Pain Physician 2013; 16:379-389 • ISSN 1533-3159

Multi-Center Study

Pain and Its Interference with Daily Activities in Medical Oncology Outpatients

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Disclaimer: This study was funded by KWF (Dutch Cancer Society) and 'Bergh in het Zadel' (Private funding Association). .
Conflict of interest: None.

Manuscript received:03-06-2013
Revised manuscript received: 04-04-2013
Accepted for publication: 04-30-2013

Free full manuscript: www.painphysicianjournal.com

Background: Pain prevalence at various stages of cancer ranges from 27% to 60% for outpatients. Yet, how pain is managed in this patient group is poorly understood.

Objectives: The primary objective was to assess pain prevalence and intensity, and its interference with daily activities, in medical oncology outpatients. The secondary objectives were the adequacy of analgesic pain treatment and to identify independent predictors for moderate to severe pain.

Study design: A cross-sectional study.

Setting: Oncology outpatient clinics of 7 Dutch regional hospitals.

Methods: Four hundred twenty-eight medical oncology outpatients were assigned to the study. Pain prevalence and interference of pain with daily activities were assessed using the Brief Pain Inventory. Adequacy of analgesic treatment was determined by calculating the Pain Management Index (PMI). Descriptive statistics, non-parametric tests, and logistic regression analysis were conducted.

Results: More than one third of all participants reported pain (39%). Eighty-three patients (20%) had moderate to severe pain (NRS 5-10). Analgesic treatment was inadequate in more than half of the patients with pain (62%). Interference of pain with daily activities increased with increased intensity, yet even 10%-33% of patients suffering mild pain reported high interference with daily activities. High current pain intensity and high interference with general daily activities predicted moderate to severe pain.

Limitations: No characteristics of nonparticipants were available.

Conclusion: Pain remains a significant problem in medical oncology outpatients, and often pain is insufficiently managed.

Patients with a high pain intensity were more at risk to experience pain related interference with daily activities, but even some patients suffering mild pain experienced this. As adequate pain relief for up to 86% of the patients with cancer should be feasible, pain in medical oncology outpatients is still undertreated. Taking into account the interference of pain with daily activities and predictors of pain will facilitate cancer pain management.

The study has been approved by the Medical Ethics Committee (CMO) in all 7 hospitals (METC protocol number 2011/020) and has been registered by the Dutch Trial register (NTR): NTR2739.

Key words: Pain, prevalence, cancer, interference with daily activities, pain management, Brief Pain Inventory, Pain Management Index, neuropathic pain

Pain Physician 2013; 16:379-389

Pain is one of the most prevalent symptoms in patients with cancer (1) and appears to interfere with daily activities in patients with advanced cancer (2). In patients with cancer visiting outpatient clinics, pain prevalence ranged from 27% (3) to 60% (4). Additionally, 19% to 39% of patients with cancer suffered from neuropathic pain caused by the tumor, the operation, or the treatment (5). Adequate pain relief in 71% (6) to 86% (7) of cancer pain is considered feasible. As inadequate pain treatment ranged from 31% (8) to 65% (3) in patients with cancer, pain is still undertreated.

Undertreatment is the result of different patient and care provider related barriers. A key patient related barrier in pain management is the reluctance of many patients to discuss pain with their doctor or to ask for pain medication (9). This hesitation has a variety of reasons, such as concerns about addiction and fear that reporting pain will distract the physician from the treatment of their cancer (9). Care providers also experience barriers in cancer pain diagnosis. These include ineffective pain communication with patients (10) and inadequate pain assessment (11). This underassessment and undertreatment of cancer pain influences the quality of life of these patients.

Moreover, cancer pain is associated with anxiety, depression, and sleep disturbances (12-14). It hampers daily activities (15), which also affects the quality of life. Putting it in day-to-day terms: If you are unable to work because you experience severe pain when moving your arm, this obviously reduces the quality of your life.

Pain related interference with daily activities has been well studied (16-19). However, pain management patterns are poorly understood in medical oncology outpatients. To get more insight in these patterns, our study explored pain prevalence and intensity, analgesic pain treatment, neuropathic pain components, breakthrough pain, pain related interference with daily activities, and predictors of pain in outpatients with cancer.

The primary objective was to assess pain prevalence and intensity, and its interference with daily activities in medical oncology outpatients. The secondary objectives were the adequacy of analgesic pain treatment and to identify independent predictors for moderate to severe pain.

Methods

Patients and Procedures

A cross-sectional survey study was performed. Patients with cancer visiting the medical oncology outpatient clinic of one of 7 Dutch regional hospitals were invited to participate.

Patients were eligible to participate if they had been diagnosed with cancer and were 18 years or older. Exclusion criteria were severe cognitive dysfunction or inability to understand or read the Dutch language. In each hospital, in both 2011 and 2012, over a period of 5 consecutive working days, all patients visiting the medical oncology outpatient clinic were asked to participate.

