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Drugs in palliative care: results from a representative survey in Germany

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Abstract: The development of palliative medicine in inpatient units in Germany has been impressive in the last years. As a first step of quality assurance, a core documentation form was developed in 1996. In 2001, 55 of the 83 palliative inpatient units in Germany and one unit each in Switzerland and Austria participated in the third phase of the evaluation of the core documentation. A total of 1304 patients were documented consecutively in the 57 units for a period of up to three months. This study investigates the frequency of drugs used in palliative care units in Germany. During inpatient treatment, the most common drug classes were strong opioids (68% of the patients), nonopioids (59%), corticosteroids (32%), laxatives (31%), antiemetics (27%), gastric protection agents (24%), neuroleptics (19%), sedatives/anxiolytics (18%), antidepressants (16%) and diuretics (15%). These ten drug classes made up for 72% of all prescriptions in the palliative care units. The substances used most frequently were dipyrone (47% of the patients), morphine (42%), fentanyl (28%), dexamethasone (27%), metoclopramide (21%), sodium picosulfate (15%), haloperidol (13%), pantoprazole (11%), macrogol (11%), amtriptyline (11%), furosemide (10%), omeprazole (9%), lactulose (8%), rofecoxib (8%) and lorazepam (7%). The 15 most commonly used drugs accounted for 54% of the prescriptions in the palliative care units in Germany. Drug treatment was related to sex, age and functional status of the patients. Patients who died in a palliative care unit had received significantly more frequent doses of neuroleptics ($P < 0.001$), corticosteroids ($P < 0.001$), sedatives/anxiolytics ($P < 0.001$) and strong opioids ($P < 0.001$). This study is the first representative and systematic evaluation of drug treatment in palliative care units in a European country. Many of the 'top 15' drugs were drugs included in the list of essential drugs of the World Health Organisation though availability and cultural differences have an effect on the use of drugs, e.g., the high usage of dipyrone in Germany. Age and sex-related differences in drug therapy were seen, and more research is needed to recognize possible undertreatment of symptoms in subgroups of patients, e.g., treatment of depression in older or male patients. *Palliative Medicine* 2004; **18:** 100–107

Key words: drugs; nonopioids; opioids; palliative care units; survey; symptom management

Introduction

In 1996, the German Ministry of Health initiated a meeting of physicians from palliative care units to define a core instrument to be recommended for use in the inpatient units to enable the evaluation of the concepts and procedures used in the different units. A working group from several palliative care units, the German Cancer Association and the German Association of Palliative Medicine produced a draft for such an instrument, which was tested in evaluation periods in 1999 and 2000.[1–3] The instrument was modified after each evaluation period.

Until now there has been no systematic evaluation on the drugs used in palliative care in Germany. In the two previous core documentation series, the main emphasis was placed on pain management. Checklists were used to document analgesic drugs but little information was

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obtained on the management of other symptoms than pain. In 2001, the core documentation system used free text entries for physical symptoms, psychosocial problems and for drug therapy. It was hoped that the assessment with free text entries would result in the documentation of those problems, symptoms and drugs that the staff members perceived to be of highest importance, that documentation of drugs would not be focused on pain management and that the free entries would be less susceptible to differences in documentation discipline encountered with checklists. The documentation of symptoms and problems is published separately,[4] as well as the evaluation of nondrug interventions and procedures.[5] This paper will look at the drug use in palliative care in Germany and on the factors influencing the strategies in drug treatment.

Methods

All palliative care units in Germany were identified from the hospice directory[6] and were contacted in January 2001. From May to June 2001 the 57 participating units (55 German units, one unit each in Switzerland and Austria) assessed up to 30 patients consecutively admitted to the unit with the core documentation. Demographic data, diagnosis and stage of the disease, concomitant diseases, physical symptoms, psychological, social, nursing, as well as other problems, previous therapies and medication were assessed at the time of admission. Symptoms, problems, therapies performed and medication during inpatient treatment were also documented at the end of treatment, either at the time of discharge or death. Structural data from the units, such as staff resources, were assessed in a separate survey before the core documentation series had started.[3]

The medication had to be documented in free text entries. Eight fields for medication at admission and during inpatient treatment were provided. The units were asked to document the generics with dose and route of application. Additional checklists were provided for classification of the analgesic therapy according to the WHO ladder.

