Palliative Medicine 2005; **19:** 477–484

Pain and pain treatments in European palliative care units. A cross sectional survey from the European Association for Palliative Care Research Network

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The Research Network of the European Association for Palliative Care (EAPC) performed a survey of 3030 cancer patients from 143 palliative care centres in 21 European countries. The survey addressed pain intensity and the use of non-opioid analgesics, adjuvant analgesics and opioids.

Patients were treated with analgesics corresponding to the WHO pain ladder step I ($n=855$), step II ($n=509$) and step III ($n=1589$). The investigators assessed 32% of the patients as having moderate or severe pain. In general there were small differences between pain intensities across different countries. Cancer primary sites and the presence of metastasis had only minor influences on pain intensity. The most frequently used non-opioid analgesics were NSAIDs (26%) and paracetamol (23%). Adjuvant analgesics or co-analgesics used by >1% of the patients were corticosteroids (39%), tricylic antidepressants (11%), gabapentin (5%), bisphosphonates (4%), clonazepam (2%), carbamazepine (4%) and phenytoin (2%). The use of non-opioid analgesics and co-analgesics varied widely between countries. Opioids administered for mild to moderate pain were codeine (8%), tramadol (8%), dextropropoxyphene (5%) and dihydrocodeine (2%). Morphine was the most frequently used opioid for moderate to severe pain (oral normal release morphine: 21%; oral sustained-release morphine: 19%; iv or sc morphine: 10%). Other opioids for moderate to severe pain were transdermal fentanyl (14%), oxycodone (4%), methadone (2%), diamorphine (2%) and hydromorphone (1%). We observed large variations in the use of opioids across countries. Finally, we observed that only a minority of the patients who used morphine needed very high doses. *Palliative Medicine* 2005; **19:** 477–484

Key words: analgesics; cancer; opioid; pain; palliative care; survey

Introduction

Pain is one of the most frequent symptoms among cancer patients with metastatic disease. The prevailing principle for treatment of cancer pain is the WHO three-step pain ladder in which pain treatment is escalated from the use of non-opioids as the first step, through a second step using opioids for mild to moderate pain, up to the third step applying opioids for moderate and severe pain.[1] Based on the WHO pain ladder, a more detailed European recommendation for the use of morphine and alternative opioids has been published by an expert committee of the European Association for Palliative Care (EAPC),[2] which parallels its US counterpart's guidelines for the treatment of cancer pain.[3]

Despite the widespread use and recognition of recommendations for the treatment of cancer pain, results from retrospective and prospective surveys consistently show that pain is still prevalent in patients with malignant disease. Cleeland *et al*. surveyed the intensity of pain in 1308 outpatients with metastatic cancer and observed that 42% of those with pain were not given adequate analgesic therapy.[4] The inadequacy of cancer pain treatment was also demonstrated by an IASP Task Force on Cancer Pain survey which reported that among 1095 patients treated by pain specialists, 20% reported average pain intensity of ≥ 7 on a 10-point numerical rating scale and 67% reported worse pain of ≥ 7.[5] A recent

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10.1191/0269216305pm1054oa

Norwegian survey observed that 13% of cancer patients on ongoing morphine treatment reported an average pain score of ≥ 7. These data suggest that there has been little improvement in pain treatment since the IASP task force project was completed.[6]

In 2000, the Research Network of the EAPC initiated a questionnaire survey among 141 palliative care centres in 21 European countries. One of the main objectives of the survey was to provide detailed information on the use of strong opioids and other key drugs by specialist palliative care services. This was a select sample of patients in the care of palliative care services, but the data provide some insights into the epidemiology of symptoms and the use of non-opioid and opioid analgesic drugs in a palliative care patient population across European countries.

