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Gastrointestinal symptoms under opioid therapy: A prospective comparison of oral sustained-release hydromorphone, transdermal fentanyl, and transdermal buprenorphine

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ABSTRACT

Introduction: The purpose of this trial was to evaluate the effect of long-term treatment with oral sustained-release hydromorphone, transdermal fentanyl, and transdermal buprenorphine on nausea, emesis and constipation.

Patients and methods: Randomly selected outpatients with cancer pain receiving one of the study medications were enrolled in a prospective, open-labeled, controlled trial ($n = 174$). Mobility, pain, and gastrointestinal symptoms were assessed directly and per selected item on the ECOG (Eastern Cancer Oncology Group), EORTC (European Organisation for Research and Treatment of Cancer) questionnaires, NRS (Numerical Rating Scales), and analyzed statistically.

Results: Demographic and medical data were comparable in all groups. Only 15% of patients suffered from constipation. 59% took the prescribed laxatives. The incidence of stool free periods >72 h was significantly higher with transdermal opioids (transdermal fentanyl: 22%; transdermal buprenorphine: 21%; oral hydromorphone: 2%; $p = 0.003$). 21% of patients revealed nausea and emesis. The mean NRS for nausea (transdermal fentanyl:1.3; transdermal buprenorphine: 1.2; oral hydromorphone: 1.5; $p = 0.6$), the consumption of antiemetics (transdermal fentanyl: 42%; transdermal buprenorphine: 33%; oral hydromorphone: 36%; $p = 0.6$) and laxatives (transdermal fentanyl:53%; transdermal buprenorphine:66%; oral hydromorphone: 61%; $p = 0.2$) did not differ significantly, in contrast to the score for emesis (transdermal fentanyl: 16%; transdermal buprenorphine:13%; oral hydromorphone: 33%; $p = 0.02$). Morphine equivalent opioid doses differed (mg/d transdermal fentanyl: 183; transdermal buprenorphine: 89; oral hydromorphone: 143; $p = 0.001$), because of obvious tolerance varying after long-term treatment.

Conclusions: Gastrointestinal symptoms of cancer pain patients undergoing an opioid therapy are related to multifactorial causes. Transdermal opioids showed no benefit over oral controlled-release hydromorphone with regard to gastrointestinal symptoms. The conversion ratios for transdermal fentanyl, transdermal buprenorphine, and oral hydromorphone did not accord to the literature, because of differing occurrences of opioid tolerance after long-term therapy.

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1. Introduction

Gastrointestinal symptoms are common side effects of opioid therapy in cancer pain patients, severely impairing their quality of life. More than a quarter of this population suffers from adverse effects such as constipation, nausea and emesis. Numerous other etiologies and risk factors, such as age and gender, type, growth

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and stage of the cancer, inadequate nutrition, dehydration and immobilization contribute to these symptoms besides the opioid therapy (Derby and Portenoy, 1998; Lagman et al., 2005). Despite various treatment schemes, previous publications indicate that the management of gastrointestinal symptoms can be more difficult than therapy of the pain itself (Davis and Walsh, 2000; Levy, 2003). The occurrence of gastrointestinal adverse effects often leads patients to discontinue their opioid therapy which results in analgesic undertreatment (Cherny et al., 2001). The use of different opioids can be associated with a difference in the incidence of gastrointestinal symptoms. Previous studies indicate a lower incidence of gastrointestinal symptoms with *transdermal* administration of opioids compared with opioids administered orally. The transdermal mode of opioid administration is therefore often regarded as more advisable, but prospective comparisons of transdermal with oral opioids are rare and mostly refer to the "gold standard," morphine (Ahmedzai and Brooks, 1997; Payne et al., 1998; Haazen et al., 1999; Menten et al., 2002; Glare et al., 2006). The semi-synthetic opioid, hydromorphone, is however also reported to produce a low incidence of symptoms, but in spite of this, this substance has never been prospectively compared with transdermal opioids (Hays et al., 1994; Sarhill et al., 2001; Wirz et al., 2006). Most studies on opioids and symptoms are on *hospitalized patients* suffering from advanced stages of cancer rather than on outpatients, although the majority of cancer patients are actually treated as outpatients and do not stay in palliative care units (PCU) (Bruera et al., 1994; Fallon and Hanks, 1999).