Data Collection

Patients were asked to complete the questionnaire during their stay at the outpatient clinic. A medical student helped them to fill in the questionnaire. The questionnaire consisted of the Brief Pain Inventory (BPI), Douleur Neuropathic 4 (DN4) interview, a question about breakthrough pain, intake of medication in the last 24 hours, demographics, and medical data. Of those patients that took part in 2012, additional information was extracted from their medical records after they had provided their informed consent.

BPI

The BPI was used to assess pain prevalence and interference with daily activities (21). This BPI is linguistically validated in many languages (21), including Dutch. The BPI consists of 7 questions with 15 items and an 11-point Numeric Rating Scale (NRS) of 0 (no pain) to 10 (worst pain imaginable), in which patients are asked to rate their mean pain over the last 24 hours. Additionally, the BPI was used to ask for interference of pain with daily activities over the last 24 hours (mood, walking ability, normal work [including household], relationships, sleep, and enjoyment of life).

Pain Management Index (PMI)

To determine the adequacy of analgesic pain treatment, Cleeland et al's (22) and Ward et al's Pain Management Indexes (PMI) (9) were used. The PMI, based on the WHO pain ladder (23), is the most frequently used measure for adequate pain treatment and is useful for evaluating the Quality of analgesic care). Ward et al's PMI was calculated for participants when prescribed analgesics were not described in the medical record (9,24). Pain treatment is considered adequate if there is a congruence between the patient's reported level of worst pain and the prescribed analgesics (25). Cleeland et al's PMI compares the most potent analgesic prescribed with the patient's reported worst pain on the BPI (22). Ward et al's PMI compares the most potent

analgesic drug therapy actually used by the patient with his worst pain (1,9).

In both variations of the PMI, the levels of analgesic drug therapy are scored as 0, no analgesic; 1, a non-opioid analgesic; 2, a weak opioid analgesic; and 3, a strong opioid analgesic. Absence of pain is defined as 0, mild pain as 1, moderate pain as 2, and severe pain as 3 (9,22). The PMI can be determined by subtracting the pain level from the analgesic level. The outcome ranges from -3 (a patient with severe pain receiving no analgesic drug) to +3 (a patient with no pain receiving a strong opioid or equivalent). Negative scores indicate inadequate pain treatment, whereas scores of 0 or higher represent adequate pain treatment (9,22).

DN4

Neuropathic pain (NP) was, as accepted by the International Association for the Study of Pain (IASP), defined as "pain arising as a direct consequence of a lesion or disease affecting the somatosensory system" (26,27). We identified NP components by using the 7-item DN4-interview (28). The complete DN4 has been validated in Dutch (29). The DN4-interview tests the presence of NP components and includes pain descriptors namely burning, painful cold, electric shocks and associated abnormal sensations, tingling, pins and needles, numbness, and itching. Each positive answer is assigned a score of one. If at least 3 answers out of 7 are positive, pain includes neuropathic components and this might be an indication that neuropathic pain is present.

Additional Data from Medical Records

Of those patients participating in 2012, additional data were retrieved from their medical records, namely disease characteristics, prescribed analgesics, and treatment intention.

Statistical Analysis

Descriptive statistics were conducted with SPSS version 2.0. Outcome variables were pain prevalence, pain intensity, and interference of pain with daily activities. Worst, least, average, and current pain levels were obtained. A numeric rating scale (NRS) from one to 4 was categorized as mild, 5 to 6 as moderate, and 7 to 10 as severe pain (30). This categorization was used because the present study was based on the principles of the Dutch clinical practice guideline (CPG) on cancer pain, being one of the most recent and best CPGs in Europe (30,31).

Disease groups were categorized as 1a: patients treated with curative intention more than 6 months ago; 1b: patients treated with curative intention less than 6 months ago; 2: patients with palliative anti-cancer treatment; 3: patients for whom anti-cancer treatment was not or no longer feasible and patients with palliative treatment more than 6 months ago (1). Differences in proportions were tested with Chi-squared test or Fisher's exact test. Reported *P*-values are 2-tailed and considered significant at the $P < 0.05$ level. Kruskal-Wallis tests were conducted to compare median pain scores and median pain related interference with daily activities scores.

Additionally, multiple regression analyses were conducted to determine the extent to which pain intensity rating (least, worst, average, and current) was related to interference of pain with daily activities once other ratings were controlled. Mean interference of the 6 daily activities was the dependent variable and each pain intensity rating (least, worst, average, and current) was added as a predictor of interference in the second step of the regression after the other 3 were entered in the first step (32).

