Original Article

The Burden of Opioid Adverse Events and the Influence on Cancer Patients' Symptomatology

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Abstract

Context. Opioids are frequently used for the treatment of moderate-to-severe pain and their use may produce a number of unwanted adverse events (AEs).

Objectives. The objective of this study was to understand the burden of opioid-induced AEs in cancer patients with pain after the introduction of strong opioids (WHO Step III).

Methods. This is a cohort study derived from a randomized controlled trial involving 498 cancer patients with pain who received strong opioids. During 28-day follow-up, we analyzed frequency, intensity, and changes over time of the main opioid-induced AEs; the influence of previous pain therapy on AEs; and the relationships between the presence of AEs and analgesic response.

Results. After starting strong opioids, dry mouth, nausea, and vomiting immediately increased and persisted over time, constipation continued to increase, while drowsiness and confusion tended to decrease. Patients previously treated with weak opioids had more frequent and severe AEs. While at all observation points the percentage of patients without AEs was 37%−39%, considering all the five scheduled visits, from Day 3 to Day 28, 17% of patients never experienced any AEs, while 48% of patients had four or more concomitant AEs. Patients with no AEs experienced significantly lower pain intensity.

Conclusion. Opioid introduction induces various AEs that persist over time and worse patients' symptomatology. Moreover, there seems to be a different expression of the opioid toxicity among patients, and a possible interaction between AEs and the analgesic response. The balance between the opioids analgesic effect and induced toxicity is fundamental in deciding the best management for pain in cancer patients. J Pain Symptom Manage 2019;57:899−908.

Key Words

Cancer pain, opioids, adverse events, symptoms

Introduction

Pain affects 39% to 64% of cancer patients depending on the stage of the disease and needs appropriate treatments.[1] Opioids are frequently used for the treatment of moderate-to-severe pain as suggested by major international guidelines and recommendations.[2−4] Most of the studies showed a good effectiveness of opioids for cancer pain treatment[5−7] but their use may cause a variable analgesic response and produce a number of unwanted adverse events (AEs). Good analgesic response to opioids, with a pain intensity decrease ≥30%, was recently observed in 75% of

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cancer patients,[7] but the remaining 25% of the patients were classifiable as poor responders, with a pain decrease <30% (13%), or as nonresponders, when their pain did not change or worsened (12%).

Opioid use could induce the onset of various AEs, sometimes severe and not always easy to handle. The most common opioid-induced AEs are nausea, vomiting, constipation, dry mouth, drowsiness, and confusion, whereas other AEs, such as hallucinations, breathlessness, myoclonus, dysuria, and itching, have been less frequently reported.[8,9] Some of these negative effects, for example nausea, may not only be a consequence of the opioid treatment but also derive from the disease itself, its localization, concurrent chemotherapy, or other concomitant medications.[10–13] Opioid-induced AEs often overlap with the symptoms that cancer patients experience during the course of the disease.

In general, the prevalence and characteristics of various AEs have been reported among the safety evaluations of clinical trials aimed to test opioid efficacy on cancer pain.[8,9] Only a few studies, however, specifically focused on such AEs and evaluated their frequency and intensity at different times after the opioid introduction.[5,14–16]

We carried out this analysis with the aim of understanding how starting a treatment with strong (WHO step III) opioids in patients with moderate-to-severe cancer pain could change patients' clinical symptomatology. We evaluated the distribution, intensity, and duration of AEs in the cancer patients' population, the influence of previous pain therapy on these AEs, the distribution of AEs frequency among the patients, and the possible relationship between AEs and analgesic response.

Methods

This is a cohort study derived from a randomized, open-label, longitudinal (28 days), Phase IV clinical trial on 520 cancer patients with moderate-to-severe pain requiring WHO Step III opioids conducted in 2010–2011.[17] Patients were recruited at 44 Italian centers and randomized (1:1:1:1 ratio) to receive either oral morphine (active comparator), or transdermal buprenorphine, or oral oxycodone, or transdermal fentanyl. Patients' eligibility criteria included diagnostic evidence of locally advanced or metastatic tumor, persistent moderate-to-severe cancer pain, need for strong opioids never previously administered, and age ≥18 years. Exclusion criteria included cerebral tumors and leukemia, concurrent radiotherapy, first-line chemotherapy during the seven days before randomization, nonpharmacological analgesic treatment, and preexisting renal failure. Titration of the initial dose of opioids was based on the recommendations of the European Association for Palliative Care,[1] which suggest starting with 30 to 60 mg daily of morphine-equivalent, depending on the patient's age, general clinical condition, and previous analgesic treatment. The changes of opioid doses over the period of observation were chosen by the physicians on the basis of the patients' clinical needs. The study was approved by the institutional review boards of each center, and patients gave written informed consent before any study-related activities were carried out.

Patients received six evaluations, one at Day 1 (baseline) and at five subsequent visits (at Days 3, 7, 14, 21, and 28). The last available visit could be either the visit at the end of the follow-up (Day 28) or at the moment of a premature discontinuation of the study for any reason occurred.

At the baseline, patients' clinical aspects recorded were as follows: oncological medical history (primary tumor site, presence and localization of metastases, previous and ongoing cancer treatments), concomitant diseases and treatments, Karnofsky Performance Status (KPS), average pain intensity (API), and worst pain intensity (WPI) experienced by the patients in the 24 hours before the visit, measured on a numeric rating scale from 0 (no pain) to 10 (worst imaginable pain), and psychological status (anxiety, worry, irritability, and depression).

At all visits, AEs due to previous pain therapies (i.e., nonopioid analgesics or weak opioids) (at Day 1) or to strong opioids (at Day 3 to 28) were assessed by means of a four-point verbal rating scale (i.e., no, mild, moderate, and severe), partially adapted from the Therapy Impact Questionnaire.[18] The questionnaire was self-reported by the patients who attributed to the presence and intensity of the AEs. Twelve AEs were considered: breathlessness, confusion, constipation, drowsiness, dry mouth, dysuria, gastralgia, hallucinations, itching, myoclonus, nausea, and vomiting.

Four hundred ninety-eight patients without major violations of the eligibility criteria and with at least a second pain evaluation after baseline were considered.[19] Because no difference in the frequency of the AEs was observed across the four assigned opioids,[17] in this secondary analysis, we considered the population of treated patients as a unique sample, without distinction according to the opioid assigned.

Statistical Analysis

We calculated the absolute and relative frequency of the AEs by dichotomizing the original variables as absence versus presence of symptoms at any degree (i.e., mild, moderate, and severe). For the six most frequent AEs (i.e., confusion, constipation, drowsiness, dry mouth, nausea, and vomiting), we also

analyzed intensity, combining moderate and severe categories, due to the low number of AEs of severe intensity. *P*-values for the differences between the frequency/intensity at Day 1 and at Day 3, and between Day 3 and Day 28 were tested using the McNemar test.

Furthermore, to analyze the patterns of the six most frequent AEs during the five visits (from Day 3 to Day 28) and the modifying effect of selected patients' characteristics (i.e., sex, age, previous pain therapy, pain therapy assigned at random, primary site of tumor, ongoing anticancer therapy, and KPS), we used mixed-effects models for repeated measures. These models allow a general unstructured covariance matrix and enable the inclusion of data from patients who had missing data at some scheduled time points.

We also computed total number of the six major AEs experienced at single visits and overall from Day 3 to Day 28. We then categorized patients according to the total number of these six major AEs and estimated the linear trend in API and WPI across AE categories using ANOVA. All analyses were carried out with the SAS software (version 9.4; SAS Institute, Cary, NC).

