TO BE IN PAIN OR NOT

research to improve cancer-related pain management

Wendy Oldenmenger

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CHAPTER 1

General Introduction

Cancer is a growing problem. In the Netherlands, the twenty years prevalence of cancer is rising during the years. In 1990, 223 540 persons were living with cancer (twenty years prevalence). In 2002, the twenty years prevalence was 386 361 persons, and in 2010 540 371 persons. The prevalence of cancer increased with 3% – 3.5% per year since 1990. This increase was mainly provoked by an increase in the national population, especially elderly[1-2].

In cancer patients, pain is one of the most frequent and feared symptoms[3]. Pain can interfere with all aspects of daily life and pain relief is an important component of patients' quality of life. The prevalence of cancer-related pain remained stable over the years, although the knowledge on pain treatment did improve. For cancer patients with all disease stages, the studies before 1990 showed that the prevalence of cancer-related pain varied between 41% - 72%[4-5], of whom 35% scored their pain as moderate to severe (pain intensity score ≥ 5)[6]. The studies between 1990 and 2005 showed a prevalence between 28% - 87%[4-5], of whom between 23% - 65% scored their pain as moderate to severe[7], and studies after 2005 reported a prevalence of 52% - 72%, of whom between 20% - 56% scored their pain as moderate to severe[8-10]. The prevalence of pain in cancer patients is related to the stage of cancer. The review of Van den Beuken et al.[5] showed that the prevalence of cancer-related pain was 33% (95% Confidence Interval (CI) 21-46%) in cancer patients after curative treatment (n=726); 59% (95% CI 44-73%) in patients during anti-cancer treatment (n=1408); and 64% (95% CI 58-69%) in patients with advanced disease (n=9763)[5].

Cancer-related pain can be caused by (a) the direct growth and penetration by the tumor and/ or metastases (70%) (e.g. bone metastases, compression or infiltration of nerves); (b) diagnostic procedures; (c) antitumor treatment, such as chemotherapy, surgery or radiotherapy (20%); (d) and comorbidity or associated factors (10%) (e.g. constipation, infections, muscular spasms)[11-12]. Cancer-related pain can be distinguished into nociceptive pain and neuropathic pain. Nociceptive pain is caused by tissue damage. This pain is often the result of bone metastases or infiltration in soft tissues or viscera. Neuropathic pain can be defined as pain resulting from damage to the peripheral or central nervous system. Damage to the nervous system may be caused by compression or invasive growth by a tumor, by chemotherapy or after surgical interventions. About 65%-68% of cancer-related pain is nociceptive and 8-9% is neuropathic. In 23-27% of cases both types of pain can be found[12-15].

The aim of pain management is to reduce the pain intensity to a tolerable level with acceptable side-effects. Cancer-related pain management consists of a combination of anti-tumor treatment (i.e. therapy directed at the cause of the pain) and pharmacotherapy. The aim of the anti-tumor therapy is to reduce tumor load with the intention to decrease patients' pain intensity. Examples of the use of anti-tumor therapy are radiotherapy when patients have local pain due to bone metastases, or chemotherapy

in patients with potentially chemotherapy-sensitive tumors. Besides this, analgesic pharmacotherapy is the mainstay of cancer pain management. In 1986, the World Health Organization (WHO) published the analgesic ladder[11]. The WHO analgesic ladder categorizes analgesics into three steps which, depending on the pain intensity, progress from non-opioid analgesics (Step 1: acetaminophen and Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)) to Step 2 opioids (e.g. codeine and tramadol), to Step 3 opioids (e.g. morphine, fentanyl, hydromorphone). When patients have neuropathic pain, adjuvant analgesics like tricyclic antidepressants or anticonvulsants may help. The WHO ladder can be summarized in five phrases:

1. by the mouth (if possible, analgesics should be given by mouth; continuous subcutaneous infusion offers an alternative route);
2. by the clock (e.g. drugs should be taken at regular time intervals and not 'as needed');
3. by the ladder (according the WHO analgesic ladder);
4. for the individual (there are no standard doses for opioid drugs, the right dose is the dose that relieves the patient's pain);
5. attention to detail (it is essential to monitor the patient's response to the treatment to ensure that the patient obtains maximum benefit with as few side-effects as possible)[11-12,14].

By the introduction of the WHO analgesic ladder, it was estimated based on practical experience that this approach combined with appropriate dosing guidelines would provide adequate pain relief to 70%-90% of patients[11]. In the years after this publication several studies evaluated the effectiveness of the WHO analgesic ladder. The two articles that reviewed these validation studies, questioned the feasibility and effectiveness of the analgesic ladder due to methodological limitations (e.g. small sample size or high rates of exclusion) of the included studies[16,17]. In these two validation reviews, adequate analgesia was described as a pain intensity of ≤ 4 measured with an NRS; description of pain intensity as none, slight or mild; or a ≥70% reduction of the pain intensity. Adequate analgesia was achieved in approximately 76% (range 45% - 100%) of the patients with cancer-related pain who were treated using the WHO analgesic ladder[16-17].

In general, various reasons exist why patients' pain is not always adequately managed (NRS ≥ 5, Figure 1). First, a substantial part of the cancer patients have complex pain problems. Approximately 35% of all cancer patients' pain has a neuropathic component. Breakthrough pain occurs in 50%-65% of the cancer patients[12,14]. Besides this, not all patients could be treated effectively with oral morphine. For these patients, an opioid rotation, a change in opioid *or* route of administration has been shown to be beneficial[18-19].

Secondly, health care providers do not always have enough knowledge regarding pain management and have various misconceptions about pain and pain treatment.

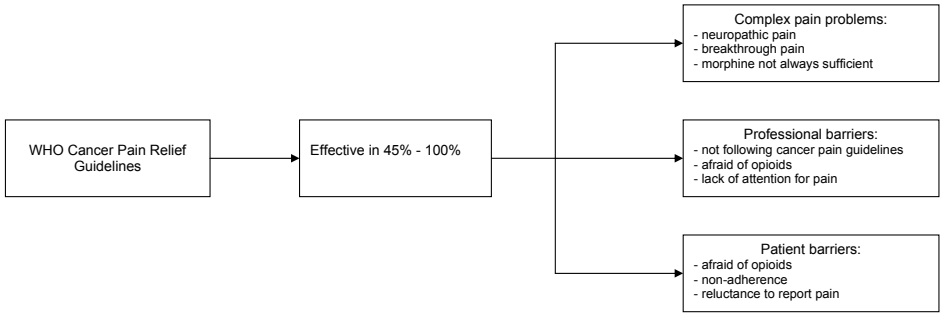

Figure 1. Reasons for inadequate pain relief

Physicians do not always follow the existing pain guidelines; the potential of anti-tumor therapy is not always included as an option. Besides this, not all physicians always pay attention to patients' pain. In a recent pan-European survey of 5084 adult cancer patients, 72% reported to have pain[9]. In total, 56% of the surveyed patients rated their pain as ≥ 5 (on a 0-10 Numeric Rating Scale (NRS)). An in-depth survey to increase the understanding of cancer-related pain took place in a sample of 573 patients with NRS ≥ 5, in whom 69% described that their pain interfered with daily life. Pain was primary managed by medical oncologists (42%) or general practitioners (19%). In only 5% of the patients a pain specialist or palliative care specialist was involved. According to these patients, the physician asked them about their pain at every consultation (55%), at most consultations (16%) or occasionally (22%)[9]. According to the patients, 38% believed that their physician mainly focused on their cancer, rather than the cancer-related pain, 33% believed that their physicians did not have time to discuss their pain and 26% thought that their physician did not know how to treat pain. Moreover, eleven percent of the patients with NRS ≥ 5 were not receiving any analgesics at all. Of the patients with a prescription of analgesics, only 40% received a prescription for WHO Step 3 opioids[9].

Thirdly, besides health care providers, also patients have various misconceptions about pain and pain treatment, which could contribute to inadequate pain treatment. It is known that many patients have misconceptions about their pain and analgesics, especially concerns about opioid use, and a reluctance to report pain and to use prescribed analgesics[20].

AIMS

Despite the existing guidelines and the increased attention for cancer-related pain, adequate pain management is still not possible for all cancer patients. The percentage of patients with adequate pain relief has a broad range and the reasons for inadequate

pain relief are divers: patients with complex pain problems, misconceptions and insufficient knowledge in both professionals and patients. Therefore attention to improve pain management remains necessary.

This thesis describes research that was performed in order to get more insight in the factors that influence cancer-related pain management and research to evaluate interventions aimed to improve patients' pain. The aims of this thesis are:

1. to evaluate the prevalence of cancer-related pain and quality of cancer-related pain treatment at our own outpatient clinic;
2. to identify and summarize the available information on barriers hindering adequate pain management and interventions aiming to overcome these barriers;
3. to study methods to measure patients' adherence to analgesics in cancer patients;
4. to evaluate whether an intervention based on the barriers hindering adequate pain management will improve patients' pain intensity and interference in daily life;
5. to evaluate whether an opioid rotation to parenteral hydromorphone will improve patients' pain intensity in patients with complex pain problems.

OUTLINE OF THIS THESIS

Chapter 2 describes a survey designed to determine the prevalence and quality of cancer-related pain in the outpatient clinic of the Erasmus MC Daniel den Hoed Cancer Center.

Chapter 3 describes a systematic review to identify the major barriers hindering adequate pain management and the randomized controlled trials on interventions aiming to overcome these barriers (aim 2).

Chapter 4 evaluates the feasibility of using Medication Event Monitoring System (MEMS) vials in comparison with medication diaries in cancer patients with chronic pain (aim 3).

Chapter 5 reports the results of a randomized clinical trial in which we investigated if a pain consult combined with pain education including weekly monitoring leads to an overall reduction in average pain intensity over the 8-week study period (aim 4).

In **chapter 6** we describe the results of a retrospective study in advanced cancer patients, with a complex pain problem, who were rotated to parenteral hydromorphone (aim 5).

Chapter 7 summarizes the main results of this thesis. Finally, the main conclusions and implications for clinical practice are discussed and recommendations for future research in pain management are given.

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CHAPTER 2

The effects of analgesic prescription and patient adherence on pain in a Dutch outpatient cancer population

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ABSTRACT

Insufficient awareness of cancer pain, including breakthrough pain, inadequate analgesic prescriptions, and nonadherence contribute to inadequate cancer pain management. There are insufficient data about the contribution of each of these factors. In a cross-sectional survey among 915 adult cancer outpatients, pain was assessed by the Brief Pain Inventory. Breakthrough pain was defined as a *worst* pain intensity rated as '7 or more' and an *average* pain intensity rated as '6 or less' in patients on 'around-the-clock' (ATC) analgesics. The Pain Management Index (PMI) was calculated to measure the quality of treatment. Adherence was considered inadequate when below 100% of the dose prescribed. Pain was present in 27% of patients. Worst pain was rated as moderate in 26%, and as severe in 54%. Breakthrough pain was present in 45% of patients with ATC medication. The PMI indicated inadequate treatment in 65% of patients. The proportions of patients' adherent to ATC analgesics varied from 59% (tramadol) to 91% (Step 3 opioids). The management of cancer pain will benefit most from improving analgesic prescriptions and patient adherence.

INTRODUCTION

Cancer pain management is complex and consists of anticancer treatment, analgesics, adjuvant analgesics (e.g., anti-epileptic drugs for neuropathic pain), and strategies to improve side effects [1-4]. The selection of the appropriate analgesic therapy is based on the intensity of the pain according to the three-step analgesic ladder of the World Health Organization (WHO)[5]. Analgesics should be given around the clock (ATC). In addition, patients may need supplemental rescue doses for breakthrough pain[4-5]. Accurate knowledge of the prevalence of pain among cancer patients is vital to improve treatment of cancer pain. In the past 10 years, the Pain Management Index (PMI) was developed as a simple and objective tool for evaluating the quality of analgesic prescriptions, and breakthrough pain was recognized as a separate entity[6-7].

The PMI is a composite measure computed by subtracting a patient's *worst* pain intensity from the rating of the most potent analgesic prescribed[7]. The PMI is considered a conservative estimate, since it does not take into consideration the doses of the analgesics used or the schedule (ATC or 'as needed' [PRN]). The PMI is the single most often used outcome measure for quality of pain treatment[7-21].

Breakthrough pain was originally described as a transitory exacerbation of pain to greater than moderate intensity that occurs in addition to otherwise stable persistent pain of moderate intensity or less among patients on stable doses of opioids[1]. The definition of breakthrough pain, however, differs between research groups[6]. Breakthrough pain is associated with greater functional impairment, and more pain-related hospitalizations and physician office visits[22-23].

Even though health care providers mention nonadherence as one of the most common reasons for uncontrolled cancer pain, surprisingly little attention has been paid to this issue[24]. The few studies that measured adherence to analgesic regimens among cancer patients reported adherence rates for fixed-schedule opioids averaging 80 – 90%[25-26]. Even fewer data are available about adherence to nonopioid drugs in cancer patients. Furthermore, it has been demonstrated outside the field of cancer pain that simple measures of adherence, e.g., patient's self-report, are useful since they correlate with clinical outcome[27-29].

The present cross-sectional study was designed to determine the prevalence of pain, including breakthrough pain; to assess the quality of pain management; and to evaluate adherence to ATC analgesics in a cohort of outpatients treated in a tertiary cancer center in Rotterdam, The Netherlands.

METHODS

Study subjects

During one week, we studied 915 adult outpatients with cancer. All patients were treated in the Daniel den Hoed Cancer Center in Rotterdam, the 136-bed tertiary cancer center of the Erasmus Medical Center, Rotterdam, the Netherlands. The study was approved by the Medical Ethics Committee of the Erasmus Medical Center. All patients gave written informed consent.

Study procedure

Sixteen advanced medical students were trained by two of the authors (RHE, WHO) to interview the patients. A pain questionnaire was developed for the purpose of this study. The following sociodemographic and medical variables were collected for all participating patients: age; gender; Eastern Cooperative Oncology Group (ECOG) Performance Status[30]; year and month of cancer diagnosis; type of cancer; tumor status (no evidence of disease [NED], locoregional, or distant metastases); current (previous six weeks) anti-tumor treatment; intent of current anti-tumor treatment (curative or palliative, according to the treating physician); and use of bisphosphonates. All data were checked by one of the authors (RHE). Subsequently, the interviewer asked the patients if they had experienced pain in the past week other than everyday kinds of pain. This represents the first question of the Brief Pain Inventory (BPI)- Dutch Language Version[31]. In addition, patients were asked if they had been prescribed any analgesic. All patients who had pain or were taking analgesics were asked to fill in the written part of the questionnaire. After completion, the questionnaire was checked and patients received additional questions about their analgesic use. If patients were unable to give details about current analgesic use, a telephone call was made in the following days to complete the questionnaire.

Measures

Pain, Pain Interference with Activities, and Breakthrough Pain

The questionnaire started with the BPI- Dutch Language Version[31]. Patients were asked to rate their present pain on an 11-point numeric pain rating scale of 0-10, and their least, worst, and average degree of pain in the past week. They were asked to rate how much their pain interfered with level of activity, mood, ability to walk, work, relations with others, sleep, and enjoyment of life on a four-point scale commonly used in protocols of the European Organization of Research and Treatment of Cancer (EORTC) (not at all, a little, quite a bit, very much)[31]. Breakthrough pain was operationalized as a worst pain intensity rated as '7 or more' superimposed on controlled background pain (average pain intensity rated as '6 or less'). We included patients using all kinds of ATC

medication instead of ATC opioids, contrary to the definition used by Portenoy et al., but in accordance with other research groups[1,22].

Analgesics

Each patient was asked to describe current prescriptions for analgesics (PRN and / or ATC, drugs, doses, and routes used). Analgesics were categorized as WHO Step 1 (non-steroidal anti-inflammatory drugs [NSAIDs], acetaminophen), WHO Step 2 (tramadol, codein), WHO Step 3 (morphine, fentanyl patch, oxycodone, methadone), or WHO 'Step 4' (invasive opioids)[5]. The opioid dose was converted to oral morphine equivalent dose using published analgesic tables[23,32]. The median oral morphine equivalent doses were calculated for the total dose prescribed (ATC, and maximum dose allowed of PRN) and the total dose taken. Patients were further asked if they took any of the adjuvant analgesics gabapentin, carbamazepine or amitriptyline.

Quality of analgesic treatment

The PMI relates the patients' worst pain intensity (categorized as 1, mild (1-3); 2, moderate (4-7); or 3, severe (8-10)) to the most potent pain medication prescribed by the clinician (0, no analgesics; 1, WHO Step 1; 2, WHO Step 2; and 3, WHO Step 3 or 4). It is calculated by subtracting the pain level from the analgesic level[7]. Negative PMI scores are considered to be indicators of inadequate pain management, while scores of 0 or higher are considered 'adequate'.

Adherence

Adherence rates for the past 24 hours were calculated for ATC regimens (i.e., dose taken divided by dose prescribed, multiplied by 100) for all classes of medication[26]. Inadequate adherence was defined as an adherence rate of <100%.

Contribution of Quality of Prescription and Adherence

For the evaluation of the contribution of inadequate prescriptions vs. inadequate adherence, we compared adherence rates to the PMI data.

Statistical analysis

Proportions are reported with their 95% confidence intervals (95% CIs) as appropriate. Differences in proportions were tested with the Chi-squared test or Fisher's exact test as appropriate. Means are reported with their standard deviation (SD), medians with their range. Differences in means were tested with Student *t*-test. Reported *P*-values are two-tailed and were considered significant at $P < 0.05$ level.

RESULTS

Prevalence and Intensity of Pain, and Breakthrough Pain

A total of 246 of 915 patients (27%, 95% CI: 24%-30%) had pain or used analgesics in the past week. Table 1 shows the prevalence of pain among categories defined by sociodemographic or medical variables. Pain was seen more often in female patients, in patients with poor performance status, in patients with distant metastases, in patients who had received antitumor treatment within the previous six weeks, and among those treated, in patients who were treated with a palliative intent. Furthermore, pain was not distributed equally among cancer types, and was present most frequently among breast cancer patients. The mean pain intensities were 3.8 $\pm$ 2.4 (present pain), 6.4 $\pm$ 2.4 (worst pain), and 4.1 $\pm$ 2.2 (average pain). One hundred thirty-three patients (54%) reported a worst pain score of 7 or above, while 34 (14%) reported an average pain score of 7 or above in the last 24 hours (Figure 1). Pain interfered 'quite a bit' or 'very much' with the patients' daily activities (51%), work (47%), and sleep (41%) (Figure 2).

Table 1 Sociodemographic and Medical Variables (n=915)

	N (%) with pain	P
Male (n=416)	98 (24)	0.04
Female (n=499)	148 (30)	
ECOG 0-1 (n=758)	165 (22)	<0.001
ECOG 2-4 (n=119)	57 (48)	
NED (n=344)	57 (17)	<0.001
Locoregional (n=328)	92 (28)	
Distant metastases (n=243)	97 (40)	
With antitumor therapy (n=403)	145 (36)	<0.001
Without antitumor therapy (n=512)	101 (20)	
With curative intent of therapy (n=213)	58 (27)	<0.001
With palliative intent of therapy (n=190)	87 (46)	
Breast cancer (n=286)	91 (31)	0.02
Head and neck cancer (n=155)	41 (26)	
Hematological malignancies (n=120)	21 (18)	
Urological cancer (n=107)	22 (21)	
Other cancer (n=247)	71 (29)	

Breakthrough pain was present in 57 patients (45%, 95% CI: 36%-54%) of the 126 patients with ATC analgesics. The mean average pain of these patients was 4.5 ± 1.5, and the mean maximum pain was 7.8 ± 0.9.

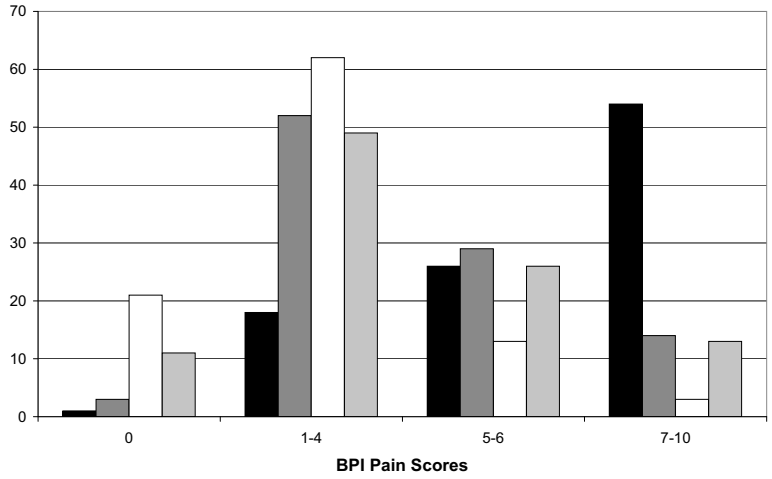

Figure 1. BPI pain scores. Percentage of patients reporting pain scores in the BPI. Worst pain = black bars; average pain = dark gray bars; least pain = white bars; current pain = light gray bars.

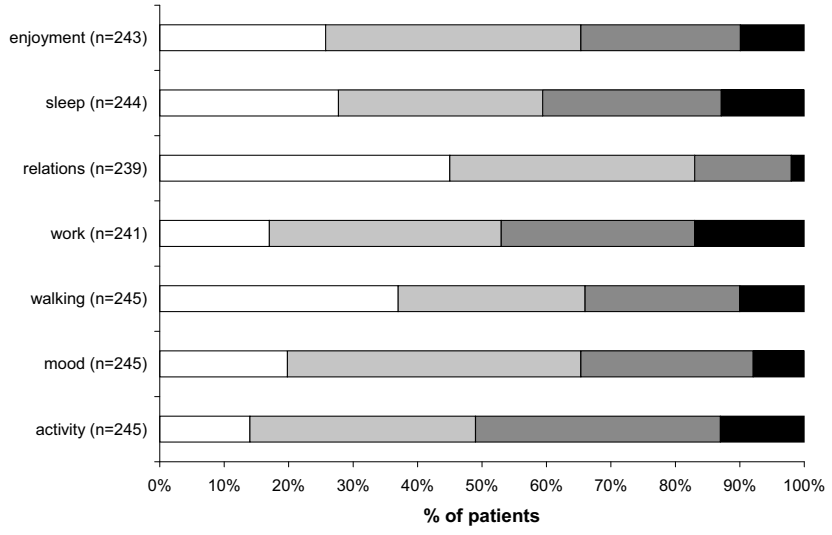

Figure 2. Interference of pain with various activities of daily living. Very much interference = black; quite a bit interference = dark gray; a little interference = light gray; no interference at all = white.

Analgesics

A total of 180 of 246 (73%, 95% CI: 68%-79%) patients with pain had been prescribed analgesics (Table 2). Only 70% of patients with a prescription had ATC analgesics, and 58% had access to PRN analgesics for breakthrough pain. The median oral equianalgetic morphine dose of patients taking WHO Step 2 or Step 3 opioids (including one patient who had parenteral opioids) was 60 mg/day (range: 7-360 mg). Of the patients with WHO Step 1 and Step 2 prescriptions, the analgesics were prescribed ATC in 61%, whereas WHO Step 3 analgesics were prescribed ATC in 94% of patients (Table 2). The adjuvant analgesics were prescribed infrequently: gabapentin in 3%, carbamazepine in 1% and amitriptyline in 3% of patients.

Table 2 Analgesic prescriptions 'by the clock' and 'by the ladder'

	ATC N (%)	PRN N (%)	ATC and PRN N (%)	N
WHO 1	80 (51)	60 (38)	17 (11)	157
WHO 2	29 (58)	20 (40)	1 (2)	50
WHO 3	22 (47)	3 (6)	22 (47)	47
WHO 4	0	1 (100)	0	1
Any analgesic	75 (42)	54 (30)	51 (28)	180
No analgesics				66

ATC = around-the-clock; PRN = as needed

Quality of Pain Management

Poor (worst pain score 7 – 10) or very poor (average pain score 7 – 10) pain control was seen across all analgesic categories, suggesting that patients were receiving inadequate opioid therapy (Figure 3)[33]. The PMI was negative in 158 of 244 patients (65%, 95% CI: 59%-71%), indicating inadequate pain management (Figure 4).

Adherence

The proportions of patients adherent to ATC analgesics varied from 59% (tramadol), to 78% (NSAIDs) and 91% (Step 3 opioids), but proportions were not significantly different due to small numbers. A total of 125 patients had a prescription for ATC analgesics and were evaluable for comparison of PMI and adherence (Figure 5). By PMI, 68 patients (55%) were adequately managed and 57 (46%) were not. Overall, 91 patients (73%) adhered to their analgesic prescription, while 34 (27%) were nonadherent. Of the 57 patients with inadequately managed pain, 19 (33%) were nonadherent to their analgesic medication.

Of the 57 patients with breakthrough pain and a prescription for ATC medication, 16 (28%) were nonadherent. Of the 23 patients with breakthrough pain and a PRN prescription, only 4 (17%) actually took ≥ 80% of the PRN medication allowed.