Methods

Palliative care centres

The project was organized by the Research Network of the EAPC. Palliative care centres were recruited from 15 states in the European Union (in June 2000), as well as Norway, Switzerland, Iceland, Israel, Romania and Cyprus. In each country a national co-ordinator recruited individual centres with a maximum of ten in each country. In the countries where the national co-ordinators identified more than ten palliative care centres, a representative selection based upon the distribution of palliative care programmes in that country was identified. Data on contributing centres, patient demographics and symptoms will be reported in a separate paper.

Study period

This was a cross-sectional survey performed during week 23 of the year 2000. All patients treated in the palliative care programme, either as in-patients or out-patients, during this week were eligible.

Study procedure

A physician or other health care professional completed a questionnaire for each patient currently in the care of the palliative care service. The questionnaire included the demographics, age, gender, cancer diagnosis and presence of metastasis. Current medications used for pain control at the time of inclusion into the study were recorded as yes or no in respect of predefined categories of medications. These categories included the non-opioid drugs: paracetamol, dipyrone, aspirin, NSAIDs, dexamethasone, prednisolone, other corticosteroids, amitriptyline, other antidepressants, gabapentin, carbamazepine, phenytoin and clonazepam. The opioid drugs recorded were codeine, tramadol, dextropropoxyphene, dihydrocodeine, morphine, fentanyl, methadone, oxycodone, diamorphine, hydromorphone and hydrocodone. Doses were registered for those patients who used morphine. The investigators assessed the patients' symptom severity over 24 hours applying a 4-point verbal rating scale with the descriptors none, mild, moderate or severe. The symptoms rated were pain, fatigue, generalized weakness, focal weakness, anxiety, anorexia, depression, confusion, constipation, diarrhoea, nausea, vomiting, sleep disturbance, dyspnoea, itching, hallucination and hiccups.

Statistics

All data are descriptive in character. Collection and organization of the data were performed at the Unit for Applied Clinical Research, Norwegian University of Science and Technology. The SPSS statistical software for Windows v.10.07 was used for all statistical analyses.

Results

Patients

Reports were submitted on 3030 patients from 143 centres located in 21 countries. The patients were admitted to cancer hospital departments (8%), general hospital departments (28%), hospices (39%) or treated as outpatients (26%). The patients mean age was 66 years (0–19 years: 24 patients; 20–39 years: 127 patients; 40–59 years: 798 patients; 60–79 years: 1555 patients; 80–99 year: 504 patients, >100 years: three patients). The majority of patients suffered from a malignant disease (94%). Other diseases were neurological (3%), respiratory (0.5%), cardiac (0.5%), renal (0.3%) or AIDS (0.3%).

Among those patients with cancer, breast cancer was the most prevalent malignant diagnosis with lung cancer and colorectal cancer as the second and third most prevalent cancer diagnosis (Table 1). Some 30% of the patients had bone metastases. Liver and lung were the two other sites of metastasis observed in more than one-tenth of the patients (Table 2).

Pain and other symptoms

A total of 32% of the patients had pain of intensity that was moderate or severe (Table 3). The reported pain intensity varied between countries: on a 4-point scale, the lowest mean score of 1.6 was reported from Austria and the highest mean score of 2.6 was reported from Romania. However, in general there were small differences in pain intensity across different countries (data can be supplied from the first author).

The percentage of patients who were considered to have moderate or severe pain were 11% of those receiving WHO pain ladder step I treatment ($n = 855$), 30% for step II treatment ($n = 509$) and 43% for step III treatment ($n = 1589$). Overall, there were only minor differences in

Table 1 Malignant diagnosis

Primary site	Number of patients	%
Breast	471	17
Lung	395	14
Colorectal	349	12
Prostate	214	8
Female reproductive organs	201	7
Head and neck	189	7
Stomach	134	5
Pancreas	121	4
Haematological malignancy	114	4
Bladder	87	3
Renal	71	3
Skin (including malignant melanoma)	54	2
Oesophagus	44	2
Sarcoma	37	1
Brain	32	1
Liver	25	1
Thyroid	18	1
Others	228	8
Unknown	59	2
Total	2843	100