Results

Table 1 shows demographic and main clinical characteristics of 498 cancer patients at Day 1. Mean age was 66.9 years; 44.4% were females; major primary sites of the tumor were lung and respiratory systems (28.3%), followed by digestive (22.9%), genitourinary, and reproductive (18.9%) systems; 85.1% of patients presented metastasis; 38.4% of patients had ongoing anticancer therapy; API was 6.0 and WPI was 8.0; 73.5% of patients were previously treated with weak opioids. Patients were administered with either oral morphine, or oral oxycodone, or transdermal buprenorphine, or transdermal fentanyl (about 25% in each treatment group); 11.5% of patients had KPS ≤40; and 64.3% presented at least one concomitant disease.

Table 1
Demographic and Main Clinical Characteristics of 498 Cancer Patients at Day 1 (Baseline)

Patients' characteristics	Cancer Patients *n* (%)
Age (yrs), mean (SD)	66.9 (11.8)
Sex, female	221 (44.4)
Primary site of tumor	
Lung/Respiratory system	141 (28.3)
Digestive system	114 (22.9)
Genitourinary/Reproductive system	94 (18.9)
Breast	65 (13.1)
Other	84 (16.8)
Presence of metastasis	424 (85.1)
Pain	
Average pain intensity, mean (SD)	6.0 (1.4)
Worst pain intensity, mean (SD)	8.0 (1.5)
Previous pain therapy	
No analgesics (WHO Step 0)	48 (9.6)
Nonopioids (WHO Step I)	84 (16.9)
Weak opioids (WHO Step II)	366 (73.5)
Pain therapy assigned at random	
Oral morphine	122 (24.5)
Oral oxycodone	125 (25.1)
Transdermal buprenorphine	127 (25.5)
Transdermal fentanyl	124 (24.9)
Karnofsky Performance Status, mean (SD)	66.9 (17.0)
≤40	57 (11.5)
41–70	273 (54.8)
≥71	168 (33.7)
Ongoing anticancer therapy	191 (38.4)
Concomitant diseases	320 (64.3)
Concomitant medications	278 (86.9)

Table 2 depicts the distribution of the 12 AEs at Day 1, Day 3, and Day 28 after the introduction of WHO III opioids, both overall and according to previous pain therapy (no opioids, WHO Step 0–I, and weak opioids, WHO Step II). At Day 1, the most frequent reported AEs (>10%) were constipation, dry mouth, drowsiness, nausea, and confusion. At Day 3, the frequency of all AEs significantly increased, with the exception of breathlessness, gastralgia, and myoclonus. At Day 28, only the frequency of breathlessness and constipation significantly increased as compared to Day 3, whereas it significantly declined for drowsiness and itching and was not significantly reduced or stable for the remaining AEs.

In opioid-naïve patients, the frequency of all AEs was low (0%–3.8%) at Day 1, whereas in patients treated with weak opioids, it was already >10% for most AEs, except hallucinations, dysuria, vomiting, and itching (0.8%–5.7%; Table 2). In opioid-naïve patients, the frequency of all AEs largely increased from Day 1 to Day 3 (significantly for breathlessness, confusion, constipation, drowsiness, dry mouth, nausea, and vomiting); at Day 28, it further increased, though not significantly, for constipation, gastralgia, hallucinations, myoclonus, and vomiting. The time patterns of patients treated with weak opioids were consistent with those among the overall study patients.

The frequency of the six more frequent opioid-induced AEs for all patients during the period of observation (from Day 1 to Day 28) is presented in Fig. 1. After the significant increases between Day 1 and Day 3, the frequency of dry mouth, nausea, and vomiting remained almost stable in the following visits; conversely, frequency of confusion and drowsiness significantly declined, while frequency of constipation significantly increased.

Fig. 2 shows the frequency of the six AEs in patients treated with no opioid medications and weak opioids. At Day 1, the frequency of all AEs was significantly higher in patients previously treated with weak opioids than in opioid-naïve patients, except for vomiting. This difference remained significant for constipation,

Table 2
Frequency of Adverse Events (AEs) at Day 1 (Baseline) and After the Introduction of Strong Opioids (WHO Step III), Overall and According to Previous Opioid Treatment, Among 498 Cancer Patients

	Overall			Previous Treatments					
				No Opioids (WHO Step 0–I) ($N = 132$)			Weak Opioids (WHO Step II) ($N = 336$)		
	Day 1	Day 3	Day 28[a]	Day 1	Day 3	Day 28[b]	Day 1	Day 3	Day 28[c]
AEs	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
Breathlessness	40 (8.0)	36 (7.2)	38 (9.7)[d]	1 (0.8)	7 (5.3)[e]	5 (5.2)	39 (10.7)	29 (7.9)[e]	33 (11.1)[d]
Confusion	52 (10.4)	119 (23.9)[e]	76 (19.3)	1 (0.8)	24 (18.2)[e]	18 (18.8)	51 (13.9)	95 (26.0)[e]	58 (19.5)
Constipation	142 (28.5)	192 (38.6)[e]	181 (46.1)[d]	3 (2.3)	37 (28.0)[e]	38 (39.6)	139 (38.0)	155 (42.4)	143 (48.2)
Drowsiness	116 (23.3)	219 (45.0)[e]	145 (36.9)[d]	2 (1.5)	41 (31.1)[e]	25 (26.0)	114 (31.2)	178 (48.6)[e]	120 (40.4)[d]
Dry mouth	119 (23.9)	176 (35.3)[e]	139 (35.4)	3 (2.3)	36 (27.3)[e]	26 (27.1)	116 (31.7)	140 (38.3)[e]	113 (38.1)
Dysuria	21 (4.2)	38 (7.6)[e]	19 (4.8)	0 (0.0)	7 (5.3)	4 (4.2)	21 (5.7)	31 (8.5)[e]	15 (5.1)[d]
Gastralgia	49 (9.8)	45 (9.0)	34 (8.7)	5 (3.8)	6 (4.6)	5 (5.2)	44 (12.0)	39 (10.7)	29 (9.8)
Hallucinations	3 (0.6)	14 (2.8)[e]	11 (2.8)	0 (0.0)	2 (1.5)	2 (2.1)	3 (0.8)	12 (3.3)[e]	9 (3.0)
Itching	21 (4.2)	41 (8.2)[e]	20 (5.1)[d]	0 (0.0)	5 (3.8)	3 (3.1)	21 (5.7)	36 (9.8)[e]	17 (5.7)[d]
Myoclonus	37 (7.4)	33 (6.6)	31 (7.9)	1 (0.8)	3 (2.3)	4 (4.2)	36 (9.8)	30 (8.2)	27 (9.1)
Nausea	66 (13.3)	145 (29.1)[e]	94 (23.9)	3 (2.3)	34 (25.8)[e]	22 (22.9)	63 (17.2)	111 (30.3)[e]	72 (24.2)
Vomiting	24 (4.8)	57 (11.5)[e]	38 (9.7)	3 (2.3)	14 (10.6)[e]	12 (12.5)	21 (5.7)	43 (11.6)[e]	26 (8.8)

[a]Based on 393 subjects.
[b]Based on 96 subjects.
[c]Based on 297 subjects.
[d]Significant difference between Day 3 and Day 28 ($P < .05$).
[e]Significant difference between Day 1 and Day 3 ($P < .05$).

drowsiness, and dry mouth. The time patterns in the two groups of patients were similar.

The frequency of the six most frequent AEs across strata of selected patients' demographic and clinical characteristics is shown in Figs. S1–S6. Nausea and vomiting were significantly more frequent in women than in men (Fig. S1) and in patients aged 68 years or more than those younger than 68 years (Fig. S2). A significantly higher frequency of constipation, dry mouth, and nausea was observed in patients with ongoing anticancer therapy (Fig. S5). No significant differences were observed across strata of pain therapy (Fig. S3), primary site of the tumor (Fig. S4), and KPS (Fig. S6).