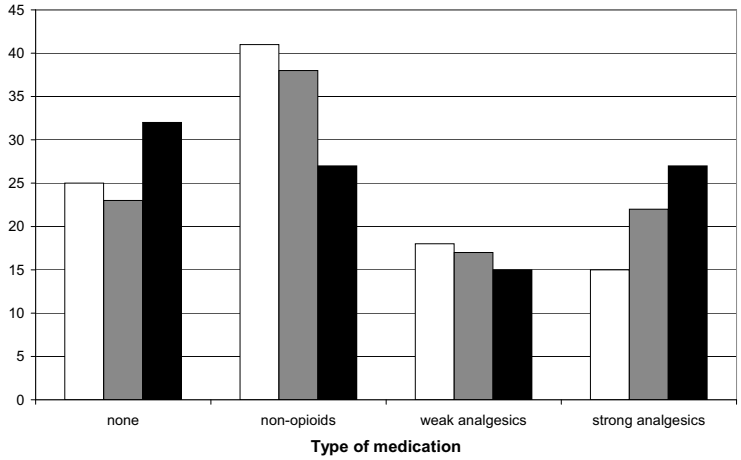

Figure 3. Percentage of patients receiving no pain medications, nonopioid analgesics, weak opioids, or strong opioids. BPI average pain score 0 - 4, *n=136* (good pain control) = white bars; BPI worst pain score 7 - 10, *n=133* (poor pain control) = gray bars; BPI average pain score 7 - 10, *n=34* (very poor pain control) = black bars.

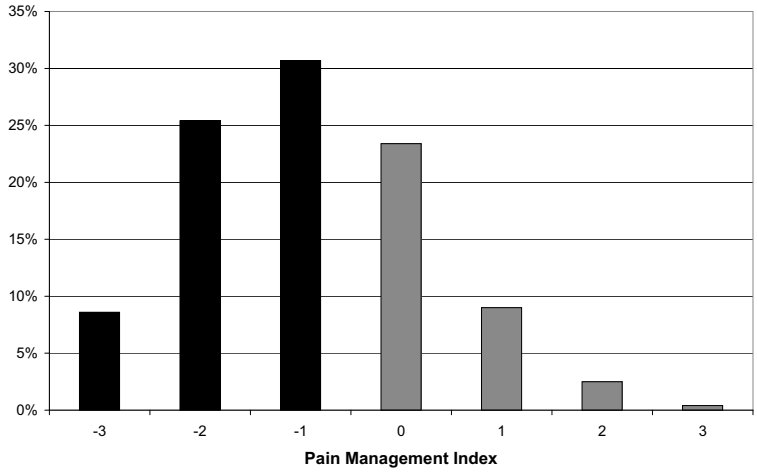

Figure 4. Percentage of patients by Pain Management Index (PMI).

DISCUSSION

Studies to date show a wide variation in the reported prevalence of cancer pain. In the present study, 27% of outpatients treated in a cancer center reported to have pain, which is lower than found in previous prospective studies in outpatients. Among outpatients at various stages of cancer, the prevalence varied from 40% to 61%[14,34-36]. The prevalence of cancer pain in outpatients with advanced cancer varied in prospective

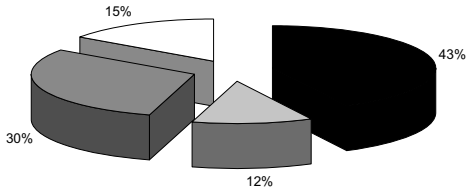

Figure 5. Relative contribution of prescription (PMI) and adherence to efficacy of pain management (n=125). Positive PMI and adherent *(43%)* = black piece; positive PMI and non-adherent (*12%)* = light gray; negative PMI and adherent *(30%)* = gray; negative PMI and non-adherent *(15%)* = white.

studies between 67% and 78%, compared to 40% in our series[7,37-38]. The different clinical settings may explain these differences.

In the present study, 45% of patients with a prescription for ATC analgesics had breakthrough pain in the past week. The incidence of breakthrough pain varies widely from 40% to more than 90% of patients, depending on the definitions used and the clinical setting[39-43]. Less restrictive criteria have been used both for the definition of pain and for the analgesics used. Alternative definitions of breakthrough pain included *any* transient exacerbation of pain that could be distinguished from baseline pain, or any pain that varied with time, including episodes of pain on a pain-free background[40,43]. In several studies, a fixed schedule of opioids was a prerequisite for the diagnosis[1,23]. However, as in previous studies, we accepted any medication taken on a fixed schedule[22]. We used a stricter definition of pain and, as may be expected, found a lower prevalence (45% compared to 63%)[22].

Seventy-three percent of patients with pain were treated with analgesics. Most (87%) of them had WHO Step 1 analgesics, approximately 25% had WHO Step 2 analgesics, and 25% had WHO Step 3 analgesics.

A negative PMI was seen in 65% of patients with pain. Since the PMI is considered a conservative estimate, this result is disappointing. Most would consider a low dose of WHO Step 3 opioids or a PRN opioid schedule inadequate for patients who experience severe background pain, but both examples would be considered adequate according to the PMI. One might hypothesize that the pain could be neuropathic in a large amount of patients, and since the PMI does not consider adjuvant analgesics, it would not reflect the quality of treatment in such patients. However, since fewer than 5% of our patients were treated as such, this hypothesis does not hold. A negative score on the PMI was seen in 13%-79% of patients in previous studies (Table 3)[7-21]. There are no prior data available for Dutch outpatients.

Self-reported adherence is fraught with difficulties, but it has been used in all previous studies on adherence among cancer patients[25-26,44-46]. We found that the proportions of patients adherent to ATC analgesics varied from 59% (tramadol) to 91% (Step 3 opioids). In earlier reports, patients took an average of 80%-89% of their ATC opioids[25-26,44-46].

Table 3 Adequacy of treatment (Cleeland Pain Management Index)

Country	n	% worst PI > 4	mean worst PI	% strong opioids	% inadequate treatment	95% CI	Reference
Germany	905	NS	NS	71%	13%	11-15%	Sabatowski[12]
Japan	121	NS	4.9	NS	27%	20-36%	Uki[16]
USA	139	66%	5.7	39%	29%	22-37%	Wells[17]
South Africa	426	74%	5.7	36%	30%	26-35%	Beck[13]
Korea	508	47%	NS	25%	41%	37-45%	Hyun[14]
USA	597	62%	NS	NS	42%	38-46%	Cleeland[7]
Italy	117	NS	NS	NS	43%	34-52%	Cascinu[20]
Netherlands	313	91%	7.7	36%	49%	44-55%	de Wit[49]
France	270	69%	NS	26%	51%	45-57%	Larue[8]
Korea	464	64%	5.5	NS	53%	48-57%	Yun[19]
USA	281	67%	5.7	37%	65%	59-70%	Cleeland[15]
China	147	70%	NS	27%	67%	59-74%	Wang[10]
Taiwan	113	65%	5.7	NS	69%	60-77%	Ger[18]
Greece	220	85%	7.4	10%	75%	69-80%	Mystakidou[11]
Israel	218	80%	NS	NS	75%	69-80%	Shvartzman[21]
India	200	84%	7.4	NS	79%	73-84%	Saxena[9]
Netherlands	*244*	*81%*	*6.4*	*26%*	*65%*	*59-71%*	*present study*

NS= not stated; PI= pain intensity

In 125 patients with a prescription for ATC analgesics, we estimated the contribution of patient adherence to pain management. Sixty-eight (54%) of these 125 patients were adequately managed, as indicated by a positive PMI. However, of the 57 (46%) with a negative PMI, 33% were nonadherent despite the presence of pain. Of the 23 patients with breakthrough pain and a PRN prescription, only four (17%) actually took ≥ 80% of the PRN medication allowed. These findings indicate that improvement of patient adherence may contribute to better pain management.

There are several limitations that should be considered in interpreting the results of this study. First, information about analgesic prescriptions was based on patients' report and may not have been accurate. To overcome this problem, patients who could not reproduce their prescriptions had follow-up phone calls. Second, recently, sophisticated methods of measuring adherence have become available, e.g., a medication event monitoring system (MEMS) in which a microprocessor in a special pill-bottle cap records the number of times that the pill bottle is opened. MEMS was not used since it is expensive, especially when evaluating a complex analgesic regimen, but MEMS will be used in a longitudinal study in our center. Third, the cutoff for adherence in the present study was 100%, while the traditional cutoff for adherence derived from studies on hypertension

was 80%[47]. For HIV-1 infection, it has been demonstrated that ≥ 95% adherence is necessary for successful treatment[48]. It is not clear which cutoff should be taken for cancer pain. However, in our study there was no difference between patients > 80% adherent and patients 100% adherent.

In summary, 27% of cancer outpatients were found to have pain, and 45% of patients on ATC analgesics had breakthrough pain. Sixty-five percent of patients were undertreated, as indicated by a negative PMI. About one-third of patients with a negative PMI did not adhere to their analgesic prescription. Apparently, both poor analgesic prescriptions and poor adherence contribute to ineffective cancer pain treatment. We have begun a longitudinal study where quality of pain treatment will be monitored by pain experts, and adherence will be measured by MEMS.

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CHAPTER 3

A systematic review on barriers hindering adequate cancer pain management and interventions to reduce them: a critical appraisal

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ABSTRACT

The aim of this paper is to identify the major barriers hindering adequate pain management and critically review interventions aiming to overcome them. We searched relevant literature on PubMed published between January 1986 and April 2007. The most frequently mentioned barriers for both patients and professionals were knowledge deficits, inadequate pain assessment and misconceptions regarding pain. Four interventions were identified: patient education, professional education, pain assessment and pain consultation. These interventions were never combined in multidisciplinary study protocols. Most RCTs included small groups of patients and reported no power analysis. Studies on professional education and pain assessment did not evaluate patients' outcomes. In 5 of 11 RCTs on patient education, pain intensity decreased statistically significantly. In two RCTs on pain consultation, patients' pain decreased statistically significantly, although the adequacy of pain treatment did not change. In conclusion, international guidelines on multidisciplinary interventions in pain management are partly substantiated by clinical trials.

INTRODUCTION

Pain is one of the most frequent and distressing symptoms in cancer. Pain is present in 36 - 61% of patients depending on cancer type, stage of disease and patient setting, e.g. in- or outpatients[1-3]. Of patients with advanced cancer 64% experience pain[4]. Management of cancer pain is considered to be complex. In 1986, the World Health Organization (WHO) published the analgesic ladder[5]. The WHO analgesic ladder categorizes analgesics into three steps which, depending on the pain intensity, progress from non-opioid analgesics to weak opioids and then to strong opioids. Analgesics should be prescribed 'around-the-clock' (ATC) for continuous pain and 'as needed' (PRN) for breakthrough pain[5]. The WHO analgesic ladder has been generally accepted as the foundation of cancer pain treatment. The fact remains, however, that despite the existing guidelines and knowledge about pain and pain management, cancer pain relief is still inadequate[6].

Cleeland et al. developed the 'Pain Management Index' (PMI), a tool to assess the congruence between severity of pain and medication prescribed[7]. The PMI relates the patients' worst pain intensity (categorized as none, mild, moderate or severe) to the most potent analgesic prescribed (no analgesics; nonopioid analgesics; weak opioids; strong opioids). It is calculated by subtracting the worst pain from the most potent analgesic prescribed. Negative PMI scores are considered to indicate suboptimal medication prescription and scores of zero or greater are considered indicating acceptable analgesic potency[7]. According to the PMI, 43% of patients, outpatients as well as inpatients, are treated inadequately[8].

However, although almost half of the patients are treated inadequately[8], it has been proposed that effective treatment of pain should be feasible for 70-90% of oncology patients[6]. Numerous barriers have been documented that prevent patients from receiving effective pain treatment and avert physicians from providing adequate pain management. The first aim of this paper is to identify the major barriers hindering adequate pain management, patient – related barriers as well as professional – related barriers. The second aim is to critically review RCTs on interventions aiming to overcome these barriers with respect to the methodological quality of these studies and the effect on clinically relevant outcome measurements.

METHODS

Relevant literature published in English was searched on PubMed from 1986 to April 2007. The search was limited to adults, cancer and humans. The terms 'pain management' and 'barrier* or concern*' were used as keywords to identify relevant titles and abstracts. We restricted the search to patients and health care providers. We found

121 articles of which 40 were relevant. Additionally we conducted a search using the medical subject headings terms of 'pain management' and 'health knowledge, attitudes, practice' (n=80), which produced twelve supplementary articles. The reference list of each relevant article and the senior author's personal library was checked to retrieve additional relevant publications, which were not identified by means of the computerized search (n=18) (Figure 1). For the study of interventions to overcome the published barriers we selected randomized clinical trials (RCTs). The methodological quality of the RCTs was assessed using the criteria of Van Tulder et al[9]. We added a criterion to what extent the power analysis was reported. The main outcome measurements used were patients' pain intensity (average pain, worst pain and current pain), patients' or professionals' knowledge or barriers, adherence to analgesics and adequacy of pain treatment, measured with the pain management index (PMI)[7]. To give an indication of the effect of the intervention studied in the RCT on pain, we calculated the difference in the decrease of pain intensity, with respect to baseline, between the intervention and the control group. A clinically relevant effect was defined as a difference in the reduction of pain intensity with 30% or ≥ 2 points on a 0-10 scale[10]. If insufficient data on pain intensities were reported in the articles (e.g. only in graphs), we tried to contact the first author in order to gain access to the source data. All data on the statistical significances, reported in this review, were retrieved from the original papers (Table 3).

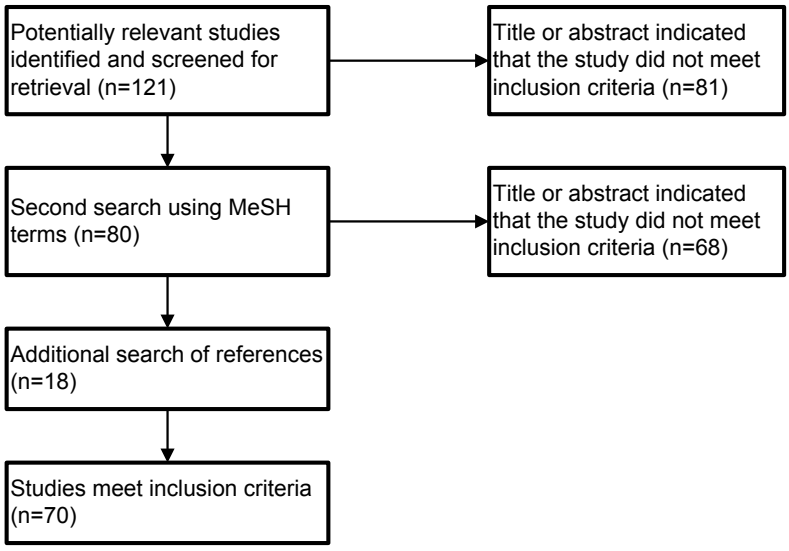

Figure 1. Flow chart.

RESULTS

1. Patient-related barriers

Patients often impede their own treatment due to misconceptions about analgesics and their side effects, non-adherence to treatment regimens, and poor communication of their pain and their concerns about pain to health care providers[11-12]. In 1993, Ward et al. designed a 27-item questionnaire containing eight barriers, the Barriers Questionnaire (BQ)[13]. The BQ is a self-report instrument designed to measure the extent to which patients have barriers reflecting two general factors: beliefs that hinder communication about pain and beliefs and attitudes that may interfere with the use of analgesics. In Table 1, an overview of 10 studies is given, in which the BQ was used.

The sample size varied between the studies, ranging from 35 to 270 patients. Four studies included more than 100 patients. In two studies, no BQ total score could be determined. Patients were most concerned about addiction, side-effects of analgesics, and that increased pain means progression of disease[13-22].

Several studies using the BQ examined to what extent patients' barriers influenced pain management. These studies described that the patients who hesitated to report pain indeed had significantly higher BQ total scores as compared with the patients who did not hesitate[15,20,23-24]. Patients with a negative PMI, which indicates suboptimal use of analgesics[7], had significantly higher BQ total scores than those patients who were adequately medicated[13,15-16,18,21,24-27]. Patients who hesitated to use analgesics had significantly higher BQ total scores as well[15-17].

Fourteen studies were published about adherence to analgesics by cancer patients. Adherence rates varied from 20% to 95%[25,28-40]. Two of these studies examined the relation between adherence and patients' barriers. According to the study of Thomason et al., patients taking their medications only as needed (48%) had more barriers[25]. The study of Lai et al. showed that the stronger patients believed that they could control their pain themselves, the less likely they were to adhere to the prescribed regime. In addition, the stronger they believed that medication was necessary for their pain, the more likely they adhered to their analgesic regime[34].

2. Intervention to reduce patient-related barriers: patient education

Patient education has been suggested as a method to overcome patients' barriers. Various Pain Education Programmes (PEPs) were developed to improve patients' knowledge and to stimulate them to participate actively in their own pain treatment. We found 11 RCTs evaluating PEP. The programmes varied greatly in type, content and duration. The educational interventions ranged in complexity from a single session (approximately 20 min)[41] to an academic detailing session tailored to patients' prior knowledge in

Table 1. Patients' barriers (BQ).

	Year	Number cancer patients	Country	Fear of addiction	Fatalism	Concerns about tolerance	Desire to be a good patient	Concerns regarding side effects	Fear of injections	Fear of distracting one's physician from treating the disease	Concern that increased pain means progression of disease	Misconception toward the interval of taking analgesics	Religious fatalism	Belief that pain medications are better given as needed instead of on an around-the-clock scheduled basis	Total BQ score
Ward[13]*	1993	270	USA	2.20 (1.41)	1.04 (1.03)	1.47 (1.28)	1.11 (1.14)	2.03 (1.06)	1.68 (1.38)	1.27 (1.25)	2.08 (1.54)				1.65 (0.81)
Ward[20] *	1994	53	USA	2.54 (1.38)	1.04 (1.01)	1.74 (1.40)	1.01 (1.21)	2.07 (1.02)	2.26 (1.49)	1.31 (1.33)	2.21 (1.61)				1.76 (0.79)
Ward[19]*	1996	35	USA	2.34 (1.39)	1.29 (1.05)	1.39 (1.35)	1.73 (1.59)	2.50 (1.00)	1.52 (1.27)	1.67 (1.28)	2.59 (1.39)				1.94 (0.85)
Potter[22]+	2003	93	Australia	76%	42%	59%	46%	67%	65%	49%	71%				
Ward[21]*	1994	263	Puerto Rico	3.05 (1.41)	2.37 (1.30)	3.20 (1.42)	2.78 (1.39)	2.68 (0.99)	2.45 (1.52)	3.00 (1.37)	3.20 (1.57)				2.82 (0.82)
Lin[15]*	1995	63	Taiwan	2.98 (1.97)	2.32 (1.33)	4.17 (1.51)	1.42 (1.47)		2.55 (2.00)	2.82 (1.74)	3.99 (1.61)				2.98 (0.85)
Wang[18]*	1997	128	Taiwan	2.94 (1.62)	2.56 (0.98)	3.62 (1.29)	2.04 (1.10)	2.49 (0.85)	3.21 (1.59)	2.40 (1.14)	3.80 (1.69)	3.75 (1.15)			2.98 (0.60)
Wills[14]*	1999	48	China	2.46 (0.83)	2.30 (0.66)		2.80 (0.76)	2.65 (0.56)							
Chung[17]*	1999	39	Hong Kong	2.46 (0.92)	2.64 (0.74)	2.51 (0.72)	2.77 (1.13)	2.87 (0.95)	2.72 (1.26)	3.44 (0.67)	3.64 (0.82)	3.62 (0.86)			2.96 (0.36)
Lin[16]*	2000	159	Taiwan	3.21 (1.67)	1.45 (1.05)	3.66 (1.71)	0.95 (1.21)	3.08 (1.06)		2.55 (1.34)	3.48 (1.73)		2.16 (1.70)	3.29 (1.72)	2.56 (0.79)

Barriers according to the Barriers Questionnaire (BQ); * = mean (sd) (0=do not agree at all; 5=agree very much); + = % patients with some agreement.

combination with written instructions, pillbox and three follow-up phone calls and two follow-up home visits[42] (Tables 2 and 3).

The sample size varied widely between the studies. Four studies included >100 patients while four other studies included <60 patients (Table 2). Two studies reported their power analysis. Two other studies did not describe their dropout rate, in the remaining studies the dropout rate was acceptable (<25%). Only four studies clearly described the method used to randomize their patients. The study duration differed from 5 days to 8 weeks. Five studies measured a long-term effect (> 4 weeks) of the intervention (Table 3).

All studies used patients' pain intensity as the main outcome measurement. One study did not specify what type of pain intensity was measured[39,43]; and three other studies measured one type of pain intensity[35,41,44]. The seven remaining studies measured several types of pain intensity (e.g. average pain, current pain and worst pain) according to

Table 2. Methodological Quality Assessment of Pain Intervention RCTs.

		Method of randomization presented	I/C similar at baseline	Outcome assessor blinded to intervention	Interventions by independent care provider	Number of patients randomized	Dropout rate	Assessment times similar in I/C groups	Intention-to-treat analysis	Power analysis reported*
PEP	Lin[46]	+	+	uk	-	61	uk	+	+	-
	Miaskowski[42]	-	+	uk	+	212	18%	+	+	+
	Yates[44]	+	+	uk	+	189	12%	+	+	-
	Anderson[45]	-	+	uk	uk	97	17-31%~	+	+	+
	Lai[47]	-	+	uk	uk	34	12%	uk	+	-
	Chang[39]	-	+	uk	-	37	0%	+	+	-
	De Wit[49-50]	-	+	uk	+	313	11-25%~	+	+	-
	Oliver[41]	+	+	uk	+	87	23%	+	+	-
	Ward[48]	-	+	uk	-	43	23-37%~	+	+	-
	Rimer[35]	-	+	uk	uk	230	15%	+	+	-
	Dalton[43]	+	+	uk	-	30	uk	+	+	-
Nursing education	Camp-Sorrell[71]	-	+	uk	n/a	60	27%	+	+	-
	Vallerand[72]	-	+	uk	n/a	202	22%	+	+	-
Pain assessment	Kravitz[73]	+	+	uk	+	87	10%	+	+	-
	Trowbridge[74]	-	+	uk	+	320	uk	+	+	-
Pain consultation	Du Pen[32]	+	+	+	+	96	16%	+	+	-
	Cleeland[75]	+	+	uk	+	129	11%	+	+	+

+ = measured; - = not measured; uk = unknown; ~ = % at different assessment times; n/a = not applicable; * = added item.

Table 3. Pain Education Programs: Clinically relevant results.

				Differences in the decrease of pain between I and C groups					
	Year	Intervention/Control	Assessment times	Average Pain NRS (%)	Current Pain NRS (%)	Worst Pain NRS (%)	Pain not specified NRS (%)	Patients' knowledge/ barriers measured	Adherence measured
		I: Education program (30-40 min), and booklet. After 2 and 4 weeks visit in clinic.	2 wks			0.8 (14)		+*	+
Lin[46]	2006	C: Care as Usual	4 wks	NR	NR	1.3 (24)*	n/a	+*	+*
		I: Trained nurses educate and instruct patients for pain, 2 follow-up visits & 3 phone calls, coached how to communicate							
Miaskowski[42,51]	2004	C: AHCPR patients' version and 3 home visits and 3 phone calls by nurse.	5 wks	**1.4 (34)***@	-	1.5 (28)*	n/a	+*	+
		I: Education program (30 min), booklet and phone call after 1 week	1 wk	0.6 (15)				+*	-
Yates[44]	2004	C: Education about cancer in general	8 wks	0.1 (2.4)	-	-	n/a	+	-
		I: Education program in English and Spanish, including video's and consult nurse (30 min). After 48-72 hrs phone call							
		C: Education program about nutrition (English	2 wks			0.4 (5)#			+
Anderson[45]	2004	and Spanish)	8 wks	NR	NR	-0.9 (-12)#	n/a	-	+
		I: Pain education 10-15 min per day for 5 days							
Lai[47]	2004	C: Care as Usual and 10-15 min visit per day	5 days	**1.6 (30)***	**2.3 (61)***	0.1 (1.5)	n/a	+*	-
		I: Pain education (30-40 min) and booklet. After 2 weeks visit in clinic							
Chang[39]	2002	C: Care as Usual	2 wks	NR	NR	NR	0.6 (8)	+*	+*
		I: Pain Education inclusive promotion of 'help-seeking' behavior & booklet, 1 phone call, and audiotape.	2 wks	0.3 (7)	0.8 (24)	0.8 (10)		+*	-
			4 wks	1.0 (22) *	0.8 (24) *	0.5 (6)		-	-
De Wit[49-50]	2001	C: Care as Usual	8 wks	0.4 (10)	0.5 (15)	0.0 (0)	n/a	-	-

Oliver[41]	2001	I: Pain education by Health Educator (20 min) C: Standard education cancer pain (20 min)	2 wks	0.9 (18)*@	-	-	n/a	+	+
		I: Individual tailored information about barriers and side effects. Phone-call after 1 week	4 wks		0.5 (**42**)@	0.7 (12)@		+	-
Ward[48]	2000	C: Care as Usual	8 wks	-	-0.7 (-**69**)@	**-2.0** (**-59**)@	n/a	+	-
Rimer[35]	1987	I: Brief nurse counseling session (15 min) and printed materials C: Care as Usual	4 wks	-	not possible	-	n/a	+*	+*
Dalton[43]	1987	I: Pain education (< 1 hr), printed materials, phone call after 1 week. C: Care as Usual	7-10 days	-	-	-	-3.8 (-12%)^	+*	-

bold = clinically relevant outcome; * = statistically significant; NR = measured but not reported; + = measured; - = not measured; ^ = 0-100 pain scale; @ = data received by email; # = data only reported in graph; n/a = not applicable.

the method sections of the respective papers[39,42,45-49]. However, three of these studies reported only one type of pain intensity[39,45-46], in one of them not further specified[48]. The pain intensities that were measured but not reported in the original paper were described as 'not reported' in Table 3.