Table 3 Symptom severity: clinician assessment*

Severity	None (%)	Mild (%)	Moderate (%)	Severe (%)
Pain	31	37	24	8
Fatigue	16	33	33	18
Generalized weakness	17	30	33	20
Anxiety	40	30	21	9
Anorexia	43	30	18	9
Depression	52	28	14	5
Constipation	54	27	14	6
Poor sleep	57	27	13	4
Dyspnoea	65	20	12	4
Focal weakness	70	10	11	9
Nausea	70	21	8	2
Confusion	79	11	6	3
Vomiting	84	10	5	2
Diarrhoea	91	5	3	1
Itch	92	5	2	1
Hallucination	95	3	1	1
Hiccups	96	2	1	0.5

*Overall severity for the past 24 hours.

pain intensities between different cancer diagnoses (data can be supplied from the first author). The only notable exception was for primary brain tumours, which were associated with reports of lower pain intensity than other sites. Pain severity was not influenced by the presence of bone, liver, lung or brain metastases (data can be supplied from the first author).

Symptoms other than pain were prevalent in this population. Commonly reported symptoms of moderate or greater severity were generalized weakness (53%), fatigue (51%), anxiety (30%), anorexia (27%), constipation (20%), mood disorder (19%), lack of sleep (17%), dyspnoea (16%) and nausea (10%) (Table 3).

Non-opioid analgesics

NSAIDS and paracetamol were the most frequently used non-opioid analgesics. Acetylsalicylic acid (1%) and dipyrone (2%) were given only to a small number of patients.

Use of adjuvant analgesics was commonplace. Various types of corticosteroids were used by 39% of the patients and dexamethasone was the most frequent choice. Less commonly used adjuvant analgesics were tricylic antidepressants, most often amitriptyline (11%), gabapentin (5%), bisphosphonates (pamidronate and clodronate) (4%), clonazepam (2%), phenytoin (2%), carbamazepine (4%), sodium valproate (1%), baclofen (1%), calcitonin (0.4%) and sodium channel blockers (lidocaine and mexiletine) (0.2%). The use of non-opioid analgesics and adjuvant analgesics varied widely between countries (Table 4).

Table 2 Localization of metastases

Site	Number of patients	%
Bone	901	30
Liver	605	20
Lung	450	15
Peritoneum	283	9
Brain	231	8
Skin	124	4
Pleural	119	7
Others	325	11

Opioid analgesics

The opioids administered for mild to moderate pain were codeine (8%), tramadol (8%), dextropropoxyphene (5%) and dihydrocodeine (2%). Morphine was the most frequently used opioid for moderate to severe pain (oral normal release morphine: 21%; oral sustained-release morphine: 19%; iv or sc morphine: 10%). Other opioids used in the management of severe pain were transdermal fentanyl (14%), oxycodone (normal release oxycodone: 2%; sustained release oxycodone: 2%), methadone (2%), diamorphine (2%) and hydromorphone (1%).

Of those patients receiving morphine, approximately three-quarters were treated with doses <150 mg/24 hours, and only a very small minority used a dose >1000 mg (Table 5). Similar sets of data were not reported for the other opioids.

The use of step II opioids varied across countries (Table 6). Codeine was not given to cancer patients in Austria and Portugal, while 25% of the patients from Greece received this drug. The Greek patients, however, did not use tramadol, a drug used frequently in Romania (23%), Italy (23%), Finland (17%), Portugal (14%) and Spain (13%). Also the prescription practice of another WHO step II drug, dextropropoxyphene, varied between countries. One quarter of Romanian patients received dextropropoxyphene, a drug not used at all in nine of the countries.

