletal complaints is scarce and more studies are needed to identify patients who would benefit from amitriptyline.

In Chapter 6, the study design of the DUO trial is presented. In the DUO trial the effectiveness and cost-effectiveness of duloxetine added to usual care was compared to usual care alone for patients with chronic pain due to hip or knee OA. Furthermore, it was assessed whether the presence of symptoms of central sensitization (measured using the modified painDETECT questionnaire) would improve the response to duloxetine. The DUO trial was a cluster randomised trial with a follow-up time of 12 months. Patients were included in the trial if they had suffered from OA pain on most days of the past three months and if paracetamol and NSAIDs did not reduce pain sufficiently, were contra-indicated or had side-effects. General practitioner (GP) practices were randomly assigned to treatment with duloxetine (60mg/day) plus usual care or to usual care alone. Usual care was provided according to the Dutch GP guidelines. The primary outcome was WOMAC pain (0-20) at three months. Secondary outcomes were WOMAC pain at 12 months, WOMAC function (0-68) at 3 and 12 months, side-effects, cost-effectiveness, patients' satisfaction, patients' perceived improvement and the quality of life. 224 patients needed to be included to detect a clinically relevant difference in WOMAC pain of 1.9 points (pooled SD 4.8) with an effect size of 0.4. 44 patients with symptoms of centrally sensitized pain were needed in each group to detect a larger effect in these patients (effect size 0.6, a difference in WOMAC pain of 2.9 points).

The results of the DUO trial are presented in Chapter 7. In total, 133 patients were included in the trial and 132 patients were randomised; 66 patients (31 GP practices) were assigned to duloxetine and usual care, and 66 patients (35 GP practices) were assigned to usual care alone. No clinically relevant or statistically significant differences were found for WOMAC pain at three months (adjusted difference -0.58 [95% CI -1.80; 0.63]) or at 12 months (adjusted difference -0.26 [95% CI -1.86; 1.34]). This ruled out the smallest clinically relevant effect (differences of WOMAC pain of 1.9 points, effect size

0.4). No effect of duloxetine was found either for the subgroup of patients with symptoms of centralized pain (adjusted difference -0.32 95% CI[-2.32; 1.67]). Furthermore, the intervention was not cost-effective; a small positive difference of 0.04 QALYs was found for the duloxetine group, which is not considered clinically relevant. Based on the results we can rule out a clinically relevant effect of duloxetine (difference in WOMAC pain of 1.9 points (effect size 0.4)) and we conclude that duloxetine should not be implemented in usual care. For patients with symptoms of centralized pain, a larger effect (difference in WOMAC pain of 2.9 points (effect size 0.6)) of duloxetine can be ruled out, but the smallest clinically relevant effect cannot be ruled out due to the small sample size of the subgroup. Our results for this subgroup need to be confirmed in another clinical trial.

Finally, chapter 8 discusses the main findings and limitations of this thesis. Furthermore, implications for clinical practice and future research are given.

SAMENVATTING

Artrose is een chronische aandoening van het bewegingsapparaat. Pijn en functieverlies zijn twee belangrijke klachten van patiënten met artrose. De behandelmogelijkheden zijn uitleg, dieetadviezen en gewichtsverlies, fysiotherapie en pijnstillers. Pijnstillers die (stapsgewijs) worden voorgeschreven zijn: paracetamol, (topicale) niet-steroïde anti-inflammatoire geneesmiddelen (NSAID's) en opioïden. Deze pijnstillers verminderen de pijn echter niet altijd voldoende, kunnen bijwerkingen veroorzaken of gecontra-indiceerd zijn. Er zijn daarom alternatieven nodig om deze pijn te verminderen. Een mogelijk alternatief kan neuropathische pijnmedicatie zijn. Deze heeft mogelijk een effect op centraal gesensitiseerde pijn. Dit type pijn is bij ongeveer 23% van de patiënten met artrose aanwezig. Het meest onderzochte alternatief is duloxetine, een serotonine- en noradrenaline re-uptake inhibitor (SNRI), waarvan een klein tot gemiddeld effect is gevonden in *efficacy* studies.