The intensity distribution of the six most frequent AEs from Day 1 to Day 28 is displayed in Fig. 3. For all AEs, the frequency of moderate/severe AEs significantly increased between Day 1 and Day 3, ranging between 4% for confusion and vomiting to 16% for constipation. The frequency of all AEs significantly decreased from Day 3 to Day 28, with the exception of a nonsignificant reduction for confusion.

The concomitant presence of the six most frequent AEs is displayed in Table 3. At Day 3, the percentage of patients who did not have any of the six AEs was 37.2%, 42.4% reported 1–3 AEs, and 20.5% had ≥4 AEs. At Day 28, the corresponding percentages were 39.2%, 41.2%, and 19.6%. From Day 3 to Day 28, 16.5% of patients never experienced any of the six major AEs, while 35.1% reported 1–3 AEs, and 48.4% of patients had ≥4 AEs.

At Day 3, Day 28, and between Day 3 and Day 28, patients with any AEs over the entire period of follow-up experienced a lower level of API and WPI compared to patients with AEs, significantly proportional to the number of the coexisting AEs (Table 4).

Discussion

The present analysis shows that opioid introduction for pain control in cancer patients induces various AEs that persist over time and worse patients' symptomatology. Moreover, it suggests a different degree of opioid toxicity among patients, and a possible interaction between opioid-induced AEs and the analgesic response.

Among the aspects investigated, we first considered how the introduction of strong opioids had an effect on the general symptomatology of cancer patients. Our analysis showed that all the considered AEs increased soon after the administration of strong opioids: in particular, constipation, dry mouth, drowsiness, nausea, confusion, and vomiting were present in 10% to 45% of patients immediately after the opioid introduction. Moreover, the proportion of patients with AEs of moderate/severe intensity at Day 3 ranged between 4% for confusion and vomiting and 16% for constipation. These results were consistent with previous investigations, reporting that nausea, vomiting, constipation, drowsiness, and dry mouth are the most frequent AEs due to opioid treatments, despite the high variability in the reported frequency.[8,9] Indeed, in a recent review,

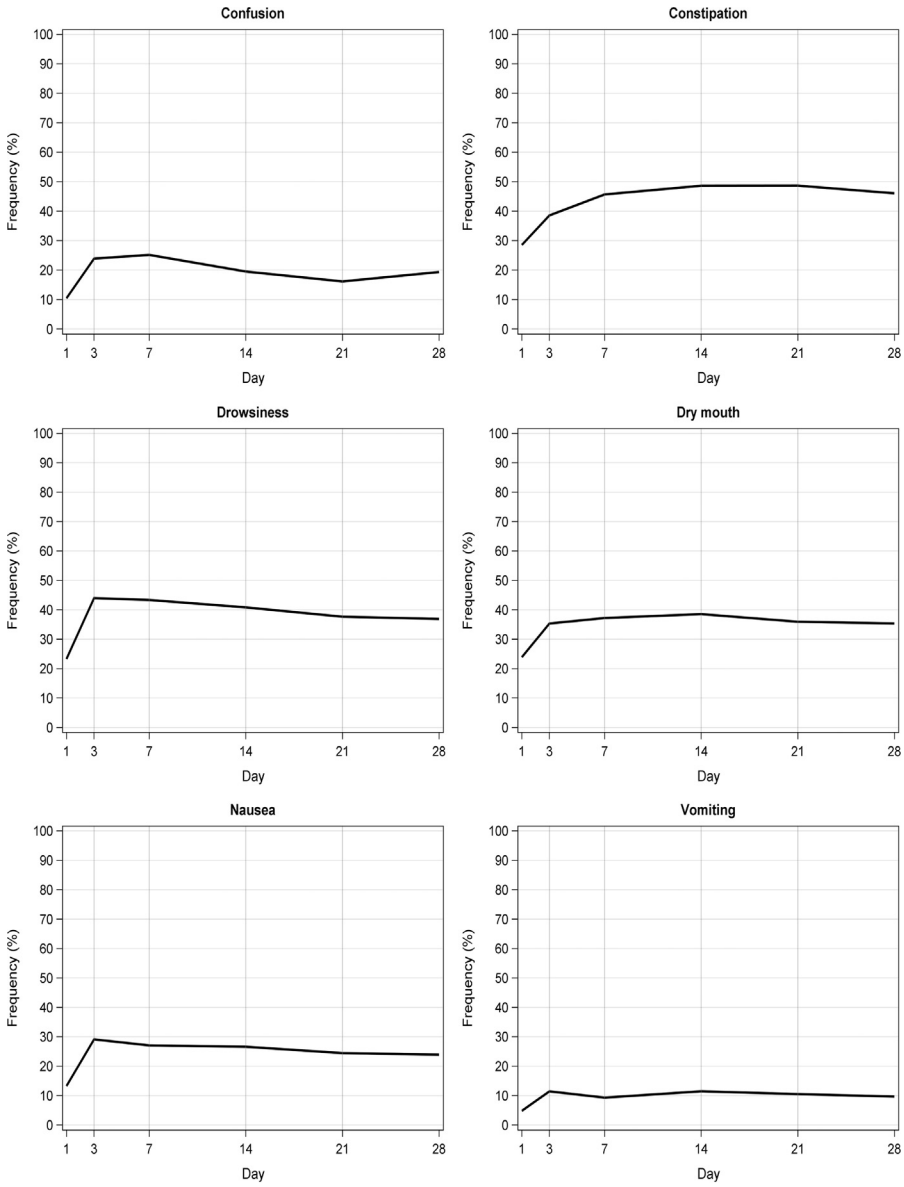

Fig. 1. Distribution (%) of six major adverse events from Day 1 (baseline) to Day 28 among 498 cancer patients treated with strong opioids (WHO Step III).

the frequency was 5%−50% for nausea, 4%−50% for vomiting, 11%−38% for constipation, 3%−50% for drowsiness, 1%−94% for dry mouth, and 70%−80% for confusion.[9] Moreover, a Cochrane review reported that the frequency of AEs was present in 14%−23% of patients for nausea, 7%−15% for vomiting, 17%−30% for constipation, and 3%−47% for dry mouth.[8]

Second, we analyzed the persistence of the AEs over time. We found that the frequency of dry mouth, nausea, and vomiting remained almost stable over time after the introduction of strong opioids. We also observed that the frequency of confusion and drowsiness slightly declined, while only that of constipation increased over time. Consistently, some authors reported that the persistence of opioid-induced AEs varies for each AE due to the different time onset of tolerance: in agreement with our findings, AEs such as drowsiness and confusion have been reported to rapidly disappear, while little or null tolerance has been observed for other AEs, such as constipation.[5,14−16]

Third, we examined possible differences in the prevalence and duration of the AEs between opioid-naïve patients and those already treated with weak opioids before the study enrollment. Only a few studies investigated this issue and reported controversial results.[9,15,20,21] We found that baseline AEs levels were rather low in opioid-naïve patients compared to those with pretreatment with weak opioids. Moreover, we