Finally, univariable and multivariable logistic regression analysis were conducted with the presence of moderate to severe pain (yes/no) as a dependent variable. The following independent variables were examined: age, gender, education, cancer type and disease group, current pain, metastasis, more than 5 years after diagnosis (yes/no), and interference with daily activities. Criterion to add a variable into the multivariable logistic regression analysis was $P < 0.10$. Moreover, sub-analysis was conducted for gender as gender might be a potential confounder for the effect of tumor type on the prevalence of moderate to severe pain. All values given are worst pain values, unless otherwise stated. Pain intensity values are given as median with the inter quartile range (IQR).

Results

Of 629 invited patients, 428 (68%) completed the questionnaire. Median age of the participants was 67 (range: 58-74). For characteristics of patients see Table 1. Nonparticipants were patients who had no time to participate because of another appointment, being too ill or tired to participate, or patients who said that this would be too confrontational.

Pain Prevalence

One hundred and sixty-seven patients (39%) reported pain in the last 24 hours and 36 (8%) experienced breakthrough pain. Table 1 shows that pain prevalence appeared higher in patients with metastates than in patients without ($P = 0.022$). A subgroup of 231 patients

Table 1. *Demographic characteristics of patients (N = 428) N (%).*

Characteristics	All (N = 428) N	With pain (N = 167) N (%)	Without pain (N = 261) N (%)
Gender			
Men	177	64 (36.2)	113 (63.8)
Women	251	103 (41.0)	148 (59.0)
Age groups in years			
< 45	21	9 (43.0)	12 (57.1)
45-60	97	45 (46.4)	52 (53.6)
60-75	216	81 (37.5)	135 (62.5)
≥ 75	93	31 (33.3)	62 (66.7)
Unknown	1	1 (100)	0 (0.0)
Education level			
Secondary school or less	117	41 (35.0)	76 (65.0)
Lower vocational education	97	37 (38.1)	60 (61.9)
Middle vocational education	128	52 (40.6)	76 (59.3)
Higher vocational education or higher	84	36 (43.0)	48 (57.1)
Unknown	2	1 (50.0)	1 (50.0)
Primary cancer type			
Gastrointestinal	123	47 (38.2)	76 (61.8)
Urogenital	59	25 (42.4)	34 (57.6)
Breast	153	68 (44.4)	85 (55.6)
Lymphatic-hematological	67	18 (26.9)	49 (73.1)
Other (lung, skin, glands, bone)	21	7 (33.3)	14 (66.7)
Unknown	5	2 (40.0)	3 (60.0)
Presence of metastatis [a]			
Yes	222	98 (44.1)	124 (55.9)
No	203	67 (33.0)	136 (67.0)
Unknown	3	2 (66.7)	1 (33.3)
Period with cancer in years			
≤ 1	184	70 (38.0)	114 (62.0)
2 - 5	124	46 (37.1)	78 (62.9)
≥5	118	51 (43.2)	65 (55.1)
Unknown	2	0 (0.0)	2 (100)
Disease group[b]			
1a	11	2 (18.2)	9 (81.8)
1b	58	26 (44.8)	32 (55.2)
2	93	46 (49.5)	47 (50.1)
3	18	7 (39.0)	11 (61.1)
Unknown[c]	197	65 (38.9)	132(50.6)

aChi-square test or Fisher's exact test significant at P < 0.05 (2-sided); b Adapted from van den Beuken et al 2007 (1): disease group 1a, patients who had been treated with curative intent, last treatment more than 6 months ago; 1b patients receiving anti-cancer treatment with curative intention or last treatment less than 6 months ago; 2, patients who were receiving palliative anti-cancer treatment; 3, patients for whom anti-cancer treatment was not or no longer feasible and patients with palliative treatment more than 6 months ago. c Obtained from medical records, these data were only available for a subgroup of 231 participants.

completed the DN4-interview. Fifty-three of them (23%) scored at least 3 NP components.

Pain Intensity

Pain intensity was obtained for worst, least, average, and current pain. Forty-three patients out of 167 patients in pain (26%) rated their worst pain as moderate and 40 patients (24%) as severe. This means that 83 patients out of all 428 patients (20%) had moderate to severe pain. Patients experienced a median worst pain of 4.0 (IQR 2.0-6.0), least pain of 2.0 (IQR 0.0-4.0), average pain of 4.0 (IQR 2.0-5.0), and current pain of 2.0 (IQR 1.0-5.0).

Table 2 shows median pain intensities in relation to demographics of patients with pain. Median pain

Table 2. Median and IQR of pain intensity (NRS) in the last 24 hours for different demographic characteristics of patients with pain (N = 167).