In one study, we could not calculate the effect of PEP on pain intensity because of insufficient information[35]. Although five studies described statistically significant differences in the decrease of pain, with respect to baseline, between the intervention and control group[41-42,46-47,50], in only two of them[42,47] the differences in the decrease of pain could be classified as clinically relevant (reduction of pain intensity with ≥ 30% or ≥ 2 points on an 11-point scale)[10]. However, one of these studies had a small sample size (n=30), no power analysis performed and a follow-up of 5 days[47]. In three studies, the control group reported less pain at the end of the study, although this was not statistically significant[43,45,48].

Ten studies evaluated patients' knowledge or barriers (Table 3). Eight of them reported a statistically significant improvement in knowledge about cancer pain and its management in the intervention group compared to the control group[35,39,43-44,46-47,49,51], while two studies found no differences[41,48]. Three studies measured this knowledge at long-term (> 4 weeks) follow up[44,48,51]. Only one study reported a statistically significant improvement in the intervention group at long-term follow-up[42].

Three out of six studies reported a statistically significant improvement on patients' adherence to analgesics in the intervention group compared to the control group.

3. Professional - related barriers

Several studies have found professional-related barriers that may hamper therapeutic strategies. Most of these data were collected by surveys. In these surveys, the investigators used a list of possible barriers to effective pain management developed by the Pain Research Group at the University of Wisconsin, which included factors related to health care system, professionals and patients. In Table 4, an overview of the barriers that were reported most frequently by physicians and nurses is given.

Physicians and nurses reported the following barriers most frequently: (a) inadequate assessment of pain and pain management[52-60], (b) patients' reluctance to report their pain or to give a pain score[13,52,54,56-60] and (c) inadequate knowledge of pain management of professionals (both physicians and nurses)[52-60].

Other studies, not mentioned in Table 4, also supported the notion that professionals may have inadequate knowledge. These studies used self-constructed questionnaires to measure professionals' knowledge on the topics: pain assessment, principles of pain management and management of side-effects[61-69]. Between 34% and 86% of the professionals overestimated the likelihood of addiction or tolerance[52,55,59,65,70] and approximately 35% of the physicians believed that morphine has an upper limit[62].

Table 4. Professionals' barriers.

	Year	Number		Inadequate pain assessment and pain relief	Inadequate staff knowledge of pain management	Medical staff reluctance to prescribe opioids	Patient reluctance to report pain	Lack of psychological support services	Patient reluctance to take opioids	Nursing staff reluctance to administer opioids	Lack of access to professionals who practice specialized methods	Excessive state regulation of prescribing opioids
Yu et al.[53]^	2001	427	physicians	74.9	64.8	41.4			39.7	22.8		74.7
Ger et al.[52]^	2000	204	physicians	54	57	25	7	54	15	10		19
Sapir et al.[55]^	1999	176	physicians	65	58	49			40	20.3		19.4
Von Roenn et al.[59]^	1993	897	physicians	76	52	61	62	11	62	38		18
Anderson et al.[54]^	2000	57	physicians and nurses	71	54	40	56	16	36	21	13	17
O'Brien et al.[57]#	1996	148	nurses	86	79	69	87	75	68	58	70	
Ryan et al.[58]#	1994	61	nurses	77	75	61	75	62	49	54	59	
Ryan et al.[58]#	1994	116	oncology nurses	61	53	48	79	45	77	32	29	
Vortherms et al.[60]#	1992	327	nurses	77.1	72	59.1	79.8	62.3	56.6	50.3	53.1	
Furstenberg et al.[56]*	1998	188	physicians	1.6 (0.8)	1.49 (0.9)	1.26 (0.95)	1.12 (0.77)	1.32 (0.98)	1.13 (0.78)	1.08 (0.97)	0.87 (0.91)	0.92 (0.90)
Furstenberg et al.[56]*	1998	248	nurses	1.58 (0.86)	1.55 (0.91)	1.52 (1.01)	1.29 (0.87)	1.34 (1.0)	1.25 (0.89)	1.19 (1.01)	1.43 (1.12)	0.76 (0.91)

^ = % of respondents who selected item as one of the top four barriers in the survey; # = % that rated that item as a barrier to optimal pain management in their setting; * = mean (sd); degree to which item represented a barrier 0-3 scale (0=no barrier; 3=major barrier).

4. Interventions directed at professionals to improve pain management

Our review identified three interventions directed at professionals that intended to improve the management of cancer pain, namely professional education, pain assessment and pain consultation or protocol. In total, six RCTs were identified concerning these interventions (Tables 2 and 5). The sample size varied from 60 to 320 respondents (Table 2). One of the six studies reported their power analysis. One study did not describe the drop out rate. Four studies described clearly how they randomized their respondents.

For the first intervention, to increase professionals' knowledge through education, we found two RCTs. The educational interventions targeted nursing staff in both studies (Tables 2 and 5). The first RCT by Camp-Sorell et al.[71] reported none of the outcome measurements that we considered relevant (Table 5). In the study of Vallerand and colleagues[72], the intervention showed no significant differences in perceived nurses' barriers or perception of control over patients' pain, but significantly increased nurses' knowledge[72].

Two RCTs evaluated the effect of pain assessment[73-74]. In the RCT conducted by Kravitz et al.[73], research staff assessed pain intensity in all patients. However, only of the patients randomly assigned to the intervention group, they recorded the pain scores on bedside charts without active communication with the professionals. Health care providers were not actively involved in the study. Current and worst pain intensity was measured in every patient, but these data were not reported. The intervention did not result in improved pain control[73]. In the study conducted by Trowbridge et al.[74] all patients completed pain assessments (e.g. average and worst pain intensity; pain treatment regimen and degree of pain relief). Only the clinical charts of the intervention group contained a summary of the pain scales. Oncologists were instructed to review the summary sheet prior to an evaluation. Data on the pain intensities were not reported in the article, but the authors suggest that the study resulted in a significant decrease in the proportion of patients with pain in the intervention group (from 70% to 55%). However, the proportion of patients with pain in the control group was not reported. In addition, they reported no differences between the intervention and control group in the percentages of patients with negative PMI scores (35% versus 38%)[74].

The third intervention was the implementation of a pain consultation[32] or pain protocol[75] to improve pain management (Tables 2 and 5). In the study of Du Pen et al., a specialized physician evaluated patients' pain following the Agency for Health Care Policy and Research (AHCPR) guidelines. With respect to the outcome measurements we defined, they found no statistically significant difference for worst pain or patient adherence between the intervention and control group (Table 5). In this study, they reported a statistically significant reduction in 'usual' pain intensity in the intervention group compared to the control group (not in table). This reduction was clinically relevant after 3 months (approximately 35%). Cleeland et al.[75] introduced in their RCT a pain manage-

Table 5. Pain Interventions: Clinically relevant results.

				Differences in the decrease of pain between I and C groups				
	Year	Intervention/Control	Assessment times	Average Pain NRS (%)	Current Pain NRS (%)	Worst Pain NRS (%)	Nurses' Knowledge/ barriers measured	PMI measured
Nursing education								
Camp-Sorell[71]	1991	I: education of pain documentation (45 min) Received laminated assessment tool. C: education of pain documentation; N: non-responders, no education	1 week 1 month 2 months	-	-	-	-	-
Vallerand[72]	2004	I: education session (4 hr); 4-6 weeks own practice; advanced session. C: no education	4 weeks	-	-	-	+*	-
Pain assessment								
Kravitz[73]	1996	I: assessing pain intensity by research staff and displaying results on bedside charts. C: assessing pain intensity by research staff. Results were not displayed.	3 days 5 days	-	NR	NR	-	-
Trowbridge[74]	1997	I: patients completed pain assessments. Oncologists were instructed to review summary sheet of pain assessments prior to patient evaluation. C: patients completed pain assessments	4 weeks	NR	-	NR	-	+
Pain consultation/ pain protocol								
Du Pen[32]	1999	I: study physician and nurse used multilevel treatment algorithm for pain management; C: pain management by patients' own oncologist	2 weeks 4 weeks 2 months 3 months	-	-	0.5 (8)# 0.7 (12)# 0.2 (3)# 0.9 (15)#	-	-
Cleeland[75]	2005	I: pain management protocol; C: care as usual	15 days 29 days	0.9 (21)# **1.3 (30)#**	NR	1.3 (20) 0.9 (15)	-	+

bold = clinically relevant outcome; * = statistically significant; + = measured; - = not measured; NR = measured but not reported; # = data only reported in graph.

ment protocol in the intervention centers, randomizing by center. Although they used the BPI, they only reported on the intensities of worst pain, the primary end-point of the study, and average pain. Worst pain decreased statistically significantly in the intervention group, although not clinically relevant. In the control group, a non-significant reduction was reported (Table 5). A between-groups analysis was not described. The study was terminated early because of slow accrual. Since the study was underpowered they examined differences in proportions of responders, defined as patients whose worst pain scores changed from moderate or severe to none or mild, rather than mean levels of worst pain scores. The proportions of patients responding to pain treatments were 48% (protocol) versus 15% after 15 days (p=0.008) and 52% versus 19% after 29 days (p=0.045). This study showed no differences in PMI[75].

DISCUSSION

According to the multidisciplinary task force of the American Pain Society (APS), the adequacy of cancer pain management will only improve when a multidisciplinary and multilevel approach will be chosen. All cancer patients should be routinely screened for pain during their visit in the clinic and their pain intensity should be documented and frequently reassessed. When patients are in pain, this should be adequately treated with a multidisciplinary evidence-based pain protocol. As a part of this, patients and their relatives should be educated regarding pain and analgesics[76].

Although, internationally, this approach is considered the only way to effectively improve daily cancer pain management, it is not substantiated in the studies here reported. Our review of the literature identified the most important patient-related as well as professional-related barriers hampering patients' pain treatment and also identified the studied interventions to overcome these barriers. Unfortunately, we were incapable to identify interventions that unequivocally demonstrated clinically relevant improvements in patients' pain using the outcome measurements and criteria we selected for this systematic review. Of note, the results of the studies on patient education could even be flattered because some of the studies did not report all measured pain intensities (Table 3). The negative findings from the studies may be due to several factors.

The first factor is the quality of the design and reporting the studies. Many studies used small groups of patients and did not substantiate the sample size with a power analysis. Furthermore, most studies on professional education and pain assessment did not study or report the effect of the intervention on patients' pain. Although pain is a major problem in patients with cancer, internationally there is no consensus on the most important end-points for pain research, for example which pain intensity is most relevant (e.g. current, average or worst pain intensity). According to the recommenda-

tions formulated by Dworkin et al. pain intensity is one of the core end-points in clinical pain trials[77]. However, in the various studies in which pain intensity was used as the main outcome measurement, e.g. studies on patient education and pain consultation or pain protocol, different types of pain intensity were measured, making an overall analysis impossible. In this review, we chose to report clinically relevant results (reduction of pain intensity with ≥ 30% or ≥ 2 points on an 11-point scale) according to Farrell et al.[10]. Other possibilities as 'numbers needed to treat' would have been potential alternatives, but in this review it is not possible because the included RCTs did not report these data.

Another explanation for the negative findings in the reviewed RCTs is that most of these trials studied a monodisciplinary intervention without standardizing and optimizing the practice of other disciplines, especially the medical one. For example, when studying the effect of patient education, in all RCTs it was only described as a nursing intervention, without taking the role of physicians into account. Adequate medical treatment may be pivotal before patient education becomes effective[45].

We think that adequate medical treatment is a prerequisite for other interventions. As reported in the survey of Enting et al.[28], insufficient awareness of cancer pain, inadequate analgesic prescription and non-adherence contribute to inadequate cancer pain treatment. In this study, 27% of the outpatients treated in a cancer clinic reported to have pain. Sixty-five percent of these patients were undertreated, as indicated by a negative PMI. Besides this, 27% declared to be non-adherent[28]. These data indicate that most patients will benefit from more effective analgesic prescription besides education to improve adherence to the treatment. Indeed, in our review of the literature the two studies on optimizing medical treatment, by pain consult or the introduction of a pain protocol, both found a statistically significant effect on pain intensity.

In conclusion, over the years professionals as well as patients still report many barriers regarding pain and pain management. The most frequent barriers for both groups are inadequate pain assessment and inadequate knowledge and misconceptions regarding pain management. Our review indicates that despite all the studies and guidelines, there is no convincing study that showed a multidisciplinary intervention to improve cancer-related pain treatment. Future research should focus on a multilevel approach: structural identification of cancer-related pain, implementation of a multidisciplinary protocol to improve the quality of pain treatment and education of patients and their relatives to enhance their involvement in the pain treatment. Furthermore, international consensus about the primary outcome measurement in pain research is urgently needed.

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CHAPTER 4

Analgesic adherence measurement in cancer patients: comparison between electronic monitoring and diary

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ABSTRACT

Adherence to analgesics in cancer patients has scarcely been studied. In this study, the Medication Event Monitoring System (MEMS) and medication diaries were compared with respect to feasibility and adherence measurements. Forty-six outpatients with nociceptive pain caused by cancer were asked to use MEMS for their analgesics and to record their medication usage in a diary for four weeks. Seventy-nine percent of the patients used MEMS for the full four-week period; 70% did so for the diary. The majority of patients were satisfied with both MEMS and diary. Adherence data assessed by MEMS and diary were comparable. Patients used the amount of analgesics adequately (taking adherence: 87%) but took them irregularly (timing adherence: 53%). Subgroup analyses in patients using single and multiple analgesic regimens confirmed the comparable suitability of both methods. MEMS and a medication diary are equally useful for analgesic adherence measurement in cancer patients with pain.

INTRODUCTION

In 2003, the World Health Organization (WHO) adherence project made the following definition of patients' adherence: "the extent to which a person's behavior, taking medication, following a diet, and/ or executing lifestyle changes, corresponds with agreed recommendations from a health care provider"[1]. Of all treatment recommendations, pharmaceutical interventions are the easiest interventions to which patients can adhere[1]. Patients are expected to take their medication as prescribed. However, patients' adherence to long-term therapies averages merely 50% in developed countries; in developing countries, the rates are even lower[2].

Medication adherence has been extensively studied in patients with various diseases or conditions[3-10]. In chronic diseases, both direct and indirect methods have been used. Direct methods provide proof of ingestion of the studied drug by measuring the drug or its metabolite in plasma, urine or hair. However, measured drug concentrations do not necessarily correlate with overall adherence[10-11]. Indirect methods include self-report, prescription refills based on pharmacy records, pill counts, and electronic monitoring. Of these methods, the most frequently used assessment tool is self-report, for example, by interview, questionnaires and diaries. Advantages of self-report include the low costs, and the fast and easy documentation and collection of data. Furthermore, diaries can provide information on adherence to multiple medications used in combination. Especially for research purposes, self-report also can provide insight into patients' barriers to medication intake[6,12]. Self-report, however, is limited by patient memory. Moreover, the use of diaries over time is variable, and patients tend to complete them retrospectively[6,11-13].

Electronic monitoring of medication intake has been introduced during the last decade, in particular by using the Medication Event Monitoring System (MEMS)[14-15]. MEMS is available in various packages: vial-type containers; eye drop dispensers; inhalers time-stamp; and blister packages. MEMS vials are most frequently used. A MEMS vial is a standard medication vial with a cap containing a microprocessor that accurately records time and date of each opening and closing. Information regarding medication intake can easily be displayed and used for statistical analysis using specially designed software.

MEMS allows long-term monitoring with detailed information about patterns of medication use. However, the tablets have to be removed from the original container or blister, and medication changes within a study period can yield inaccuracies[12,14,16]. Similar to all indirect adherence methods, MEMS does not confirm ingestion of medication[11].

Several studies in various nonmalignant diseases compared MEMS with self-report for medication adherence measurement. In all these studies, self-report assessments overestimated adherence in comparison to MEMS[3,5,17-20]. An average of 30% of diary entries

were in error compared with MEMS data[17]. These studies concluded that MEMS was the most accurate adherence measurement instrument available[14,17,20].

Although adherence has been studied in various chronic diseases, adherence to analgesics in cancer patients has not been studied extensively. Pain occurs in 30%-50% of cancer patients in the early stages of disease, and in 70%-80% in advanced stages[21-24]. Lack of adherence to pain medication is one of the reasons that patients do not achieve adequate pain control[25]. From 1981 to 2005, 14 studies were published about adherence to analgesics by cancer patients. In all these studies, adherence was measured by self-report. In only three studies, investigators used diaries; in the other studies, questionnaires or interviews were used. Adherence rates varied between 20% - 90%[25-38]. In oncology, patients are often treated with a combination of various opioid and nonopioid analgesics. In the studies on electronic monitoring of medication adherence mentioned above, MEMS was always used for only one drug. In case of multiple drug use, patients were asked to transfer the medication with the most complex prescription into a MEMS vial[16]. Therefore, studies investigating adherence to multiple analgesic regimens, such as used in cancer pain, are lacking.

In this study, we determined the feasibility of using MEMS vials in comparison with medication diaries in cancer patients with chronic pain on single as well as on multiple analgesic regimens. We also compared medication adherence as obtained by MEMS and by diary.

METHODS

Patients

Between July 1 and December 31, 2004, 46 outpatients of the Erasmus MC Daniel den Hoed Cancer Center were included in a prospective study. Patients were eligible if they met the following criteria: cancer or treatment-related nociceptive pain; pain duration of at least two weeks; a prescription for one or more analgesics for the duration of the study with at least one around-the-clock (ATC) regimen; life expectancy of at least three months; and able to read and speak Dutch. Patients who used medication-dispensing devices, such as pillboxes, and patients who were residing in a nursing home or retirement home, were ineligible. Fifteen patients used one analgesic preparation, 16 patients used two, and 15 patients used three different analgesic preparations.

Procedure

After written informed consent was obtained, patients entered the study for a period of four to five weeks, depending on the next appointment at the outpatient clinic. At study entry, patients received separate MEMS vials for each monitored analgesic, a

medication diary, and prescriptions for analgesics. Patients were subsequently referred to their pharmacy to obtain a fresh supply of medication in the MEMS vials. Patients were requested to take all their pain medication from the MEMS vials and to open the MEMS vials only if they intended to take medication. All patients were informed about the nature of MEMS vials. They were also asked to write their medication intake in the diary each day. At the end of the study period, an exit interview was planned. Patients who returned their diary and MEMS, and answered the exit interview, were considered evaluable for feasibility and medication adherence calculation. The Medical Ethics Committee of the Erasmus Medical Center approved the study.

Instruments and measurements

Sociodemographic and Medical variables.

At study entry, sociodemographic variables, including age, gender, and education level, were collected by patient interviews. The WHO performance status[39] was assessed, and patients were asked to rate the severity of their current pain, their 'worst' pain, and 'average' pain of the past week using a numeric rating scale[40-42]. Medical variables, including type of cancer, tumor status, anti-tumor therapy, and analgesic prescription, were obtained from the medical records.

Adherence measurement.

Instruments. Electronic adherence measurement was performed using the Medication Event Monitoring System version 6 (MEMS®, Aardex, Zug, Switzerland). A separate MEMS vial was used for each analgesic preparation. Medication events or openings occurring within one hour of a prior vial opening were interpreted as not to represent dosing. For adherence measurement per diary, an investigator-constructed medication diary was used, with one page allocated for each day.

Feasibility. Two aspects of feasibility were assessed: the actual use of the instruments and patients' satisfaction. The actual use of MEMS and diary was calculated as: 1) the median number of days the respective instrument was used, and 2) the number of patients who used the instrument during the entire evaluable study period (with a margin of two days). Days at which patients were hospitalized were omitted from analysis.

Patients' satisfaction was assessed in the exit interview with six self-constructed questions. The questions 'How satisfied are you using MEMS/ medication diary?' and 'Did you have any problems using MEMS/ medication diary?' were answered on a 5-points Likert-type scale. The questions 'Did you use your diary every day?' and 'Did you take your medication from MEMS every day?' were answered by yes or no. In addition, patients were given the opportunity to provide comments on MEMS and medication diary.

Medication adherence. Adherence was assessed for the ATC medication only. Adherence rates according to MEMS and diary were calculated separately. Medication adherence was calculated over the days the respective instrument had actually been used. If a patient used multiple ATC analgesic preparations, the separate adherence rates for the different preparations were averaged for that patient. Adherence was differentiated into 1) 'taking adherence': percentage of total prescribed drugs taken; 2) 'correct dosing': the percentage of days on which the correct doses were taken; and 3) 'timing adherence': the percentage of days on which all medication doses were taken within 25% of the correct dosing interval, with a maximum of four hours for medication prescribed once a day or less[8].

Data analysis

Data were analyzed using the Statistical Package for the Social Science for Windows, version 13.0. Descriptive statistics were used to describe patients' sociodemographic and medical characteristics. Differences in feasibility between MEMS and diary were analyzed with the nonparametric Wilcoxon signed rank test. Differences between MEMS and diary in adherence were analyzed with parametric tests. A test for repeated measures ANOVA was performed to test the differences in adherence between MEMS and diary, and one versus multiple analgesic prescriptions. MEMS and diaries were included as the "within" variable, and the number of analgesics was included as the "between" variable. A P-value of < 0.05 (two-tailed) was considered significant.

RESULTS

Sociodemographic and medical data

The median age of the 46 patients included was 56 years (range 32-77 years); the WHO performance status was ≤ 1 in 91% of the patients. Half of the patients received antitumor therapy during the study period. Additional demographic characteristics are summarized in Table 1. Twenty-nine patients were prescribed 32 ATC strong opioids (three patients with two different dose preparations): fentanyl patches (n=15), and morphine (n=11), oxycodone (n=5) and methadone (n=1) tablets. Seven of these patients also had a prescription for opioids 'as needed'.

Of the 46 patients, 43 (93%) were evaluable for feasibility and adherence assessment; one patient died early, one patient's MEMS vial was lost, and one patient refused further participation in the study one week after inclusion.

Table 1. Demographic and Disease-Related Characteristics.

		Median (Range)	n	%
Age (median, range)		56 yr (32-77 yr)		
Gender	male		20	44
	female		26	56
WHO performance status				
	Grade 0		15	32
	Grade 1		27	59
	Grade 2		4	9
Cancer status				
	No evidence of disease		8	17
	Locoregional		14	31
	Metastatic disease		24	52
Cancer type				
	Breast		16	35
	Lung		11	24
	Head and Neck		9	20
	Sarcoma		3	7
	Gynecological		2	4
	Hematological		2	4
	Other		3	7
Anti-tumor therapy				
	Chemotherapy		17	37
	Radiotherapy		2	4
	Hormonal therapy		3	7
	Surgery		1	2
	None		24	52
Bisphosphonates			11	24
Pain duration		8 months (1 - 216)		
Pain intensity				
	current pain	3.0 (0 - 8)		
	average pain	5.0 (0 - 10)		
	worst pain	7.5 (0 - 10)		
Analgesics				
	Nonopioids*		36	78
	Weak opioids		8	17
	Strong opioids**		29	63
Number of analgesic preparations				
	one		15	33
	two		16	34
	three		15	33

*Nine patients used both acetaminophen and NSAID.

**Ten patients used two strong opioid preparations.

Feasibility

Actual use of MEMS and Medication Diary. The median evaluable study period per patient was 28 days (range 24-34 days). Patients used MEMS and medication diaries both for a median duration of 26 days (range for MEMS and diary 9-34 and 0-34, respectively). Also, in subgroup analyses for patients using single and multiple analgesic regimens, no differences were found between the use of MEMS and medication diaries (Table 2). Thirty-four patients (79%) used MEMS during the entire study period, whereas 30 patients (70%) did so for the diary. Twenty-seven patients (63%) used both instruments, and six patients (14%) used neither MEMS nor diary during the entire study period (Figure 1).

Table 2. Usage of MEMS and Diary.

Prescription	MEMS*	Diary*	*P*-value
One analgesic preparation (n=14)	28.5 (22 – 34)	28.5 (0 – 34)	NS
Multiple analgesic preparations (n=29)	25.5 (9 – 34)	25.5 (4 – 34)	NS

*usage in days, median (range).