Het doel van dit proefschrift was om 1) inzicht te krijgen in het huidige voorschrijfgedrag en gebruik van opioïden en neuropathische pijnmedicatie (derde keuze pijnmedicatie) bij patiënten met artrose en 2) bewijs te leveren voor het gebruik van neuropathische pijnmedicatie bij patiënten met artrose.

Aantal voorschriften en gebruik van derde keuze pijnmedicatie

In hoofdstuk 2 onderzochten we welke pijnstillers worden gebruikt door patiënten voor artrose gerelateerde pijn en hoe zij deze pijnstillers gebruiken. We voerden een cross-sectionele studie uit bij patiënten die deelnamen aan het patiëntenpanel van ReumaNederland. Patiënten vulden een vragenlijst in over het gebruik van pijnstillers in de voorafgaande maand, wat resulteerde in een totaal van 842 ingevulde vragenlijsten. Van deze patiënten had 70% gegeneraliseerde artrose, daarnaast had 26% van de deelnemers ook fibromyalgie en 34% had nog andere musculoskeletale aandoeningen. 71% van de deelnemers had ten minste 1 soort pijnstillers gebruikt. Paracetamol was de meest gebruikte pijnstiller (51%). Het merendeel van de patiënten (ongeveer 70%) gebruikte de pijnstillers gedurende meer dan 14 dagen van de maand. De dosering was over het algemeen lager dan de geadviseerde gemiddelde dosering. Dit was zo bij 58% van de patiënten die paracetamol gebruikten, bij 31% van patiënten die een NSAID gebruikte en bij 76% van de patiënten die zwakke opioïden gebruikten. Patiënten zonder fibromyalgie of andere musculoskeletale aandoeningen gebruikten vaker geen pijnstillers ($p<0.01$) en minder vaak twee of drie soorten pijnstillers ($p<0.05$).

In hoofdstuk 3 onderzochten we het aantal voorschriften voor opioïden bij patiënten met artrose in de Integrated Primary Care Information (IPCI) database tussen 2008 en 2017. De IPCI-database bevat huisartsgegevens van meer dan 1,5 miljoen patiënten in Nederland. Het cohort bestond uit 157.904 patiënten met artrose. Patiënten werden

geëxcludeerd uit het cohort een jaar voordat een maligniteit, neuropathische pijn aandoening of fibromyalgie werd gediagnosticeerd. Ook werden patiënten een jaar voor overlijden geëxcludeerd. Incidente en prevalente voorschriften per 1000 persoonsjaren werden berekend per opioïde.

Het totaal aantal voorschriften opioïden bleef stabiel tussen 2008 en 2017. Het aantal incidente voorschriften was ongeveer 100 per 1000 persoonsjaren en het aantal prevalente voorschriften ongeveer 170 per 1000 persoonsjaren. Echter welke opioïden werden voorschreven aan patiënten veranderde. Het aantal voorschriften van de sterke opioïden oxycodon en fentanyl steeg tijdens deze periode: het incidente aantal voorschriften voor oxycodon steeg van 7.1 per 1000 persoonsjaren in 2008 naar 40.7 per 1000 persoonsjaren in 2017 en voor fentanyl steeg het aantal voorschriften van 4.2 naar 7.4 per 1000 persoonsjaren. Het zwakke opioïde paracetamol/codeïne werd minder vaak voorgeschreven in deze periode: het aantal incidente recepten voor paracetamol/codeïne daalde van 63.0 naar 13.3 per 1000 persoonsjaren in deze periode. Bijna 75% van de patiënten met incidente artrose kreeg geen opioïde voorschreven tijdens de follow-up periode en 3% van de patiënten kreeg een opioïde voor langer dan drie maanden voorgeschreven. Opioïden werden vaker voorgeschreven aan patiënten met twee of meer bijkomende musculoskeletale aandoeningen (odds ratio (OR) 4.91 [95% betrouwbaarheidsinterval (BI) 4.76; 5.05]), op hogere leeftijd, en bij patiënten met artrose in twee of meer gewrichtsgroepen (OR 1.58 [95%BI 1.51; 1.65]). Opioïden werden minder vaak voorgeschreven aan mannen (OR 0.78 [95% BI 0.76; 0.80]).