Characteristics	N	Worst pain *	Least pain *	Average pain *	Current pain *
Gender		***P* = 0.015**	***P* = 0.119**	***P* = 0.006**	***P* = 0.005**
Men	64	*3.5 (2.0-6.0)*	*1.5 (0.0-3.0)*	*3.0 (2.0-4.8)*	*2.0 (1.0-3.0)*
Women	103	*5.0 (3.0-7.0)*	*2.0 (0.0-5.0)*	*4.0 (2.8-6.0)*	*3.0 (1.0-6.0)*
Age groups (years)		***P* = 0.324**	***P* = 0.988**	***P* = 0.876**	***P* = 0.776**
< 45	*9*	*3.0 (2.5-5.0)*	*2.0 (0.0-4.0)*	*4.0 (2.0-6.0)*	*2.0 (1.0-3.5)*
45-60	*44*	*4.0 (3.0-6.0)*	*2.0 (1.0-3.0)*	*4.0 (2.0-5.0)*	*3.0 (1.0-5.0)*
60-75	*81*	*4.0 (2.0-6.0)*	*2.0 (0.0-4.0)*	*3.0 (2.0-5.0)*	*2.0 (0.5-5.0)*
≥ 75	*31*	*5.0 (3.0-7.0)*	*2.0 (0.0-4.0)*	*4.0 (2.0-5.0)*	*2.0 (1.0-6.0)*
Education level		***P* = 0.341**	***P* = 0.259**	***P* = 0.511**	***P* = 0.553**
Secondary school or less	*41*	*5.0 (2.0-7.0)*	*2.0 (1.0-5.0)*	*4.0 (2.0-6.0)*	5.0 *(1.0-6.0)*
Lower vocational education	*37*	*4.0 (3.0-7.0)*	*2.0 (1.0-4.0)*	*3.0 (2.0-5.0)*	3.0 *(1.0-5.0)*
Middle vocational education	*51*	*4.0 (2.0-5.8)*	*1.5 (0.0-3.8)*	*3.0 (2.0-5.0)*	2.0 *(1.0-4.8)*
Higher vocational education or higher	*36*	*5.0 (3.0-6.0)*	*1.5 (0.0-3.0)*	*4.0 (2.0-5.8)*	2.0 *(1.0-6.0)*
Primary cancer type		***P* = 0.835**	***P* = 0.333**	***P* = 0.654**	***P* = 0.711**
Gastrointestinal	47	5.0 *(2.0-7.0)*	2.0 *(0.0-4.0)*	3.0 *(2.0-5.0)*	2.0 *(1.0-5.0)*
Urogenital	24	4.0 *(2.0-5.0)*	1.0 *(0.0-3.0)*	3.5 *(2.0-5.0)*	2.0 *(0.0-5.0)*
Breast	68	5.0 *(3.0-6.8)*	2.0 *(0.0-5.0)*	4.0 *(2.0-6.0)*	3.0 *(1.0-6.0)*
Lymphatic-hematological	18	4.0 *(2.8-6.0)*	2.0 *(0.8-4.0)*	3.5 *(2.0-6.0)*	3.0 *(1.0-6.0)*
Other (lung, skin, glands, bone)	7	3.0 *(3.0-6.0)*	2.0 *(1.0-3.0)*	3.0 *(3.0-4.0)*	3.0 *(1.0-3.0)*
Presence of metastatis		***P* = 0.491**	***P* = 0.824**	***P* = 0.552**	***P* = 0.781**
Yes	98	5.0 *(0.0-4.3)*	2.0 *(2.0-5.0)*	4.0 *(1.0-5.0)*	2.0 *(1.6-5.0)*
No	67	4.0 *(3.0-6.0)*	2.0 *(0.0-3.0)*	4.0 *(2.0-5.0)*	3.0 *(1.0-5.0)*
Period with cancer (years)		***P* = 0.419**	***P* = 0.976**	***P* = 0.468**	***P* = 0.805**
≤ 1	70	4.0 *(2.0-6.0)*	2.0 *(0.0-4.0)*	3.0 *(2.0-5.0)*	2.0 *(1.0-5.0)*
2 – 5	47	4.0 *(3.0-6.0)*	2.0 *(0.0-3.0)*	4.0 *(3.0-5.0)*	3.0 *(1.0-5.0)*
≥5	49	5.0 *(2.0-7.0)*	2.0 *(0.0-4.3)*	4.0 *(2.0-6.0)*	2.5 *(0.8-6.0)*
Disease group[a]		***P* = 0.022**	***P* = 0.318**	***P* = 0.313**	***P* = 0.355**
1a	2	5.0 (4.0-6.0)	1.0 (0.0-2.0)	4.5 (3.0-6.0)	3.0 (0.0-6.0)
1b	26	3.0 (2.0-5.3)	1.5 (0.0-4.3)	3.0 (2.0-5.0)	1.5 (1.0-5.0)
2	46	3.5 (2.0-5.0)	1.0 (0.0-2.3)	3.0 (2.0-5.0)	2.0 (0.0-3.3)
3	7	7.0 (5.0-9.0)	3.0 (2.0-4.0)	4.0 (3.0-7.0)	3.0 (2.0-7.0)