We therefore evaluated whether oral hydromorphone, transdermal fentanyl and transdermal buprenorphine differ with respect to gastrointestinal symptoms in *outpatients* undergoing cancer pain therapy. We explored the incidence and severity of nausea, emesis and constipation, and the consumption of laxatives and antiemetics, with an opioid therapy consisting of either oral sustained-release hydromorphone, transdermal fentanyl, or transdermal buprenorphine.

2. Methods

2.1. Study design and assessment

This investigation was a prospective, open-labeled, controlled study enrolling outpatients consulting in our pain clinic, whereas many investigations on opioids for cancer pain are *retrospective* (Bruera et al., 1994; Lawlor et al., 1997; Fallon and Hanks, 1999). Demographic and general medical data – such as age, sex, cancer diagnosis, tumor grade and stage of disease, concurrent diseases or disorders, complete list of medication – were obtained directly by examining and interviewing the patients in the Outpatients clinic. They were asked to come to the pain clinic daily for examination and for data to be recorded. The data were collected by an investigator over a period of five consecutive days (Monday to Friday) using a standardized questionnaire.

In our experience, larger questionnaires with many elaborate items often overtax outpatients. We therefore confined ours to a small number of questions. The investigator assessed patients' mobility using the ECOG Performance Status scale and items 1–5 of the EORTC questionnaire (EORTC QLQ 30, version 3) (1: not at all, 2: a little, 3: quite a bit, 4: very much). The intensity of pain at rest, the intensity of nausea, and constipation was assessed once daily using the numerical rating scale (NRS, 0–10, 0 = no symptom, 10 = worst symptom imaginable), and the use of analgesics, laxatives or antiemetics was recorded. Additionally, categorical parameters were assessed by *counting* such events as the incidence of emesis and defecation, which cannot be rated by the NRS. The definition of constipation is that it is a subjective symptom involving complaints of decreased stool frequency (Oken et al., 1982; McShane and McLane, 1985; Portenoy, 1987), but for pragmatic reasons, we defined *constipation as* a stool free interval of more than 72 h in combination with an NRS score for constipation greater than 4. Furthermore, items 14 (nausea), 15 (emesis), and 16 (constipation) of the validated EORTC questionnaire were assessed by the investigator (Aaronson et al., 1993).

Legend 1 ECOG performance status

Grade 0: Fully active, able to carry on all pre-disease performance without restriction.
Grade 1: Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work.
Grade 2: Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
Grade 3: Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
Grade 4: Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
Grade 5: Dead.

Legend 2 Selected EORTC items

Mobility
Item 1 "Do you have trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?"
Item 2 "Do you have any trouble taking a long walk?"
Item 3 "Do you have any trouble taking a short walk out of the house?"
Item 4 "Do you need to stay in bed or in a chair during the day?"
Item 5 "Do you need help with eating, dressing, washing yourself or using the toilet?"
Nausea, Emesis, Constipation
Item 14: "Have you felt nauseated?"
Item 15: "Have you vomited?"
Item 16: "Have you been constipated?"

2.2. Patients

Considering ethical concerns about randomizing cancer pain patients, we chose the alternative methodical approach of random selection. After identifying outpatients undergoing pain therapy consisting of one of the study medications, patients were selected for participation by a computer generated random selection scheme. In accordance with the requirements of the local ethics committee, we *first* selected patients by randomly and *then* asked them to participate after giving their informed consent. To avoid opioid-naïve patients being enrolled, only patients who had already taken one of the study medications for longer than 4 weeks were included. After the enrolment of 62 patients per group the study was finalized.

Inclusion criteria were cancer related pain, pure nociceptive pain, opioid therapy with one of the study medications for longer than 28 days, strictly ambulatory treatment, the patient's cooperation, and a score of 0–3 on the ECOG Performance Status scale. Criteria for exclusion included referral for inpatient treatment,

diarrhea and diseases that are likely to cause diarrhea (e.g. carcinoma of the pancreas), neuropathic or mixed pain, breakthrough pain, severe incidental pain (NRS > 5), communication deficits, hepatic or renal impairment with the risk of accumulation, conditions likely to interfere with transdermal or oral administration or with drug absorption, current chemotherapy, radiotherapy, immobilization or inability to walk, entering the terminal phase, infections, prior history of drug addiction or alcohol abuse, and concomitant treatment with other opioid analgesics during the study period. Modification of the dose of study opioids was a particular reason for exclusion.