For statistical analysis, the drugs had to be recoded because drugs were not always documented as generics, but also with trade names or general terms, e.g., 'mo' for morphine. Obvious mistakes in spelling were corrected. First, all drug entries were recoded into generics. In a second step, these generics were combined into drug classes, as listed below (Table 1). The classification into

Table 1 Drugs and drug classes

Drug class	Common substances within classes
Antiarrhythmics	amiodarone, digitoxin, digoxin, verapamil
Antibiotics	amoxicillin, ciprofloxacin, metronidazole
Anticonvulsants	carbamazepine, gabapentin, phenytoin, clonazepam
Antidepressants	amitriptyline, doxepin
Antidiarrhoea agents	loperamide
Antiemetics	cyclizine, diphenhydramine, metoclopramide, odansetron
Antihypertensives	amlodipine, enalapril, metoprolol, nifedipine
Antimycotics	flucanozole, nystatin
Bisphosphonates	clodronate, pamidronate
Bronchiolytics	ipatropium, fenoterol, theophylline
Chemotherapeutics	carboplatin
Other coanalgesics	clonidine, ketamine
Corticosteroids	dexamethasone
Diuretics	furosemide, hydrochlorthiazide
Electrolytes	calcium, potassium
Enzymes	pancreatic enzyme
Gastric protection	omeprazole, pantoprazole, ranitidine
Heparins	dalteparin, nadroparin
Hormones/and antagonists (antineoplastic)	cyproterone, tamoxifen
Insulins	humane insulin
Laxatives	lactulose, macrogol, paraffin
Local anaesthetics	lidocaine, ropivacaine
Mucolytics	acetylcysteine, ambroxol
Muscle relaxing	baclofen
Neuroleptics	haloperidol, promethazine
Nonopioids	diclofenac, dipyrone, ibuprofen, rofecoxib, flupirtine, paracetamol
Oral anticoagulants	phenprocoumon
Oral antidiabetics	glibenclamide, glimepiride
Other hormones (substitution)	thyroxin
Sedatives/anxiolytics	diazepam, lorazepam, flunitrazepam
Spasmolytics	hyoscine hydrobromide
Strong opioids	fentanyl, hydromorphone, levomethadone, morphine
Weak opioids	tramadol, tilidine

drug classes was done under consideration of the drug formulary of the German Federal Association of Pharmaceutical Industry,[7] based on the WHO 'Guidelines for ATC Classification and DDD Assignment'.[8] In contrast to the drug formulary weak opioids, strong opioids and nonopioids were recoded as drugs of different classes. As dosage and route of application were documented only rarely, it was decided not to evaluate these parameters. Recoding was done by one of the authors (C.O.).

The programme package SPSS 10.0 was used for statistical evaluation. The incidences of generics and drug classes at the time of admission and at the end of therapy were compared. The frequency of drugs and drug classes during inpatient treatment were compared for sex, age and level of performance status, as well as between patients discharged and patients treated until death in the palliative care units. To investigate the influence of age on drug classes, patients were dichotomised with the median age. Fisher's Exact Test was used to test between-group differences and compare patients with a low functional status (ECOG 3–4) with patients with a good to medium functional status (ECOG with 0–2) and patients with no to moderate pain (NRS 0–2, observer-assessment, using NRS 0 = no pain/NRS 4 severe pain) and patients with strong and severe pain (NRS 3–4).

The core documentation is a long-term quality assurance project in palliative care supported by the German Association of Palliative Medicine (Deutsche Gesellschaft für Palliativmedizin – DGP) and the German Cancer Society (Deutsche Krebsgesellschaft – DKG). As a survey of drug practice, the project was not submitted to an ethics committee.

Results

A total of 57 units – 55 palliative care units in Germany, one unit in Switzerland and one in Austria – participated in the evaluation period of the core documentation in 2001.