Abbreviations: P = P-value, IQR= Inter Quartile Range, NRS= Numeric rating Scale. Note: The red values are reaching significance with Kruskal-Wallis tests at P < 0.05 (2-sided); a Adapted from van den Beuken et al 2007 (1): disease group 1a, patients who had been treated with curative intent, last treatment more than 6 months ago; 1b patients receiving anti-cancer treatment with curative intention or last treatment less than 6 months ago; 2, patients who were receiving palliative anti-cancer treatment; 3, patients for whom anti-cancer treatment was not or no longer feasible and patients with palliative treatment more than 6 months ago: Obtained from medical records, these data were only available for a subgroup of 231 participants.* = in last 24 hours)

intensity was higher in women than in men for worst, average, and current pain (P = 0.015; P = 0.006; P = 0.005). Additionally, Table 2 shows that median worst pain intensity was higher in disease group 3 than in the other disease groups (= 0.003) (n = 7).

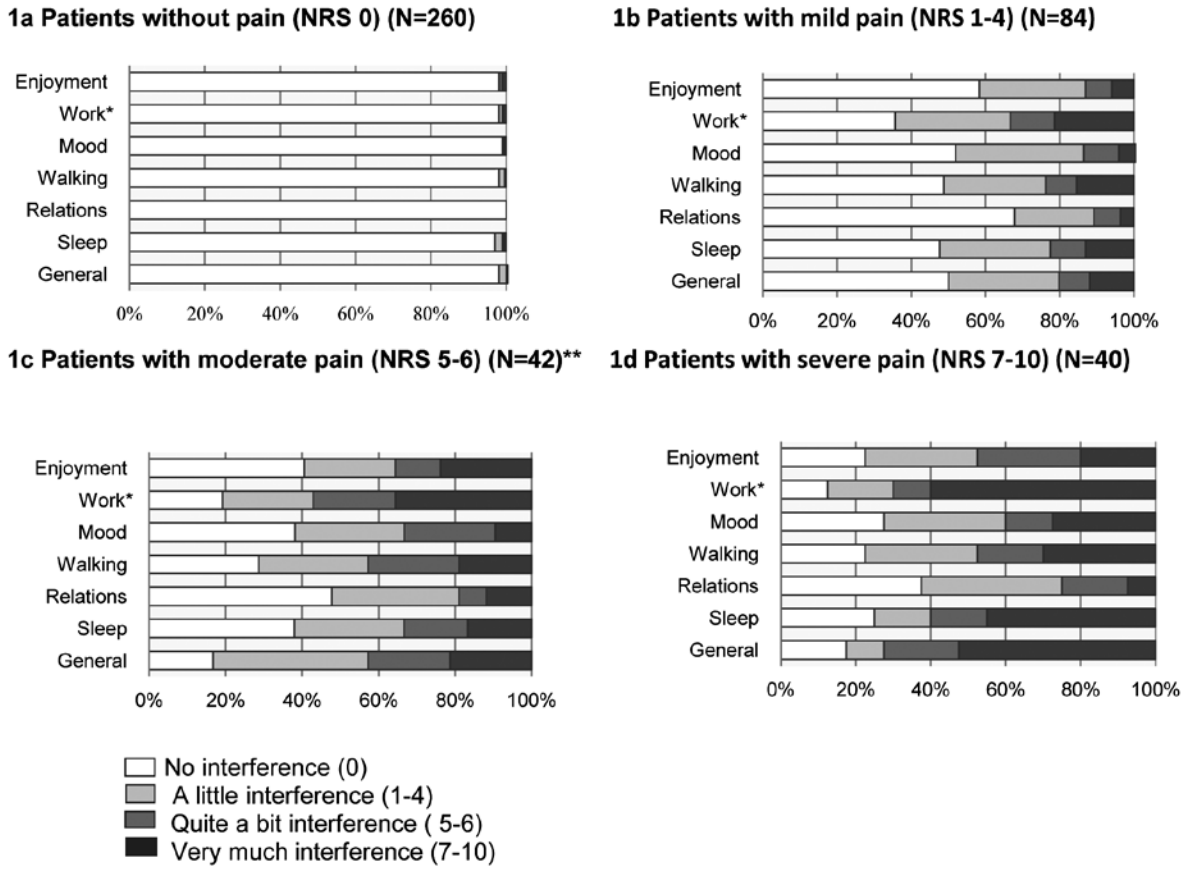
Patients with metastasis had an increased risk for pain (= 0.025), but did not have an increased risk for higher pain intensity than patients without metastasis. Finally, there were no significant differences in mean scores per pain intensity category between different tumor types and presence of metastasis.