2.3. Medication

Patients received an oral formulation of hydromorphone with a prolonged duration of action of 12 h, transdermal fentanyl, or transdermal buprenorphine. We calculated morphine equivalent daily doses according to the data of previous publications (Donner et al., 1996; Menten et al., 2002; Payne et al., 1998; Pereira et al., 2001; Sittl et al., 2003; Sittl et al., 2005, 2006). With regard to oral hydromorphone we used 2 different conversion ratios producing a ratio of oral hydromorphone:oral morphine = 1:5 and a ratio of oral hydromorphone:oral morphine = 1:7.5 because of contradictory previous publications (Bruera et al., 1994; De Stoutz et al., 1995; Hays et al., 1994; Lawlor et al., 1997; Miller et al., 1999; Moriarty et al., 1999; Sarhill et al., 2001; Wirz et al., 2006). If necessary, fast-acting formulations of the same drug were allowed (hydromorphone group: 1.3 mg or 2.3 mg hydromorphone, transdermal fentanyl group: 200 μg transmucosal fentanyl, transdermal buprenorphine group: 0.2 mg sublingual buprenorphine). However, severe breakthrough or incidental pain (NRS > 5) was an exclusion criterion. No opioids other than the study opioids were permitted during the course of the study. The investigators checked daily whether the administration of all analgesics (opioids, nonsteroidal anti-inflammatory drugs (NSAIDs), antidepressants, anticonvulsants), and adjuvants (laxatives, antiemetics) had been continued at the same dose levels. The opioid doses and all other medication, including for symptom control, were adjusted prior to the study. No variation was allowed during the course of the observation period.

2.4. Data documentation and analysis

All data obtained were documented in an electronic SPSS database (SPSS 12 for Windows) created for this purpose. The demographic and medical data, the data on the use and dosage of all the drugs, NRS scores of the parameters described were analyzed at all time points by descriptive statistics. Confirmatory statistical analysis of pain intensity and symptoms was used to detect differences in all treatment groups (ANOVA, Analysis of Variance). The primary statistical hypothesis examined whether the treatment groups differed with regard to the following points: the occurrence of stool free periods >72 h, the NRS or EORTC items of constipation, nausea, emesis, medication for symptom control, the use of analgesics and co-analgesics.

We assessed 'numerical parameters', such as NRS, and 'categorical parameters', such as numbers of patients revealing a symptom. Using ANOVA we analyzed mean NRS group scores for pain, constipation, nausea, ECOG scores, EORTC items (constipation, nausea, emesis), age, weight, length, duration of opioid therapy, opioid daily doses, daily doses of substances with constipating effects (when appropriate) (significance level 0.05). Analogously, we used the χ^2 test for analyzing the numbers of patients with several medications or symptoms, such as dipyrone, lactulose, the use of antiemetics, or emesis (significance level 0.05). The numbers of substances used in all groups were analyzed by the χ^2 test, and the doses of them by ANOVA. A post hoc power analysis examined whether the number of at least 3×50 participants was sufficient. To ensure that despite possible withdrawals, the number of patients enrolled with completely evaluable data would be adequate, the sample size was enlarged to 62 subjects per group (186). Statistical significance was defined as $p < 0.05$ for a two-tailed hypothesis.

3. Results

Between July 1st 2000 and December 31st 2006, 467 individuals of the 1212 outpatients with cancer pain were prescribed controlled release hydromorphone, transdermal fentanyl, or transdermal buprenorphine. After random selection of 298 patients being treated with one of the study opioids, 186 patients gave their consent to take part in the study. These patients met *all* inclusion criteria. Data could be evaluated completely from 174 patients. Fifty-eight patients received oral sustained-release hydromorphone, 61 transdermal buprenorphine, and 55 transdermal fentanyl. A post hoc power analysis was performed to cross-check the sample size of the participants, which yielded a power of 100% (effect size $w = 1.7860$, $\alpha = 0.05$; total sample size = 174, df = 2, power: 1.000, critical $\chi^2 = 5.9915$; $\lambda = 555.0245$). Inconsistent appearance at the pain clinic ($n = 7$), the occurrence of incidental pain ($n = 4$; NRS > 5), intermittent pain at rest ($n = 3$) or the use of other substances ($n = 2$) which had been prescribed by other doctors led to exclusion of these patients.

Medical and demographic data, medication and symptoms are presented in Tables 1–4.