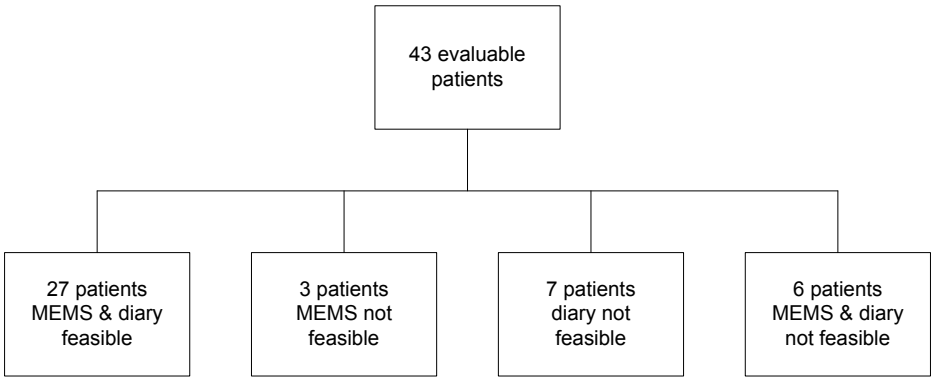

Figure 1. Feasibility of the instruments. Feasibility is defined as the use of the respective instrument during the entire evaluable study period.

Patients' Satisfaction. Thirty-one patients (72%) indicated that they were moderately or very satisfied using MEMS, whereas 26 patients (61%) were moderately or very satisfied with the medication diaries. Most patients had no problems using MEMS (84%) or diary (81%). Thirty-five patients (81%) answered that they had used MEMS every day; 30 patients (70%) said they had filled in the diary every day. No statistically significant differences were found between the evaluations of MEMS and diary. The use of one or multiple analgesics did not influence patients' satisfaction.

Patients' Comments on MEMS and Medication Diary. Eight patients reported that they were too ill to fill in a diary every day. Nine patients stated that they had filled out

their diary retrospectively after a few days, and one patient filled in the diary several days ahead. Seven patients considered MEMS vials easier to use than usual packaging (blister pack). Six patients who were prescribed fentanyl patches experienced difficulties with handling the patches from MEMS vials. Five patients reported that they were more adherent to their pain medication because of the use of the medication diary and the MEMS vials.

Medication Adherence

The overall adherence rates as assessed by medication diary and MEMS are presented in Figure 2. For all three adherence measurements, taking adherence, correct dosing and timing adherence, similar results were found for MEMS and diary. Of note, clinically relevant differences were found between the different adherence measurements, with the highest scores for taking adherence (mean 87% and 85% for MEMS and diary, respectively) and the lowest scores for timing adherence (53% and 57%, respectively). In Figure 3, adherence rates are presented separately for patients using one or multiple analgesic preparations. Using repeated measures ANOVA testing, no significant differences between MEMS and diary were found for the three adherence rates and no significant interaction between instrument and the number of analgesic preparations. Only for correct dosing was the difference between one and multiple analgesics statistically significant [F(1,39)=0.08, P=0.013].

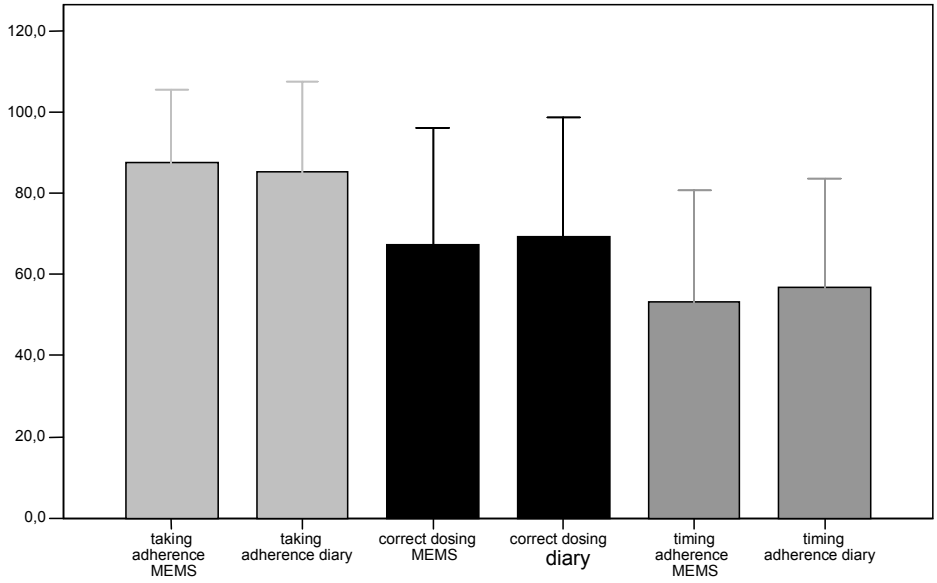

Figure 2. Mean (sd) adherence rates for MEMS and diary.

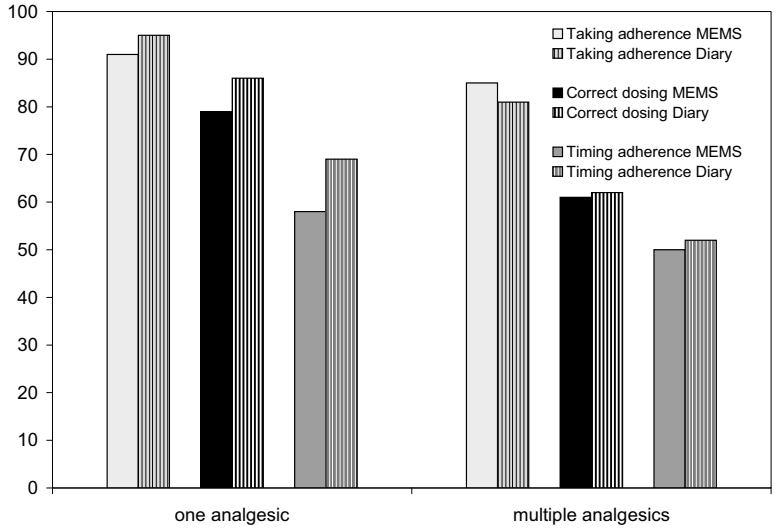

Figure 3. Mean adherence rates: one analgesic in comparison to multiple analgesics.

Adherence was not related to WHO performance status, age, or sex. Adherence did not differ between patients using fentanyl patches and patients using other opioids ATC (data not shown).

DISCUSSION

This study evaluated the feasibility of MEMS in comparison with medication diaries for adherence measurement in cancer patients with chronic pain who were receiving single-drug or multiple-drug analgesic regimens. In the four-week study period, we found no differences between MEMS and diaries in feasibility and adherence measurements. Seventy-nine percent of the evaluable patients used MEMS for the entire study period, whereas 70% did so for the medication diary. The majority of patients were satisfied with both MEMS and diary and used both instruments every day. Adherence rates measured by MEMS and diary were similar. Subgroup analyses in patients using single and multiple analgesics confirmed the comparable suitability of both methods. We conclude that both MEMS and diary are useful and manageable methods for adherence measurement in chronic cancer pain.

In our study, we could not confirm the results from comparative studies on medication adherence measurements performed in nonmalignant diseases. In these studies, electronically monitored adherence rates consistently ranged between 10% and 30% lower than adherence rates as assessed by self-reports[16-18,43]. We found similar adherence rates by MEMS and diary. These results may be explained by the rather high taking adher-

ence rates (mean 85%-87%) found in our study. Indeed, the measured adherence rates were high in comparison with results from earlier studies in cancer pain (30%-91%)[25-38]. The rather frequent use of fentanyl patches for pain management may explain the high adherence rates. Furthermore, five patients reported to be more adherent because of the use of medication diary as well as MEMS. The fact that nine patients had filled out their diary retrospectively while mean adherence results were similar for MEMS and diary supports the idea that patients had indeed taken their analgesics quite regularly.

Although the study was designed to compare the feasibility of MEMS and diary, the study also showed that patients may use their medication with different intervals over the day. Patients appear to use the total amount of medication prescribed, but take doses at wrong intervals. In future research, it will be interesting to study the relation between timing adherence and efficacy of pain treatment.

Limitations of the study may be the sample size, the selection of patients, and the duration of the study. We did not perform a power-analysis before start of the study. The sample size may be too small to detect small differences in feasibility and usefulness between MEMS and diary. Many patients included in this study used fentanyl patches, which may increase adherence. Furthermore, it is possible that we included a selected group of patients. A substantial part of the patients was treated in the pain clinic. These patients may be more motivated to adhere to their analgesics. Furthermore, patients' participation might have increased their awareness of medication intake during the study. Because we included patients for four weeks, feasibility for using MEMS and diary over a longer period remains unknown.

MEMS and diaries have different advantages. In clinical practice, diaries may be preferred because they are cheap and easy to handle. Patients, however, have to be able to remember to complete their diaries accurately and in a timely manner[13,16]. However, for research purposes, data extraction from diaries is time consuming. MEMS allows easy analysis of the more detailed patterns of adherence without additional effort from the patient, because computer programs are available that can read the information from the vials. For daily practice, limitations of MEMS are its costs and that it excludes the use of common adherence strategies such as pillboxes.

In conclusion, both MEMS and medication diaries are useful for adherence measurement in cancer patients with pain using single and multiple medication regimens. Medication diaries are an inexpensive method and very useful in daily practice. MEMS is the appropriate method for research, when more detailed insight in patients' adherence is required.

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CHAPTER 5

A combined pain consultation and pain education program decreases average and current pain and decreases interference in daily life by pain in oncology outpatients: A randomized controlled trial

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ABSTRACT

Pain Education Programs (PEP) and Pain Consultations (PC) have been studied to overcome patient-related and professional-related barriers in cancer pain management. These interventions were studied separately, not in combination, and half of the studies reported a significant improvement in pain. Moreover, most PEP studies did not mention the adequacy of pain treatment. We studied the effect of PC combined with PEP on pain and interference by pain with daily functioning in comparison to standard care (SC). Patients were randomly assigned to SC (n=37) or PC&PEP (n=35). PEP consisted of patient-tailored pain education and weekly monitoring of pain and side effects. We measured overall reduction in pain intensity and daily interference over an 8-week period as well as adequacy of pain treatment and adherence. The overall reduction in pain intensity and daily interference was significantly greater after randomization to PC&PEP than to SC (average pain 31% vs. 20%, *P*=0.03; current pain 30% vs. 16%, *P*=0.016; interference 20% vs. 2.5%, *P*=0.01). Adequacy of pain management did not differ between the groups. Patients were more adherent to analgesics after randomization to PC&PEP than to SC (*P*=0.03). In conclusion, PC&PEP improves pain, daily interference, and patient adherence in oncology outpatients.

INTRODUCTION

Pain is one of the most frequent and distressing symptoms in cancer. Pain is present in 36% to 61% of patients, depending on cancer type, stage of disease and patient setting, e.g. inpatient or outpatient departments[1-4]. Management of cancer pain is considered to be complex. Despite the existing guidelines and knowledge about pain and pain management, almost half of the patients are treated inadequately[5]. Nevertheless, it has been proposed that effective pain treatment should be feasible for 70% to 90% of oncology patients[6].

Inadequate pain management seems to be caused by professional-related as well as patient-related barriers. The most reported barriers in professionals include inadequate assessment of pain and inadequate knowledge of pain management[7]. Patients often impede their own treatment due to misconceptions about analgesics and their side effects, non-adherence to treatment regimens, and poor communication about their concerns about pain to health care providers[7].

To improve the adequacy of pain management both professional-related and patient-related barriers should be reduced. Professional-related barriers could be decreased by a pain consultation (PC) or the implementation of a pain protocol[8-9]. Both Du Pen et al.[9] and Cleeland et al.[8] described a reduction in patients' pain intensity by the introduction of a pain protocol. However, they did not discover an improvement in the adequacy of pain treatment and patient adherence or a reduction of the interference by pain in daily living (daily interference)[7-9]. To diminish patient-related barriers Pain Education Programs (PEPs) were developed to improve patients' knowledge and to stimulate participation in their own pain treatment[10-28]. PEP decreased patients' pain intensity in 10 of 18 studies and improved pain knowledge in 13 of 18 studies. Similar to the studies on the introduction of a pain protocol, the adequacy of pain treatment was not improved, although this was investigated in only a few studies. Furthermore, PEP did not improve adherence to analgesics, nor did it decrease daily interference[7,10-28].

In summary, interventions to diminish professional-related and patient-related barriers in pain treatment found beneficial effects on pain in about half of the studies, with no definite effects on other pain-related outcomes. Furthermore, they were only studied separately. Herein, we report the results of a randomized controlled trial (RCT) that tested the effectiveness of standard care versus standard care supplemented with a PC combined with PEP. The primary end point of this study was the overall reduction of average pain intensity over the 8-week study period with respect to baseline. The predefined secondary end points were worst and current pain intensity, interference in daily life by pain, pain treatment, adherence and patients' pain knowledge.

PATIENTS AND METHODS

Patient population

All patients were treated in the outpatient oncology clinic of the Erasmus University Medical Center in Rotterdam. Patients were eligible for inclusion in the study if they met the following criteria: (1) 18 years of age or older; (2) confirmed diagnosis of cancer; (3) diagnosis of nociceptive pain related to cancer or cancer therapy by the treating physician; (4) average pain intensity in the last week ≥ 4; (5) life expectancy of at least three months; (6) able to comprehend, speak, and read Dutch; (7) signed informed consent. Patients were excluded in case of residing in a nursing home or retirement home, invasive pain treatment (e.g. subcutaneous or intravenous infusion of opioids) or radiotherapy planned or received within the last two weeks before inclusion.

Procedure

The study started in March 2006. Recruitment was conducted through oncology health care professionals. The investigators (WHO; PJdR) explained the study, obtained written informed consent, and coordinated the study assessments. Patients were stratified for treatment with chemotherapy, hormonal therapy or no antitumor treatment. Eligible and consenting patients were initially randomly assigned to (1) Standard Care (SC), (2) Pain Consult (PC), or (3) Pain Consult combined with Pain Education Program (PC&PEP). The randomization was based on a computer-generated randomization procedure with a variable block length (1 to 4 repetitions per block). Patients completed a baseline assessment before randomization. For patients allocated to one of the intervention groups, the intervention was planned within one week after randomization. Study assessments for all groups were conducted 2 weeks (T1), 4 weeks (T2) and 8 weeks (T3) after randomization. The questionnaires were sent to the patients by mail. All patients filled in their questionnaires at home, independently from the health care professionals or the investigators.

In January 2009 the 3-arm study turned out to be not feasible because of slow accrual. Since then, patients were randomized between (1) SC and (3) PC&PEP. The study protocol and the amendment were approved by the Institutional Review Board of the Erasmus MC. The study was performed according to the ICH-GCP principles.

Intervention

Pain Consultation

Patients were evaluated thoroughly with a complete history and physical examination, including a pain assessment by a neuro-oncologist. This pain specialist determined whether

the cause of the pain was clear; advised on antitumor therapy and optimized symptomatic treatment according to national and international cancer pain guidelines[29-30], if indicated.

Pain Education Program

The PEP was developed by De Wit et al.[31]. The intervention included the use of multiple teaching methods, which were provided both in the outpatient clinic and by telephone. The pain information (brochure) and instruction was tailored to the needs and the abilities of the individual patient. Patients in the PEP group received the intervention by a specialized nurse trained in palliative care. The specialized nurse conducted the academic detailing session at the outpatient clinic in the first week after inclusion. The PEP consists of two components: (1) Enhancing patients' knowledge about pain and pain treatment. Patients were educated about relevant pain topics that were assessed by a nurse as insufficient. The verbal instruction was accompanied by a pain brochure. (2) Stimulating patients' help-seeking behavior. An extensive description of PEP can be found in the article of the original study[31]. Until the end of the study at 8 weeks, the specialized nurse contacted patients weekly by telephone and reviewed their pain intensity scores and opioid-related side effects. She contacted the physician if necessary. Furthermore, the educational content of the PEP was reinforced if needed.

Outcome assessment

Sociodemographic variables were assessed at study entry. Health-related variables included cancer diagnosis; tumor status (no evidence of disease (NED), locally advanced disease, or metastatic disease) and antitumor therapy.

Pain intensity and daily interference were measured on 0-10 numerical rating scales with the Brief Pain Inventory (BPI). Pain intensity was measured as current pain and as average and worst pain in the last 24 hours. Interference by pain in daily life (daily interference) was assessed by seven items (general activity, mood, walking ability, normal work, sleep, relations with other people, and enjoyment of life). A mean interference score is computed by taking the average of the 7 items[32-33].

Analgesics were categorized to World Health Organization (WHO) step 1 (nonsteroidal anti-inflammatory drugs, acetaminophen), WHO step 2 (tramadol, codeine), WHO step 3 (morphine, fentanyl patch, oxycodone, and hydromorphone). The various analgesic dosages were converted to oral morphine equivalent daily doses (MEDD) (mg/day) according to published equi-analgesic dose tables[29-30]. In addition, the percentage of patients with an around-the-clock and as needed (ATC+PRN) analgesic prescription was calculated.

The adequacy of analgesic prescription was assessed using the Pain Management Index (PMI), which related the worst pain intensity to the most potent analgesic prescribed. It is calculated by subtracting the pain level from the analgesic level. Negative

PMI scores were considered to be an indicator of inadequate pain management, whereas scores of 0 or higher were considered adequate[34].

Adherence (the percentage of total prescribed drugs taken) for the ATC (ATC) medication was measured using the Medication Event Monitoring System version 6 (MEMS®, Aardex, Zug, Switzerland). A separate MEMS vial was used for each ATC analgesic preparation[35]. If a patient used multiple ATC analgesic preparations, the separate adherence rates for the different preparations were averaged for that patient. Mean adherence was measured in the time intervals: week 1&2; week 3&4; and week 7&8.

Pain knowledge was assessed using a translated version of the Ferrell Patient Pain Questionnaire[36]. The scores of the eight items were linearly transformed to a 0 to100 scale (0=lowest knowledge score, 100=highest knowledge score). A mean total score was computed for overall pain knowledge at T0 and at T1[31].

Data analysis

Definitions outcome measures pain and interference

To give a clear representation of the effect of our study over the complete period of interest (e.g. 8 weeks), we chose for a weighted mean reduction in pain intensity. For average, worst and current pain, the overall reduction in pain intensity over the 8-week period compared with baseline was calculated using the formula:

$$m\Delta PI = [\Sigma_{i=1}^{N} (PI_i + PI_{i-1})(T_i - T_{i-1}) / (2 \times (T_N - T_0))] - PI_0$$

in which mΔPI was the weighted mean reduction in pain. Pain intensity at time point T_i, i = 2, 4 or 8 weeks was reported as PI_i and T_n was the last available measurement. The overall reduction in interference with daily living was calculated similarly.

Power analysis

Originally the study required a sample size of 156 patients, randomized over the three groups, using the assumptions as given in Table 1. The baseline pain intensity was based on patients' pain in a former study in our hospital[35]. Because of slow accrual, we performed an interim analysis with 54 patients at the end of 2008. According to the interim analysis, the most realistic scenario was to continue the study with (1) SC and (3) PC&PEP. Based on the results of the interim analysis, a total sample of 72 evaluable patients was required ($\alpha = 0.029$ (one-sided), power of 80%; Table 1).

Data analysis

Data were analyzed using the Statistical Package SPSS version 15 and STATA version 10. Descriptive statistics and frequency distributions were generated for the patients' demographic, disease, and pain-related characteristics. Independent Student *t* tests

Table 1. Assumptions for the original power analysis and the interim analysis (N=54) for average pain intensity.

	Baseline mean (sd)	2 weeks mean (sd)	4 weeks mean (sd)	8 weeks mean (sd)	mPI mean (sd)
1. Standard Care					
Original power analysis	*4.5 (2.0)*	*4.5 (2.0)*	*4.0 (2.0)*	*4.0 (2.0)*	*-0.31 (1.12)*
Interim analysis	5.8 (1.4)	5.1 (1.7)	4.4 (1.9)	4.4 (1.8)	-0.70 (1.51)
2. Pain Consult					
Original power analysis	*4.5 (2.0)*	*3.8 (2.0)*	*3.2 (2.0)*	*3.5 (2.0)*	*-0.93 (1.12)*
Interim analysis	5.8 (1.5)	4.0 (1.7)	4.5 (2.8)	4.5 (2.8)	-1.04 (1.27)
3. Pain Consult & PEP					
Original power analysis	*4.5 (2.0)*	*3.0 (2.0)*	*2.5 (2.0)*	*2.5 (2.0)*	*-1.61 (1.12)*
Interim analysis	5.7 (1.3)	4.3 (1.5)	3.7 (1.4)	3.3 (2.2)	-1.62 (1.33)

Assumptions of the original power analysis (*italic*), and the data of the interim analysis (*N*=54). mPI = weighted mean, an overall reduction over the 8-week period compared to baseline.

and χ^2 analyses were performed to determine if there were differences in the baseline characteristics between patients randomized to SC and PC&PEP.

An overall analysis was performed for the pain intensities and daily interference using the above mentioned formula. Before that, for these outcome measures the missing values were substituted using an imputed method (i.e. multivariate regression). The differences between the groups for the other secondary end points were tested at T1, T2, and T3.

For the primary and secondary end points, the distributions of scores were examined for normality by using the Shapiro-Wilk test. When the scores were not normally distributed, we used non-parametric tests (2-sample Mann-Whitney test), otherwise we used independent Student *t* tests. A *P* value of less than 0.05 (one-sided) was considered statistically significant. The limited number of patients in the PC group did not allow for statistical testing.

RESULTS

Patient Characteristics

In total, 73 patients with nociceptive cancer-related pain were included in the SC and the PC&PEP groups. One patient was not evaluable because he dropped out before T1 (too ill; Figure 1). Patient characteristics of the evaluable patients are summarized in Table 2. The baseline results of the outcome measurements are reported in Table 3. No significant differences were found in the demographic, disease, or baseline outcome measurements.

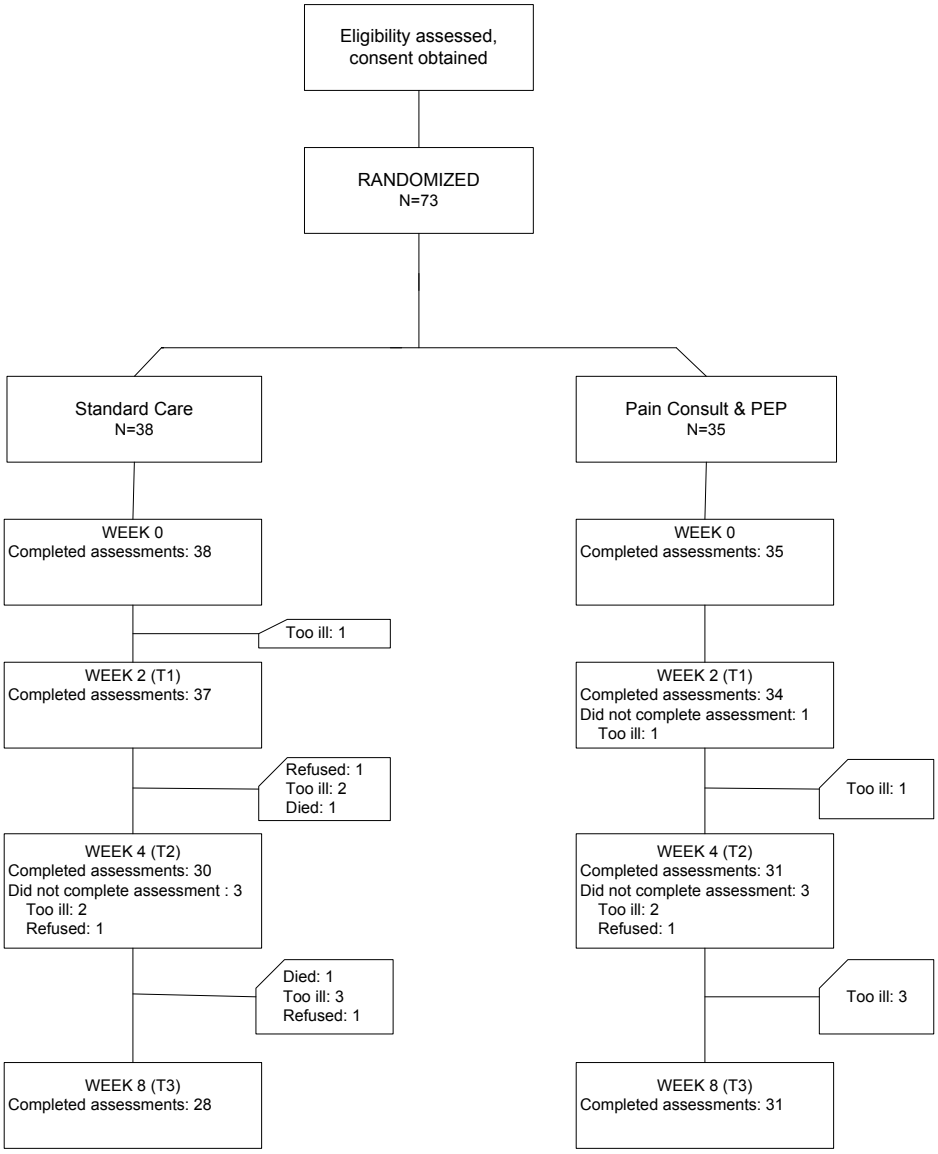

Figure 1. Flow of patients through the trial

Outpatient department and hospital admissions

Forty-eight patients were referred for a PC (Table 4). Thirteen patients (35%) received a PC as part of the standard care. Patients having a PC met the pain specialist for a median of 2 appointments (range 1 to 5). Diagnostic imaging (computed tomography/ magnetic resonance imaging) was requested in 57% of the patients, more frequently in the PC&PEP than the SC group (*P*=0.004). Twenty-six percent of the patients had a

Table 2. Baseline Demographic and Disease Characteristics

		Total (N=72)	Standard Care (N=37)	Pain Consult & PEP (N=35)
Gender	male	25 (35%)	14	11
	female	47 (65%)	23	24
ECOG	0	7 (10%)	3	4
	1	56 (78%)	29	27
	2	9 (13%)	5	4
Age, mean (sd)		59 (11)	61 (12)	56 (10)
Tumor (n)				
	breast	24 (33%)	11	13
	urogenital	12 (17%)	6	6
	gastrointestinal	16 (22%)	10	6
	lung	5 (7%)	2	3
	melanoma	3 (4%)	1	2
	head and neck	4 (6%)	3	1
	ACUP	4 (6%)	2	2
	sarcoma	2 (3%)	2	0
	others	2 (3%)	0	2
Tumor status				
	Locally advanced	12 (17%)	5	7
	Metastatic	59 (82%)	32	27
	Unknown	1 (1%)	0	1
Anticancer treatment				
	Chemotherapy	24 (33%)	12	12
	Hormonal therapy	12 (17%)	7	5
	No anticancer therapy	36 (50%)	18	18
Bisphosphonates		7 (10%)	3	4
Pain duration, months, median (IQR)		5 (3-14)	4 (2-8)	6 (3-24)
Number of pain locations				
	1	32 (44%)	17	15
	2	31 (43%)	14	16
	≥ 3	10 (14%)	6	4

Abbreviations: ACUP= Adenocarcinoma of Unknown Primary; IQR=Inter Quartile Range

hospital admission during the study, in 13% due to pain-related issues. The number of hospital admissions and the frequency radiotherapy used did not differ between the groups (Table 4).