Pain Related Interference with Daily Activities

Fig. 1 shows interference with daily activities per pain intensity category. One patient did not respond to the questions on interference with daily activities and therefore was excluded from this part of the analysis (n = 166 patients with pain). One hundred and forty-eight out of 166 patients with pain (89%) experienced interference of pain with one or more daily activities. The overall median interference of pain with daily activities of patients with pain was 2.6 (IQR 0.8-5.0). Five percent of patients without pain reported interference with daily activities (Fig. 1a).

Patients who rated their worst pain in the last 24 hours as mild (n = 84) had an overall median interference of pain with daily activities of 1.1 (IQR 0.2-3.3). This figure is 3.1 (IQR 2.0-4.9) for patients with moderate pain (n = 42) and 4.9 (IQR 2.7-5.8) for patients with severe pain (n = 40) (P < 0.0001).

However, prevalence of interference with daily activities ≥ 5 in patients with mild pain ranged from 8 out of 84 (10%) to 27 out of 84 (33%) over the various activities. Even up to 8 out of 42 patients (19%) with



Note: Pain intensity categories used were adapted from the Dutch guideline: Pain in patients with cancer (28).
*Includes households. ** Data was missing on one patient (Patient was excluded from figures). NRS = Numeric Rating Scale

Fig. 1. *Pain related interference with daily activities of patients with cancer by pain intensity category (%)*

a pain intensity of NRS 1-2 reported interference with daily activities ≥ 5 for work (including household). Most often pain negatively interfered with work/household and general activity.

Fig. 1 also shows that median interference with daily activities was higher in patients with moderate pain than in those with mild pain for all activities ($P < 0.05$) except for sleep ($P = 0.125$). Severe pain interfered significantly more than moderate pain with sleep and general activity. Severe pain interfered significantly more with each daily activity than mild pain ($P < 0.05$).

Additionally, Fig. 1 shows higher interference with daily activities in patients with high pain intensity. Negative interference with enjoyment, work, mood, sleep, and general activities with an NRS 7-10 was more common regarding severe pain than regarding mild and moderate pain.

Worst pain contributed most to interference with daily activities (R2 = 0.014; F change 16.15; $P = 0.00$). Worst pain contributed more to interference with daily activities than current pain (R2 = 0.008; F change 9.37; $P = 0.002$).

Evaluation of Analgesic Pain Treatment

Analgesic pain treatment in relation to pain severity is summarized in Fig. 2. Strong opioids were used by one out of 8 patients with mild pain and moderate pain, whereas in patients with severe pain one out of 3 used strong opioids. Of patients with moderate to severe pain 28.6% were not treated with analgesics and 42.9% were treated with a non-opioid.

Due to unclear recording of prescribed analgesics, data of 22 patients could not be included in calculating Cleeland et al's PMI. For these patients Ward et al's PMI was calculated. One hundred and three out of 167 patients in pain (62%) were inadequately treated according to the PMI. Patient characteristics did not influence adequacy of analgesic treatment. However, breast cancer patients with pain were more often inadequately treated than patients with other tumor types (P = 0.001). Forty-seven percent of patients who scored at least 3 neuropathic pain components were inadequately treated for their pain compared to 20% of patients who scored less than 3 neuropathic pain components ($P = 0.00$).

Logistic Regression

Gender, having a lymphatic-hematological tumor, presence of metastasis, current pain, and interference with daily activities were related to moderate to severe

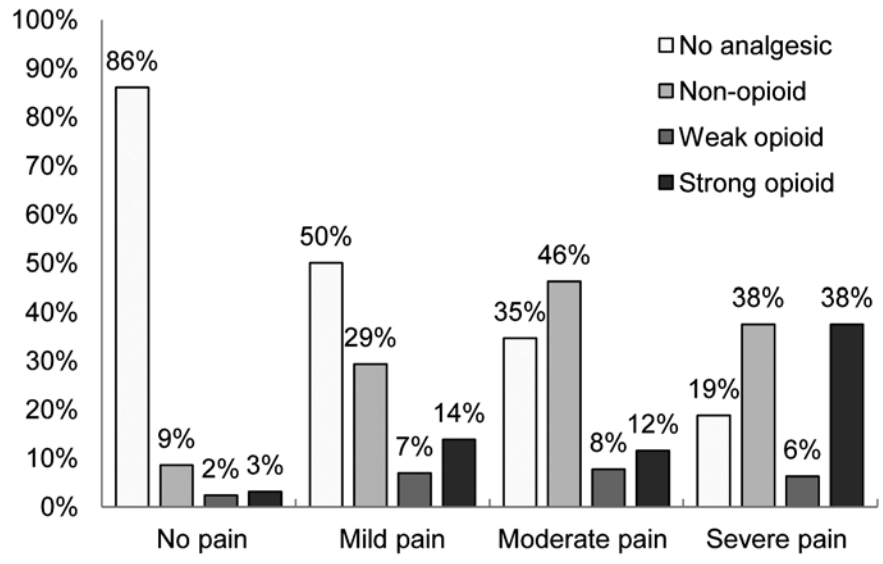


Fig. 2. *Analgesic pain treatment in relation to pain severity.*
Note: Analgesic pain treatment categories adapted from WHO categories