Besides their cancer (Fig. 1), patients suffered from diseases such as hypertension (transdermal fentanyl: $n = 5$, transdermal buprenorphine: $n = 4$, oral hydromorphone: $n = 6$), mild coronary heart disease (transdermal fentanyl: $n = 2$, transdermal buprenorphine: $n = 6$, oral hydromorphone: $n = 6$), pulmonary diseases (transdermal fentanyl: $n = 4$, transdermal buprenorphine: $n = 1$, oral hydromorphone: $n = 1$) or had a history of cardiac arrhythmia (transdermal fentanyl: $n = 0$, transdermal buprenorphine: $n = 2$, oral hydromorphone: $n = 1$). In compliance with the exclusion criteria, treatment of all these diseases was well adjusted. No patients suffered from renal or hepatic impairment.

All patients were pretreated with their current opioid therapy for more than 28 days and experienced pure nociceptive pain. Overall, mean pain intensity in all groups was comparable (Table 1). Several patients reported an overall pain intensity at rest higher than 5 (transdermal fentanyl: $n = 4$, transdermal buprenorphine: $n = 5$, oral hydromorphone: $n = 5$), but they continued their analgesic therapy unwilling to modify their opioid medication.

For the treatment of *incidental* pain (osseous metastases, pain due to movement or scars) 18 patients used additional medication with fast-acting formulations of their opioids (transdermal fentanyl: transmucosal fentanyl $n = 5$, transdermal buprenorphine: sublingual buprenorphine $n = 5$, oral hydromorphone: fast-acting oral hydromorphone $n = 8$), but all reported NRS scores for pain lower than 5. More patients treated with oral hydromorphone and transdermal buprenorphine used dipyrone (metamizole) as an additional analgesic.

Overall, nausea and emesis persisted in 20.7% of patients after long term treatment with opioids. The *mean* intensity scores (NRS) for nausea and constipation did not differ significantly between the treatment groups (Nausea: $p = 0.632$, ANOVA; Constipation: $p = 0.935$; Table 4), despite a slight tendency to higher NRS scores for nausea and constipation in the transdermal fentanyl group. In addition there were no significant differences in the calculated *daily mean defecation rate* per group and the use of antiemetics between treatment groups. The number of patients with

Table 1
Demographic and medical data, mobility scores, use of analgesics, pain at rest (all days)

	Transdermal fentanyl	Transdermal buprenorphine	Oral hydromorphone	*p*
Age (years, mean, SD) (min, max, median)	64.1 ± 11.6 (37, 85, 66)	65.3 ± 10.7 (39, 85, 66)	67.8 ± 11.2 (31, 79, 62)	0.078 (ANOVA)
Gender (male/female)	28/27	36/25	34/24	0.019 (ANOVA)
Height (cm, mean, SD) (min, max, median)	168.2 ± 9.3 (152, 182, 168)	169 ± 9.2 (152, 186, 168)	170.6 ± 9.3 (155, 189, 171)	0.357 (ANOVA)
Weight (kg, mean, SD) (min, max, median)	64 ± 11.6 (47, 104, 64)	68.9 ± 9.2 (50, 90.1, 68)	64.5 ± 11.2 (51, 93.1, 60)	0.30 (ANOVA)
ECOG score (0–5) (mean, SD)	2.1 ± 1.3	1.9 ± 0.8	2.4 ± 0.8	0.012 (ANOVA)
EORTC item 1 (1–4) (mean, SD)	3 ± 1.2	3.5 ± 0.8	2.9 ± 1	0.003 (ANOVA)
EORTC item 2 (1–4) (mean, SD)	3 ± 1.1	3.4 ± 0.7	2.8 ± 1.1	0.003 (ANOVA)
EORTC item 3 (1–4) (mean, SD)	2.5 ± 1.2	2.2 ± 1	2.1 ± 1	0.062 (ANOVA)
EORTC item 4 (1–4) (mean, SD)	2.4 ± 1.4	2.2 ± 0.9	1.9 ± 1	0.029 (ANOVA)
EORTC item 5 (1–4) (mean, SD)	1.6 ± 1	1.4 ± 0.8	1.6 ± 0.7	0.511 (ANOVA)
Pain at rest (NRS, mean, SD) (min, max, median)	2.8 ± 2.8 (0, 5.1, 2.6)	3 ± 2.3 (0, 4.8, 2.9)	3.3 ± 1.9 (0, 4.6, 3.2)	0.505 (ANOVA)
Duration of opioid use (days, mean, SD) (min, max, median)	206.9 ± 291.2 (28, 1250, 90)	174.1 ± 222.5 (28, 750, 90)	92.9 ± 115.9 (28, 730, 60)	0.019 (ANOVA)
Opioid daily dose (mg, mean, SD) (min, max, median)	ME: 1:100 183.3 ± 131.74 (60, 720, 120)	ME: 1:75 88.52 ± 39.8 (30, 180, 90)	ME 1:5 143.2 ± 125.4 (20, 520, 80) ME 1:7.5 214.8 ± 188.2 (30, 780, 120)	<0.001 (ANOVA) <0.001 (ANOVA)
Use of dipyrone (*n*)	26	23	31	0.221 (χ^2)
Use of NSAIDs (*n*)	14	14	22	0.159 (χ^2)