Table 3. Baseline Characteristics for Outcome Measures.

		Standard Care (N=37)	Pain Consult & PEP (N=35)
BPI - Pain mean (sd)			
	Average pain (0-10)	5.7 (1.3)	6.2 (1.5)
	Worst pain (0-10)	7.9 (1.4)	8.1 (0.9)
	Current pain (0-10)	4.2 (2.1)	5.0 (1.6)
BPI - Interference - mean (sd)			
	Mean score (0-10)	4.4 (2.2)	4.6 (1.8)
Pain Management n(%)			
Analgesic use			
	No Analgesia	0	0
	Acetominophen ± NSAIDs	37 (100)	34 (97)
	Weak opioids	8 (22)	2 (6)
	Strong opioids	19 (51)	23 (66)
	Antidepressant drugs	2 (5)	1 (3)
	Antiepileptic drugs	2 (5)	4 (11)
Opioid prescription both ATC + PRN*		13 (50)	12 (48)
MEDD mg/day, mean (sd)		84 (74)	70 (59)
PMI			
	Inadequate analgesia	14 (38)	14 (40)
	Adequate analgesia	23 (62)	21 (60)
Pain Knowledge mean (sd) (0-100)		65 (12)	62 (13)

Abbreviations: MEDD = Morphine Equivalent Daily Dose; NSAID = Non-Steriodal Anti-Inflammatory Drug; ATC = around the clock; PRN = as needed. *of the patients with an opioid prescription

Table 4. Pain Treatment during the study.

	Total (N=72) N(%)	Standard Care (N=37) N(%)	Pain Consult & PEP (N=35) N(%)	P value
Patients with Pain Consult	48 (67)	13 (35)	35 (100)	<0.001
Number appointments PC 0	24 (33)	24 (65)	0	<0.001
1	22 (31)	6 (16)	16 (46)	
2-3	21 (29)	6 (16)	15 (43)	
> 4	5 (7)	1 (3)	4 (11)	
CT/ MRI	41 (57)	15 (41)	26 (74)	0.004
Hospital admissions	19 (26)	8 (22)	11 (31)	0.250
due to pain	9 (13)	5 (14)	4 (11)	
Radiotherapy	19 (26)	10 (27)	9 (26)	0.556

Effect on Pain Intensity and Daily Interference over Time

Figure 2 illustrates the mean reductions in pain intensity over time compared with baseline for patients randomized to SC and PC&PEP. For average pain intensity, the mΔPI was 1.13 for SC and 1.95 for PC&PEP (20% vs. 31%; *P*=0.03). For current pain intensity, the mΔPI was 0.67 for SC and 1.50 for PC&PEP (16% vs. 30%; *P*=0.016). No significant difference was found between SC and PC&PEP groups for worst pain (1.16 vs. 1.28). For daily interference, the mean reduction was 0.11 for SC and 0.91 for PC&PEP (2.5% vs. 20%; *P*=0.01; Figure 2).

Changes in Medication

The number of patients with an opioid prescription, the type of prescription, the MEDD, and the adequacy of the prescription at the beginning of the study are listed in Table 3. The percentage of patients with a WHO 3 opioid prescription increased from 51% at baseline to 64% at T3 in the SC group and from 66% to 77% in the PC&PEP group. At the separate time points, differences between SC and PC&PEP groups were not statistically significant.

In the PC&PEP group, the percentage of patients with both an around-the-clock and an as needed (ATC+PRN) opioid prescription increased from 48% at baseline to 88% at T3. In the SC group, the percentage remained stable at 50%. The difference between the two groups was statistically significant at T3 (*P*=0.003; Figure 3A).

In the PC&PEP group, the median MEDD increased by 60 mg (range 60 to 2150 mg) over the eight weeks, compared with 33 mg (range 130 to 380 mg) in the SC group (Figure 3B). Differences between the two groups were not statistically significant at any time point.

The adequacy of the analgesic prescription as measured with the PMI increased from 62% to 75% (SC) and from 60% to 77% (PC&PEP) at T3 (not significant).

During the study, the percentage of patients with antidepressant or antiepileptic drugs did not differ between the groups.

Adherence to pain medication

Patients' adherence in week 1&2 did not differ between the groups (SC 79% and PC&PEP 81%). In the last 2 weeks, mean adherence scores were changed to 74% and 85%, respectively (*P*=0.028; Figure 3C).

Patients' Pain knowledge

Patients' pain knowledge was measured at baseline and after 2 weeks. The baseline data are described in Table 3 and did not differ. At week 2, the level of pain knowledge (0 to 100) was significantly better after randomization to PC&PEP (71, SD=13) than to SC (64, SD=10); *P*=0.002).

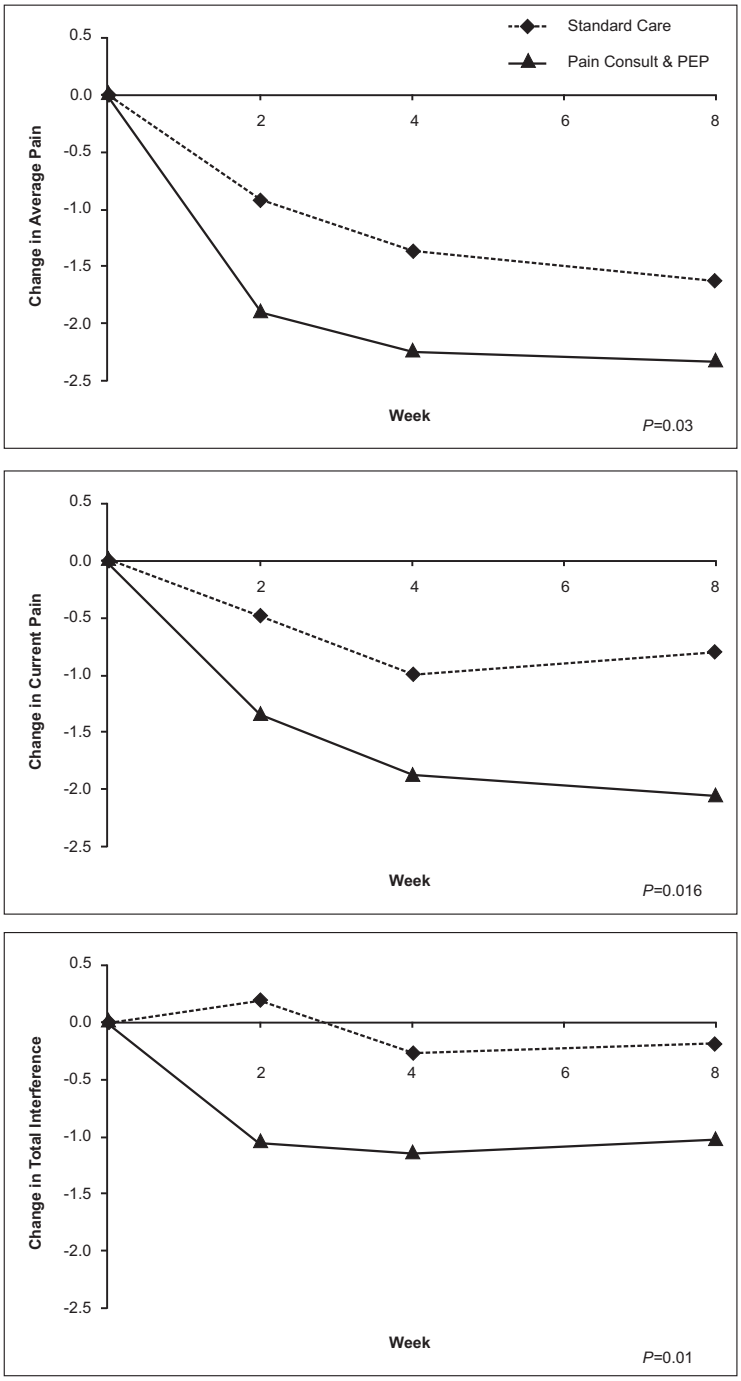

Figure 2. Mean changes in pain scores and daily interference, compared to baseline, over time in the Standard Care (*N*=37) and Pain Consult & PEP (*N*=35).

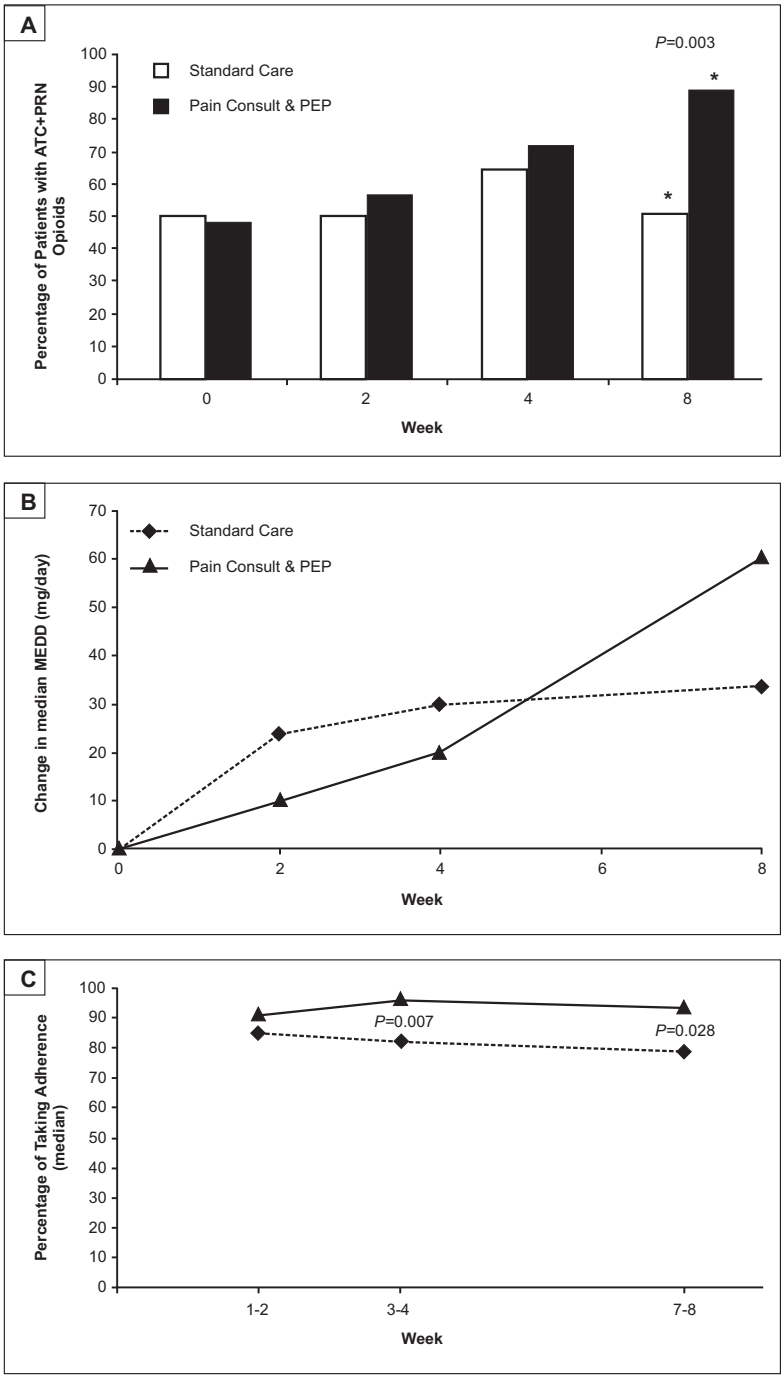

Figure 3. Opioid analgesics. A. Percentage of patients with ATC + PRN opioids; B. Median change in total dose of opioid analgesics as prescribed (morphine equivalent daily dose), compared to baseline; C. Mean adherence week 1&2, week 3&4 and week 7&8.

Pain Consult

Before the change in study design, 20 patients were randomized for a PC. The baseline characteristics of the group with PC were comparable with the SC and PC&PEP groups (Supplementary Tables S1-S3). For the PC group, the mΔPI was 1.58 for average pain; 1.03 for current pain; 1.16 for worst pain. The reductions in pain were larger than the reductions found in the SC group but smaller than the reductions in the PC&PEP group. The reduction in mean daily interference was 1.06. Because the study was underpowered for a three-arm design, statistical testing was not performed (Supplementary Table 4).

DISCUSSION

In the present study in oncology outpatients with pain, a PC combined with a PEP is more effective than SC in reducing average and current pain intensity and the interference by pain in daily living. In addition, patients' knowledge and adherence increased significantly. To the authors' knowledge, this is the first study demonstrating a long-term effect of an intervention on daily interference.

Various articles measured the effect of PEP or a pain protocol on daily interference[8-9,11,13-15,19-21,23-24,28], but only two studies found a significant, although short-term effect[15,24]. A possible explanation why we found a significant effect over the 8-week period in our study is that, in addition to PEP, the patients in the intervention group were monitored weekly by our specialized nurses. Thereby the pain treatment could be changed rapidly and PEP could be repeated, adjusted to patients' daily life.

In all PEP studies, pain intensity was an outcome measure. However, contrary to our study, 3 of 18 studies did not describe how they defined pain intensity[10,21,26] and 5 of 18 studies did not report all measured pain intensities[7,11-12,15,19,21], preventing proper interpretation of the results of these studies[7]. In this study, we found a comparable decrease in average pain intensity and current pain intensity as was found in the meta-analysis of Bennett et al.[28]. However, the results of this meta-analysis are difficult to interpret because it is unclear if they included the overall results over the assessment periods. In addition, as they described in their discussion, they did not consider the duration of the assessment periods in the studies, which varied between 5 days[20] and 6 months[13]. Unlike Bennett et al., we could not show an effect in worst pain intensity. It is possible that our patients, experiencing less average pain and less interference by pain in daily living, increased their daily activities until the occurrence of painful moments. The specialized nurses who educated the patients using PEP, indeed aimed to improve patients' daily activity level.

Unlike our study, most of the articles regarding PEP or a pain protocol did not substantiate the sample size with a power analysis[7,9-10,13,15,18,20-21,23-27,31] or studied small groups of

patients (< 50 patients) [20-21,24,26-27]. Five studies reported the PMI[34]. Like the present study, all found no effect in PMI [10-11,14,19,24]. Only Syrjala et al. [13] found a significant effect in MEDD.

Seven studies described the results of patient adherence to their analgesics. Four studies described no differences in adherence[9,17,19,23], three other studies were able to found an increase in adherence[13,21,25]. However, 5 of these 7 studies used a questionnaire to measure adherence, like the Morisky questionnaire[15,19,21,23,25], whereby they ask for patients' perception and therefore did not actually measure medication adherence. The 2 other studies measured actual analgesic use in a medication diary[9,17]; both found no significant effects on adherence to opioids. In this study, we measured adherence using MEMS. However, in an earlier study, we demonstrated that adherence measured with a medication diary and with MEMS gave comparable results[35]. Possibly, our weekly reinforcement of information may have increased the adherence to the analgesics.

In the present study, 59% of the included patients had a prescription for strong opioids, and 49% of the included patients already had a prescription for both ATC+PRN opioids at baseline, as advised by various national and international pain guidelines[29-30]. This contrasts with the study by Miaskowski et al.[17], the only PEP study that described the analgesic prescription. In that study, 29% of the included patients had an ATC+PRN prescription for their opioids at baseline. Moreover, in our study patients' pain knowledge was higher at baseline than in previous studies that used the same questionnaire (64% vs 55%)[12,31]. In addition, 35% of the patients in de SC group were referred for a PC. At our outpatient clinic, therefore, doctors pay attention to cancer pain treatment. Nevertheless, we were able to further optimize pain treatment. At T3, 50% of patients randomized to SC and 88% of patients randomized to PC&PEP were given a prescription for ATC+PRN opioids. This again contrasts with the study by Miaskowski et al.[17], in which 37% of the patients in the intervention group had a prescription for ATC+PRN opioids at the end of their study[17].

The most important limitations of this study were the slow accrual and change in study design. In a previous study performed at the same outpatient clinic, we identified 107 patients with moderate or severe pain in one week[33]. Despite the apparent feasibility, it proved very difficult to accrue patients for this study. The major reasons for the slow accrual were the strict exclusion criteria we used. Patients who had radiotherapy either planned or started within the two weeks before inclusion were excluded. Patients were also excluded when they already had been referred to a pain specialist or already had received pain education. Because the recruitment of our study was conducted through oncology health care professionals, we were dependent on the oncologists for inclusion, and therefore we were not able to screen all patients ourselves. During the study, we took a sample of 100 patients who used WHO analgesics and checked whether they were eligible. Patients were not eligible because of concurrent radiotherapy (28%), earlier referral to a pain specialist (15%), language barrier (8%), hospitalization (not for

pain) (10%), and other exclusion criteria (17%). Of the remaining 22 patients, we could not find a note about patients' pain in the medical record, so eligibility remained unclear. The slow accrual forced us to change our study design into a two group RCT, preventing us from assessing the contribution of a PC or PEP separately. However, it is reasonable that patient education and monitoring has an added value to a PC, because one-third of the SC also received a PC and the differences in pain treatment between SC and PC&PEP were limited. We could not prevent a referral to a pain specialist because in our hospital this referral often is considered as part of the standard pain treatment. However, this does not take place systematically. Our patients did not receive any form of palliative service in the outpatient clinic or in the community. During this study, the patients could be admitted to the unit for Palliatieve Care and Symptom Control. In the SC, 4 of the 37 patients (11%) and in the PC&PEP 7 of the 35 patients (20%) were admitted to this unit during the study. However, during this study, PEP was not embedded in the standard care at this unit or at the outpatient clinic. In this study we investigated the added value of a systematic referral to a pain specialist (PC) and PEP in comparison with the SC.

In conclusion, PC&PEP improves overall pain intensity, daily interference, patient adherence and pain knowledge in oncology outpatients.

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Table S1. Baseline Demographics and Disease Characteristics.

		Total (N=91)	Standard Care (N=37)	Pain Consult & PEP (N=35)	Pain Consult (N=19)
Gender	male	31 (34%)	14	11	6
	female	60 (66%)	23	24	13
ECOG	0	9 (10%)	3	4	2
	1	67 (73%)	29	27	11
	2	15 (17%)	5	4	6
Age, mean (sd)		58 (11)	61 (12)	56 (10)	57 (12)
Tumor, n					
	Breast	29 (32%)	11	13	5
	Urogenital	20 (22%)	6	6	8
	Gastrointestinal	17 (19%)	10	6	1
	Lung	6 (7%)	2	3	1
	Melanoma	5 (5%)	1	2	2
	Head and neck	4 (4%)	3	1	0
	ACUP	5 (5%)	2	3	0
	Sarcoma	2 (2%)	2	0	0
	Others	3 (3%)	0	1	2
Tumor status					
	Locally advanced	19 (21%)	5	8	6
	Metastatic	71 (78%)	32	26	13
	Unknown	1 (1%)	0	1	0
Anticancer treatment					
	Chemotherapy	32 (35%)	12	12	8
	Hormonal therapy	12 (13%)	7	5	0
	No anticancer therapy	47 (52%)	18	18	11
Biphosphonates		10 (11%)	3	4	3
Pain duration (months), median (IQR)		5 (3-16)	4 (2-8)	6 (3-24)	10 (2-17)
Number of pain locations					
	1	41 (45%)	17	15	8
	2	37 (41%)	14	16	7
	≥3	14 (15%)	6	4	4

Abbreviations: ACUP= Adenocarcinoma of Unknown Primary;
IQR=Inter Quartile Range.

Table S2. Baseline Characteristics for Outcome Measures.

		Standard Care (N=37)	Pain Consult & PEP (N=35)	Pain Consult (N=19)
BPI - Pain mean (sd)				
	Average pain (0-10)	5.7 (1.3)	6.2 (1.5)	6.0 (1.8)
	Worst pain (0-10)	7.9 (1.4)	8.1 (0.9)	7.8 (1.4)
	Current pain (0-10)	4.2 (2.1)	5.0 (1.6)	5.0 (1.9)
BPI - Interference - mean (sd)				
	Mean score (0-10)	4.4 (2.2)	4.6 (1.8)	5.5 (1.5)
Pain Knowledge	mean (sd) (0-100)	65 (12)	62 13)	65 (13)
Pain Management n(%)				
Analgesic use				
	No Analgesia	0	0	0
	Acetominophen ± NSAIDs	37 (100)	34 (97)	16 (84)
	Weak opioids	8 (22)	2 (6)	2 (11)
	Strong opioids	19 (51)	23 (66)	12 (63)
	Antidepressant drugs	2 (5)	1 (3)	0
	Antiepileptic drugs	2 (5)	4 (11)	1 (5)
PMI				
	Inadequate analgesia	14 (38)	14 (40)	9 (47)
	Adequate analgesia	23 (62)	21 (60)	10 (53)
Opioid prescription both ATC + PRN*		13 (50)	12 (48)	7 (50)
MEDD mg/day, mean (sd)		84 (74)	70 (59)	93 (90)

Abbreviations: MEDD = Morphine Equivalent Daily Dose; NSAID = Non-Steriodal Anti-Inflammatory Drug; ATC = around the clock; PRN = as needed. *of the patients with opioid prescription

Table S3. Pain Treatment during the study.

	Total (N=91) N(%)	Standard Care (N=37) N(%)	Pain Consult & PEP (N=35) N(%)	Pain Consult (N=19) N(%)
Patients with Pain Consult	67 (74)	13 (35)	35 (100)	19 (100)
Number appointments PC				
0	24 (26)	24 (65)	0	0
1	30 (33)	6 (16)	16 (46)	8 (42)
2-3	31 (34)	6 (16)	15 (43)	10 (53)
> 4	6 (7)	1 (3)	4 (11)	1 (5)
CT/ MRI	55 (60)	15 (41)	26 (74)	14 (74)
Hospital admissions	25 (27)	8 (22)	11 (31)	6 (32)
due to pain	12 (13)	5 (14)	4 (11)	3 (16)
Radiotherapy	21 (23)	10 (27)	9 (26)	2 (11)

Table S4. Overall reduction in pain and interference.

	Standard Care (*N*=37)	Pain Consult (*N*=19)	Pain Consult & PEP (*N*=35)
mΔPI Average pain	1.13	1.58	1.95
mΔPI Current pain	0.67	1.03	1.50
mΔPI Worst pain	1.16	1.16	1.28
mΔPI Daily interference	0.11	1.06	0.91

CHAPTER 6

Efficacy of opioid rotation to continuous parenteral hydromorphone in advanced cancer patients failing on other opioids

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ABSTRACT

The effectiveness of an opioid rotation to parenteral hydromorphone in advanced cancer patients has never been investigated. Therefore, the purpose of this study was to investigate the analgesic efficacy and side effects of parenteral hydromorphone on serious cancer-related pain. We included 104 consecutive advanced cancer patients who were extensively pretreated with opioids. They were rotated to parenteral hydromorphone because they failed to achieve adequate pain relief on other opioids. Pain intensity and side effects were daily assessed. The moment of adequate pain control was defined as the first of at least 2 consecutive days when the mean pain intensity at rest was ≤ 4 (on a 0-10 numeric rating scale) and side effects were tolerable.