Table 4 Use of non-opioids by country (No. of patients (% of patients))

	Total ($n=3030$)	Austria ($n=59$)	Belgium ($n=109$)	Cyprus ($n=133$)	Denmark ($n=88$)	Finland ($n=139$)	France ($n=160$)	Germany ($n=101$)	UK ($n=783$)	Greece ($n=72$)	Iceland ($n=72$)
Paracetamol	700 (23)	0	16 (15)	60 (45)	38 (43)	8 (6)	28 (18)	2 (2)	261 (33)	11 (15)	7 (10)
NSAIDs	792 (26)	11 (19)	9 (8)	38 (29)	13 (15)	40 (29)	23 (14)	33 (33)	222 (28)	28 (39)	20 (28)
Acetylsalicylic acid	43 (1)	0	0	0	0	2 (1)	1 (1)	0	37 (5)	0	0
Dipyrone	66 (2)	6 (10)	1 (1)	0	0	0	3 (2)	30 (30)	1 (0.1)	0	0
Corticosteroids	1179 (39)	27 (46)	36 (24)	30 (23)	57 (65)	51 (37)	68 (43)	41 (41)	228 (29)	20 (28)	30 (42)
TCA	337 (11)	4 (7)	5 (5)	5 (4)	19 (22)	11 (8)	37 (23)	23 (23)	89 (11)	16 (22)	11 (15)
Gabapentin	152 (5)	1 (2)	2 (2)	1 (1)	15 (17)	6 (4)	11 (7)	4 (4)	30 (4)	4 (6)	0
Bisphosphonates	132 (4)	3 (5)	0	1 (1)	2 (2)	6 (4)	9 (6)	5 (5)	30 (4)	1 (1)	0
Clonazepam	57 (2)	1 (2)	1 (1)	0	0	1 (1)	29 (18)	4 (4)	1 (0.1)	0	1 (1)
Phenytoin	64 (2)	0	2 (2)	9 (7)	0	2 (1)	0	1 (1)	16 (2)	2 (3)	1 (1)
Carbamazepine	108 (4)	5 (9)	3 (3)	2 (2)	0	9 (7)	3 (2)	6 (6)	24 (3)	3 (4)	3 (4)

	Ireland ($n=205$)	Israel ($n=107$)	Italy ($n=269$)	Luxembourg ($n=5$)	Netherlands ($n=42$)	Norway ($n=121$)	Portugal ($n=43$)	Romania ($n=94$)	Spain ($n=195$)	Sweden ($n=168$)	Switzerland ($n=65$)
Paracetamol	27 (18)	6 (6)	10 (4)	5 (100)	15 (36)	47 (39)	12 (28)	11 (12)	32 (16)	82 (49)	22 (34)
NSAIDs	79 (37)	8 (8)	94 (35)	3 (60)	13 (31)	16 (13)	11 (26)	41 (44)	42 (21)	33 (20)	15 (32)
Acetylsalicylic acid	1 (0.5)	0	0	0	0	1 (1)	0	0	0	0	1 (2)
Dipyrone	0	14 (13)	0	0	0	0	0	0	11 (6)	0	0
Corticosteroids	93 (44)	41 (38)	206 (54)	4 (80)	11 (25)	38 (31)	21 (49)	30 (32)	85 (44)	90 (54)	32 (49)
TCA	13 (6)	5 (5)	32 (2)	1 (20)	1 (2)	9 (7)	7 (16)	30 (22)	9 (5)	9 (5)	1 (2)
Gabapentin	21 (10)	0	16 (6)	1 (20)	2 (5)	5 (4)	2 (5)	9 (10)	14 (7)	5 (3)	3 (5)
Biphosphonates	5 (5)	11 (10)	20 (8)	2 (40)	1 (2)	0	5 (12)	5 (5)	7 (4)	9 (5)	4 (6)
Clonazepam	2 (1)	7 (7)	0	0	0	0	0	0	6 (3)	0	4 (6)
Phenytoin	10 (5)	3 (3)	0	0	2 (5)	0	2 (5)	1 (1)	9 (5)	2 (1)	2 (3)
Carbamexapine	3 (1)	2 (2)	9 (3)	0	0	5 (4)	2 (5)	13 (14)	6 (3)	8 (5)	2 (3)

Distribution by countries for non-opioid analgesic drugs and co-analgesics used by >1% of the patients. Some patients may have received a non-opioid drug or a co-analgesic drug for indications other than pain.