EORTC 1: not at all, 2: a little, 3: quite a bit, 4: very much Opioid doses include sustained-release and additional fast-acting opioids as rescue medication. ME: Morphine equivalence.
The ANOVA results refer to differences of mean daily doses, demographic parameters, ECOG score, EORTC items.

Table 2a
Additional use of a medication with potentially constipating effects

	Transdermal fentanyl	Transdermal buprenorphine	Oral hydromor-phone	*p*
Patients with a constipating medication (*n*)	28	28	26	0.788 (χ^2)
Number of different substances (sum)	44	36	57	
Amitriptyline (*n*)	4	10	18	0.004 (χ^2)
mg/d, mean, SD (min, max, median)	31.3 ± 12.5 (25, 50, 25)	30 ± 10.5 (25, 50, 25)	22.5 ± 5.8 (10, 25, 25)	0.043 (ANOVA)
Verapamil (*n*)	0	2	0	n.d.
mg/d, mean, SD (min, max, median)		170 ± 14.1 (160, 180, 170)		
Nifedipine (*n*)	0	3	4	n.d.
mg/d, mean, SD (min, max, median)		20 ± 0 (20, 20, 20)	25 ± 10 (20, 40, 20)	0.437 (ANOVA)
Furosemide (*n*)	7	8	4	0.484 (χ^2)
mg, mean, SD (min, max, median)	33.3 ± 11.5 (20, 40, 40)	20	20 ± 0 (20, 20, 20)	0.658 (ANOVA)
Pantoprazole (*n*)	24	15	22	0.138 (χ^2)
mg, mean, SD (min, max, median)	47.1 ± 21 (10, 80, 40)	34.5 ± 20.9 (10, 80, 25)	38.6 ± 14.1 (20, 80, 40)	0.094 (ANOVA)
Antiemetics (*n*) (except metoclopramide)	16	12	9	0.197 (χ^2)

The ANOVA results refer to differences of mean daily doses.
n.d.: Not determined.

Table 2b
Antiemetic medication (except metoclopramide)

Antiemetics	Transdermal fentanyl	Transdermal buprenorphine	Oral hydromor-phone
Haloperidol (*n*)	4	0	2
mg/d, mean, SD (min, max, median)	1.9 ± 1.2 (0.6, 3.5, 1.75)		1.3 ± 0.4 (1, 1.5, 1.3)
Promethazine (*n*)	2	0	1
mg, mean, SD (min, max, median)	17.5 ± 10.6 (10, 25, 17.5)		20
Dimenhydramine (*n*)	1	1	3
mg/d, mean, SD (min, max, median)	25	50	50 ± 0 (50, 50, 50)
Ondansetrone (*n*)	0	0	4
mg/d, mean, SD (min, max, median)			12 ± 4.6 (8, 16, 12)

No calculation of *p* values due to the small numbers.

emesis was significantly lower in both transdermal groups whereas the *mean* NRS score for nausea did not differ.

In the transdermal buprenorphine and transdermal fentanyl group, more patients were treated with substances with potentially constipating effects. There were obvious differences in the number of patients with a stool-free interval of more than 3 days ($p = 0.003$, χ^2; Table 4). Twenty-six patients (14.9%) met the definition of constipation by combining NRS scores for constipation of at least 5, an EORTC item score of 4, and a stool-free interval of more than three days (transdermal fentanyl: 12, transdermal buprenorphine: 13, oral hydromorphone: 1). Differences in the use of laxatives were insignificant ($p = 0.217$, χ^2; Table 4). Regardless of the policy of prescribing laxatives, 72 outpatients (41.4%) refused to take them.