The reasons for rotation to parenteral hydromorphone were inadequate pain control with/without expected delivery problems due to high opioid dosages (n=61) and intolerable side effects with persistent pain (n=43). Adequate pain control was achieved in 86 patients (83%) within a mean of 5 days. Eight of 86 patients still had side effects, but these were scored as acceptable. The mean pain intensity at rest decreased from 5.4 [standard deviation (sd)=2.1] to 2.4 (sd=1.5; $p<0.001$). The median failure-free treatment period was 57 days and covered a substantial part of the median survival of 78 days in the responding patients. In conclusion, in advanced cancer patients with serious unstable cancer-related pain refractory to other opioids, continuous parenteral administration of hydromorphone often results in long-lasting adequate pain control and should be considered even after extensive pretreatment with opioids.

INTRODUCTION

Pain is a serious problem in patients with advanced solid cancer. Two thirds of these patients experience pain of whom 20% grade their pain as moderate to severe[1]. The World Health Organization set up guidelines for treating chronic cancer pain up to high doses of around-the-clock opioids, striving for an acceptable pain control for the majority of cancer patients[2-3]. However, despite following these guidelines accurately, 10-30% of patients do not achieve adequate pain relief, mainly because of uncontrolled side effects restraining them from further dose increment[3]. For these patients, an opioid rotation, a change in opioid *or* route of administration has been shown to be beneficial in several studies[4-5]. Parenteral administration of opioids (here defined as subcutaneous or intravenous) is especially useful for rapid titration in case of severe pain, but it is also indicated for patients with pain in whom dose escalations are needed to doses that are no longer convenient for oral use[6-7]. When high doses of opioids are indicated, potent opioids that can still be delivered in small volumes are necessary, especially when subcutaneous administration is desirable[8]. When parenteral treatment fails, more invasive techniques like epidural and intrathecal opioid treatment are possible, although these techniques are more expensive and hazardous[8].

Hydromorphone is a semisynthetic derivate of morphine, with comparable efficacy and side effects to morphine when administrated subcutaneously in low concentrations[9]. Since hydromorphone is more lipophilic than other opioids[9-10] it can be administrated subcutaneously in highly concentrated solutions, making it particularly useful for subcutaneous administration when high doses of opioids are needed[7,9,11]. Based on this knowledge, it can be hypothesized that in case of inadequate pain control and/or uncontrolled side effects in patients who already use opioids in high doses for moderate to severe pain, rotating from a certain opioid to parenteral hydromorphone might be a useful alternative. In practice, this situation will especially occur in cancer patients with progressive disease for whom antitumor therapy is no longer available and life expectancy, therefore, is limited. These patients are also often treated with earlier opioid rotations in an effort to treat pain with tolerable side effects. However, data on the effect of parenteral hydromorphone in such patients are lacking.

We therefore performed a descriptive, retrospective study in extensively pretreated advanced cancer patients with inadequate pain control or uncontrolled side effects on the current opioids who were rotated to parenteral hydromorphone. The objective of this study was to investigate the analgesic efficacy and side effects of opioid rotation to parenteral hydromorphone, continuously administrated, on serious cancer-related pain among this patient population.

METHODS

Data were collected in our 13-bed Unit for Palliative Care and Symptom Control (PCSC unit) in the Erasmus MC Daniel den Hoed Cancer Center in the Netherlands. Most of the patients admitted to our PCSC unit have already been set on pain medication by their general practitioner or treating physicians, either from the cancer center or from other hospitals. Patients with severe pain despite the use of around-the-clock opioids or patients who suffer intolerable side effects to the used opioids are admitted for titration of parenteral opioids. At our PCSC unit, we generally use morphine or fentanyl for parenteral administration, depending on the opioid used before. In general, opioid rotation to another opioid is used in case of inadequate pain control combined with limiting opioid-related side effects; otherwise, dose escalation is applied with the opioid in use. Patients who suffer intolerable side effects on morphine and fentanyl and patients with persistent pain despite multiple dose escalations, particularly when high doses of subcutaneous opioids are needed to such an extent that delivery problems (are expected to) occur because of needed volumes, can be rotated to parenteral hydromorphone. The decision for rotating to parenteral hydromorphone is made by our multidisciplinary pain team. In general, patients who are rotated to parenteral hydromorphone start with 50-75% of the equianalgesic dose of the former opioid to allow for incomplete cross tolerance[12]. Published equianalgesic dose tables were used[10,13-14]. The subcutaneous route is preferred unless the infusion volume of the opioid administrated per hour is too large. Parenteral hydromorphone is not commercially available in the Netherlands, but can be prepared by our hospital pharmacy in a concentration of 10 mg/ml.

In this retrospective study, consecutive patients with nociceptive pain set on parenteral hydromorphone between December 2004 and June 2010 were included, thereby using the unit's standard systematic registration of pain intensity and side effects. Baseline characteristics including age, gender, type of cancer, tumor status, anti-tumor therapy (radiotherapy, chemotherapy, and hormonal therapy), prior analgesic prescription, pain intensity, side effects, and the reason for rotation to hydromorphone were obtained from medical records. Reasons for rotation to hydromorphone were classified as inadequate pain control {pain intensity > 4 [on a 0-10 numerical rating scale (NRS)] or uncomfortable} often while reaching the maximum feasible volume for subcutaneous administration of morphine or fentanyl, and intolerable (moderate to severe; see next paragraph) opioid-induced side effects (i.e., nausea or vomiting, constipation, confusion, somnolence, hallucinations, and myoclonus). In case of a combination of intolerable side effects and persistent pain or delivery problems of subcutaneous administration of large volumes, the reason for rotation was classified as intolerable side effects.

After starting parenteral administration of hydromorphone, pain intensity and side effects were recorded twice daily. Patients were asked to rate their pain intensity at rest

and with movement on the NRS[15]. The mean pain scores were calculated as the means of two pain intensity scores per day for pain at rest and pain with movement separately. Side effects were systematically rated using a Likert scale as none, mild, moderate, or severe. Side effects were further dichotomized into tolerable (none or mild) or intolerable (moderate or severe) categories. The used dosages of the different opioids were converted to oral morphine equivalent daily doses (MED, in milligrams per day) according to published equianalgesic dose tables: oral morphine 60 mg/day = parenteral morphine 20 mg/day = transdermal fentanyl 25 mcg/hr = parenteral fentanyl 25 mcg/hr = oral oxycodone 30 mg/day = oral hydromorphone 8 mg/day = parenteral hydromorphone 4 mg/day[13-14,16-17].

The effectiveness of continuous administration of parenteral hydromorphone was evaluated by determining the percentage of patients whose pain got adequately controlled with continuous administration of parenteral hydromorphone without intolerable side effects, the change in mean pain intensity at rest and mean pain with movement in these patients, and the time needed to achieve adequate pain control. The moment that adequate pain control was reached was defined as the first day of at least 2 consecutive days in which the mean pain score at rest was 4 or less[18-19], or in case pain measurement was not reported, patients and physicians were documented to be satisfied both in the absence of intolerable side effects. Moreover, to get an impression of the duration of the effect of parenteral hydromorphone, the failure-free period was determined among all patients who reached adequate pain control after rotation to parenteral hydromorphone. Failure-free period was defined as the period from the start of hydromorphone until death or the application of more invasive techniques. In some patients pain was adequately controlled with dosages of hydromorphone for which rotation back to an oral or transdermal opioid formulation was feasible. These patients were not considered as failures on parenteral hydromorphone and therefore were included in the calculation of the failure-free treatment period. Overall survival was calculated from the start of hydromorphone until death or end of the study.

Statistical analysis

Data were analyzed using the Statistical Package for the Social Science for Windows version 15.0. Descriptive statistics was used to describe patients' sociodemographic and medical characteristics. Differences in mean pain intensity overtime were tested with the *t* test. The failure-free treatment period and overall survival was visualized using the Kaplan-Meier method. July 31, 2010 was the censoring date for survival. Reported *p* values are two-tailed, and $p < 0.05$ was considered to be statistically significant.

RESULTS

One hundred and four consecutive patients were rotated to hydromorphone between December 2004 and June 2010. The baseline characteristics are shown in Table 1. All patients had advanced cancer, predominantly lung (18%), urological (17%), breast (14%), gastrointestinal (14%), or gynecological carcinoma (9%). The main reasons for rotation to parenteral hydromorphone were inadequate pain control combined with/without

Table 1. Patient characteristics.

	N (%)
Age (years), mean (sd)	57 (13.5)
Gender	
Male	57 (55%)
Female	47 (45%)
Stage of disease	
Metastatic disease	91 (88%)
Local recurrence	13 (13%)
More than one pain location	82 (79%)
Anticancer treatment at start hydromorphone	
No anticancer therapy	84 (81%)
Radiotherapy (within 2 weeks before start)	12 (12%)
Chemotherapy	5 (5%)
Hormonal therapy	3 (3%)
Use of atc opioids until start hydromorphone[a]	
Oral morphine	5 (5%)
Parenteral morphine	14 (13%)
Transdermal fentanyl	38 (37%)
Parenteral fentanyl	41 (39%)
Oral oxycodone	6 (6%)
Oral hydromorphone	5 (5%)
Oral morphine equianalgesic dose (mg), median (range)	600 (72-2,592)
Atc opioids ever used before hydromorphone	
Fentanyl (transdermal or parenteral)	92 (88%)
Morphine (oral or parenteral)	66 (63%)
Oxycodone (oral)	30 (29%)
Tramadol (oral)	21 (20%)
Hydromorphone (oral)	7 (7%)
Methadone (oral)	1 (1%)

HM hydromorphone, SD = standard deviation, atc = around the clock

[a] Five patients used combination of analgesics

expected delivery problems due to high opioid dosages [n=61, (59%)] and intolerable side effects with persistent pain [n=43, (41%); Figure 1].

All patients had received opioids before the start of parenteral hydromorphone (Table 1); 19 patients (18%) used morphine, and 79 patients (76%) used fentanyl as last opioid before the start of hydromorphone. Patients included in this study had serious cancer-related pain, which became obvious in the fact that most patients were extensively pretreated; 91 patients (88%) had been treated with two or more opioid rotations (drug and/or route) before rotating to hydromorphone. In addition, before rotating to parenteral hydromorphone, 74% of the patients had ever used at least two different types of opioids and 31% at least three different opioid types (Table 1).

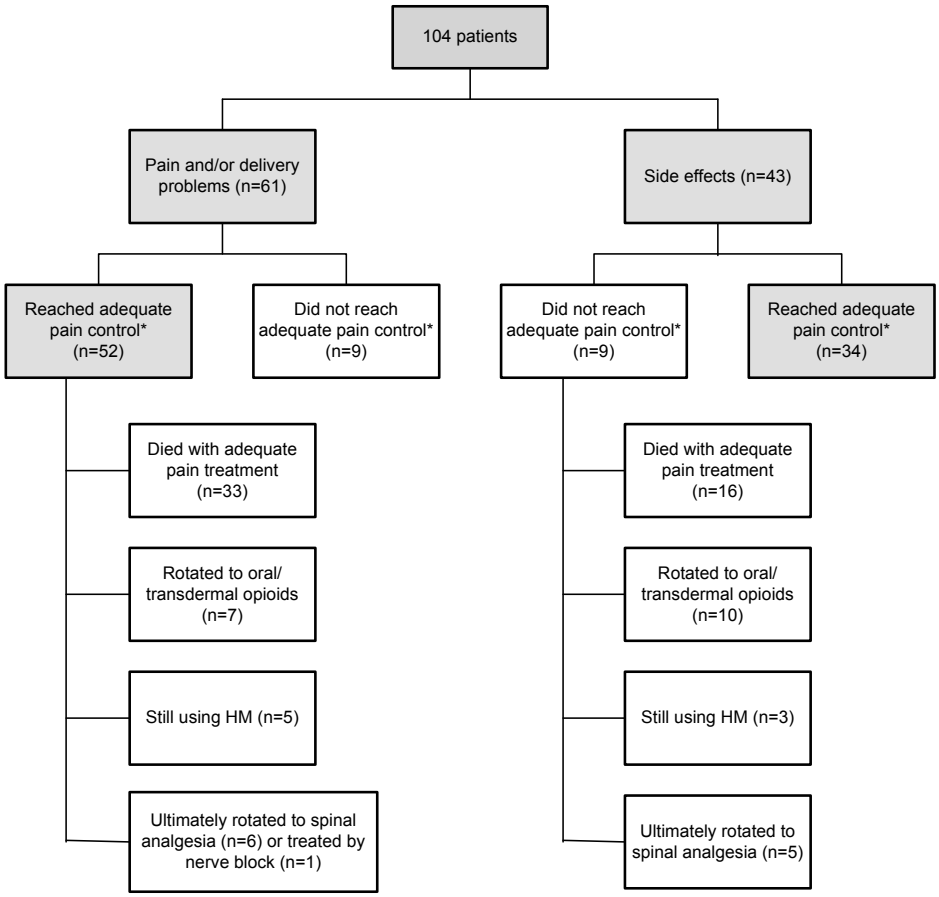

Figure 1. Opioid rotation to parenteral hydromorphone: summary of indications and clinical effectiveness
* adequate pain control = mean pain score in rest ≤ 4 (or when patients and physicians were satisfied) in the absence of intolerable side effects

The median oral MED was 600 mg/day (range 72-2,592 mg/day) before the start of hydromorphone (Table 1). Ninety-one patients were rotated to subcutaneous administration and 13 patients to intravenous administration of hydromorphone. The median daily dose of parenteral hydromorphone at start was 48 mg/day (range 5-216 mg/day).

Achievement of pain control

Adequate pain control (without intolerable side effects) was achieved in 86 out of 104 patients (83%) within a mean of 5.0 days [standard deviation (sd) = 3.4; Figure 1]. There was no relationship between number of opioids patients used before rotating to hydromorphone and percentage of patients achieving adequate pain control on parenteral hydromorphone. Before this rotation, 54 patients (52%) had side effects [mostly somnolence (n=22) or nausea (n=18)]. Eight of the 86 patients had side effects at adequate pain control [mostly nausea (n=3), constipation (n=4)], although these patients and their physicians were satisfied with the management of the side effects and both were unwilling to change policy. The mean pain intensity at rest in these 86 patients significantly decreased from 5.4 (sd =2.1) to 2.4 (sd=1.5; n=78; $p< 0.001$). The mean pain intensity with movement significantly decreased from 7.4 (sd=1.6) to 3.8 (sd=1.5; n=53; $p< 0.001$).

Among the 61 patients who were rotated to hydromorphone mainly because of inadequate pain control with/without (expected) volume problems with parenteral administration, 52 (85%) reached adequate pain control. In addition, a subgroup analysis, comparing patients with and without expected delivery problems due to high opioid dosages, showed similar percentage of patients receiving adequate pain control (90% vs. 83%; p=0.47). Among the 43 patients who were rotated to hydromorphone mainly because of opioid-related side effects, adequate pain control with tolerable side effects was reached in 34 (79%, Figure 1). In both groups of successfully treated patients, mean pain intensity scores at rest and with movement decreased significantly with titration of hydromorphone (Table 2).

Eighteen patients (17%) did not reach adequate pain control. Six patients died before reaching adequate pain control with parenteral hydromorphone (2-13 days); two of them were treated with palliative sedation in their terminal phase because of refractory pain and dyspnea. Twelve patients failed because of inadequate pain control and/or uncontrolled side effects. Ten of them were given spinal analgesia; one patient received a nerve block, and in one patient the intervention used was unknown.

Duration of effect on hydromorphone and overall survival

Among the 86 patients who achieved adequate pain control on parenteral hydromorphone, 74 patients (86%) did not undergo further invasive procedures, 49 patients (57%) died while still on parenteral hydromorphone, 17 patients (20%) were rotated to oral or transdermal opioids, and eight patients (9%) were still using parenteral hydromorphone

Table 2. Pain intensity scores in patients successfully rotated to parenteral hydromorphone.

	Total (n=86)		Pain (n=52)		Side effects (n=34)	
	T0	T1	T0	T1	T0	T1
Daily dose hydromorphone (mg), median (range)	48 (5-144)	48 (5-144)	48 (12-144)	65 (10-144)	24 (5-72)	34 (5-96)
Pain at rest, mean (sd)	5.4 (2.1)	2.4 (1.5)*	5.7 (2.2)	2.6 (1.5)*	4.8 (1.8)	2.1 (1.4)*
Pain with movement, mean (sd)	7.4 (1.6)	3.8 (1.5)*	7.5 (1.7)	3.5 (1.6)*	7.1 (1.6)	4.2 (1.4)*

* $p < 0.001$; *T0* baseline, *T1* at adequate pain control

at the time of data collection. Eleven patients ultimately rotated to spinal analgesia and one patient received a nerve block (Figure 1).

The median failure-free treatment period of the 86 responding patients was 57 days (range: 2-1,094 days), whereas their median duration of survival was 78 days (range 3-1,094 days). At the end of follow-up, ten patients were still alive (Figure 2).

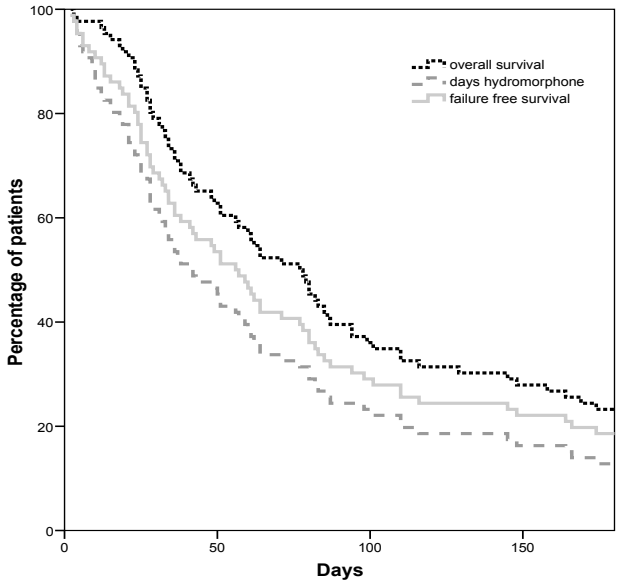

Figure 2. Failure-free treatment duration and overall survival in patients who reached adequate pain control on parenteral hydromorphone (n=86)
Overall survival was calculated from the start of hydromorphone until death or end of the study (black dotted line); duration of hydromorphone use (grey dashed line). Failure-free survival was defined as the period from the start of hydromorphone until death or the application of more invasive techniques (light grey line).

Other possible influencing factors

At baseline, 100 patients (96%) used adjuvant analgesics while rotated to parenteral hydromorphone (Table 3). Ninety-one of them used two or more adjuvant analgesics at baseline. In the 86 patients who reached adequate pain control, adjuvant analgesics were changed in 41 of them (Table 3). For example, six patients already used S(+)-ketamine before starting parenteral hydromorphone, three of them stopped with S(+)-ketamine before their pain was adequately treated. Thirteen other patients started with S(+)-ketamine between the start of parenteral hydromorphone and the moment adequate pain control was achieved (Table 3). A subgroup analysis comparing patients with and without the use of S(+)-ketamine, showed similar percentages of patients achieving adequate pain control (87% vs. 82%, p=0.54). Although a longer period was needed to achieve adequate pain control in those patients who used S(+)-ketamine compared to those who did not (median of 7 vs. 3 days; p=0.004), the median dosage of hydromorphone at start and at the moment of reaching adequate pain control was similar in both groups. Haloperidol was added in four patients to control their side effects. Dexamethasone was added in three patients while having radiotherapy (Table 3). Thirteen patients received radiotherapy within two weeks before starting parenteral hydromorphone or during therapy with hydromorphone (Table 1), and achieved adequate pain control within a median of 6 days.

Table 3. Adjuvant (analgesic) medication

	All patients (n=104)	All patients who reached adequate pain control (n=86)	
	At the start of hydromorphone treatment, n (%)	At the start of hydromorphone treatment, n (%)	At adequate pain control, n (%)
Acetaminophen	89 (86)	74 (86)	74 (86)
NSAIDs	77 (74)	65 (76)	68 (79)
S(+)-ketamine	9 (9)	6 (7)	16 (19)
Antidepressants	19 (18)	16 (19)	11 (13)
Anticonvulsants	48 (46)	39 (45)	15 (18)
Dexamethasone	5 (5)	5 (6)	8 (9)
Haloperidol	15 (14)	10 (12)	14 (16)
Methylphenidate	3 (3)	3 (4)	4 (5)

NSAIDs nonsteroidal anti-inflammatory drugs

DISCUSSION

In the present study, we have shown that parenteral hydromorphone is highly effective in advanced cancer patients with serious cancer-related pain who were extensively

pretreated with opioids. Eighty-three percent of the patients achieved adequate pain control with tolerable side effects within a mean of 5 days. Moreover, among 86% of these patients, the pain was adequately controlled until death without the need of further invasive procedures. The median failure-free treatment period of 57 days covered a substantial part of the median survival of 78 days in the responding patients. Thus, in advanced cancer patients with severe cancer-related pain despite the use of several lines of opioids, rotation to continuous parenteral administration of hydromorphone seems an elegant, highly effective option.

For patients who fail on a certain opioid, opioid rotation is regularly used, either as a change in the opioid drug or as a change in the route of administration. However, it is unknown whether opioid rotation is the choice to make in extensively pretreated cancer patients. In Table 4 all currently published prospective and retrospective studies on opioid rotation are described. In most studies the patient population was unclearly described. Moreover, only five studies gave some indication that advanced cancer patients were included in the study[20-24]. Unfortunately, these studies reported only over a short period of follow-up (7-28 days) and clear information on previous opioid use was lacking (Table 4). Finally, none of these studies reported a rotation to parenteral hydromorphone. Thus, with the current study, we are the first to show that an opioid switch to parenteral hydromorphone in a well-described, extensively pretreated advanced cancer patient population is a suitable and highly effective possibility.

In advanced cancer patients, subcutaneous administration of opioids is preferable to intravenous administration since it is more useful in the outpatient setting, has a lower risk of complications like infections, and is less expensive[11,25]. Since hydromorphone can be administered in high concentrations in very low volumes subcutaneously, it has been found to be useful when high doses of opioids are needed[11]. In our center, the maximum volume given subcutaneously is 2 ml/h for morphine and hydromorphone and 4 ml/h for fentanyl. Morphine and hydromorphone are available in concentrations of 10 mg/ml; fentanyl in a concentration of 50 µg/ml. In a substantial part of our patients, it was not possible to titrate morphine or fentanyl subcutaneously anymore because of too large volumes needed. To circumvent this problem, higher concentrations of opioids per milliliter could be prepared. However, in our experience, this often leads to an unacceptable high percentage of annoying local skin infiltrations.