From the participating 57 palliative care units, 1304 patients (687 women, 604 men, not documented 13 patients) were included in the evaluation. Mean age was 65.1 ± 12.8 years (range 20–100 years, median 66.2 years). Malignant diseases were predominant (Table 2) and less than 5% of the patients in palliative care suffered from other diseases. The predominant malignancy for women was cancer of the breast (24% of all women) and for men cancer of the lung (22% of all men). The majority of patients (80.7%) were suffering from a metastatic progression of their disease. The main symptoms at admission and reasons for treatment on the palliative care units were pain (81.7% of the patients), weakness (29.4%), anxiety (28.1%), dyspnoea (20.2%) and nausea (16.1%).

Table 2 Diagnosis

ICD-code	Diagnosis	Patients (%)
C00-C14	mouth and pharynx	4.4
C15-C26	gastrointestinal tract	28.6
C30-C39	respiratory tract	16.7
C40-C41	skeletal system	0.2
C43-C44	skin	1.5
C45-C49	connective tissue	1.9
C50	breast	12.7
C51-C58	female genital tract	6.9
C60-C63	male genital tract	5.0
C64-C68	urinary tract	6.5
C69-C72	eye and central nervous system	1.9
C73-C75	endocrine glands	0.9
C76-C80	undefined primary cancer	3.8
C81-C96	lymphoma, leukaemia	4.6
	others	4.2
	not documented	0.2

Values are given as percentage of patients.

Five hundred and thirty one patients (40.7%) died on the palliative care units, 773 (59.3%) were discharged home or to other places of care (nursing home, 54 patients; inpatient hospice, 59 patients; other hospital departments, 40 patients; others, 16 patients). The mean stay on the palliative care units was 14.7 days (median 13, range 0–92 days). Patients who were discharged were treated for 16 days (median 13, 0–92 days), the mean stay of patients who died on the units were 13 days (median 9, range 0–84 days).

Overall 10 396 drugs were documented, 4203 at admission (mean 3.2 ± 2.4 per patient) and 6193 (mean 4.8 ± 2.3) during inpatient treatment. No drugs were documented for 148 patients at the time of admission, and 35 patients were without drug treatment during their stay on the units. In contrast to the instructions of the core documentation, about half of the entries were not documented as generics but in trade names or in general terms. After recoding, 131 different generic substances were distinguished. At the time of admission, 299 (7.1%) entries could not be allocated, and 306 not (4.9%) allocated during inpatient treatment, mainly because the substances were not found in the drug formulary or notation was incomprehensible. The substances not identified in the formulary were mainly homeopathic and phytotherapeutic agents or alimentary additives.

The most common drugs during inpatient treatment, as listed in Table 3, were dipyrone, morphine, fentanyl, dexamethasone, metoclopramide, sodium picosulfate, haloperidol, pantoprazole, macrogol and amitriptyline. At the time of admission, tramadol, diclofenac and acetylsalicylic acid were more frequently used and haloperidol, lorazepam and rofecoxib were not among the most common drugs. The 'top 15' drugs accounted for 54% of the prescriptions in the palliative care units.

During inpatient treatment, the most common drug classes were: strong opioids, nonopioids, corticosteroids,

Table 3 List of most common drugs

Drug	Admission (%)	Inpatient treatment (%)
Dipyrone	30.1	46.5 ***
Morphine	25.5	42.3 ***
Fentanyl	25.5	28.2
Dexamethasone	14	27.0***
Metoclopramide	12.9	21.1***
Sodium picosulfate	5.1	15.1***
Haloperidol	3.1	12.7***
Pantoprazol	6.7	11.3***
Macrogol	3.8	11.3***
Amitriptyline	6.4	10.5***
Furosemide	7.7	9.7
Omeprazole	7.3	9.2
Lactulose	7.4	7.7
Rofecoxib	3.1	7.7***
Lorazepam	2.5	6.6***
Tramadol	7.7	6.1
Diclofenac	5.4	4.7
Acetylsalicylic acid	4.8	3.4

Values are given as percentage of patients treated with drugs at admission respectively during inpatient treatment, significant differences are marked with *** for $P < 0.001$, ** for $P < 0.01$ and * for $P < 0.05$.