Table 5 Distribution of daily doses of morphine

Dose (mg)	Morphine oral (%)	Morphine parenteral (%)
<30	28	32
>30–60	26	26
>60–150	22	19
>150–300	13	11
>300–600	6	6
>600–1000	3	3
>1000–1500	1	2
>1500	0.2	0.5

The formulation of morphine varied between countries. Oral normal release morphine is most frequently used in Ireland, Denmark and Norway, while Romania, Luxembourg, Iceland and Italy rarely use this formulation. The use of sustained release morphine varied from 3% in Greece to 43% in Iceland. The use of sc or iv morphine varied from $<5\%$ in several countries (Cyprus, Finland, UK, Greece) to $>30\%$ in Austria and Portugal. Fentanyl was the most used opioid for moderate or severe pain in Belgium, Denmark, Greece and Netherlands. Oxycodone was most used in Denmark, Finland and Israel, hydromorphone most often used in Germany, Ireland and Switzerland and diamorphine was used only in Belgium and the UK.

Opioids for severe pain were often combined with a non-opioid analgesic drug. Of the 1416 patients treated with a WHO step III opioid analgesic, 334 received paracetamol and 504 received a NSAID.

Discussion

This paper presents a cross-sectional survey of the incidence and intensity of pain and of the use of analgesic medications prescribed for pain in European palliative care units. The principal findings of the survey are that most patients are treated with moderate doses of morphine, that there is considerable variability between countries in the use of non-opioids, and a similar large variability between countries in the selection of opioids.

In this survey about one-third of the patients were assessed as having moderate or severe pain. This result confirms that pain is still prevalent in cancer patients. The number of patients with pain observed in this palliative care patient population was similar to reported incidences of pain in other cancer patient populations, such as those treated as out-patients,[4] or those admitted to a general hospital.[6] The reasons why such a high proportion of patients had moderate or severe pain are not clear. Potential causes are lack of knowledge of adequate pain treatment,[7,8] fear of prescribing opioids,[9] or patient related barriers towards the use of opioids.[10,11] Lack of compliance may cause inferior pain treatment, especially if opioids are prescribed on an 'as required' basis.[12] Lack of treatment success may also be caused by failure to recognize specific cancer pain syndromes needing differential pain treatments. An IASP Task Force on Cancer Pain identified 22 pain syndromes as prevalent and observed that 40% of patients had some pain of neuropathic origin.[5] These findings indicate that in some cases poor pain control is a result of inaccurate or inadequate diagnosis.

The pain intensities were in general rather uniform across the different countries and were also similar to results obtained in US surveys.[4] However, the pain ratings were slightly higher in some countries of which Romania had the highest pain scores. It is not clear why this should be, but potential explanations are differences in the availability of opioids because of legislative or economic restrictions, doctor or patient barriers against opioid use, differences in pain assessment or different expectations about acceptable pain relief.

Patients with brain cancer had less pain compared to the other patients. For all other cancer diseases, the difference in pain from the lowest ratings (gastric and liver cancer) to the highest ratings (sarcoma and head and neck cancer) was only 0.5 on the 4-point pain verbal rating scale. Thus, cancer primary site had no major influence on pain intensities. This finding was surprising since it is assumed that highly invasive cancers generally cause a more intense pain stimulus. Previous studies have also reported that patients with bone metastases are subject to more intense pain.[13] No association was observed between the presence of bone metastases and pain intensity in this survey. The explanation may be that increased pain caused by a more invasive cancer or by a metastasis is simply counterbalanced with higher opioid doses. Another explanation not addressed in this survey may be that pain related to bone metastases is more associated with breakthrough pain,[13] which is not adequately assessed using a global pain assessment. The findings of only minor associations between pain intensity and cancer primary site suggest that clinicians should not over emphasize the implications of a particular cancer diagnosis or the presence of metastasis when considering the expected success of pain treatment.