There are several limitations that should be considered in interpreting the results of our study. First, it is a retrospective study. However, even though the definitions of the outcome measures were made retrospectively, the patients were evaluated prospectively for pain intensity and side effects. Due to the retrospective design, we were not able to give a complete overview of the analgesics patients had used before they were treated in our hospital. It is thus likely that the analgesics presented in Table 1 are an underestimation of the previously used analgesics. Second, this study was a

Table 4. Prospective and retrospective studies of opioid rotation in chronic cancer-related pain

Reference	N	Kind of rotation	Nº previous rotations	Mean follow up (days)	MED mean (mg/day)	RR (%)	Effectiveness	
							Pain Intensity	Side effects
Sawe, 1981[28]	14	Various opioids (po/im) → Me (po)	N/A	7	N/A	79	N/A	N/A
Slover, 1992[29]	5	M, HM, or O (po/iv) → F (td)	N/A	28	156	60	↓	Constipation ↓, Drowsiness ↑
Morley, 1993[30]	5	M (po) → Me (po)	N/A	N/A	N/A	80	↓	N/A
Bruera, 1995[31]	37	HM (sc) → Me (pr/po)	N/A	40	4140	84	↓	N/A
Cherny, 1995[32]	80	Various drugs and/ or routes	2	N/A	N/A	100	↓	↓
Paix, 1995[33]	11	M (po/sc/epi)→ F (sc)	N/A	32	245	73	No difference	↓
De Stoutz, 1995[34]	80	Various opioids → various opioids	N/A	N/A	1731[a]	73	↓	↓
De Conno, 1996[35]	196	Various opioids → Me (po)	N/A	N/A	N/A	N/A	No difference	No difference
Maddocks, 1996[22]	13	M (po/sc) → O (sc)	0-1	N/A	N/A	69	No difference	No difference
Hagen, 1997[36]	44	HM (po) ↔ O (po)	N/A	149	229	70	No difference	No difference
Ripamonti, 1998[37]	38	M (po/sc/iv) → Me (or)	N/A	3	145[a]	100	No difference	No difference
Ashby, 1999[20]	49	Various opioids → various opioids,	N/A	10	72[a]	65	↓	↓
Gagnon, 1999[38]	63	M or HM (sc) → O (sc)	N/A	N/A	342	51	No difference	No difference
Mercadante, 1999[39]	24	M (po) → Me (po)	N/A	48	125	79	↓	↓
Kloke, 2000[40]	103	Various drugs → Various drugs	1.38	N/A	N/A	65	N/A	N/A
Lee, 2001[41]	55	Various opioids → HM (po)	1.29	N/A	145.5	60	↓	↓
Mercadante, 2001[42]	50	M (po) → Me (po)	N/A	4	180[a]	80	↓	↓
Santiago-Palma, 2001[43]	18	F (iv) → Me (iv)	N/A	4	1159[a]	89	↓	Sedation ↓
Enting, 2002[5]	100	Various opioids (po/td) → various opioids	N/A	2	240[a]	71	↓	↓
McNamara, 2002[44]	19	M (po) → F (td)	N/A	14	60-120	47	No difference	Sleepiness ↓ drowsiness ↓
Moryl, 2002[45]	13	Me (po/iv) → various opioids (iv)	1-2	1	6946[b]	8	↑	Dysphoria ↑

Tse, 2003[23]	37	M (po) → Me (po)	N/A	14	120[a]	73	↓	↓
Benitez-Rosario, 2004[21]	17	F (td) → Me (po)	N/A	7	360[a]	80	↓	↓
Mercadante, 2005[46]	31	F (td) → Me (po) or vv	N/A	3	360	81	↓	↓
Morita, 2005[47]	20	M (po) → F (td/iv/sc)	N/A	7	64	90	↓	Delirium score ↓
Muller-Busch, 2005[24]	161	Various opioids → various opioids	N/A	28	204	N/A	N/A	N/A
Narabayashi, 2008[48]	25	M (po) → O (po)	N/A	2.3	44	84	↓	↓

Abbreviations: *po* per os, *pr* per rectal, *td* transdermal, *sc* subcutaneous, *iv* intravenous, *im* intramuscular, *HM* hydromorphone, *M* morphine, *Me* methadone, *O* oxycodone, *F* fentanyl, *vv* visa versa, *N/A* not available, *RR* response rate, definitions differ, *MED* oral morphine equivalent daily dose prerotation opioid

[a]Median instead of mean; [b]A 13.5:1 conversion was used

single-center study, which hampered the extrapolation of the results. Third, adequate pain control could be due to concomitant treatment with S(+)-ketamine or undergoing radiotherapy instead of an effect of hydromorphone alone. A pain-reducing effect of using S(+)-ketamine could not be excluded, although it seems not very likely. Besides the pain-reducing effect, S(+)-ketamine has been suggested to restore opioid sensitivity for its analgesic effects thereby diminishing the opioid doses needed to achieve adequate pain control. Due to the fact that the success rate in patients with and without S(+)-ketamine was the same in the subgroup analysis, the main effect we found in this study is most likely caused by hydromorphone. As far as radiotherapy is concerned, the effect of radiotherapy on pain relief can be expected after 2-4 weeks[26-27]. Given the fact that patients with radiotherapy received adequate pain control within a median of 6 days, a pain-reducing effect of radiotherapy in these patients cannot be fully excluded.

In conclusion, in patients with advanced cancer and serious unstable cancer-related pain refractory to other opioids, parenteral continuous administration of hydromorphone seems effective and should be considered even after extensive pretreatment with opioids. In this vulnerable patient population, often in their last weeks to months of life, adequate pain management is of the utmost importance. However, until now, opioid rotation is used by trial and error. For individual patients, underlying factors related to beneficial and detrimental effects of specific opioids are unknown. For optimizing patient-tailored opioid therapy, insights in underlying pharmacodynamic mechanisms are eagerly awaited.

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CHAPTER 7

Summary and discussion

Since 1990, the prevalence of cancer in the Netherlands has been increased with 3 – 3.5% per year, mainly provoked by an increase in the national population, especially in the elderly. In 2010, 540 371 persons were living with cancer (twenty-years prevalence) in the Netherlands[1-2]. In cancer patients, pain is one of the most frequent and feared symptoms. The prevalence of cancer-related pain remained stable during the years; approximately 53% of the cancer patients experienced pain during their disease[3]. The aim of pain management is to reduce patients' pain intensity to a tolerable level with acceptable side-effects.

Cancer-related pain management consists of a combination of anti-tumor therapy and symptomatic pharmacotherapy. Although the World Health Organization (WHO) introduced the analgesic ladder in 1986, till today adequate analgesia can be achieved in approximately 76% (range 45% - 100%) of the patients with cancer-related pain[4-5]. Possible reasons for inadequate pain management are the complexity of pain problems in a substantial part of the cancer patients, and the existence of various barriers and misconceptions regarding pain and pain management in both health care professionals and patients. Therefore, attention to the improvement of pain management remains necessary (**chapter 1**).

Because the prevalence of cancer-related pain varied across the studies, we identified the prevalence of cancer-related pain and the prevalence of inadequate pain relief at the outpatient clinic of the Erasmus MC Daniel den Hoed Cancer Center. **Chapter 2** reports a cross-sectional survey among 915 adult cancer outpatients. Patients were asked to rate their pain on an 11-point numeric rating scale (NRS) of 0-10[6]. A total of 246 of 915 patients (27%) had pain or used analgesics in the past week. Of these patients, 180 patients (73%) had been prescribed analgesics. Only 70% of patients with a prescription for analgesics had a prescription for 'around the clock' (ATC) analgesics, and 58% had access to 'as needed' (PRN) analgesics. Pain management was indicated as inadequate in 158 of 244 patients (65%)[7]. A total of 125 patients had a prescription for ATC analgesics and were evaluable for adherence measurement. Adherence rates were calculated for ATC regimens (i.e. dose taken divided by dose prescribed, multiplied by 100) and were considered inadequate when below 100% of the dose prescribed. Overall, 91 patients (73%) adhered to their analgesic prescription. From this survey, we were not able to make clear why patients did not take their analgesics and why professionals did not give the most adequate analgesic prescription. Therefore, **chapter 3** describes a systematic review of the literature to identify the major barriers hindering adequate pain management and to give a critical appraisal of interventions aiming to overcome these barriers.

Patients often impede their own treatment due to misconceptions about analgesics and their side-effects (e.g. concerned about addiction), non-adherence to their prescribed analgesics, and poor communication of their pain and their concerns about pain to health care providers (e.g. concerned that increased pain means progression of dis-

ease)[8-18]. The most frequently mentioned barriers in professionals (both physicians and nurses) that may hamper adequate pain management were: inadequate assessment of pain and pain management, patients' reluctance to report their pain or to give a pain score, and inadequate knowledge of pain management (e.g. believe that morphine has an upper limit)[19-25]. This review identified four interventions aimed to overcome these barriers: patient education, professional education, pain assessment and pain consultation. These interventions were always studied separately and were never combined in multidisciplinary study protocols. Studies on professional education and pain assessment did not evaluate patients' outcomes (e.g. pain intensity)[26-29]. In five of the eleven RCTs on patient education (PEP) and the two RCTs on pain consultation, patients' pain intensity decreased statistically significantly, although the adequacy of pain treatment, adherence or interference with daily life did not change[8,30-41]. The sample size of these studies varied widely and patients' follow-up differed per study (i.e. 5 days till 8 weeks). In addition, the RCTs measured different types of pain intensity, and the results of the studies on patient education could even be flattered because some of the studies did not report all measured pain intensities.

One of the influencing factors of adequate pain management is patients' adherence to analgesics. In cancer pain, adherence has been measured by self-report. Self-report, however, is limited by patients' memory. Moreover, the use of medication diaries over time is variable and patients tend to complete them retrospectively[42-45]. Another indirect method is the Medication Event Monitoring System (MEMS), an electronic monitoring device. A MEMS vial is a standard medication vial with a cap containing a microprocessor that accurately records time and date of each opening and closing. Similar to all indirect adherence methods, MEMS does not confirm ingestion of medication[43]. MEMS was never used in analgesic adherence measurement. In **chapter 4**, we determined the feasibility of MEMS vials in comparison with medication diaries in cancer patients with chronic pain on single as well as on multiple analgesic regimens.

Forty-six patients with nociceptive pain caused by cancer were asked to use MEMS vials for their analgesics and to record their medication usage in a diary for four weeks. Seventy-nine percent of these patients used MEMS for the full four-week period; 70% did so for the diary. The majority of patients were satisfied with both MEMS and diary. Adherence data assessed by MEMS and diary were comparable. Subgroup analyses in patients using single and multiple analgesic regimens confirmed the comparable usefulness of both methods. MEMS and a medication diary are equally useful for adherence measurement in analgesics.

To improve patients' pain treatment, we performed a multidisciplinary and multilevel randomized controlled trial. As identified in chapter 3, interventions to diminish professional-related and patient-related barriers were only studied separately, not in combination. From the literature, these interventions did not unequivocally demonstrated

clinically relevant improvements in patients' pain intensity. In **chapter 5**, we report the results of a randomized controlled trial (RCT) that tested the effectiveness of a pain consult combined with PEP. The primary endpoint of this study was the overall reduction of average pain intensity over the 8-week study period with respect to baseline.

Patients were initially randomly assigned to (1) standard care (SC), (2) pain consult (PC), or (3) pain consult combined with a patient Pain Education Program (PC&PEP). During the PC, a pain specialist determined if the cause of pain was clear; advised on anti-tumor therapy and optimized symptomatic treatment, as indicated. PEP consisted of patient-tailored pain education to enhance patients' knowledge about pain and pain management and to stimulate patients' help-seeking behavior, and weekly monitoring of pain and side-effects[41]. In January 2009, the three-arm study turned out to be not feasible because of slow accrual. Since then patients were randomized between (1) SC and (3) PC&PEP. In total, 37 patients were randomized to SC and 35 patients to PC&PEP. The overall reduction in pain intensity and daily interference was significantly greater after randomization to PC&PEP than to SC (average pain 31% vs. 20%, P=0.03; current pain 30% vs. 16%, P= 0.016; daily interference 20% vs. 2.5%, P=0.01). Adequacy of pain management did not differ between the groups. However, in the PC&PEP group the percentage of patients with both an ATC and a PRN opioid prescription increased from 48% at baseline to 88% after 8 weeks. In the SC group the percentage remained stable at 50%. The difference between the two groups was statistically significant after 8 weeks (P=0.003). Patients were more adherent to analgesics as measured with MEMS, after randomization to PC&PEP than to SC (P=0.03) and after 2 weeks the level of pain knowledge was significantly better after randomization to PC&PEP than to SC (P=0.002). In conclusion, PC&PEP improves patients' pain intensity, daily interference, patient adherence and patient knowledge in oncology outpatients. This study was the first to show an effect of PEP in daily interference.

As described in chapter 1, another reason why pain treatment is not always effective in all patients, is the complexity of pain in some patients. In our hospital, patients who suffer intolerable side effects on morphine and fentanyl, and patients with persistent pain despite multiple dose escalations, can be rotated to parenteral hydromorphone. Hydromorphone is a semi-synthetic derivate of morphine, with comparable efficacy and side effects to morphine. Hydromorphone can be administrated subcutaneously in highly concentrated solutions, making it particularly useful for subcutaneous administration when high doses of opioids are needed[46-47]. **Chapter 6** describes a study in which the analgesic efficacy and side effects of hydromorphone were investigated in advanced cancer patients with serious cancer-related pain. The reasons for rotation to parenteral hydromorphone were inadequate pain control with or without expected delivery problems due to high opioid dosages (n=61) and intolerable side effects with persistent pain (n=43). Before this rotation, 88% of the patients had been treated with

two or more opioid rotations. Adequate pain control was achieved in 86 patients (83%) within a median of 5 days. Eight of these 86 patients still had side effects, but these were scored as acceptable. The mean pain intensity at rest decreased from 5.4 (sd=2.1) to 2.4 (sd=1.5, P<0.001). The median failure-free treatment period was 57 days and covered a substantial part of the median survival of 78 days in the responding patients. In advanced cancer patients with serious unstable cancer-related pain refractory to other opioids, continuous subcutaneous administration of hydromorphone often results in a long-lasting adequate pain control and should be considered even after extensive pretreatment with opioids.

CONCLUSIONS

This thesis shows more insight in both patient-related and professional-related barriers regarding cancer-related pain and pain management, and the scientific evidence of possible interventions to overcome these barriers. This thesis has the following aims:

1. *To evaluate the prevalence of cancer-related pain and quality of cancer-related pain treatment at our outpatient clinic.*
   The prevalence of cancer-related pain at the outpatient clinic in our hospital was lower than described in the literature, but still over a quarter of the cancer patients at the outpatient clinic had pain, and in more than half of them, pain was not adequately treated.
2. *To identify and summarize the available information on barriers hindering adequate pain management and interventions aiming to overcome these barriers.*
   The key patient-related barriers are lack of knowledge about analgesia, poor adherence, and reluctance to complain about their pain. The most important professional-related barriers are inadequate pain assessment and inadequate knowledge of pain management. The identified interventions to diminish these barriers (patient education, professional education, pain assessment and pain consultation) did not unequivocally demonstrated clinically relevant improvements in patients' pain intensity.
3. *To study methods to measure patients' adherence to analgesics in cancer patients.*
   The feasibility of MEMS vials was compared with medication diaries to measure adherence in cancer patients. The majority of patients were satisfied with both MEMS and diary. Adherence data assessed by MEMS and diary were comparable. MEMS and a medication diary are equally useful for adherence measurement in analgesics.
4. *To evaluate whether an intervention based on the barriers hindering adequate pain management will improve patients' pain intensity and interference in daily life.*

In an RCT, in which a Pain Consult combined with patient Pain Education Program was compared to standard pain treatment, we show that this intervention decreased pain intensity and interference by pain in daily life and increased patients' knowledge and adherence to analgesics in oncology outpatients.

5. *To evaluate whether an opioid rotation to parenteral hydromorphone will improve patients' pain intensity in patients with complex pain problems.*
   In patients with complex pain problems, who already use opioids in high doses for moderate to severe pain, rotating from a certain opioid to parenteral hydromorphone often results in long-lasting adequate pain control.

DISCUSSION

Internationally, the prevalence of cancer-related pain remains high through the years [3]. This is always cited to demonstrate that cancer-related pain is a problem. However, is the prevalence the right indicator? The prevalence includes all patients with cancer-related pain (from almost no pain, NRS=1, till unbearable pain NRS=10), and is not an indicator of the adequacy of pain management. It would be more interesting to report the percentages of patients with moderate to severe pain, because those patients are not treated adequately.

The subsequent question is what do we mean with moderate to severe pain? What should be the cut point on the Numeric Rating Scale? According to the Dutch Adult Cancer Pain Guideline the cut point for moderate to severe cancer-related pain is NRS 5[48]. On the other hand, the National Comprehensive Cancer Network (NCCN) guideline 'Adult Cancer Pain' categorized moderate to severe pain as NRS ≥ 4[49]. However, it is unclear if one cut point is valid in all situations; different stages of cancer, gender or underlying mechanism. We need more evidence, before using such cut points, but agreement on definitions is eagerly awaited for use in clinical and epidemiologic studies.

As described in the introduction, adequate pain control is still not achieved in a substantial group of patients with cancer-related pain due to the existence of professional- and patient-related barriers and the complexity of pain problems in a part of the patients (Figure 1). Our review confirmed that both patient-related and professional-related barrier play an important role in pain management. The RCT in this thesis was designed to diminish these barriers. To reduce the influence of physician-related barriers, patients were referred to a pain specialist. To decrease patient-related barriers, patients received a Pain Education Program. However, during this RCT, we met other barriers. We were forced to change our study design because of the slow accrual of our patients. Possible explanations for the slow accrual were the strict inclusion criteria we used and that we were not able to screen all patients by ourselves. Patients' pain was

not always documented. This could be due to known barriers (chapter 3), namely that patients were often reluctant to report their pain and physicians assessed patients' pain and pain management inadequately. The RCT show that the combined intervention decreased patients' pain intensity and increased daily functioning. When decreasing the barriers, patients' pain treatment will improve. Therefore, to improve the pain treatment at the outpatient clinic, an integrated system should be implemented. Patients' pain intensity should be systematically measured and documented and actively reported to the treating professionals. Besides this, an oncology pain protocol should be easily accessible for all professionals and referral to a pain specialist and to a pain nurse for tailored pain education should be integrated in cancer care for patients with moderate to severe cancer pain.

A third reason why not all patients achieved adequate pain control is that some patients have complex pain problems (Introduction, Figure 1). The study in chapter 6 showed that a rotation to parenteral hydromorphone, as an example of a treatment for a group of patients with complex pain, was successful in 83% of the included advanced cancer patients with unstable pain refractory to other opioids. Therefore, when pain management failed with the more common opioids, a rotation to parenteral hydromorphone could be a useful option.

The interventions in the studies described in this thesis showed an improvement in patients' pain. However, in a part of the patients pain was still not adequately managed. At the end of a study, these patients scored their pain as moderate to severe despite the changes in pain treatment or education. Some patients made a conscious decision between pain and side effects and decided to tolerate some pain. In other patients, much attention had been given to all treatment options but despite all efforts, prolonged pain relief could not be achieved. It is still unclear which factors may influence patients' pain and whether it is possible to achieve adequate analgesia in all patients. For individual patients, the underlying factors related to beneficial and detrimental effects of specific opioids are unknown. For optimizing patients' tailored opioid treatment, insight in underlying pharmacodynamic mechanisms is eagerly awaited. Besides this, it is possible that the currently available analgesics are not sufficiently effective and that novel treatment options with other physical targets are necessary.

This leads to the following recommendations:

1. More research is necessary to know which scores on a 0-10 Numeric Rating Scale represent moderate to severe pain.
2. To improve patients' pain management at the outpatient clinic, an integrated system should be implemented, concerning systematic pain measurement; pain protocol, including guideline for referral to a pain specialist; and referral to a pain nurse for tailored instruction how to cope with their pain and their analgesics.

3. In palliative care priority should be given to stimulate research on pharmacodynamic and pharmacokinetic mechanisms of the WHO analgesics; furthermore, research on novel therapies may be eagerly awaited.

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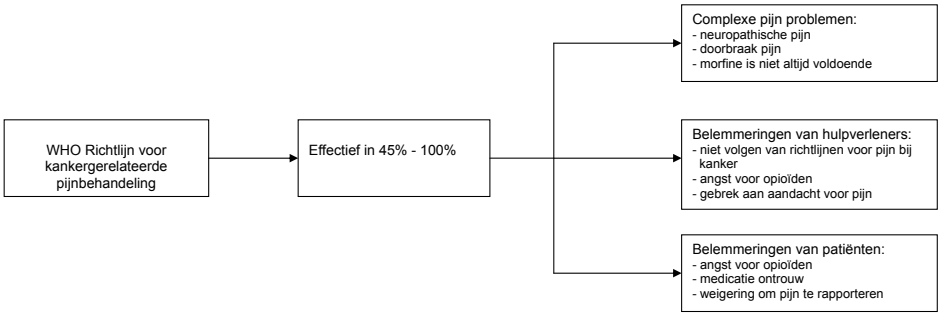
APPENDIX

Samenvatting en discussie

Sinds 1990 is de prevalentie van kanker in Nederland toegenomen met 3 – 3.5% per jaar. Deze toename werd vooral veroorzaakt door een bevolkingstoename, in het bijzonder van de ouderen. In 2010 leefden er in Nederland 540 371 mensen met kanker (20-jaars prevalentie)[1-2]. Voor patiënten met kanker is pijn één van de meest voorkomende en gevreesde symptomen. De prevalentie van kankergerelateerde pijn is door de jaren heen stabiel gebleven; ongeveer 53% van de patiënten met kanker ervaart pijn tijdens hun ziekte[3] **(hoofdstuk 1)**. Het doel van de pijnbehandeling is om de mate waarin patiënten pijn hebben te verminderen tot een draaglijk niveau met acceptabele bijwerkingen.

De behandeling van kankergerelateerde pijn bestaat, zo mogelijk, uit een combinatie van een antitumor behandeling (behandeling die de oorzaak van de pijn aanpakt, bijv. radiotherapie bij botmetastasen) en een symptomatische behandeling met pijnstillers. Hoewel de Wereld Gezondheidsorganisatie (WHO) in 1986 een pijnladder introduceerde, kan, tot de dag van vandaag, maar ongeveer 76% (range 45% - 100%) van de patiënten met pijn bij kanker, adequaat behandeld worden voor hun pijn[4-5]. Mogelijke redenen voor deze inadequate pijnbehandeling zijn de complexiteit van de pijnproblemen bij een substantieel deel van de patiënten met kanker en het bestaan van diverse misverstanden en vooroordelen met betrekking tot pijn en pijnbehandeling bij zowel zorgverleners als patiënten. Daarom blijft aandacht voor verbetering van de pijnbehandeling nodig (**hoofdstuk 1**, Figuur 1).



Figuur 1. Redenen voor inadequate pijnbehandeling.

Omdat de prevalentie van kankergerelateerde pijn varieerde tussen de diverse studies, hebben wij een onderzoek uitgevoerd op de polikliniek van het Erasmus MC Daniel den Hoed ter bepaling van de prevalentie van kankergerelateerde pijn; daarbij werd beoordeeld hoe vaak een adequate pijnbehandeling was voorgeschreven. **Hoofdstuk 2** geeft de resultaten weer van de prevalentie meting bij 915 volwassen poliklinische patiënten met kanker. Patiënten werden gevraagd hun pijn aan te geven op een 11-punts numerieke beoordelingsschaal (NRS) van 0 (geen pijn) tot 10 (ergst denkbare pijn)[6]. In totaal gaven 246 van de 915 patiënten (27%) aan dat zij de afgelopen week pijn hadden gehad

of pijnmedicatie hadden gebruikt. Van deze patiënten hadden 180 patiënten (73%) een voorschrift voor pijnmedicatie. Van de patiënten met een voorschrift voor pijnmedicatie had 70% een voorschrift voor medicatie op vaste tijden ('around the clock' (ATC)). Daarnaast had 58% 'zo nodig' pijnmedicatie voorgeschreven gekregen. Voor 158 van de 244 patiënten (65%) was de pijnbehandeling inadequaat[7]. In totaal hadden 125 patiënten een voorschrift voor pijnmedicatie op vaste tijden en waren daarmee evalueerbaar voor een meting van medicatietrouw. Medicatietrouw werd berekend voor de ATC-medicatie en werd als inadequaat beschouwd indien minder dan 100% van de voorgeschreven dosering ingenomen werd. Eén en negentig patiënten (73%) met een voorschrift voor ATC-medicatie waren medicatietrouw. Wij konden in deze studie niet bepalen waarom patiënten hun pijnmedicatie niet innamen en waarom zorgverleners niet het meest optimale voorschrift voor pijnmedicatie gaven. Daarom beschrijft **hoofdstuk 3** een systematisch overzicht van de literatuur over de belangrijkste barrières die een adequate pijnbehandeling bij patiënten met kanker verhinderen en over de interventies die bedoeld zijn om deze barrières te verminderen.

Patiënten belemmeren hun eigen pijnbehandeling door de vooroordelen die zij hebben over pijnmedicatie en bijwerkingen (bijv. angst voor verslaving), onvoldoende medicatietrouw aan de voorgeschreven pijnmedicatie, slechte communicatie met zorgverleners over de ervaren pijn en bezorgdheid over pijn (bijv. angst dat toename van pijn progressie van ziekte betekent)[8-18]. Zorgverleners, zowel artsen als verpleegkundigen, geven als belangrijkste barrières aan: inadequate beoordeling van de pijn en pijnbehandeling, terughoudendheid van patiënten om pijn aan te geven of de pijn in een cijfer uit te drukken, en onvoldoende kennis van pijn en pijnbehandeling bij zorgverleners (bijv. morfine heeft een maximale dosering)[19-25]. In dit review wordt een overzicht gegeven van de in de literatuur beschreven interventies die als doel hebben de barrières te verminderen: patiënteneducatie, educatie van zorgverleners, pijnmeting en een pijn consult. Deze interventies zijn slechts afzonderlijk bestudeerd en nooit gecombineerd in multidisciplinaire studies. Studies over educatie aan zorgverleners en over systematische pijnmeting rapporteerden geen patiëntgerelateerde uitkomstmaten (bijv. pijnintensiteit)[26-29]. In vijf van de elf gerandomiseerde studies (RCTs) over patiënteneducatie ('Pijn Educatie Programma' (PEP)) en in de twee RCTs over pijn consulten, nam de mate waarin patiënten pijn hadden statistisch significant af. Echter er werd geen verandering gezien in de adequaatheid van de pijnbehandeling, de medicatietrouw of de invloed van de pijn op het dagelijks functioneren[8,30-41]. De studies verschilden sterk van elkaar wat betreft het aantal bestudeerde patiënten en de duur van de follow-up. De steekproefgrootte van deze studies verschilde zeer en de follow-up van patiënten was per studie anders (5 dagen tot 8 weken). Daarnaast werden in de RCTs verschillende maten gebruikt om pijnintensiteit te meten (bijv. pijn op dit moment of ergste pijn). Ook is het mogelijk dat de resultaten van studies over patiënteneducatie geflatteerd

zijn, omdat enkele van deze studies niet alle verschillende typen pijnintensiteiten rapporteerden die wel gemeten waren.