Table 3
Constipation, nausea, and emesis

	Transdermal fentanyl	Transdermal buprenorphine	Oral hydromor-phone	*p*
Constipation (NRS) mean, SD (min, max, median)	2.4 ± 3 (0, 9, 0)	2.2 ± 2.7 (0, 9, 1)	2.2 ± 2.3 (0, 8, 1)	0.935 (ANOVA)
EORTC (1–4) item – constipation mean, SD (min, max, median)	2.1 ± 1.3 (1, 4, 2)	2.3 ± 1.3 (1, 4, 2)	1.9 ± 1 (1, 4, 2)	0.163 (ANOVA)
Mean defecation rate (1/day) mean, SD (min, max, median)	0.7 ± 0.6 (0, 2.6, 0.6)	0.8 ± 0.6 (0, 2.4, 0.8)	0.8 ± 0.5 (0, 2.4, 0.6)	0.577 (ANOVA)
Stool-free interval >72 h: number of patients[a] (*n*)	12	13	1	0.003 (χ^2)
Use of laxatives: number of patients (*n*)	27	39	36	0.217 (χ^2)
Nausea (NRS) mean, SD (min, max, median)	1.3 ± 2.2 (0, 9.8, 0)	1.2 ± 1.7 (0, 5.4, 0)	1.5 ± 1.9 (0, 8, 0.7)	0.632 (ANOVA)
EORTC item – Nausea (1 – 4) mean, SD (min, max, median)	1.8 ± 1.1 (1, 4, 1)	1.7 ± 0.9 (1, 4, 1)	1.8 ± 1 (1, 4, 2)	0.887 (ANOVA)
Emesis: number of patients (*n*)	9	8	19	0.019 (χ^2)
Emesis (1/day) mean, SD (min, max, median)	0.1 ± 0.3 (0, 2, 0)	0.1 ± 0.3 (0, 1.8, 0)	0.1 ± 0.3 (0, 1.6, 0)	0.553 (ANOVA)
EORTC item – Emesis (1–4) mean, SD (min, max, median)	1.6 ± 0.9 (1, 4, 1)	1.4 ± 0.8 (1, 4, 1)	1.4 ± 0.8 (1, 4, 1)	0.346 (ANOVA)
Use of antiemetics: number of patients (*n*)	23	19	22	0.601 (χ^2)

The ANOVA results refer to differences of mean NRS, EORTC items, mean defecation rates.
[a] Stool-free interval >72 h together with an NRS score (constipation) >4.

Table 4
Use of laxatives and metoclopramide

	Transdermal fentanyl	Transdermal buprenorphine	Oral hydromor-phone	*p*
Laxatives: number of patients (*n*)	27	39	36	0.217 (χ^2)
Cumulative number of different substances (sum)	43	53	49	n.d.
Sodium picosulphate (*n*)	8	9	11	0.766 (χ^2)
mg/d, mean, SD (min, max, median)	11.5 ± 7.2 (5, 25, 11)	10 ± 0 (10, 10, 10)	11.5 ± 5.5 (5, 22.5, 10)	0.774 (ANOVA)
Lactulose (*n*)	11	9	5	0.225 (χ^2)
g/d, mean, SD (min, max, median)	18.8 ± 5.8 (7, 27, 20)	16.3 ± 8.9 (13.3, 40, 13)	32 ± 17.9 (13.3, 53.4, 40)	0.030 (ANOVA)
Polyethylene glycol (*n*)	12	19	20	0.311 (χ^2)
g/d, mean, SD (min, max, median)	20.7 ± 7.2 (13.8, 27.6, 20.7)	21.8 ± 7.0 (13.8, 27.6, 27.6)	20 ± 9.5 (13.8, 41.4, 13.8)	0.790 (ANOVA)
Paraffin (*n*)	0	0	1	n.d.
mg/d			30	
Bisacodyl (*n*)	0	2	0	n.d.
mg/d		20 ± 14.1 (10, 30, 20)		
Metoclopramide (*n*)	12	14	12	0.956 (χ^2)
mg/d	22.5 ± 13.1 (5, 40, 20)	12.4 ± 6.5 (4, 24, 10)	23.7 ± 10.7 (12, 40, 22)	0.014 (ANOVA)

The ANOVA results refer to differences of mean daily doses.
n.d.: Not determined.