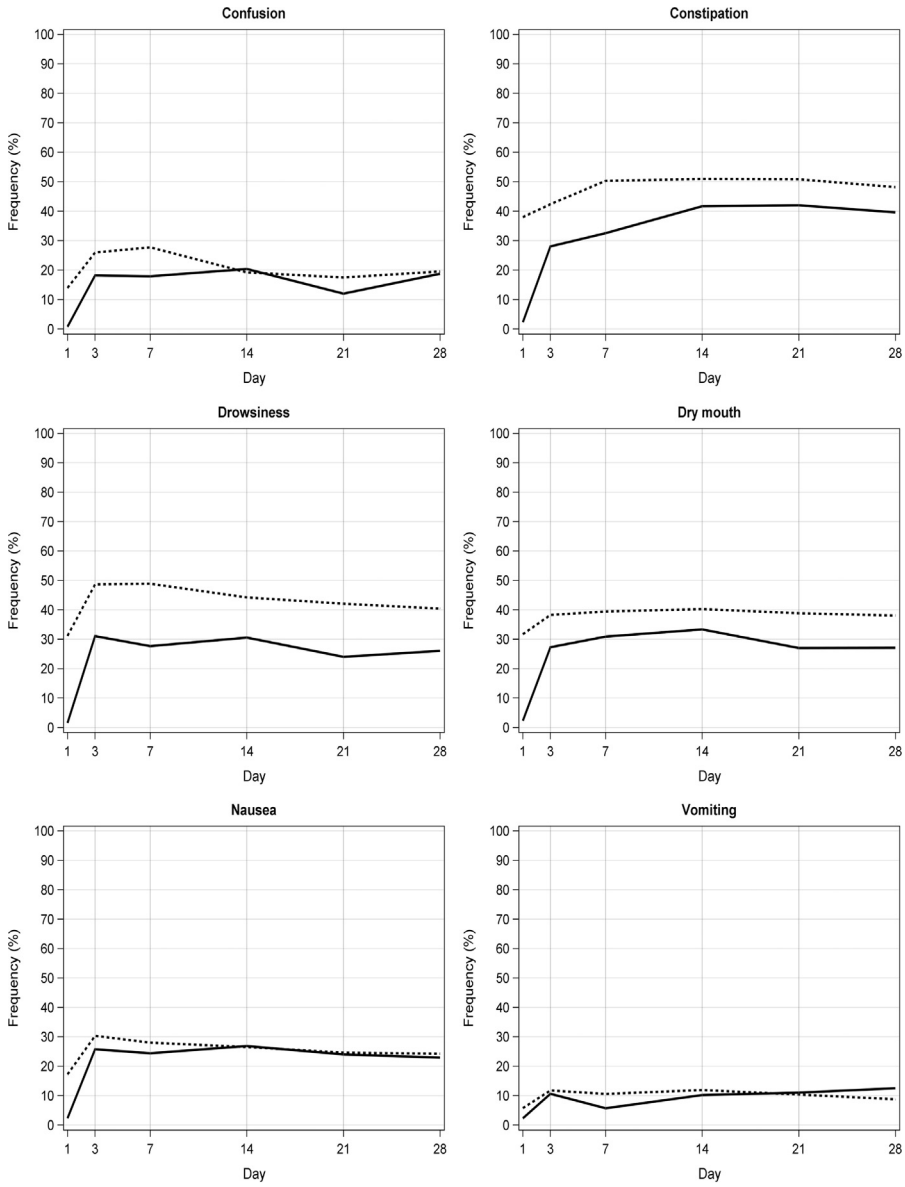

Fig. 2. Distribution (%) of six major adverse events from Day 1 (baseline) to Day 28 among 498 cancer patients treated with strong opioids (WHO Step III), according to previous pain therapy. ——— No opioids (WHO Step 0–I) ·····. Weak opioids (WHO Step II).

observed that not only opioid-naïve patients experienced a strong increase in the AEs, but also patients previously treated with weak opioids had further increases in previous AEs after starting the strong opioids. In particular, constipation, drowsiness, and dry mouth were more frequent over the entire period of observation in patients previously treated with weak opioids than in opioid-naïve ones. These observations were somewhat unexpected because we believed that a change in the opioid WHO step, as a switch,[22] could reduce the toxic effects. However, it is possible that the higher frequency of AEs in patients pretreated with weak opioids indicates more advanced disease in those patients. The change to the next step of the analgesic ladder often comes at crucial times in the disease trajectory, when cancer has suddenly spread, new metastases have appeared, or complications from cancer or treatment have emerged.

Fourth, we evaluated the influence of sex, age, and some patients' clinical factors in modulating opioid-induced AEs. We found that nausea and vomiting were more frequent in women. These findings were in line with some previous studies that showed less opioid-induced analgesia and more collateral effects in women than in men.[23,24] Sex hormones, different expression and drug affinity to opioid receptors, and variable immune response seem to be the most likely reasons for the difference between sexes. As also

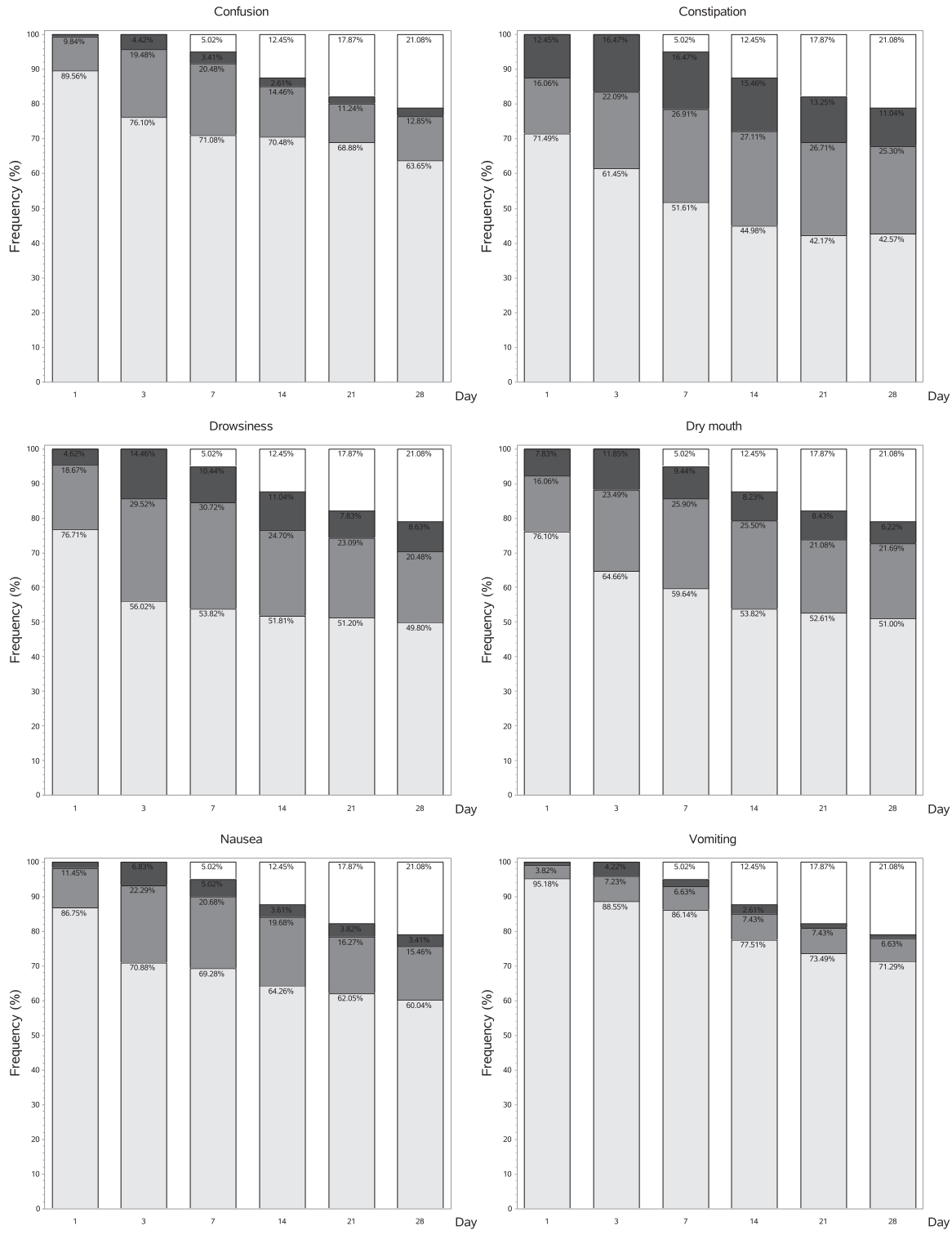

Fig. 3. Distribution (%) of six major adverse events intensity from Day 1 (baseline) to Day 28 among 498 cancer patients treated with strong opioids (WHO Step III). No. Mild. Moderate/Severe. Missing.