Het doel van hoofdstuk 4 was om het aantal voorschriften voor neuropathische pijnmedicatie voor patiënten met artrose te onderzoeken in de IPCI database tussen 2008 en 2017. Deze neuropathische pijnmedicatie wordt misschien al voorgeschreven aan patiënten met artrose, ondanks het ontbreken van bewijs hiervoor. Er werden 164.292 patiënten met artrose geïncludeerd in het cohort. Patiënten werden geëxcludeerd een jaar voor een diagnose van een maligniteit of een jaar voor overlijden. Daarnaast onderzochten we in een subgroep van patiënten (n=99.099), namelijk patiënten zonder comorbiditeiten waarvoor neuropathische pijnmedicatie wordt voorgeschreven, of het aantal voorschriften en beloop over de tijd verschilde van de totale groep. Hiervoor onderzochten we het aantal eerste recepten, het aantal episoden van gebruik en het aantal prevalente voorschriften van de antidepressiva amitriptyline, nortriptyline en duloxetine en van de anti-epileptica gabapentine en pregabaline (gabapentinoiden).

Amitriptyline werd het meest voorschreven en het aantal episoden van voorschriften nam toe tot 15.1 per 1000 persoonsjaren in 2017. De stijging in het aantal episoden van voorschriften was het meest opvallend voor pregabaline: deze verdubbelde bijna van 7.1 per 1000 persoonsjaren in 2008 naar 13.9 per 1000 persoonsjaren in 2017 (gemiddelde jaarlijkse verandering 8.3% [95% BI 5.9-10.5]). Het aantal episoden met voorschriften van gabapentine steeg naar 3.9 per 1000 persoonsjaren in 2017. Het

aantal episoden met voorschriften van nortriptyline (3.0 per 1000 persoonsjaren) en duloxetine (2.0 per 1000 persoonsjaren) bleef stabiel tussen 2008 en 2017. De trends voor de eerste voorschriften, episoden en prevalente voorschriften waren gelijk. In de subgroep van patiënten zonder aandoeningen waarvoor neuropatische pijnmedicatie kan worden voorgeschreven zagen we dezelfde trends als in de totale groep. Echter lag het absolute aantal voorschriften lager. Over het algemeen werd de neuropathische pijnmedicatie vaker voorgeschreven aan vrouwen, aan oudere patiënten (uitgezonderd duloxetine), aan patiënten waarbij artrose in 2 of meer gewrichtsgroepen aanwezig is, aan patiënten met artrose in de rug en aan patiënten met bijkomende musculoskeletale aandoeningen.

Bewijs voor het gebruik van neuropathische pijnmedicatie

Amitriptyline is de meest voorgeschreven neuropathische pijnmedicatie bij patiënten met artrose. De plaats voor amitriptyline bij de behandeling van musculoskeletale pijn is minder duidelijk dan bij neuropathische pijn aandoeningen. In hoofdstuk 5 beschrijven we de resultaten van een systematisch review waarin we de effectiviteit van amitriptyline voor musculoskeletale klachten onderzochten. Gerandomiseerde trials (RCT's) werden geïncludeerd die amitriptyline vergeleken met een placebo, usual care of met een andere pijnstiller. In totaal werden er 2066 artikelen geïdentificeerd waarvan er uiteindelijke zeven werden geïncludeerd. Vier studies werden uitgevoerd bij patiënten met lage rugpijn, twee bij patiënten met reumatoïde artritis en één studie bij patiënten met armklachten (KANS/RSI). Vanwege klinische heterogeniteit van de studies werd geen meta-analyse verricht. Twee studies, met een laag risico op bias vonden positieve resultaten (lage rugpijn amitriptyline vs. pregabaline en armklachten amitriptyline vs. placebo). We concludeerden dat er weinig bewijs is voor het gebruik van amitriptyline bij musculoskeletale pijn en dat er meer onderzoek nodig is om patiënten te identificeren die baat kunnen hebben van amitriptyline.