An interesting finding of this survey is the wide variation in use of analgesics across countries. This variability is evident for non-opioids, opioids for mild to moderate pain, and opioids for moderate and severe pain. The EAPC guidelines recommend morphine as the first choice step III opioid.[2] Despite the EAPC recommendation, some countries such as Belgium (fentanyl), Finland (oxycodone), Greece (fentanyl) and Israel (fentanyl) do not use morphine as the opioid of first choice. Another interesting opioid in terms of differences in use between countries is diamorphine, which is exclusively used in Belgium and the UK. In the UK, diamorphine is the most frequently used opioid for

Table 6 Use of opioids by country (No. of patients (% of patients))

	Total ($n=3030$)	Austria ($n=59$)	Belgium ($n=109$)	Cyprus ($n=133$)	Denmark ($n=88$)	Finland ($n=139$)	France ($n=160$)	Germany ($n=101$)	UK ($n=783$)	Greece ($n=72$)	Iceland ($n=72$)
Codeine	227 (8)	0	3 (3)	7 (5)	2 (2)	8 (6)	11 (7)	1 (1)	82 (10)	18 (25)	14 (19)
Dextropropoxyphene	155 (5)	0	0	45 (34)	1 (1)	1 (1)	8 (5)	0	51 (7)	5 (7)	0
Dihydrocodeine	53 (2)	1 (2)	0	0	0	0	4 (3)	0	38 (5)	1 (1)	0
Tramadol	229 (8)	3 (5)	7 (6)	3 (2)	2 (2)	23 (17)	14 (9)	10 (10)	31 (4)	0	3 (4)
Morphine oral normal release	520 (17)	3 (5)	8 (7)	13 (10)	31 (35)	7 (5)	36 (23)	25 (25)	172 (22)	5 (7)	1 (1)
Morphine oral sustained release	561 (19)	6 (10)	8 (7)	11 (8)	18 (21)	21 (15)	34 (21)	26 (26)	132 (17)	2 (3)	31 (43)
Morphine parenteral	302 (10)	20 (34)	14 (13)	1 (1)	21 (24)	4 (3)	39 (24)	20 (20)	4 (0.5)	3 (4)	4 (6)
Fentanyl	417 (14)	10 (17)	29 (27)	4 (3)	35 (40)	26 (19)	31 (19)	24 (24)	68 (9)	30 (42)	12 (17)
Oxycodone	111 (4)	0	0	0	13 (15)	32 (23)	0	4 (4)	25 (3)	0	0
Methadone	66 (2)	0	2 (2)	0	8 (9)	3 (2)	1 (1)	1 (1)	5 (0.5)	1 (1)	1 (1)
Hydromorphone	62 (2)	3 (5)	0	0	0	0	9 (6)	4 (4)	10 (1)	0	0
Diamorphine	52 (2)	0	5 (5)	0	0	0	0	0	47 (6)	0	0
Hydrocodone	4 (0.1)	0	0	0	0	0	1 (1)	0	0	0	0
Other opioids	89 (3)	0	3 (3)	0	8 (9)	5 (4)	4 (2)	9 (9)	6 (1)	0	3 (4)

