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Title page

Original manuscript

Title: Non-responsiveness and susceptibility of opioids side effects related to cancer patients' clinical characteristics: a post-hoc analysis

Running head: Clinical factors and opioids response

Oscar Corli[1], Anna Roberto[1], Michael I. Bennett[2], Francesca Galli[3], Nicole Corsi[1], Eliana Rulli[3], Raffaella Antonione[4].

[1]Pain and Palliative Care Research Unit, Oncology Department, IRCCS Istituto di Ricerche Farmacologiche Mario Negri, Milan (Italy).

[2]Academic Unit of Palliative Care, Leeds Institute of Health Sciences, School of Medicine, University of Leeds, Leeds (UK).

[3]Methodology for Clinical Research Laboratory, Oncology Department, IRCCS Istituto di Ricerche Farmacologiche Mario Negri, Milan (Italy).

[4]Struttura Operativa Complessa di Medicina, Ospedale San Polo, AAS 2 Bassa Friulana Isontina, Monfalcone (Italy).

Corresponding author:

Anna Roberto, Biol Sci D

anna.roberto@marionegri.it

Department of Oncology

IRCCS Istituto di Ricerche Farmacologiche Mario Negri

Via G. La Masa 19, 20156 Milano (Italy)

Tel. 0039 02 39014648 fax 0039 02 33200231

Abstract

Background. Response to opioids is not always positive in cancer patients. A considerable proportion of patients do not respond (non-responders, NRs) or experience severe toxicity. The aim of this analysis was to assess the role of demographic characteristics, pain features, comorbidities and ongoing therapy on the lack of efficacy and on the occurrence of severe adverse drug reactions (ADRs).

Methods. This is a post-hoc analysis of a randomized controlled trial that involved 520 patients and was aimed to evaluate the efficacy and safety of four strong opioids. Patients who presented unchanged or worsened pain compared to the first visit were considered as NRs. As to toxicity, severe degree ADRs with occurrence higher than 10% were evaluated. Univariate and multivariate logistic models were used.

Results. 498 patients were analyzed. Liver metastases and breakthrough pain (BTP) were found to increase the risk of non-response. Conversely, a high basal pain intensity significantly decreased the same risk. Constipation risk was worsened by previous weak opioid therapy but decreased with aging, and the use of transdermal opioids. Risk of drowsiness was aggravated by bone metastases, concomitant treatment with anticoagulant, antidiabetic and central nervous system drugs. Risk of confusion increased with antidiabetics, antibiotics and previous weak opioid therapy but decreased when fentanyl was used. Occurrence of nausea increased in patients with high Karnofsky index. Risk of xerostomia was higher in women and in patients treated with antidiabetic or long-term opioids.

Conclusions. Several clinical variables are correlated to opioid response in cancer patients. In particular, the presence of BTP is associated with non-response. Additionally, patients with polypharmachological therapy are more likely to experience opioid adverse events.

Keywords: cancer pain, opioids, non-responders, toxicity.

Clinical Trial Registration Number: NCT01809106

https://clinicaltrials.gov/ct2/show/NCT01809106?term=cerp&rank=2

Introduction

Cancer patients with moderate to severe pain are generally treated with opioids as regulated by several guidelines and recommendations (1–3). A recent randomized study (4), called CERP, compared analgesic efficacy, changes in therapy program, and safety profile over time of four strong opioids (morphine, oxycodone, fentanyl and buprenorphine) in cancer patients. All four strong opioids achieved a similar analgesic effect characterized by remarkable variations in therapy schedules depending on the used opioid. Additionally, the occurrence and severity of ADRs, in particular neurotoxic effects (confusion, hallucinations, myoclonus), varied among the four strong opioids. A second outcome of CERP study was the considerable proportion of patients that were non-responders (NRs) to the treatment, occurred in 10-15% of the cases. This negative response was defined as the lack of pain relief, with unchanged or worsened pain intensity (PI), obtained by comparing the initial to the final visit. Additionally, 15% of patients was poor responders (PRs) showing a PI reduction lower than 30% (5). The outcomes described in the original study encouraged further in-depth analyses aimed to explore whether factors related to patients' clinical conditions might be associated with a non-response condition. Up to now, this topic has been only partially investigated in the literature. It has been described that cancer progression, the site of primary tumor, the presence of metastases and negative psychological conditions could influence the experienced pain (6,7). Also the features of pain, as in case of neuropathic and breakthrough pain, have been often related to a worse experienced pain and a poorer response to analgesics (6). Given the existing evidence, we performed this post-hoc analysis to evaluate which clinical factors might impact more on the response to opioids in cancer patients.