reported in the original study publication,[17] we did not observe significant differences across the opioid therapy used, notwithstanding the large difference in dose increases over time among the four opioids (i.e., oral morphine increased by 32.7%, oral oxycodone by 70.9%, transdermal buprenorphine by 56.4%, and transdermal fentanyl by 121.2%).[17] This is in line with previous evidence because the rates of AEs were generally consistent across different opioids. However, few studies indicated that constipation was

Table 3
Distribution in the Number of Adverse Events (AEs) at Day 1 (Baseline) and After the Introduction of Strong Opioids (WHO Step III), Among 498 Cancer Patients

	Day 1	Day 3	Day 28[b]	Day 3 to Day 28[b]
Number of Concomitant AEs[a]	*n* (%)	*n* (%)	*n* (%)	*n* (%)
0	306 (61.5)	185 (37.2)	154 (39.2)	65 (16.5)
1–3	143 (28.7)	211 (42.4)	162 (41.2)	138 (35.1)
≥4	49 (9.8)	102 (20.5)	77 (19.6)	190 (48.4)

[a]Including the six most frequent AEs, that is, confusion, constipation, drowsiness, dry mouth, nausea, and vomiting.
[b]Based on 393 subjects.

less frequent in patients treated with oxycodone and fentanyl, whereas nausea and drowsiness were less frequent in those treated with oxycodone.[9] In addition, we observed a significantly higher frequency of constipation, dry mouth, and nausea in patients with ongoing anticancer therapy, which is compatible with the adverse effects of some cancer therapies.

Fifth, we wondered whether the presence of the opioid-induced AEs after the introduction of strong opioids was either homogenously or differently distributed over the population of patients. We observed that 37%–39% of patients had no major AEs at various visits after starting the opioid treatment, whereas about 20% of patients presented simultaneously four or more AEs. Overall, about 17% of patients did not experience any major AEs across all the follow-up period, whereas 48% reported at least four AEs. These data seem to indicate a different expression of the opioid toxicity among cancer patients with pain. We do not have a clear explanation for such individual variability, and it is possible that the differences observed are caused by some confounding factors not measured in the study.

Finally, we analyzed the possible relation between the number of AEs simultaneously present and the opioid analgesic response. We found that patients with no or few AEs had better analgesia, with higher reduction in API and particularly in WPI; by contrast, the analgesic efficacy was significantly lower in patients reporting a high number of AEs. A possible explanation is linked to the change of opioids dose over time. In fact, baseline mean dose of opioids (expressed as oral morphine equivalent daily dose) was 49.4 mg/day, whereas the final dose was 86.5 mg/day, with a 70.9% mean dose increase. Moreover, the dose escalation was higher in patients with four or more AEs ($N = 42$, 22%, patients with opioid escalation index >5%) than in those with no AEs ($N = 9$, 14%). Therefore, this indicates that patients with insufficient analgesic effect required higher opioid doses and had consequently more AEs.

Among the strength of our study, there is a relatively large sample size as compared to most of the studies in the literature,[8,9] and the comprehensive evaluation of various aspects related to opioid-induced AEs. Among the limitations, we acknowledge that there was a short follow-up duration, which precluded the examination of long-term patterns in opioid-induced AEs. However, such time frame was probably adequate considering that our study population consisted of advanced-stage, often metastatic, cancer patients. Moreover, this was a post hoc analysis and the original study was not specifically designed to investigate opioids AEs. Notwithstanding that, we collected information on the prevalence and severity of AEs due to opioids, as well as to previous pain treatments, which allowed us to evaluate how opioids modified the preexisting patients' symptom profile. The items of our questionnaire were specifically formulated to identify drug-induced AEs,[18] although we acknowledge that it is not easy to disentangle opioid-induced AEs from symptoms due to the disease, and therefore, the frequency of AEs may also be an indicator of advanced disease. Moreover, the disease itself and anticancer therapies, as well as concomitant diseases and

Table 4
Average Pain Intensity (API) and Worst Pain Intensity (WPI) According to Number of Adverse Events (AEs) at Day 1 (Baseline) and After the Introduction of WHO Step III Opioids, Among 393 Cancer Patients With a Visit up to Day 28

	Day 1		Day 3		Day 28		Day 3 to Day 28	
	API	WPI	API	WPI	API	WPI	API	WPI
Number of AEs[a]	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
0	6.4 (1.4)	8.0 (1.4)	2.6 (1.9)	3.7 (2.7)	2.2 (2.0)	3.2 (2.4)	2.3 (1.5)	3.3 (2.0)
1–3	5.9 (1.4)	7.7 (1.6)	3.3 (1.8)	5.0 (2.6)	2.3 (1.7)	3.6 (2.4)	2.7 (1.5)	4.2 (2.1)
≥4	6.2 (1.4)	8.1 (1.4)	3.5 (2.0)	5.3 (2.4)	2.7 (2.0)	4.4 (2.6)	2.9 (1.5)	4.6 (1.9)
P-value for trend	.22	.29	.001	<.0001	.05	.0003	.0014	<.0001

[a]Including the six most frequent AEs, that is, confusion, constipation, drowsiness, dry mouth, nausea, and vomiting; AEs from Day 3 to Day 28.

their medications may have had some role in causing the observed AEs. In addition, procedures to manage opioid-induced AEs could also be important to interpret the trajectory of AEs. Among the six major AEs evaluated in our analysis, constipation, nausea, and vomiting were potentially responsive to symptomatic treatments. Constipation was treated with laxatives in 31% of patients at Day 1 and in 21% of patients at Day 28; antiemetic drugs were administered in 46% and 37% of patients with vomiting and in 38% and 30% of patients with nausea, respectively, at Day 2 and at Day 28. Therefore, taken together, gastroenteric symptoms were treated in a low percentage of cases, and their treatment did not seem to increase with time. With reference to switch, in another secondary analysis based on the same database,[25] we found that only 19 of the 498 patients switched specifically because of severe and unmanageable side effects, and a good improvement in the AEs was reached in only eight patients. Therefore, treatment for gastroenteric symptoms, as well as opioid switches, seems to modestly affect the global trajectory of the AEs.

A few final considerations can be drawn from the present investigation. Opioid-induced AEs importantly change cancer patients' symptomatology. In advanced conditions of illness, AEs may end up worsening the quality of life of those patients who are given palliative care with the intent to improve it. Therefore, any effort to manage the opioid-induced AEs is required to improve cancer patients' care. If patients suffer too much from opioid-related AEs, a slower titration might be indicated, starting with lower doses (especially in opioid-naïve and/or elderly patients). Patients should also be asked whether they want to have higher doses (with more side effects) or lower doses (with higher residual pain levels, but less side effects), with an evaluation of the patient's priorities and using value-based decision making. The balance between the opioids analgesic effect and induced toxicity is fundamental in deciding the best management for pain in cancer patients, and involving patients in such choices is an ethic and clinical priority.