laxatives, antiemetics, gastric protection agents, neuroleptics, sedatives/anxiolytics, antidepressants and diuretics (Table 4). These ten drug classes accounted for 72.3% of the prescriptions on the palliative care units. At admission, antihypertensive medications and weak opioids were more frequent, whereas sedatives/anxiolytics and neuroleptics were not on the list of the ten most common drug classes. At the time of admission, morphine and fentanyl were used with the same frequency for 25.5% of the patients. During inpatient treatment, the frequency of prescriptions for morphine (42.3%) increased significantly ($P < 0.001$), whereas it remained almost unchanged for fentanyl (28.2%). For 42.8% of the patients, no opioid therapy was documented at the time of admission. This ratio decreased to 26.6% during inpatient treatment. Other opioids than morphine used in the units were hydromorphone (1.6% at admission/2.8% during inpatient treatment), levomethadone (0.7%/1.2%), buprenorphine (1.4%/0.3%), piritramid (0.2%/0.2%) and sufentanyl (0.1%/0.2%) (Figure 1). At the time of admission, 19.9% received only morphine as a step III opioid, which increased to 33.5% during inpatient treatment. Fentanyl and morphine were combined frequently at the time of admission (4.9%) and during inpatient treatment (7.4%). Other combinations of opioids were rare. Only 0.2% of the patients were given a combination of three different opioids at the time of admission (inpatient treatment 0.4%). At admission, three patients were treated with a combination of an opioid agonist with a partial antagonist (buprenorphine). Of those patients without opioids at the time of admission, 55.6% remained without opioids during inpatient treatment, and for 44.4%, opioid therapy was initiated. Of those patients admitted to the palliative care units with an opioid pretreatment, opioid medication remained unchanged for 58.3% of the patients. In 5%, opioid medication was discontinued, 23.4% had to be switched to another opioid and in 11.1% of the patients, the opioid medication was supplemented by a second opioid or one substance was switched within an opioid combination. The most common switch was from fentanyl to morphine, as 18.4% of the patients treated with fentanyl at the time of admission were switched to morphine. The most frequent add-on opioid was morphine, as 16.4% of the patients treated with fentanyl at the time of admission were supplemented with morphine. A combination with nonopioids was given to 66.6% of the patients receiving opioids during inpatient treatment compared to 53.6% at the time of admission.

No differences were detected in performance status at the time of admission for men and women (ECOG 0–2, good to medium functional status; ECOG 3–4, low

Table 4 List of most common drug-classes

Drug class	Admission (%)	Inpatient treatment (%)
Strong opioids	50.3	67.9***
Nonopioids	42.0	58.9***
Corticosteroids	17.8	32.4***
Laxatives	16.3	31.1***
Antiemetics	15.0	26.9***
Gastric protection	17.6	23.7***
Neuroleptics	5.2	19.3***
Sedatives/anxiolytics	7.4	18.4***
Antidepressants	9.6	15.6***
Diuretics	12.1	14.6
Antihypertensive med.	12.3	8.7**
Weak opioids	12	10

Values are given as percentage of patients treated with drug classes at admission and during inpatient treatment respectively, significant differences are marked with *** for $P < 0.001$, ** for $P < 0.01$ and * for $P < 0.05$.

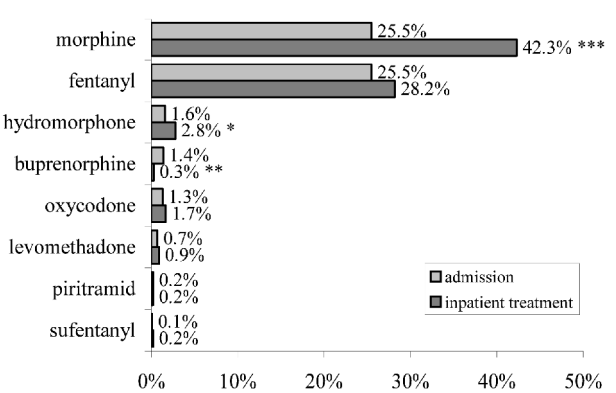

Figure 1 Strong opioids at admission and during inpatient treatment $n = 1304$, significant differences are marked with *** for $P < 0.001$, ** for $P < 0.01$ and * for $P < 0.05$.