Methods

This analysis derives from a multicenter, randomized, open-label, longitudinal (28 days), active-controlled, four-arm, of superiority, phase IV clinical trial on cancer patients with moderate to severe pain requiring WHO step-III strong opioids, never administered before the study participation (CERP study (4)). 520 patients with diagnostic evidence of advanced/metastatic solid tumors were recruited by 44 Italian centers and were randomized to receive either oral morphine (active comparator), or transdermal buprenorphine, or

oral oxycodone, or transdermal fentanyl. Eligibility criteria included diagnostic evidence of locally advanced or metastatic tumor; persistent moderate to severe cancer pain [average pain intensity (API) experienced in the last 24 h ≥ 4 points rated on a 0–10 Numerical Rating Scale (NRS)]; need for WHO step III strong opioids never previously administered; age >18 years. Exclusion criteria included: cerebral tumors and leukemia, concurrent radiotherapy, first-line chemotherapy during the 7 days before randomization, non-pharmacological analgesic treatment and pre-existing renal failure (4). At baseline, the clinical aspects recorded were the oncological medical history (primary tumor site, presence and localizations of metastases, previous and ongoing cancer treatments), the concomitant diseases and treatments, the Karnofsky Performance Status index (KPS), and the psychological status (anxiety, worry, irritability, depression) investigated by 4 items extracted from the EORTC QLQ-C30 version 3 (8). Pain was assessed by measuring the average pain intensity (API) and the worst pain intensity (WPI) experienced by the patients in the 24 hours before the visit, through a 0 (no pain) to 10 (the worst pain imaginable) Numeric Rating Scale (NRS). We additionally recorded the presence of neuropathic pain (NP), by using the DN4 questionnaire (9), and of breakthrough pain (BTP), according to the Davies algorithm (10). The measures of PI were repeated during five visits (72 hours, and day 7, 14, 21, 28) together with the ADRs, that were assessed by means of the Therapy Impact Questionnaire (TIQ) (11). The TIQ was self-reported by the patient who attributed the presence and severity of the symptoms by means of a four-points verbal rating scale (i.e. no, little, moderate, severe). During all the observational period, any change in the therapy schedule (drugs and doses) was monitored. The doses of all the opioids were reported in OMEDD (oral morphine equivalent daily dose). The titration of initial dose was suggested to the investigators, based on the EAPC recommendations (1) that suggest to start with 30 to 60 mg/daily of morphine-equivalent, depending on the age, the general clinical conditions of the patients and the previous treatment. We focused the present analysis by considering the responses to opioids observed in the main study, for both efficacy and toxicity. The patients were classified as NRs if the API of the last available visit was unchanged or worsened with respect to the initial API. The last available visit could be either the visit at the end of the follow-up (day 28) or, previously, at the moment of a switch or premature discontinuation of the study for any reason occurred.

Only ADRs reported at least once as moderate or severe (hereinafter called just severe ADRs) and with a frequency in the whole examined population higher than 10% were considered for the toxicity analysis. The

patients with these characteristics were included in the analysis to assess the role of demographic characteristics, pain and other clinical features, comorbidities and all the given treatments in influencing the lack of analgesic response and the occurrence of severe ADRs.

Statistical analysis

All analyses were performed on intention-to-treat (ITT) population, which included all CERP study randomized patients without major violations of the eligibility criteria and with at least the second pain evaluation after baseline. Each patient was observed from the baseline to the interruption of the therapy with the opioid assigned at random.

Sample characteristics were summarized using mean and standard deviation (SD) values for continuous variables, absolute and relative frequencies for categorical variables. To evaluate the impact of the demographic characteristics, clinical features and ongoing therapy on both the efficacy and safety endpoints, a logistic regression model was used for univariate and multivariate analyses.