In hoofdstuk 6 beschrijven we het onderzoeksprotocol van de DUO trial. In de DUO trial werd onderzocht wat de effectiviteit en kosteneffectiviteit is van duloxetine toegevoegd aan de *usual care* voor patiënten met chronische pijn door heup- of knieartrose, en of de aanwezigheid van centraal gesensitiseerde pijn (modified painDETECT vragenlijst) bij patiënten het effect van duloxetine beïnvloedde. De DUO trial was een cluster gerandomiseerde trial met een follow-up duur van 12 maanden. Patiënten met chronische pijn gedurende de meeste dagen in de afgelopen drie maanden werden geïncludeerd en wanneer paracetamol en NSAID's de pijn niet voldoende verminderde, waren gecontraindiceerd of bijwerkingen hadden. Huisartsenpraktijken werden gerandomiseerd naar behandeling met duloxetine (60mg/dag) toegevoegd aan de *usual care* of naar behandeling volgens *usual care*. De *usual care* werd verricht volgens de NHG-standaarden. De primaire uitkomstmaat was WOMAC pijn (schaal van 0-20) na drie maanden. Secundaire

uitkomstmaten waren WOMAC pijn na 12 maanden, WOMAC functie (schaal van 0-68) na 3 en 12 maanden, bijwerkingen, kosteneffectiviteit, patiënttevredenheid, patiënt gerapporteerde verbetering en kwaliteit van leven. Er waren 224 patiënten nodig om een klinisch relevant verschil van 1.9 punten in WOMAC pijn (standaarddeviatie 4.8, effect grootte 0.4) aan te kunnen tonen. Voor een subgroep analyse voorpatiënten met kenmerken van centraal gesensitiseerde pijn waren 44 patiënten nodig in iedere groep om een groter verschil bij deze patiënten aan te kunnen tonen (effect grootte 0.6, 2.9 punten verschil in WOMAC pijn).

In hoofdstuk 7 worden de resultaten van de DUO trial gepresenteerd. Er werden 133 patiënten in de trial geïncludeerd en 132 patiënten gerandomiseerd; 66 patiënten (31 praktijken) werden gerandomiseerd naar de duloxetine groep en 66 patiënten (33 praktijken) naar de *usual care* groep. Er werd geen klinisch relevant of statistisch significant verschil gevonden in WOMAC pijnscores na 3 maanden (geadjusteerd verschil -0.58 [95% BI -1.80; 0.63]) of na 12 maanden (geadjusteerd verschil -0.26 [95% BI -1.86; 1.34]). Hiermee kon een klinisch relevant effect van duloxetine worden uitgesloten (1.9 punten verschil in WOMAC pijnscore, effect grootte 0.4). Ook voor de subgroep van patiënten met kenmerken van centraal gesensitiseerde pijn werd geen verschil tussen de groepen gevonden (geadjusteerd verschil -0.32 95% BI [-2.32; 1.67]). Daarnaast bleek de interventie niet kosteneffectief. Er werd een klein positief verschil van 0.04 QALY's gevonden voor de duloxetine groep, wat te klein is om klinisch relevant te zijn. Op basis van de resultaten konden we een klinisch relevant effect voor de totale groep uitsluiten. Voor de subgroep met patiënten met kenmerken van centraal gesensitiseerde pijn kon een groter effect van duloxetine worden uitgesloten (verschil van 2.9 punten in WOMAC pijn (effect grootte 0.6)). Echter een kleiner effect van duloxetine kan niet worden uitgesloten gezien de kleine sample size van deze subgroep. Deze resultaten moeten daarom in een andere klinische trial worden bevestigd.

Tot slot worden in hoofdstuk 8 de belangrijkste bevindingen en beperkingen van dit proefschrift besproken. Daarnaast worden de implicaties voor de klinische praktijk en voor toekomstig onderzoek gegeven.

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CURRICULUM VITAE

Jacoline van den Driest is op 14 april 1988 geboren in Vlissingen. Na het behalen van haar gymnasium diploma aan de Christelijke Scholengemeenschap Walcheren in Middelburg in 2006 is zij begonnen aan de studie geneeskunde aan de Universiteit Maastricht. Tijdens haar afstudeeronderzoek bij de maag-, darm-, leverziekten onderzocht zij of de ziekteactiviteit bij patiënten met de ziekte van Crohn of colitis ulcerosa betrouwbaar kon worden vastgesteld in uitgeademde lucht.

Na het behalen van haar artsenexamen in 2012 heeft ze als arts achtereenvolgens een jaar gewerkt op de afdeling Interne Geneeskunde van het Maasstad ziekenhuis in Rotterdam en een jaar op de afdeling Interne Oncologie van de Daniel den Hoed kliniek in Rotterdam.