	Ireland ($n=205$)	Israel ($n=107$)	Italy ($n=269$)	Luxembourg ($n=5$)	Netherlands ($n=42$)	Norway ($n=121$)	Portugal ($n=43$)	Romania ($n=94$)	Spain ($n=195$)	Sweden ($n=168$)	Switzerland ($n=65$)
Morphine oral immediate release	77 (38)	23 (22)	4 (2)	0	7 (17)	38 (31)	8 (19)	0	21 (11)	18 (11)	18 (28)
Morphine slow release	73 (36)	20 (19)	45 (17)	1 (20)	9 (21)	35 (29)	5 (12)	7 (7)	32 (16)	33 (20)	8 (12)
Morphine parenteral	24 (127)	8 (8)	33 (12)	0	12 (29)	13 (11)	13 (30)	10 (11)	25 (13)	25 (15)	9 (14)
Fentanyl	18 (9)	31 (29)	10 (4)	0	21 (50)	18 (15)	9 (21)	0	19 (10)	17 (10)	3 (5)
Oxycodone	2 (1)	31 (29)	1 (0.4)	0	0	1 (1)	0	0	0	2 (1)	0
Methadone	2 (1)	7 (7)	10 (4)	0	0	3 (3)	0	11 (12)	11 (6)	0	1 (2)
Hydromorphone	21 (10)	0	0	0	1 (2)	1 (1)	0	0	0	6 (4)	6 (10)
Diamorphine	0	0	0	0	0	0	0	0	0	0	0
Tramadol	3 (2)	1 (1)	62 (23)	1 (20)	2 (5)	1 (1)	6 (14)	22 (23)	26 (13)	4 (2)	5 (8)
Codeine	2 (1)	1 (1)	39 (15)	1 (20)	1 (2)	13 (11)	0	13 (14)	8 (4)	2 (1)	1 (2)
Dextroporopoxyphene	8 (4)	0	3 (1)	0	0	1 (1)	1 (2)	24 (26)	0	7 (4)	0
Dihydrocodeine	1 (0.5)	1 (1)	0	0	0	0	2 (5)	0	4 (2)	1 (1)	0
Hydrocodone	1 (0.5)	0	0	0	0	1 (1)	0	0	1 (0.5)	1 (1)	0
Other opioids	4 (2)	2 (2)	6 (2)	0	4 (10)	7 (6)	0	3 (3)	1 (0.5)	22 (13)	1 (2)

sc opioid infusions. Diamorphine is preferred to morphine for parenteral administration because of its greater solubility. Few patients received methadone. The exception was observed in Romania, where methadone was the most used opioid for moderate to severe pain, however this may be related to the low cost of methadone in Romania. Methadone is a drug in which there has recently been much renewed interest and is recommended by several authorities as an alternative opioid in cases not successfully treated with morphine, especially for patients suffering from neuropathic pain.[14]

The use of step II opioids also varied considerably between countries. For example, the use of tramadol and dextropropoxyphene varied from no use in some countries to being the most frequently prescribed opioid drug in other countries (dextropropoxyphene: Cyprus and Romania; tramadol: Italy).

The reasons for these large variations in the use of opioids for cancer pain across Europe are unclear. Potential factors are clinical traditions, price, education and legal or cultural barriers to the use of opioids. There also remains little available data from high quality studies – randomized controlled trials (RCTs) – in which head to head comparisons of opioids have been made. This lack of formal evidence,[15] may be a cause of the variability in cancer pain treatment between countries.

Another finding in the subsample of patients using morphine was that relatively few patients needed very high doses of morphine (Table 4). This observation may reflect that most patients are adequately treated with low or moderate doses of opioids, and similar experience has been reported before.[16] However, the number of patients who still reported moderate or severe pain despite treatment with step III opioids suggests the possibility that some, at least, were receiving inadequate doses.

Adjuvant analgesics were used in about one-fifth of the patients. Those used in $>1\%$ of patients were tricyclic antidepressants, bisphosphonates and anticonvulsants. The findings in this survey indicate that palliative care physicians in general apply the recommended co-analgesics for selected cases. The choice of adjuvant (i.e., gabapentin versus tricyclic antidepressant) varies between countries.

All patients included in this study were in the care of a palliative care specialist service. Therefore, this study represents specialist practice in different European countries and it is not possible to draw inferences from these data about non-specialist practice in these countries.

We recognize some limitations in this cross-sectional study. First, this study used observer ratings for symptom assessments. Observer assessments are known to underestimate pain intensity.[17] If present, an under report of pain should result in a systematic error and therefore not jeopardize the validity of comparisons across countries, diagnoses, or different groups of medications. Second, in this survey we did not obtain data on the number of patients who refused inclusion or on the number of eligible patients who were not approached for study inclusion. Finally, we do not know if all non-opioids or adjuvant analgesics were prescribed with the intention of achieving improved pain control. For example, some patients may have been prescribed paracetamol for fever, corticosteroids for other diseases or anticonvulsants for prevention of epileptic seizures.