performance status). The performance status at admission of patients who died on the palliative care units was significantly lower ($P < 0.001$) than of patients who were discharged (Figures 2 and 3). Older patients (older than 66.2 years) were admitted in lower functional status than younger patients ($P = 0.001$). The frequency of patients with strong and severe pain (NRS 3–4 on a five step numeric scale) at the time of admission showed no differences between male and female patients, as well as between patients who could be discharged respectively died on the palliative care unit. Significantly, more young patients were suffering from severe or very severe pain ($P = 0.02$) at the time of admission than older patients. Correlation between symptoms respectively symptom

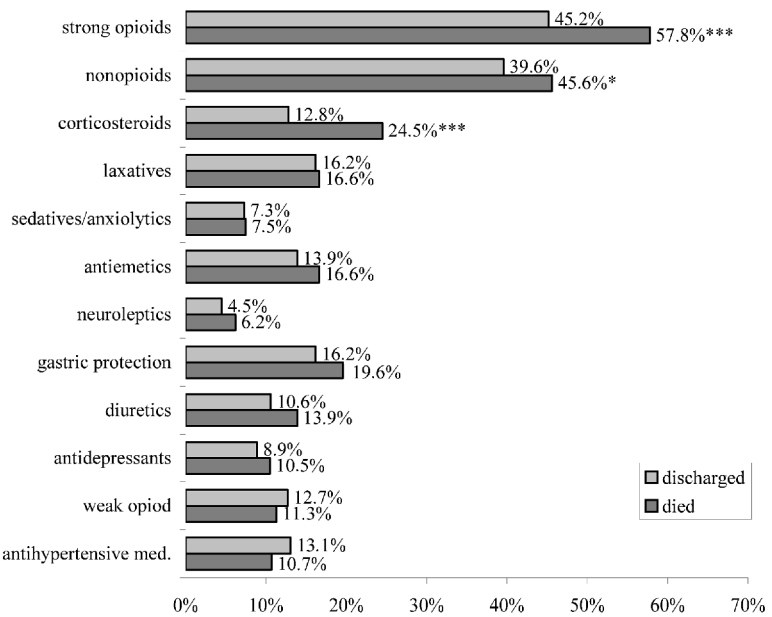

Figure 2 Drug classes at admission comparing patients who could be discharged and patients who died in palliative care units, significant differences are marked with *** for $P < 0.001$, ** for $P < 0.01$ and * for $P < 0.05$.

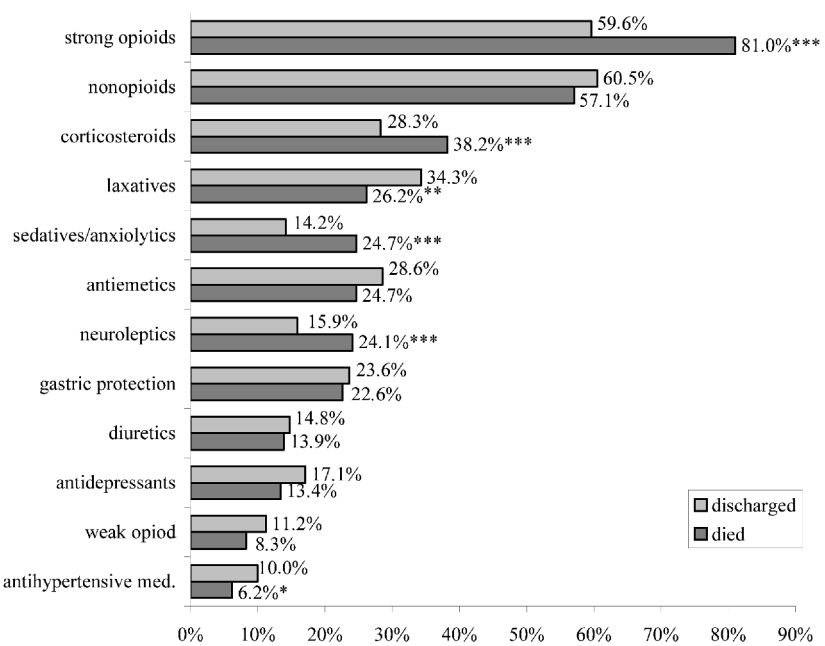

Figure 3 Drug classes during inpatient treatment comparing patients who could be discharged and patients who died in palliative care units, significant differences are marked with *** for $P < 0.001$, ** for $P < 0.01$ and * for $P < 0.05$.

intensity and frequency of drugs and drug classes was not analysed in this survey.