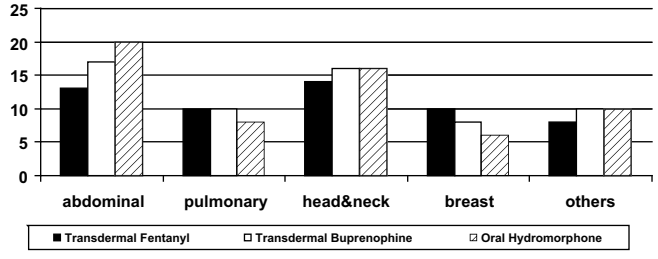

Fig. 1. Cancer diagnosis in patients treated with transdermal fentanyl ($n = 55$), transdermal buprenorphine ($n = 61$), and oral sustained-release hydromorphone ($n = 58$).

4. Discussion

Studies on cancer pain treatment in ambulatory patients are rare. Our interest focused on *outpatients* instead of inpatients with an advanced stage of cancer who are in hospitals, palliative care units or hospices (Bennett and Cresswell, 2003; Mercadante et al., 2006) The drop-out rate was very small. The demographic and medical data of all patients were comparable. No patient revealed a severe organ malfunction.

Extended symptom assessments or invasive procedures cannot be used in an ambulatory pain clinic and limitation to a few items was therefore necessary (McShane and McLane, 1985; Bruera et al., 1994; Agachan et al., 1996; Lundin et al., 2004). In our structured protocol, we used validated NRS to detect subjective discomfort produced by nausea and constipation, and in addition recorded the incidence of emesis and defecation. All assessment methods produced congruent results (Bruera et al., 1991; Aaronson et al., 1993; Derby and Portenoy, 1998).

Certain items, such as the *mean* defecation rate calculated per day or the consumption of laxatives, which is regarded as a parameter of constipation proved no tool for detecting constipation (Derby and Portenoy, 1998; Mancini et al., 2000) Using the parameter "72-h stool-free period" in combination with an NRS score >4 (Edmonton Assessment Score) led to an easily applicable assessment tool, which furthermore correlated with the corresponding EORTC item. Previous studies exhibit shortcomings such as a lack of description of the assessment modes, reference to the ICD code only, restriction to a few items, no assessment of defecation frequency, or being a retrospective study (Bruera et al., 1994; Haazen et al., 1999; Fallon and Hanks, 1999; Radbruch et al., 2001; Staats et al., 2004; Glare et al., 2006).

According to previous references nausea and emesis usually attenuate during the course of the therapy (Campora et al., 1991; Lindley et al., 1992; Cherny et al., 2001; Gralla et al., 2005; The Antiemetic Subcommittee of the Multinational Association of Supportive Care in Cancer (MASCC), 2006). However, 21% of our patients showed no attenuation, despite their long-term opioid therapy with constant dosages and sufficient analgesia, regardless of the opioid (Tables 2 and 4). We could not detect significant differences in the scores for nausea or the consumption of antiemetics. The clear differentiation between cancer-induced, cancer

associated, and therapy-induced symptoms may be difficult, as demonstrated by the emesis rates in the hydromorphone group which did not correlate. Emesis was possibly *associated with* a higher number of gastrointestinal *tumors* in the hydromorphone group, even if insignificant (Bruera et al., 1991; Campora et al., 1991; Moriarty et al., 1999).

In contrast with previous studies the incidence of constipation (14.9%) was low-approximating to the incidence in the *general* population (Drossman et al., 1993; Papagallo, 2001). O*nly 61.5%* of all patients took the prescribed laxatives, indicating obvious differences between 'healthier' outpatients and immobilized inpatients at an advanced stage of their cancer (Fallon and Hanks, 1999; Bennett and Cresswell, 2003; Lagman et al., 2005; Levy, 2003). This study did not reveal any benefits of certain laxatives, such as lactulose over other substances, maybe due to it's design.

The prescription of different laxatives and the distribution of substances with constipating potential were comparable in all groups, too (Tables 2a,b and 4). In our pain clinic, amitryptiline, an antidepressant with constipating effects, is a standard treatment for sleep disorders, and did not lead to a higher incidence of constipation in the hydromorphone group.

Surprisingly, the parameter *stool-free interval of more than 72 h* and the EORTC item 'constipation' scored higher with transdermal administration of opioids (Haazen et al., 1999). Earlier publications demonstrated a dose related increase in gastrointestinal symptoms with transdermal buprenorphine, or an incidence of constipation of up to 40% with transdermal fentanyl (Menten et al., 2002; Sittl et al., 2003), or revealed no advantages of transdermal opioids related to quality of life parameters or economic aspects (Ahmedzai and Brooks, 1997).