pain, whereas education level, tumor type, more than 5 years since diagnosed with cancer, and disease group were not (Table 3). Multiple regression analysis revealed that current pain (OR 2.96, confidence interval [95% CI] 2.28-3.85), interference with daily activities for general activity (OR 1.14, CI 1.14-1.52), and having a lymphatic-hematological tumor (OR 0.11, CI 0.02-0.54) were independently related to moderate to severe pain.

Multiple regression analysis for men revealed that current pain (OR 3.3, CI 2.19-4.96) and interference with

Table 3. Odds ratios and 95% CI of the probability of moderate to severe pain (NRS 5 - 10) in patients with cancer: univariable and multivariable logistic regression

Characteristics	N	Univariable regression Odds ratio (95% CI)	Adjusted Odds ratio (95% CI)[b]
Gender			
Men	177	1.00 (reference)	–
Women	251	1.79 (1.07 – 2.99) [a]	Not in model
Age (years)	427	1.00 (0.98 – 1.03)	–
Education level			
Secondary school or less	177	1.00 (reference)	–
Lower vocational education	97	0.87 (0.48 – 1.57)	–
Middle vocational education	128	0.60 (0.34 – 1.07)	–
Higher vocational education or higher	84	1.42 (0.80 – 2.52)	–
Primary cancer type			
Gastrointestinal	123	0.84 (0.48 – 1.47)	–
Urogenital	59	0.91 (0.44 – 1.90)	–
Breast	153	1.00 (reference)	–
Lymphatic – hematological	67	0.37 (0.15 – 0.89)[a]	0.11 (0.02 – 0.54)[a]
Other (lung, skin, glands, bone)	21	0.43 (0.10 – 1.89)	–
Presence of metastatis	425	1.76 (1.07 – 2.90)[a]	Not in model
More than 5 years diagnosed with cancer	426	1.39 (0.82 – 2.33)	–
Disease group[c]			
1a	11	0.41(0.05 – 3.33)	–
1b	58	0.71(0.31 – 1.64)	–
2	93	1.00 (reference)	–
3	18	2.39 (0.83 – 6.92)	–
Current pain	428	3.26 (2.57 – 4.13)[a]	2.96 (2.28 – 3.85)a
Daily activity interference[d]			
Enjoyment	427	1.64 (1.47 – 1.83)[a]	Not in model
Work (includes household)	427	1.53 (1.41 – 1.67)[a]	Not in model
Mood	427	1.70 (1.50 – 1.90)[a]	Not in model
Walking	427	1.58 (1.43 – 1.74)[a]	Not in model
Relations	427	1.79 (1.54 – 2.10)[a]	Not in model
Sleep	427	1.53 (1.39 – 1.70)[a]	Not in model
General	427	1.70 (1.53 – 1.90)[a]	1.14 (1.14 – 1.52)[a]

Abbreviations: NRS = Numeric rating Scale, 95% CI = 95% confidence interval. a P-value was considered significant at P ≤ 0.10.b Selection procedure was used: variables not selected in stepwise univariable regression analysis were not included in the multivariate model. Criterion to add a variable was P ≤ 0.10. c Adapted from van den Beuken et al 2007 (1): disease group 1a, patients who had been treated with curative intent, last treatment more than 6 months ago; 1b patients receiving anti-cancer treatment with curative intention or last treatment less than 6 months ago; 2, patients who were receiving palliative anti-cancer treatment; 3, patients for whom anti-cancer treatment was not or no longer feasible and patients with palliative treatment more than 6 months ago: Obtained from medical records, these data were only available for a subgroup of 231 participants.d Data of one patients was missing.

sleep (OR 1.43, CI 1.14-1.80) were related to moderate to severe pain. Multiple regression analysis for women revealed that current pain (OR 3.2, CI 2.40-4.34) and interference with general daily activities (OR 1.43, CI 1.14-1.80) were related to moderate to severe pain.

Discussion

The present study shows that more than one third of all participants, i.e., patients with cancer visiting a medical oncology outpatient clinic, reported pain. Half of those in pain had inadequate analgesic treatment. Additionally, high pain intensity strongly interfered with daily activities and even 10%-33% of patients with mild pain, which pain level is not usually treated with opioids, experienced moderate to severe interference with daily activities. High current pain intensity and high interference with general daily activities were related to moderate to severe pain.