We included the following variables in an univariate analysis: the random arm (with morphine as reference), age, sex, the primary tumor site (with the respiratory system as reference), presence of metastasis (liver, lung, bones, lymph nodes or other), concomitant diseases and therapies (metabolic/hormonal, cardiovascular, respiratory, neurological, digestive or other), previous weak opioid pain therapy, the KPS, the psychological status (anxiety, worry, irritability, depression), the presence of NP, the type of pain (only nociceptive as reference, only neuropathic or both nociceptive and neuropathic), the API at baseline $\geq$ 6 points, the WPI at baseline $\geq$ 8 points and the occurrence of at least three BTP episodes in the 24h before the baseline. Variables found to be associated with a $p \leq 0.10$ were considered for multivariate analysis, except for the random arm variable which was always included in the multivariate model. Since concomitant diseases and relative therapy could have been strictly correlated and analysis of both could lead to an unnecessary double evaluation, if both disease and therapy were associated with endpoint at univariate analysis, only the therapy was included in the multivariate analysis. To adjust both the efficacy analysis and the safety analysis for the potential different study period, the number of visits conducted during the treatment with the opioid assigned at randomization was included in the multivariate analysis. Moreover, the occurrence of a severe ADR before the interruption of the opioid assigned at randomization was used to adjust the efficacy analysis and

the mean average pain intensity reported before the occurrence of toxicity or the treatment interruption was used to adjust the safety analysis. Results are expressed as odds ratios (ORs) with their 95% confidence intervals (95% CIs). Statistical significance was set at $p<0.05$ for a bilateral test. Analyses were carried out with SAS Software, version 9.4 (SAS Institute, Cary, NC).

Results

Four hundred and ninety-eight patients were randomized in the CERP trial between May 2011 and July 2014 and were included in the ITT population.

Table 1 shows demographic and clinical patients' characteristics recorded at baseline.

Patients classified as NRs were 57 (11.4% of the whole population). As to the ADRs, 165 patients (33.1%) experienced severe constipation, 138 (27.7%) severe drowsiness, 117 (23.5%) severe dry mouth, 75 (15.1%) severe nausea, 52 (10.4%) severe confusion. Hallucinations, vomiting, muscle pain, gastralgia, dysuria and itch were recorded as severe ADRs in less than 10% of sample.

Efficacy results

Clinical factors, with a $p\leq0.10$ in univariate analysis associated with the efficacy response, are showed in **Table 2**. At the univariate analysis, the liver metastases and the occurrence of at least three episodes of BTP in the 24h before baseline were significantly associated with a higher risk of non-response. The impact of these factors on a negative analgesic response was confirmed by a multivariate analysis, in case of presence of liver metastases: OR 2.16, 95% CI 1.08 - 4.29; p=0.028; and in presence of three or more attacks of BTP: OR 2.89, 95%CI 1.44 - 5.80; p=0.003. On the contrary, high levels of API at baseline (≥6 points) were correlated with a lower risk of non-response (OR 0.49, 95%CI 0.26 - 0.91; p=0.024).

Safety results

Clinical factors, with a $p\leq0.10$ in univariate analysis, that influence the occurrence of severe adverse events are illustrated in **Table 3**. In more detail:

Constipation. At the univariate analysis, a lower risk of severe constipation was observed in older patients, while those who experienced at least three episodes of BTP in the 24h before baseline and who already received an opioid therapy were associated with a higher risk of severe constipation. Multivariate analysis confirmed the negative impact of a previous weak opioid therapy (OR 1.89, 95%CI 1.15 - 3.10; p=0.012) and the positive role of age (OR 0.81, 95%CI 0.68 - 0.96; p=0.018). A significant difference was observed by comparing the opioids used: a lower risk was detected for patients treated with either transdermal buprenorphine (OR 0.51, 95%CI 0.29 - 0.90; p=0.020) or fentanyl (OR 0.45, 95%CI 0.25 - 0.81; p=0.008) compared to morphine.