The higher mean group NRS scores for pain (even if insignificant) and the more frequent prescription of amitryptiline might hint at relatively lower opioid doses in correlation to pain levels. Hypothetically, this could indicate undertreatment producing a lower incidence of constipation in the hydromorphone group. However, this theory must be refuted because pain levels revealed no significant differences.

There is a paucity of data on the question of whether opioid induced constipation is dose related or substance related, and what data there is, is ambiguous, reporting either no significance at all or characteristic dose response curves (Portenoy, 1987; Fallon and Hanks, 1999; Sykes, 1998). Contradictory, in this trial constipation does not correlate with the dose of opioid, supporting the controversial discussion on different opioid types and their impact on constipation (Miller et al., 1999; Moriarty et al., 1999; Mancini et al., 2000; Papagallo, 2001; Lagman et al., 2005; Wirz et al., 2006).

In contradiction to the above, the occurrence of constipation might have been related to the mobility status of patients in this investigation. Whereas the ECOG score was significantly higher in the hydromorphone group, several items scored higher in the transdermal groups. Furthermore, the significant differences in mobility scores contrasted with the homogeneity of the cancer diagnoses in the groups possibly due to the lack of randomization. Nevertheless, previous studies seldom provide information on these parameters. However, the ambiguous results of the mobility scores unmistakably reverse such a conclusion, and again hint at the multifactorial causes of gastrointestinal symptoms in cancer pain patients (Hays et al., 1994; Bruera et al., 1994; Sykes, 1998; Fallon and Hanks, 1999; Bennett and Cresswell, 2003; Mercadante et al., 2006).

Mean pain intensity did not differ significantly. In contrast to other studies focusing on pain the endpoint of our investigation was gastrointestinal symptoms. Therefore we excluded various medications (rescue dosing) associated with higher mean pain levels, breakthrough pain, strong incidental pain, or end-of-dose failure, because of the possibility of inducing opioid dose related effects (Fallon and Hanks, 1999; Lawlor et al., 1997; Zeppetella et al., 2000; Mancini et al., 2000; Papagallo, 2001; Mercadante et al., 2006).

Only a few publications exist referring to long-term dosing of opioids (Pereira et al., 2001). In contrast previous data we used strictly the *oral or transdermal* route of administration, supplemented by fast-acting formulations if necessary (Hays et al., 1994; De Stoutz et al., 1995; Sykes, 1998; Moriarty et al., 1999). The different durations of use for the different products may be explained by their availability on the German market at the time of this investigation: the fast-acting formulation of hydromorphone was introduced later than transmucosal fentanyl, or sublingual buprenorphine. The significantly lower morphine equivalent doses of the partial agonist buprenorphine compared with the mu agonists, fentanyl and hydromorphone, concurs with previous publications reporting less tolerance with long-term buprenorphine. This study demonstrates for the first time prospectively the different degrees of tolerance of buprenorphine versus other mu agonists (Morgan et al., 1999; Sittl et al., 2005, 2006). It does not therefore correspond with the conversion factors which are discussed controversially (Donner et al., 1996; Ahmedzai and Brooks, 1997; Payne et al., 1998; Pereira et al., 2001; Sittl et al., 2003).

Both conversion ratios of hydromorphone (1:5, 1:7.5) resulted in *significant* dose differences because of the lower morphine equivalent doses in the buprenorphine group. However, no data are available on the ratios for conversion of the transdermal opioids to oral hydromorphone. These results might thus serve as a *preliminary* calculation for conversion ratios for *long-term therapy* (Bruera et al., 1996; Miller et al., 1999; Pereira et al., 2001; Weinstein et al., 2006). Despite lacking significance, more patients treated with hydromorphone and fentanyl received dipyrone and, patients with hydromorphone received insignificantly more NSAIDs. These differences may hint at worse tolerability, as doctors preferred opioid sparing drugs to escalating the doses of opioids, or a lower opioid tolerance under buprenorphine leading to less prescription of opioid sparing substances. However, all groups were comparable with regard to their pain scores.

5. Conclusions

In our *outpatient* cohort with cancer pain, the overall incidence of gastrointestinal symptoms was low. The use of transdermal fentanyl or buprenorphine revealed no benefit over oral controlled-release hydromorphone for gastrointestinal symptoms. Nevertheless, it remains unclear whether these effects are caused by the different opioid types, whether they are dose related, related to mobility status, or are associated with the cancer.

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