Older patients received less drugs (4.5 drugs per patient) than younger patients (5.0 drugs). Younger patients were treated more often with anticonvulsants ($P < 0.001$), corticosteroids ($P = 0.001$), antidepressants ($P = 0.007$), sedatives/anxiolytics ($P < 0.001$) and strong opioids ($P = 0.055$, n.s.) and less often with antihypertensive ($P = 0.021$) and antiarrhythmic ($P = 0.015$) medication. Female patients received significantly more antiemetics ($P = 0.004$), antidepressants ($P = 0.015$) and hormone-antagonists ($P = 0.004$) than male patients, for whom more antibronchospastic ($P = 0.018$) and mucolytic ($P = 0.009$) agents were documented.

Discussion

Pain management and symptom control are among the key issues of palliative medicine.[9] However, up to now there has been no systematic and representative evaluation of drug therapy in palliative care units. Twycross *et al*. evaluated an electronic database to monitor the drug use on a single palliative care unit.[10] Koh *et al*. analysed medication charts from three different centres (one inpatient palliative care consultation service, one hospice and one home care service),[11] and Dickerson *et al*. conducted a questionnaire survey among international experts in palliative medicine, what they deemed essential from an alleged list of drugs used in palliative care.[12] Five out of six drug classes (strong opioids, nonopioids, corticosteroids, laxatives, antiemetics), which were recognised by all experts, were also found among the six most common drug classes in the palliative care units in Germany. Medication for gastric protection was far more often documented in our study than referred to by the experts, whereas anticonvulsants were documented less often.

Compared to the list of essential drugs from the international survey by Dickerson, we found good analogy for morphine, dexamethasone, haloperidol, amitriptyline and lactulose. However, other drugs from Dickerson's list are not found in the list of the most common drugs in our study, such as midazolam, methadone, clonazepam, diclofenac, megestrol acetate or hyoscine hydromide. Fentanyl – third in our list – was only recognised as an essential drug by 50% of the respondents in the questionnaire survey. These differences may be due to the fact that the survey was conducted in 1998/1999 when fentanyl was not yet available in all participating countries, and that the questionnaire had a checklist of 83 drugs to choose from, with five more drugs that could be added by the respondents.

Opioids are one of the mainstays of cancer pain management.[13,14] At admission, half of the patients were treated with opioids, and this percentage increased to 73% during inpatient treatment. In spite of new opioids and drug formulations introduced in recent years, morphine was still the most frequently used opioid, closely followed by fentanyl. The opioid medication was switched to another opioid in a quarter of the patients, and in other patients, opioid pretreatment was supplemented with a second opioid. An evaluation of the change of routes of administration or dose adjustments was impossible because these items were documented only irregularly in the free text entries of the core documentation.

The generic used most frequently in the palliative care units in Germany is dipyrone, which is not mentioned at all in the international questionnaire that named paracetamol as the nonopioid used most frequently. This may be related to differences in availability or regulations for this drug in different countries.

In this study sex-related differences in drug therapy were evident. The administration of more hormone-antagonists in female patients was related to gender-related tumours (breast, ovary, and uterus). Women received more often antiemetic and antidepressant drugs, as nausea, anxiety and depression were reported more often in female compared to male patients (data reported separately[4]). This accords with findings of Walsh *et al*., that female patients admitted to a palliative care programme had shown more anxiety, nausea, vomiting and early satiety.[15] Male patients were treated more frequently with antibronchospastic and mucolytic agents, probably due to the fact that men suffered from lung tumours about three times as often as women, and had a higher incidence of comorbidity of nonmalignant diseases of lung and airways.