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Appendix

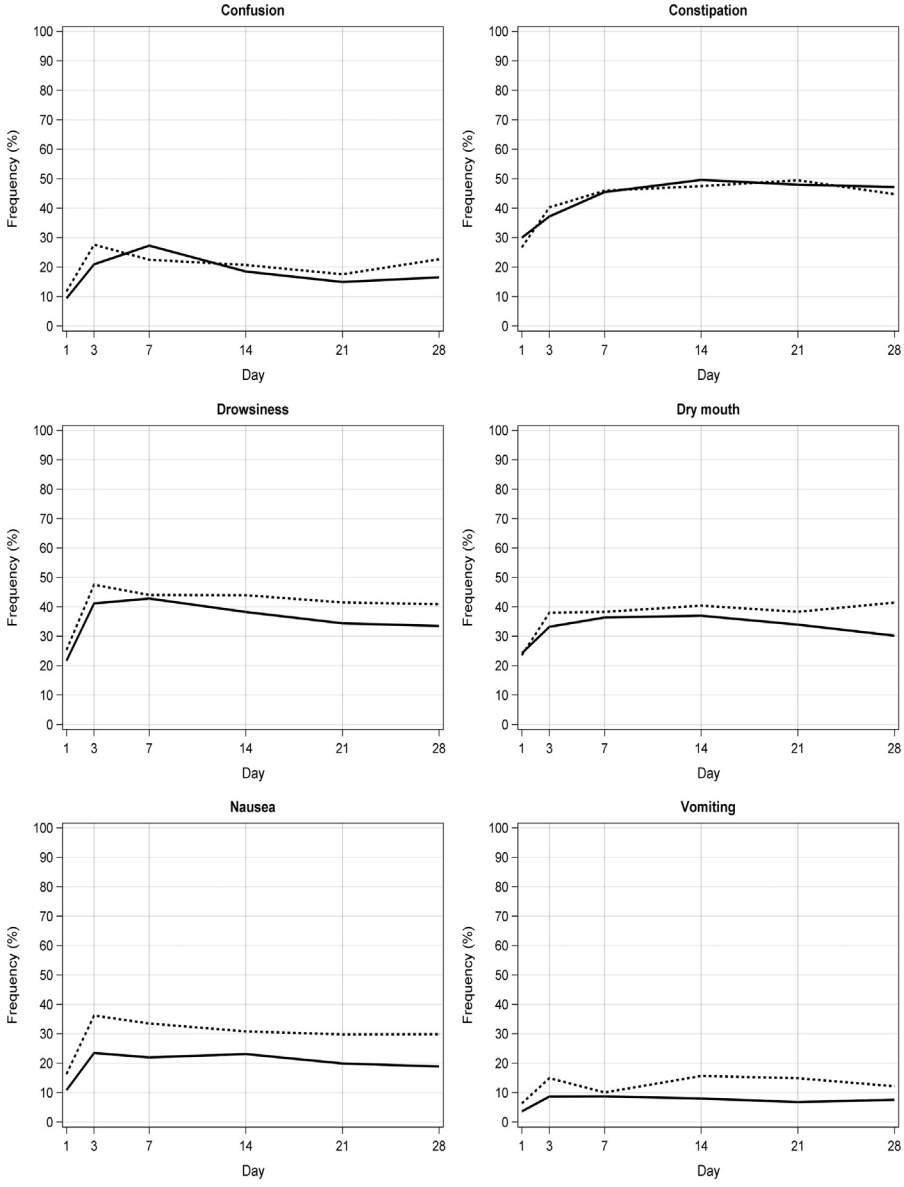

Figure S1. Distribution (%) of six major adverse events from Day 1 (baseline) to Day 28 among 498 cancer patients treated with strong opioids (WHO Step III), stratified by sex. ——— Men. ····· Women.

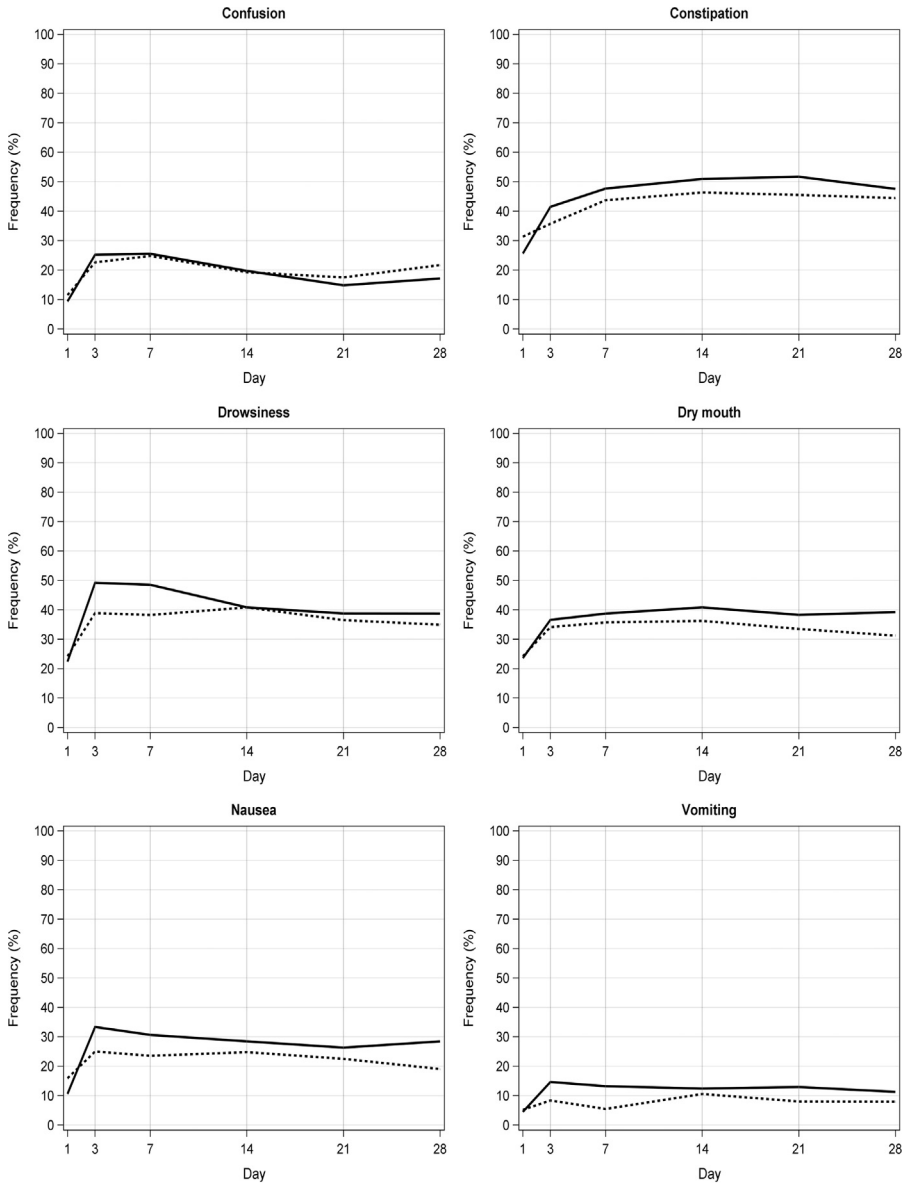

Figure S2. Distribution (%) of six major adverse events from Day 1 (baseline) to Day 28 among 498 cancer patients treated with strong opioids (WHO Step III), stratified by age. ——— ≤ 68 years. ····· > 68 years.