In januari 2015 startte zij haar promotietraject als junior onderzoeker bij de afdeling Huisartsgeneeskunde van het Erasmus MC in Rotterdam. In september 2017 is dit traject omgezet naar een AIOTHO-traject (arts in opleiding tot huisarts en onderzoeker). Dit jaar rondt zij haar huisartsopleiding af.

PHD PORTFOLIO

Erasmus MC Department: General Practice
PhD Period: January 2015- February 2021
Promotors: Prof. dr. S.M.A. Bierma-Zeinstra and Prof. dr. P.J.E. Bindels
Co-promotor: Dr. D. Schiphof

	Year	Workload (ECTS)
Courses/ training		
CPO Course Patient Oriented Research: design, conduct, analysis and clinical implications	2015	0.3
BROK course	2015	1
NIHES Biostatistical methods I: Basic Principles	2015	5.7
NIHES Biostatistical methods II: Classical regression models	2015	4.3
BKO (Basiskwalificatie Onderwijs) - Teach the Teacher	2016	1
BKO (Basiskwalificatie Onderwijs) - workshops feedback and groups	2016	1
Research Integrity	2016	0.3
Biomedical Writing	2016	3.0
NIHES Repeated Measurements	2017	1.4
BROK course, re-registration	2019	0.3
NIHES Missing Values	2019	1.7
Professional education		
Vocational training for general practitioner, Erasmus MC, Rotterdam	2017 - present	
Oral presentations		
NHG wetenschapsdag, Amsterdam, 1 presentation	2016	1
BJGP conference, London, 2 presentations	2020	2
NHG wetenschapsdag, 2 presentations	2021	2
OARSI, 1 presentation	2021	1

Poster presentations		
NHG wetenschapsdag, Amsterdam, 1 poster	2016	1
NHG wetenschapsdag, Zeist, 1 poster	2017	1
OARSI, Las Vegas, 1 poster	2017	1
Participation (inter)national conferences		
NHG Wetenschapsdag, Rotterdam	2015	0.3
OARSI, Amsterdam	2016	1
Teaching		
Clinical reasoning for bachelor and master students	2015 - 2020	3.9
Development of Clinical reasoning sessions master students	2017	9.6
Organisation		
Patient panel	2015 - 2020	5.1

LIST OF PUBLICATIONS

This thesis

Van den Driest JJ , Bierma-Zeinstra SMA, Bindels PJE, Schiphof D. Amitriptyline for musculoskeletal complaints: a systematic review. Family Practice. 2017 Apr 1;34(2):138-146

Van den Driest JJ, Schiphof D, Luijsterburg PAJ, Koffeman AR, Koopmanschap MA, Bindels PJE, Bierma-Zeinstra SMA. Effectiveness and cost-effectiveness of duloxetine added to usual care for patients with chronic pain due to hip or knee osteoarthritis: protocol of a pragmatic open-label cluster randomised trial (the DUO trial).BMJ Open. 2017 Sept 11;7(9)

Van den Driest JJ, Pijnenburg P, Bindels PJE, Bierma-Zeinstra SMA, Schiphof D. Analgesic use in Dutch patients with osteoarthritis: frequent but low doses. Journal of Clinical Rheumatology. 2019 Oct; 25 (7):297-303

Van den Driest JJ, Schiphof D, De Wilde M, Bindels PJE, Van der Lei J, Bierma-Zeinstra SMA. Opioid prescriptions in patients with osteoarthritis: a population-based cohort study. Rheumatology. 2020 Sep 1;59 (9):2462-2470

Van den Driest JJ, Schiphof D, De Wilde M, Bindels PJE, Van der Lei J, Bierma-Zeinstra SMA. Antidepressant and anticonvulsant prescription rates in patients with osteoarthritis: a population-based cohort study. Rheumatology. 2021 May 14;60 (5):2206-2216

Other publications

Schiphof D, **Van den Driest JJ**, Runhaar J. Osteoarthritis year in review 2017: rehabilitation and outcomes. Osteoarthritis Cartilage. 2018 Mar;26(3)326-340.