Subsequently, pain prevalence appeared higher in patients with metastasis than without and breast cancer patients with pain were more often inadequately treated than patients with other tumor types. Positive predictors for moderate to severe worst pain in the last 24 hours were current pain and interference with general daily activity while having a lymphatic-hematological tumor was a negative predictor.

Earlier studies in Europe found pain prevalence at various stages of cancer from 27% (3) to 60% (4) for patients with cancer visiting outpatient clinics. Inadequate pain treatment ranged from 31% (8) to 65% (3) in patients with cancer. The prevalence rates in the present study fall within the range found in previous studies. As adequate pain relief for up to 86% of patients with cancer is considered feasible, pain in patients with cancer is still undertreated (7).

In previous studies, prevalence rates of NP in patients with severe cancer pain ranged from 34% to 40% (5). In our study, in which patients without pain also participated, the NP prevalence rate was less. Additionally, our study shows that patients who scored at least 3 NP components were more often inadequately treated for their pain than patients without or with lower NP components (P = 0.00). As NP is generally treated with opioids and adjuvants and is relatively opioid resistant, this might have an impact on the PMI.

However, pain prevalence and pain intensity alone are not enough to illustrate the problem of cancer pain. Interference of pain with daily activities should also be taken into account. Although pain related interference with daily activities has been well studied (16-19), pain management patterns are poorly understood in medical oncology outpatients.

A recent study by Fisch et al reported pain prevalence, pain management adequacy, and pain related interference with daily activities (32). They found the same prevalence of moderate to severe pain as in the present study. However, they did not report on interference with daily activities of mild pain, NP components, and breakthrough pain (32). To get more insight in pain management patterns, our study explored the combination. Our findings are in line with those of Vallerand et al (33). They studied 304 oncology outpatients who experienced cancer-related pain within the past 2 weeks. In their study pain intensity was positively correlated with perceived control over functional status (33).

Shi et al (34) have previously reported that recall of worst pain in the last week contributes the most to patient reports of pain interference with daily activities. Our data confirms these findings. This indicates that ratings of worst pain in the last 24 hours, rather than current pain, might improve insight in overall experience of pain and its impact on interference with daily activities in medical oncology outpatients (34). This might guide the choice of recall period for outpatients with cancer for future studies.

Previous literature stated that patients with a pain intensity < 5 are adequately treated and that mild pain intensity hardly interferes with daily activities (15,30). However, the present study shows that some patients with mild pain (NRS 1-4) and even some patients with an NRS of 1-2 do experience moderate to high interference with daily activities, as also described by Wu et al (35).

Although Serlin and colleagues (15) established cut-off points for pain intensity based on its interference with daily activities 18 years ago, there is still no consensus on how to categorize pain intensity. Often pain is categorized as mild pain (NRS 1-4), moderate pain (5-6), and severe pain (7-10) (15,30). As a complicating but important factor in this discussion on cut-off points, we suggest including interference with daily activities as an additional factor to determine, in combination with pain intensity, whether a patient with cancer and pain needs treatment.

Little is published on predictors of the prevalence of moderate to severe pain. In our study, women were more at risk for moderate to severe pain than men. Some studies confirm this finding (36), others do not (1). Additionally, in our study patients with metastasis were more at risk for moderate to severe pain, which

confirms a previous finding that patients with more advanced disease had higher pain intensities (20). None of the previous studies explored interference with daily activities and current pain as possible related variables for moderate to severe worst pain in the last 24 hours.

Unfortunately, we were not able to obtain characteristics from the 32% non-participants, as informed consent would have been needed to obtain information from medical records.

The present study was based on the recommendations in the Dutch CPG "Pain in Patients with Cancer" (30) which is one of the most recent cancer pain guidelines in Europe. In a comparative study of European CPGs on pain management in patients with cancer, this Dutch CPG appeared to have followed a good development process (31). So far, it is not known whether this CPG has already improved adequate pain treatment in the Netherlands (37). The present study contributes to awareness on pain prevalence, pain treatment adequacy, and interference of pain with daily activities. It is an essential step in improving cancer pain management.

Conclusions

In conclusion, pain remains a significant problem in medical oncology outpatients. As adequate pain relief for up to 86% of patients with cancer should be feasible, pain in medical oncology outpatients is still undertreated.

To avoid an ongoing discussion on cut-off points, it would be interesting to focus in future research on the possibilities of using interference of pain with daily activities as an additional factor and not only as a determinating factor for pain intensity categories. As patients often are reluctant to talk about their pain, it might be interesting to ask patients additionally about interference with daily activities related to their pain intensity. Pain might become more related to daily life and less to disease and medicine. Thus multidimensional tools to assess cancer pain, taking into account interference with daily activities and predictors of pain, will facilitate improvements in cancer pain management.

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