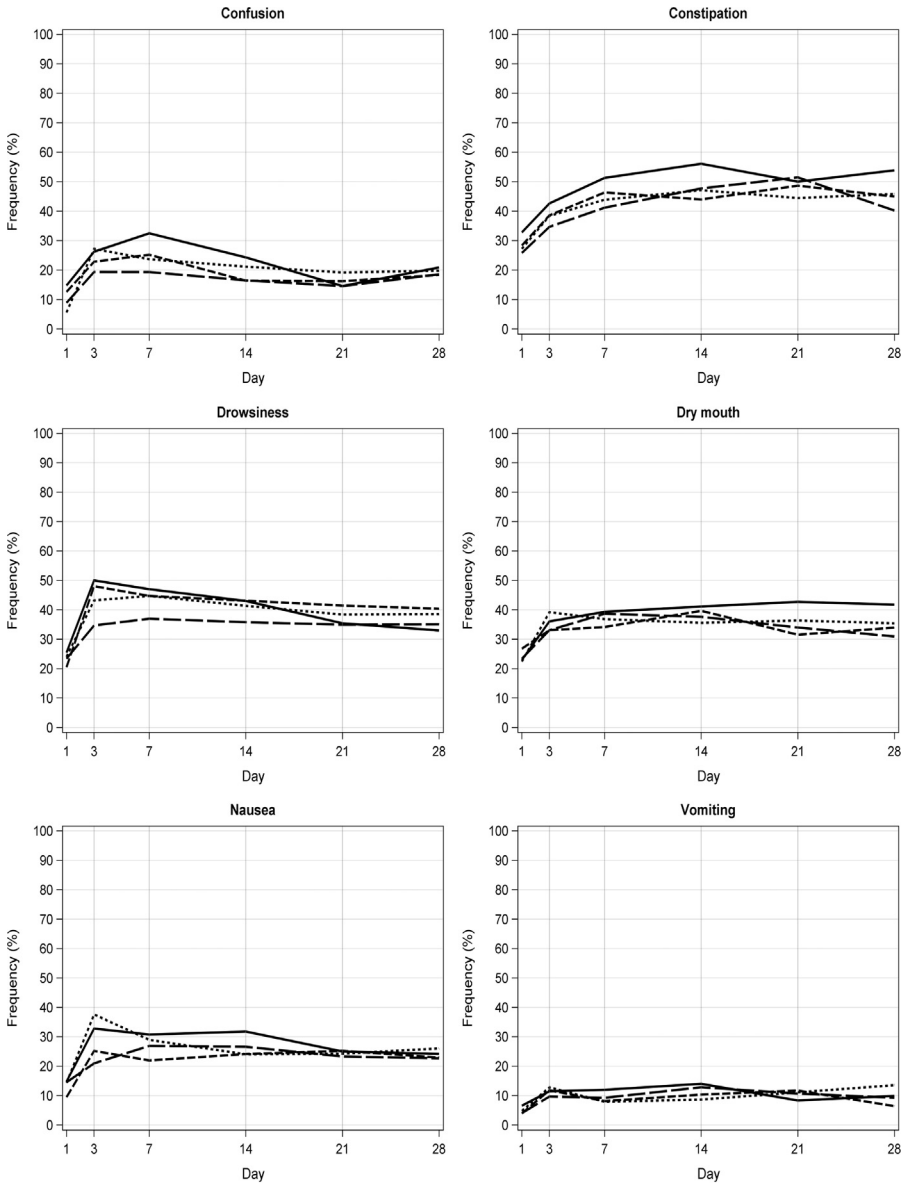

Figure S3. Distribution (%) of six major adverse events from Day 1 (baseline) to Day 28 among 498 cancer patients treated with strong opioids (WHO Step III), according to pain therapy. ——— Oral morphine. ····· Oral oxycodone. - - - - Transdermal buprenorphine. — — - Transdermal fentanyl.

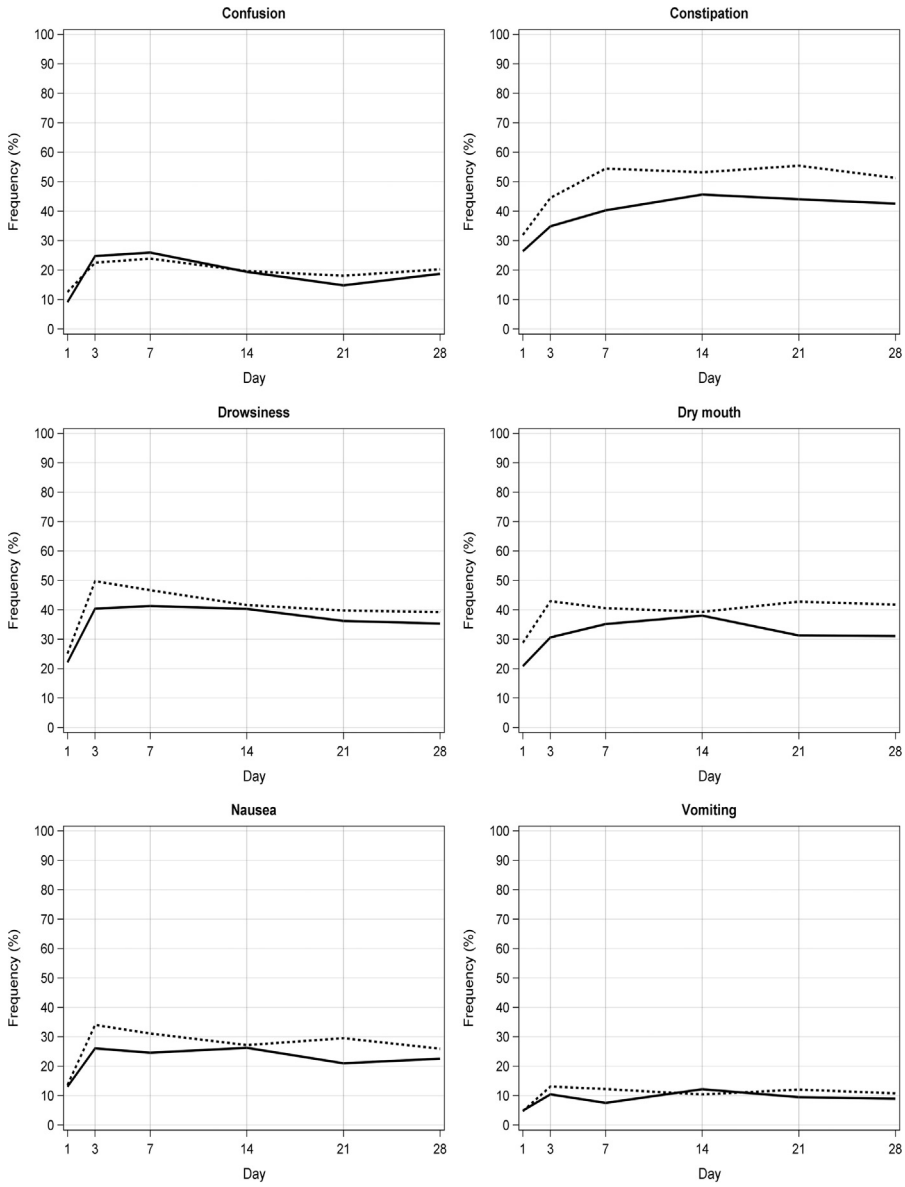

Figure S4. Distribution (%) of six major adverse events from Day 1 (baseline) to Day 28 among 498 cancer patients treated with strong opioids (WHO Step III), according to ongoing cancer therapy. ——— No ongoing cancer therapy. ····· Ongoing cancer therapy.