In conclusion, this survey presents the first European epidemiological study on palliative care patients' symptoms, use of non-opioid analgesics and use of opioids. We observed that one-third of the individual patients had clinically significant pain. There were large variations in the use of both non-opioids and opioids across countries, but the intensities of pain were still relatively evenly distributed across the participating countries. Cancer primary site and the presence of metastases had minor influence on pain intensity. Finally, we observed that for patients who used morphine, only a minority needed very high doses.

Acknowledgements

The study was performed within the Research Network of the European Association for Palliative Care. In addition to the authors the following investigators participated in the study: *study coordinator*: K Torvik (Norway). *National coordinators*: R Likar (Austria), J Menten, (Belgium), J Kakas (Cyprus), L Pedersen (Denmark), E Kalso (Finland), P Poulain (France), L Radbruch (Germany), K Mystakidou (Greece), V Sigurdardottir (Iceland), T O'Brien (Ireland), B Thill (Luxembuourg), B Zylics (Netherlands), J Ferraz Goncalves (Portugal), L Ionescu-Cälinesti (Romania), JM Nunes (Spain), CJ Fürst (Sweden), F Porchet (Switzerland), K Done (UK). *Coordinators at clinical sites*: Austria: G Forche, JP Zoidl, H Retschitzegger, M Werni-Kourik, B Stapel, C Stabel. Belgium: A Verhoeve, P Cornil, M Faignaert, T van Iersel, J Menten, K Sterckx, R Veekhoven, K Claassens, C Bieke, J Indirjian, S Michael, B Pitsillides, R Christou, N Koupi. Denmark: M Mørk, A Bonde, L Pedersen, B Enig. Finland: T Saarto, J Hänninen, T Leino. France: B Veronique, R Duclos, L Hacpille, G Laval, MHH Salamagne, P Vinan. Germany: M Cremer, F Nauck, G Hanekop, L Latasch, W Diemer, M Kloke, L Radbruch, C Bausewein, C Müller-Busch. UK: J Dale, D Alison, M Fallon, L Forman, C Sinnott, A Wilcock, C Regnard, M Nugent, K Forbes, C Higgs. Greece: K Mystakidou, E Tsiouri, A Kritikou, E Argiraki, T Christos, G Evgenia, E Kosmidou, M Tsitoura. Iceland: V Sigurdardottir, S Björnsson, N Fredriksdottir, G Thorsdottir, H Helgadottir, E Hjörleifsdottir. Ireland: L O'Siorain, S Kingston, J Flemming, R McQuillan,

M Kearney, S Donelly, T McCormack, T O'Brien. Israel: Y Zinger, R Gassner, M Bercovitch. Italy: E Arcuri, R Bortolussi, O Corli, M Gallucci, A Gottlieb, M Maltoni, M Visentin, G Zaninetta, F Zucco. Luxembourg: B Thill. Netherlands: AJM Wolf, RJ van Boxtel, Z Zylicz, R Voskamp, J Koningswoud-ten Hove, F Baar. Norway: N Magerøy, S Ottesen, S Jørgensen. Portugal: F Goncalves, AL Marques Goncalves, I Galrica Neto. Romania: C Bogdan, G Popescu, M Daniela, H Cristina. Spain: JM Nunez Olarte, G Maranon, A Tuca i Rodriguez, J Porta i Sales, C Centeno Cortes, M Nabal Vicuna, J Sanz Ortiz, N Peraz de Lucas, R Rodeles del Pozo, L Azuara Rodriguez. Sweden: G Eckerdal, I Fridegren, I Underskog, CJ Fürst, A Janson, A-M Graavgaard, M Fahlström. Switzerland: A Levorato, D Anwar, S Pautex, G Gremaud, S Eychmüller, H Gudat.

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