Not only gender, but also age had an impact on drug therapy. Walsh *et al*. found an association between symptoms and age, as younger patients suffered more frequently from anxiety and depression than older patients.[15] In our survey no difference was seen for depression, but anxiety and severe pain were reported more frequently in younger patients. These differences might explain the higher incidence of antidepressants, sedatives and anxiolytics, as well as anticonvulsants prescribed for younger patients. As would have been expected, older patients were treated more often with antihypertensive and antiarrhythmic drugs.

The evaluation also showed differences between drug treatment in dying patients and patients discharged home. Patients in the final phase may suffer from changes in symptom intensity and new symptoms may appear.[16] Oral application of drugs may no longer be possible, and medication that is not essential should be discontinued. Laxatives, antihypertensive medication, antiemetics, anti-

depressants, as well as nonopioids were given less frequent to dying patients in this study. Patients in the final phase received more often strong opioids, sedatives/anxiolytics, corticosteroids and neuroleptics, as pain, dyspnoea and restlessness were documented more often for these patients.[4] Except for steroids, the drugs correspond to the expert recommendations.[16–19] The high incidence of corticosteroids may be related to the broad range of indications of this drug and could be an interesting topic for further studies.

The results of the study may have been biased by several factors. The core documentation did provide eight fields for free text entries of drugs. For those patients treated with more than eight drugs, a selection would have to be made, and this selection may have been biased by the subjective ranking of drugs on the part of the documenting staff. Drugs considered less important, such as vitamins, mild laxatives or drugs for gastric protection may have been omitted more frequently leading to an underrepresentation of these drugs in our study. Documentation was done by physicians, psychologists or nursing staff or in team meetings, but the profession of the documenting person was not recorded. We cannot exclude that the profession of the person performing the documentation would have influenced the selection of drugs recorded, e.g., anxiolytics and antidepressants being recorded more often by psychologists than by physicians or nursing staff. However, as the mean number of drugs was below five drugs per patient during inpatient treatment, selection bias may be assumed small. The drugs given during inpatient treatment were recorded at the end of treatment, and drugs given for shorter periods of time may have been overseen in the retrospective documentation from the patients' charts. However, the mean duration of inpatient treatment in the units was around 15 days. This means that usually only two or three drug sheets had to be reviewed in the charts for documentation. Omission bias, therefore, may also be assumed small. Though the duration of inpatient treatment was usually short, it must be kept in mind that statistical comparison of data from the time of admission with those during inpatient treatment is difficult, as this means comparing prevalences at a fixed time point (admission) with incidences of a however small time interval.

The study has given detailed information on drugs and drug classes used in palliative care units in Germany. Data from an Austrian and a Swiss unit were included. The drug formularies and the prescribing guidelines in these countries are very similar to Germany, and the data from these units did not skew the evaluation.

The indications for the drugs given were not documented. It can be assumed that strong opioids generally were given to treat pain, but no information is available how often opioids were used to treat dyspnoea or other indications. No distinction was possible between the antipsychotic or antiemetic use of neuroleptics such as haloperidol.

Drug treatment of pain and other symptoms is one of the key points of palliative medicine. The study presented here is the first representative and systematic evaluation of drug treatment in palliative care units in a European country. More than 100 drugs were used for the patients in this study, though the majority of patients were treated with a small number of drugs. Many of the 'top 15' drugs were drugs included in the list of essential drugs of the World Health Organisation (WHO)[20] though cultural differences influenced the use of drugs, e.g., the high usage of dipyrone in Germany. Age and sex-related differences in drug therapy were seen, and more research is necessary to exclude possible undertreatment of symptoms in subgroups of patients, e.g., treatment of depression in older or male patients.

From the results of this study, drug checklists for the documentation forms for the next evaluation phase were constructed. The results also should be used to target the education of medical staff treating cancer patients at the 'top 15' drugs, transferring adequate knowledge on efficacy and side effects of these drugs. Adequate use of these drugs is one of the requirements of an empathic and humanistic accompaniment of patients in the last phase of their life.

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