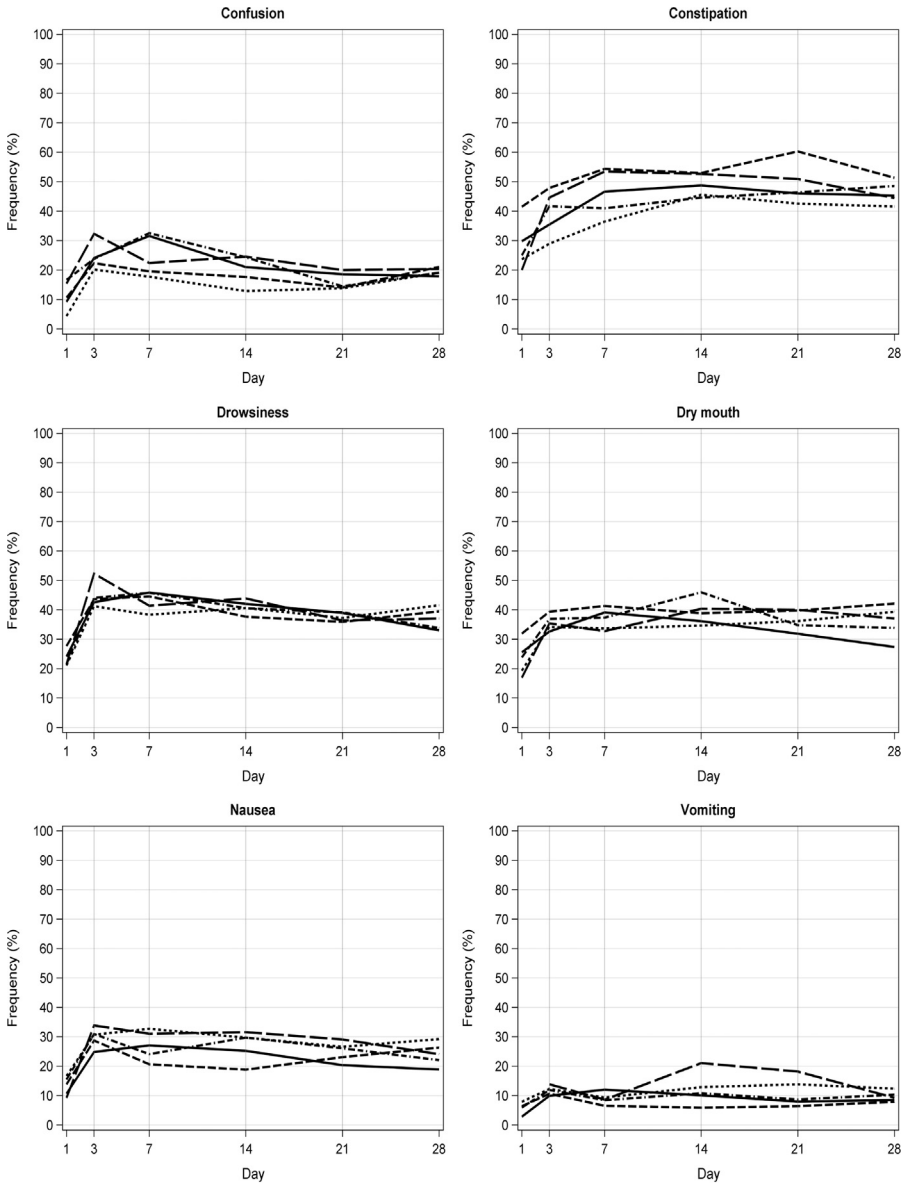

Figure S5. Distribution (%) of six major adverse events from Day 1 (baseline) to Day 28 among 498 cancer patients treated with strong opioids (WHO Step III), according to primary tumor site. ——— Respiratory. ····· Digestive. - - - - Genitourinary. — — - Breast. — · — Other.

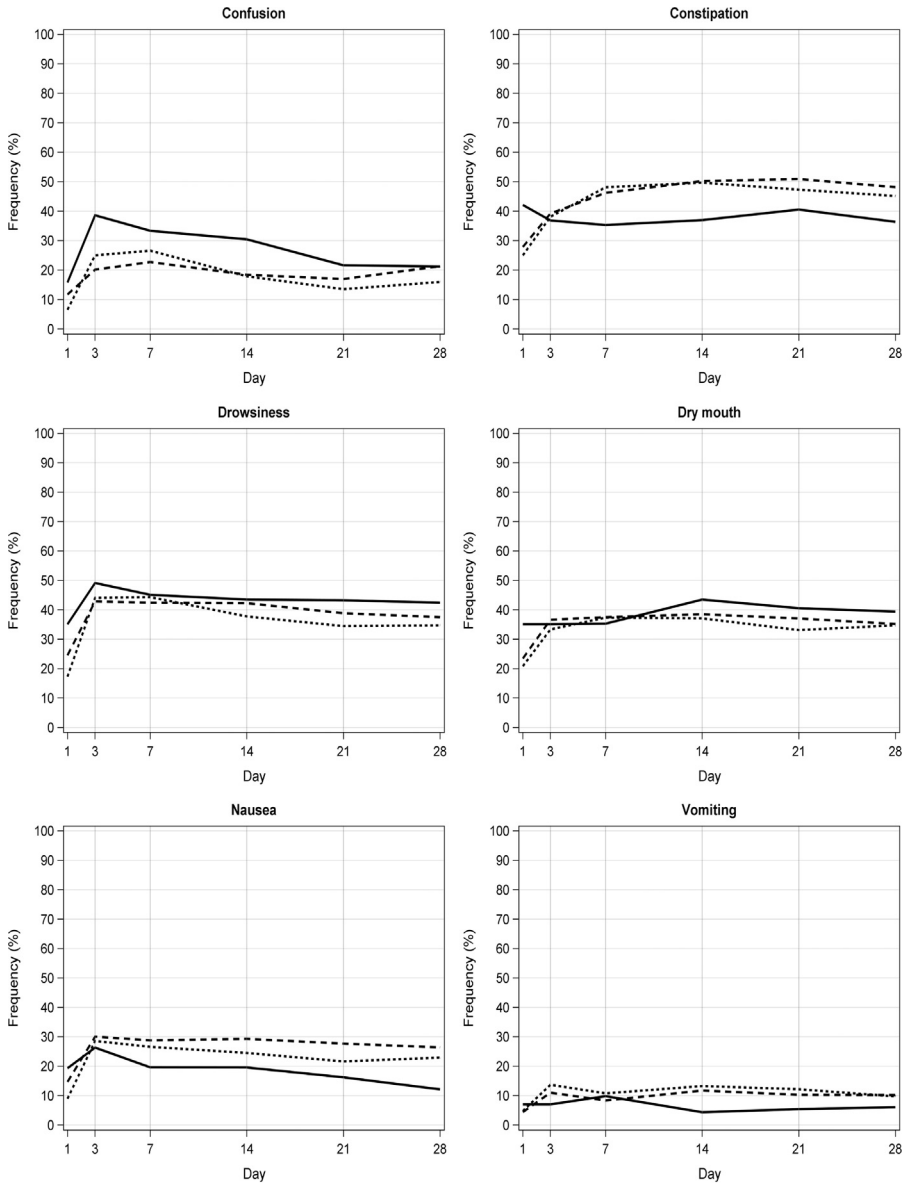

Figure S6. Distribution (%) of six major adverse events from Day 1 (baseline) to Day 28 among 498 cancer patients treated with strong opioids (WHO Step III), according to the Karnofsky Performance Status. KPS = Karnofsky Performance Status. ——— KPS ≤40. ····· 40 < KPS ≤70. – – – KPS >70.