Eén van de factoren die de adequaatheid van de pijnbehandeling kan beïnvloeden is de mate van medicatietrouw aan de voorgeschreven pijnmedicatie. Bij kankergerelateerde pijn wordt medicatietrouw meestal gemeten met behulp van zelfrapportage. Dit wordt echter beperkt door het geheugen van de patiënt. Bovendien is bekend dat een medicatiedagboek wisselend wordt ingevuld en patiënten de neiging hebben deze achteraf in te vullen[42-45]. Een andere indirecte methode om medicatietrouw te meten is het Medication Event Monitoring System (MEMS). Een MEMS potje is een standaard medicatiepotje met een deksel dat een microprocessor bevat die de exacte tijd en datum van elke opening registreert. Net zoals bij andere indirecte metingen van medicatietrouw, is het met de MEMS onmogelijk om te bepalen of de medicatie ook daadwerkelijk ingenomen is[43]. MEMS was nog niet eerder gebruikt voor het meten van pijnmedicatie. In **hoofdstuk 4** bepalen wij de bruikbaarheid van MEMS potjes in vergelijking met medicatiedagboeken in patiënten met kanker met chronische pijn die één of meerdere voorschriften voor pijnmedicatie hebben.

Gedurende vier weken gebruikten 46 patiënten met kankergerelateerde pijn MEMS potjes voor hun pijnmedicatie en registreerden zij de ingenomen pijnmedicatie in een medicatiedagboek. MEMS werd door 79% van deze patiënten gedurende de gehele studieperiode gebruikt; 70% gebruikte het medicatiedagboek gedurende deze vier weken. Het merendeel van de patiënten was tevreden met zowel MEMS als het dagboek. De mate van medicatietrouw gemeten door middel van MEMS en het dagboek was vergelijkbaar. Een subgroep analyse bij patiënten met één of met meerdere pijnstillers gaf vergelijkbare resultaten voor beide methoden. MEMS en een medicatiedagboek zijn dus even bruikbaar voor medicatietrouw meting bij pijnmedicatie.

Om de pijnbehandeling van patiënten te verbeteren, hebben wij een multidisciplinaire en multilevel gerandomiseerde gecontroleerde studie uitgevoerd. Zoals in hoofdstuk 3 is aangegeven, zijn interventies om de barrières bij zowel zorgverleners als patiënten te verminderen altijd afzonderlijk onderzocht en nooit gecombineerd. De resultaten van deze interventies op het verbeteren van de pijnintensiteit wisselde sterk tussen de verschillende studies. In **hoofdstuk 5** worden de resultaten van een RCT weergegeven. In deze RCT werd de effectiviteit onderzocht van een pijnconsult gecombineerd met patiënteneducatie over pijn. Het belangrijkste eindpunt van deze studie was de overall afname van de gemiddelde pijnintensiteit over de studieperiode van 8 weken, in vergelijking met de startwaarde.

Patiënten werden in eerste instantie gerandomiseerd tussen (1) standaard pijnbehandeling (SC), (2) pijnconsult (PC), of (3) pijnconsult gecombineerd met een pijneducatie programma voor patiënten (PC&PEP). Tijdens het pijnconsult bepaalde de pijnarts of de oorzaak van de pijn duidelijk was; gaf advies over de antitumor behandeling en

optimaliseerde zo nodig de medicamenteuze pijnbehandeling. PEP bestaat uit patiënteneducatie 'op maat' om de kennis van patiënten over pijn en pijnbehandeling te verbeteren en om patiënten te stimuleren tijdig zelf hulp te zoeken bij pijnklachten. Daarnaast werden deze patiënten wekelijks gebeld om na te vragen hoe het ging met de pijn en de bijwerkingen[41]. In januari 2009 werd duidelijk dat deze 3-armige studie niet haalbaar was omdat de patiënteninclusie te traag verliep. Vanaf dat moment werden patiënten gerandomiseerd tussen (1) SC en (3) PC&PEP. In totaal werden er uiteindelijk 37 patiënten gerandomiseerd in de SC groep en 35 patiënten in de PC&PEP groep. De overall afname van de pijnintensiteit en de invloed van pijn op het dagelijks functioneren was significant groter in de groep patiënten die gerandomiseerd waren voor PC&PEP dan voor SC (gemiddelde pijn 31% vs. 20%, p=0.03; pijn op dit moment 30% vs. 16%, p=0.016; invloed van pijn op het dagelijks functioneren 20% vs. 2.5%, p=0.01). De adequaatheid van de pijnbehandeling was niet verschillend tussen de groepen. Echter het percentage patiënten met zowel een ATC- als een zo nodig- voorschrift voor opioïden nam in de PC&PEP groep toe van 48% bij start tot 88% na acht weken. In de SC groep bleef dit percentage stabiel op 50%. Het verschil tussen de twee groepen was statistisch significant na acht weken (p=0.003). Patiënten waren na 8 weken meer medicatietrouw wanneer zij gerandomiseerd waren voor PC&PEP dan voor SC (p=0.03). Na twee weken was de pijnkennis significant beter bij de patiënten in de PC&PEP groep dan in de SC groep (p=0.002). Concluderend, PC&PEP verbeterde de pijnintensiteit, invloed van pijn op dagelijks functioneren, medicatietrouw en pijnkennis van poliklinische patiënten met kankergerelateerde pijn. Deze studie was de eerste die een effect op het dagelijks functioneren aantoonde.

Zoals beschreven in de introductie en in figuur 1, is de complexiteit van het pijnprobleem bij sommige patiënten een andere reden waarom de pijnbehandeling niet altijd effectief is. In ons ziekenhuis kunnen patiënten die ondraaglijke bijwerkingen hebben van morfine of fentanyl, en patiënten met aanhoudende pijn ondanks meerdere dosisverhogingen, een opioid rotatie krijgen naar parenteraal toegediende hydromorfon. Hydromorfon is een semi-synthetische derivaat van morfine, met vergelijkbare werking en bijwerkingen als morfine. Hydromorfon kan subcutaan gegeven worden in hoge doseringen[46-47]. **Hoofdstuk 6** beschrijft een studie waarin de pijnstillende werking en bijwerkingen van hydromorfon onderzocht werden bij patiënten met gemetastaseerde ziekte die ernstige kankergerelateerde pijn hadden. De redenen voor rotatie naar parenterale hydromofon waren inadequate pijnstilling met of zonder te verwachten toedieningproblemen als gevolg van hoge doseringen opioïden (n=61) en ondraaglijke bijwerkingen op andere opioïden met aanhoudende pijn (n=43). Voor deze rotatie was 88% van deze patiënten al behandeld met twee of meerdere opioïd rotaties. Adequate pijnstilling werd bereikt bij 86 patiënten (83%) binnen een mediaan van 5 dagen. Acht van deze 86 patiënten hadden nog steeds bijwerkingen echter deze waren acceptabel.

De gemiddelde pijnintensiteit in rust nam af van 5.4 (standaard deviatie (sd)=2.1) tot 2.4 (sd=1.5, p<0.001) op een 0-10 NRS. De mediane behandelperiode met hydromorfon was 57 dagen, een substantieel deel van de mediane overleving de responderende patiënten (78 dagen). Bij patiënten met gemetastaseerde ziekte die ernstige kankergerelateerde pijn hadden die niet reageerde op andere opioïden, gaf continue toediening van subcutane hydromorfon een langdurende pijncontrole. Daarom zou subcutaan toegediende hydromorfon overwogen moeten worden bij patiënten met moeilijk te behandelen pijn, zelfs bij patiënten die al uitgebreid zijn voorbehandeld met opioïden.

CONCLUSIES

Dit proefschrift geeft meer inzicht in zowel patiëntgerelateerde en zorgverlenergerelateerde barrières die een optimale pijnbehandeling verhinderen, en geeft inzicht in het wetenschappelijke bewijs van mogelijke interventies om deze barrières te verminderen. Dit proefschrift heeft de volgende doelstellingen:

1. *Het evalueren van de prevalentie van kankergerelateerde pijn en de kwaliteit van de pijnbehandeling op onze polikliniek*

   De prevalentie van kankergerelateerde pijn op de polikliniek in ons ziekenhuis was lager dan beschreven in de literatuur. Toch had nog steeds ruim een kwart van de patiënten met kanker op onze polikliniek pijn, en in meer dan de helft van deze patiënten werd de pijn niet adequaat behandeld.
2. *Het identificeren en samenvatten van de beschikbare informatie betreffende barrières die adequate pijnbehandeling belemmeren, en van interventies om deze barrières te verminderen.*

   De belangrijkste patiëntgerelateerde barrières zijn gebrek aan kennis over pijnmedicatie, slechte medicatietrouw, en terughoudendheid om de pijn bespreekbaar te maken. De belangrijkste zorgverlenergerelateerde barrières zijn inadequate beoordeling van de pijn en inadequate kennis over pijnbehandeling. De studies over de geïdentificeerde interventies om deze barrières te verminderen (patiënteneducatie, educatie aan zorgverleners, pijnmeting en pijnconsultatie) toonden niet eenduidig een klinisch relevante verbetering van de mate waarin patiënten pijn hebben aan.
3. *Bestuderen van methoden om medicatietrouw aan pijnmedicatie te meten bij patiënten met kanker.*

   De bruikbaarheid van MEMS medicatiepotjes werd vergeleken met medicatiedagboeken om medicatietrouw te meten aan pijnmedicatie bij patiënten met kanker. De meerderheid van de patiënten was tevreden met zowel MEMS als dagboek. De mate van medicatietrouw gemeten door middel van MEMS en het dagboek was vergelijk-

baar. MEMS en een medicatiedagboek zijn dus even bruikbaar voor medicatietrouw meting bij pijnmedicatie.

4. *Beoordelen of een interventie, die gebaseerd is op de barrières die adequate pijnbehandeling belemmeren, leidt tot een overall afname van de mate waarin patiënten pijn hebben en de invloed van pijn op het dagelijks functioneren.*
   In een RCT, waarin een pijnconsult gecombineerd met patiënteneducatie werd vergeleken met de standaard pijnbehandeling bij poliklinische patiënten met kanker, konden wij aantonen dat deze interventie de pijnintensiteit en de invloed van pijn op het dagelijks functioneren verminderd, en daarnaast de pijnkennis van patiënten en de medicatietrouw verbeterd bij poliklinische patiënten met pijn bij kanker.
5. *Het evalueren of een opioïd rotatie naar parenteraal toegediende hydromorfon de mate waarin patiënten pijn hebben, vermindert bij patiënten met complexe pijnproblemen.*
   Bij patiënten met complexe pijnproblemen, die al hoge doseringen opioïden gebruikten voor matige tot ernstige pijn, gaf rotatie van een opioïd naar parenteraal toegediende hydromorfon vaak een langdurige adequate pijnstilling.

DISCUSSIE

De prevalentie van kankergerelateerde pijn blijft hoog door de jaren heen[3]. Dit wordt altijd beschreven om aan te geven dat kankergerelateerde pijn nog steeds een probleem is. Echter, het is de vraag of de prevalentie wel een juiste indicator hiervoor is. De prevalentie houdt alle patiënten in met kankergerelateerde pijn, van bijna geen pijn, NRS=1, tot ondraaglijke pijn, NRS=10, en is daarmee geen indicator voor de adequaatheid van de pijnbehandeling. Het zou veel interessanter zijn om het percentage patiënten met matig tot ernstige pijn weer te geven, omdat deze patiënten niet goed behandeld worden voor hun pijn.

Echter, de daarop volgende vraag is, wat bedoelen wij met matig tot ernstige pijn? Wat is dan het juiste afkappunt op een numerieke beoordelingsschaal? Volgens de Nederlandse richtlijn 'Diagnostiek en behandeling van pijn bij patiënten met kanker' is het afkappunt voor matig tot ernstige kankergerelateerde pijn NRS 5[48]. Echter de 'National Comprehensive Cancer Network' (NCCN) categoriseert in haar richtlijn 'Adult Cancer Pain', matig tot ernstige pain als NRS ≥ 4[49]. Het is echter onduidelijk of één afkappunt geldig is voor alle situaties; voor de verschillende stadia van kanker, geslacht of onderliggend mechanisme. We hebben meer onderzoek nodig voordat afkappunten in de praktijk gebruikt kunnen worden, echter overeenstemming over de definities is noodzakelijk voor het gebruik in klinische en epidemiologische studies.

Zoals in de introductie en in bovenstaande figuur beschreven wordt, kan adequate controle niet altijd behaald worden in een substantieel deel van de patiënten met

kankergerelateerde pijn. Dit wordt mogelijk veroorzaakt door misverstanden en vooroordelen van zowel patiënten als zorgverleners en door de complexiteit van de pijnproblemen bij een deel van de patiënten (Figuur 1). Ons review bevestigt dat zowel patiëntgerelateerde als zorgverlenergerelateerde barrières een belangrijke rol spelen in de pijnbehandeling. De RCT die in dit proefschrift beschreven wordt, was ontworpen of deze barrières te verminderen. Om de invloed van de barrières van zorgverleners te verminderen, werden patiënt verwezen naar een pijnspecialist. Om de patiëntgerelateerde barrières te verminderen, kregen patiënten een pijneducatie programma aangeboden. Echter gedurende deze studie, liepen wij tegen andere barrières aan. We moesten ons studiedesign veranderen omdat de patiënteninclusie zeer traag verliep. Mogelijke verklaringen voor deze trage inclusie kunnen de strikte inclusiecriteria zijn die wij hanteerden en daarnaast dat wij niet alle patiënten zelf op pijn konden screenen. Of patiënten pijn hadden, was niet altijd gedocumenteerd. Dit kan veroorzaakt zijn door diverse bekende barrières (hoofdstuk 3), namelijk dat patiënten vaak terughoudend waren om aan te geven dat ze pijn hadden en daarnaast dat artsen de pijn en pijnbehandeling van patiënten niet adequaat beoordeelden. Deze RCT maakt duidelijk dat de gecombineerde interventie de mate waarin patiënten pijn hebben verminderd en het dagelijks functioneren verbeterd. Wanneer de barrières verminderd worden, verbeterd de pijnbehandeling van patiënten. Daarom, om de pijnbehandeling op de polikliniek te kunnen verbeteren, zou een geïntegreerd systeem geïmplementeerd moeten worden. De pijn van patiënten zou systematisch gemeten en gedocumenteerd moeten worden en direct aan de zorgverleners teruggeven moeten worden. Daarnaast zou een oncologisch pijnprotocol toegankelijk moeten zijn voor alle zorgverleners en een verwijzing naar een pijnspecialist en naar een pijnverpleegkundige voor 'op maat' patiënteneducatie over pijn zou in de oncologische zorg geïntegreerd moeten zijn voor alle patiënten met matig tot ernstige pijn.

Een derde reden waarom niet alle patiënten adequaat behandeld worden voor hun pijn is dat sommige patiënten complexe pijnproblemen hebben (Introductie, Figuur 1). De studie die beschreven wordt in hoofdstuk 6 laat zien dat een rotatie naar parenteraal toegediende hydromorfon, als een voorbeeld van een behandeling voor een groep patiënten met complexe pijn, succesvol was in 83% van de geïncludeerde kankerpatienten met gemetastaseerde ziekte die onstabiele pijncontrole hadden, niet reagerend op andere opioïden. Daarom, wanneer de pijnbehandeling niet effectief is met de meer gebruikelijke opioïden, kan een rotatie naar parenteraal toegediende hydromorfon een goede optie zijn.

De interventies in de studies beschreven in dit proefschrift laten een verbetering zien van de pijn van patiënten. Echter, bij een deel van de patiënten werd de pijn nog steeds niet adequaat behandeld. Aan het einde van de studie scoorden deze patiënten hun pijn nog steeds als matig tot ernstig ondanks de veranderingen in de pijnbehandeling of de

patiënteneducatie. Sommige patiënten maakten een bewuste afweging tussen pijn en bijwerkingen en besloten om wat meer pijn te accepteren. Bij andere patiënten is er veel aandacht geweest voor alle mogelijke behandelingen maar ondanks alle moeite kon er geen langdurige pijnstilling bereikt worden. Het is nog steeds onduidelijk welke factoren de pijn van patiënten mogelijk beïnvloedt en in hoeverre het mogelijk is om adequate pijnstilling te bereiken in alle patiënten. Voor individuele patiënten zijn de onderliggende factoren die gerelateerd zijn aan zowel gunstige als ongunstige effecten van specifieke opioïden onbekend. Voor het optimaliseren van een 'op maat' gemaakte pijnbehandeling met opioïden is inzicht in de onderliggende farmacodynamische en farmacokinetische mechanismen noodzakelijk. Daarnaast is het mogelijk dat de momenteel beschikbare analgetica niet voldoende effectief zijn en dat nieuwe middelen die andere aangrijpingspunten in het lichaam hebben nodig zijn om de pijnbehandeling te verbeteren.

Dit leidt tot de volgende aanbevelingen:

1. Meer onderzoek is nodig om te weten welke scores op de 0-10 numerieke beoordelingsschaal matig tot ernstige pijn weergeven.
2. Om de poliklinische pijnbehandeling te verbeteren, moet een geïntegreerd systeem geïmplementeerd worden, betreffende systematische pijnmeting; een oncologisch pijnprotocol, inclusief richtlijnen voor verwijzing naar een pijnspecialist en verwijzing naar een pijnverpleegkundige voor 'op maat' voorlichting hoe met pijn en pijnmedicatie om te gaan.
3. In de palliatieve zorg zou meer prioriteit gegeven moeten worden om onderzoek naar farmacodynamische en farmacokinetische mechanismen van de WHO analgetica te stimuleren; bovendien is onderzoek naar nieuwe therapieën nodig.

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APPENDIX

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APPENDIX

Publications

Oldenmenger WH, Sillevis Smitt PAE, Van Montfort CAGM, De Raaf PJ, Van der Rijt CCD. A combined pain consult and pain education program decreases average and current pain and decreases interference in daily life by pain in oncology outpatients: A randomized controlled trial. Pain. 2011. 152:2632-2639.

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APPENDIX

PhD Portfolio Summary

Summary of PhD training and teaching activities

Name PhD student: WH Oldenmenger
Erasmus MC Department: Medical Oncology
Research School: MolMed

PhD period: 2005 - 2012
Promotor(s): Prof. dr. CCD van der Rijt
Supervisor: Prof. dr. CCD van der Rijt

1. PhD training

	Year	Workload (ECTS)
General academic skills		
- Biomedical English Writing and Communication	2002	4.0 ECTS
- Academic Writing in English of PhD students	2007	1.0 ECTS
- NWO Talentendagen	2007	0.2 ECTS
- NWO Talentendagen	2009	0.2 ECTS
Research skills		
- Classical Methods for Data-analysis. Nihes. Erasmus MC.	2004	5.0 ECTS
- Basiscursus regelgeving en organisatie voor klinisch onderzoekers (BROK)	2010	1.0 ECTS
In-depth courses (e.g. Research school, Medical Training)		
- Methodologie van patiëntgebonden onderzoek en voorbereiding van subsidieaanvragen. CPO Erasmus MC.	2009	0.2 ECTS
- Short Introduction Course on Statistics & Survival Analysis for MD's	2010	0.4 ECTS
Oral Presentations		
- 16th ECCO/ ESMO congress	2011	1.0 ECTS
- Nursing Research Network, Erasmus MC	2011	1.0 ECTS
- IKNL, locatie Rotterdam	2011	0.4 ECTS
- Scientific Meeting Dept. of Medical Oncology Erasmus MC	2010	1.0 ECTS
- 6th EAPC research congress	2010	1.0 ECTS
- Nationaal Congres Palliatieve Zorg	2009	2.0 ECTS
- Agora meeting	2008	1.0 ECTS
- Oncologiedagen	2007	1.0 ECTS
- Oncologiedagen	2007	1.0 ECTS
- Agora meeting	2007	1.0 ECTS
- Bijscholing verpleeghuisartsen	2007	1.0 ECTS
- Symposium Wondpijn	2006	1.0 ECTS
- Symposium Kenniscentrum Palliatieve Zorg Rotterdam	2006	1.0 ECTS
Poster Presentations		
- 12th EAPC congress	2011	1.0 ECTS
- Oncologiedagen	2009	1.0 ECTS
- 11th EAPC congress	2009	1.0 ECTS
- 12th World Congress on Pain	2008	1.0 ECTS
- 10th EAPC congress	2007	1.0 ECTS
- 9th EAPC congress (April 2005, Aachen, Germany)	2005	1.0 ECTS
- Congres Vereniging van Oncologie Verpleegkundigen	2004	1.0 ECTS

International conferences

- 16th ECCO/ ESMO congress (2011, Stockholm, Sweden)	2011	0.5 ECTS
- 12th EAPC Congress (2011, Lisbon, Portugal)	2011	0.5 ECTS
- 6th EAPC Research Congress (2010, Glasgow, United Kingdom)	2010	0.2 ECTS
- 7th EONS Spring Convention (2010, Den Haag)	2010	0.2 ECTS
- 11th EAPC Congress (2009, Vienna, Austria)	2009	0.5 ECTS
- 12th World Congress on Pain (2008, Glasgow, United Kingdom)	2008	1.0 ECTS
- 10th EAPC Congress (2007, Budapest, Hungary)	2007	0.5 ECTS
- 9th EAPC Congress (2005, Aachen, Germany)	2005	0.5 ECTS

Seminars and workshops

- Autumn Symposium: Quality of Life. Consultatiecentrum voor Patiëntgebonden onderzoek, Erasmus MC.	2008	0.2 ECTS
- Symposium Pijn, IKR werkgroep Pijn (November 2008 Ridderkerk)	2008	0.1 ECTS
- Enursing course. Pijn bij kanker.	2007	1.0 ECTS
- 5e Onderzoeksforum Palliatieve Zorg NL-VL. (November 2007, Antwerpen, België)	2007	0.2 ECTS
- Evidence-based Richtlijnontwikkeling (EBRO)	2006	0.2 ECTS

Other

- Nationaal Congres Palliatieve Zorg	2010	0.5 ECTS
- Nationaal Congres Palliatieve Zorg	2008	0.5 ECTS
- Verpleegkundig congres "tijd voor palliatieve zorg"	2008	0.3 ECTS
- 3th Nationaal pijncongres	2008	0.3 ECTS
- 26th V&VN Oncologie congres	2007	0.5 ECTS
- 25th V&VN Oncologie congres	2006	0.5 ECTS
- Nationaal Congres Palliatieve Zorg (	2006	0.5 ECTS
- Wondpijn congres	2006	0.3 ECTS

2. Teaching activities

	Year	Workload (ECTS)
Lecturing		
- Specialistische verpleegkundige vervolgopleiding hemato-oncologie. Pijn. Rotterdam.	2005-2011	3.0 ECTS
- Specialistische verpleegkundige vervolgopleiding decubitus en wondverpleging. Pijn. Rotterdam.	2006-2008	0.6 ECTS
- Specialistische verpleegkundige vervolgopleiding mam-macare. Pijn. Rotterdam.	2005-2006	0.4 ECTS
- Specialistische verpleegkundige vervolgopleiding oncologie. Pijn. Rotterdam.	2005-2008	1.0 ECTS
- Specialistische verpleegkundige vervolgopleiding oncologie. Pijn. IKW Leiden.	2005-2006	0.5 ECTS

Supervising Master's theses

- PJ de Raaf	2008	1.0 ECTS
- L Voets	2009	3.0 ECTS

APPENDIX

Curriculum vitae

Wendy Oldenmenger werd geboren op 11 september 1974 te Deventer. In 1993 behaalde zij haar VWO-diploma aan het Geert Groote College te Deventer. In datzelfde jaar startte zij met de studie HBO-Verpleegkunde aan de Rijkshogeschool IJsselland te Deventer, waar zij in 1997 afstudeerde. Vervolgens studeerde ze van 1997 tot 1999 Gezondheidswetenschappen aan de Universiteit van Maastricht te Maastricht met als afstudeerrichting Verplegingswetenschap.

Aansluitend werkte zij van 1999 – 2004 als research verpleegkundige pijn bij de afdeling neuro-oncologie in het Erasmus MC – Daniel den Hoed, gecombineerd met een baan als onderzoeker bij het Pijnkenniscentrum van het Erasmus MC te Rotterdam. Hier werd haar interesse in pijn bij patiënten met kanker ontwikkeld. In 2004 kreeg zij de kans om een onderzoek op te zetten om de pijnbehandeling voor patiënten met kanker op de polikliniek te verbeteren. Vanaf 2004 kreeg zij voor dit promotieonderzoek, zoals beschreven in dit proefschrift, een aanstelling bij de afdeling interne oncologie van het Erasmus MC. Momenteel werkt zij, naast haar onderzoekstaken, als projectcoördinator voor het innovatieproject: 'Detectie en behandeling van pijn bij kanker' en als coördinator van het Kenniscentrum Palliatieve Zorg Rotterdam bij de afdeling interne oncologie.

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