Drowsiness. At the univariate analysis, cardiovascular diseases, antihypertensive, anticoagulants and antianginal drugs, metabolic/hormonal diseases, antidiabetic drugs, neurological/psychological disease and therapies with central nervous system (CNS) active drugs correlated with a higher risk of severe drowsiness. At the multivariate analysis the associations between the concomitant use of anticoagulants (OR 2.16, 95%CI 1.24 - 3.77; p=0.007), antidiabetics (OR 2.26, 95%CI 1.31 - 3.89; p=0.003), CNS drugs (OR 2.73, 95%CI 1.18 - 6.32; p=0.019) and presence of bone metastases (OR 1.63, 95%CI 1.06 - 2.51; p=0.026) were confirmed.

Dry mouth. At the univariate analysis, female gender, a previous weak opioid therapy, metabolic/hormonal diseases, digestive system diseases and therapies with anticoagulants, antidiabetics or gastrointestinal drugs increased the risk of severe dry mouth condition. At the multivariate analysis, the negative impact was confirmed for women (OR 2.00, 95%CI 1.25 - 3.18; p=0.004), previous weakopioid therapy (OR 1.94, 95%CI 1.11 - 3.39; p=0.020) and therapy with antidiabetic drugs (OR 2.05, 95%CI 1.15 - 3.67; p=0.015).

Nausea. At the univariate analysis, the female sex and high values of KPS were found to increase the risk for the severe nausea while antihypertensive therapy decreased the risk. At the multivariate analysis, only KPS was confirmed as factor of risk (OR 1.23, 95%CI 1.05 - 1.45; p=0.012).

Confusion. At the univariate analysis, the concomitant treatment with anticoagulants, cardiotonic, antianginal, antidiabetics, gastrointestinal drugs, antibiotics, previous weak opioid therapy, and the simultaneous presence of metabolic/hormonal disease, correlated with a higher risk of severe confusion while transdermal fentanyl treatment decreased the risk. At the multivariate analysis, the increased risk was

confirmed for the antidiabetic drugs (OR 2.82, 95%CI 1.34 - 5.96; p=0.006), antibiotics (OR 4.34, 95%CI 1.03 - 18.25; p=0.045) and previous weak opioid therapy (OR 2.59, 95%CI 1.06 - 6.34; p=0.038). The positive role of transdermal fentanyl was confirmed as well (OR 0.31, 95%CI 0.12 - 0.81; p=0.017).

Discussion

The aim of this analysis was to investigate whether specific patient characteristics could modulate the risk of the lack of efficacy and the occurrence of severe ADRs in cancer pain patients treated with opioids.

Several hypotheses have been proposed so far to explain the negative analgesic response. For instance, different studies have drawn the attention on the role of genetic variables in modifying the opioid receptors structure or the activity of enzymes involved in opioids metabolism, thus to effectively modulate their efficacy and toxicity (12–14). Other studies underlined the importance of either liver or kidney impairments that can alter the metabolism and the removal of the drugs and metabolites, thus enhancing the response and causing unwanted side effects (15,16).

Herein, we wanted to explore the variability of response to opioids, by evaluating whether some patients' clinical conditions could influence the analgesic efficacy and toxicity.

The risk of reduced efficacy was related to the presence of liver metastases and BTP. This last situation is consistent with a previous study where 723 cancer patients affected by BTP showed higher probability of either increasing the opioids background daily dose or having a switch due to unsatisfactory pain relief when compared to 1073 patients without BTP (17). In another study (18) incident pain was confirmed to be a relevant domain in the variability of pain outcomes. The relation between poor response and liver metastases is not clear yet: liver metastases do not automatically lead to liver dysfunction. Only a complete neoplastic substitution of hepatic tissue can produce a functional failure but this is an uncommon condition. The example of liver metastases is paradigmatic of several findings of this analysis, however there are not previous papers to rely on to support and strengthen our observations. Herein, we decided to report our results without trying to advance explanations.

Severe basal pain value correlates with an increased probability of response to opioids. In patients with widespread cancer diffusion, as in the case of our population, many nociceptive stimuli work simultaneously in leading to severe pain. In this case, strong opioids effectively relieve pain. This observation is consistent

with the outcomes of a previous study (18).

The presence of severe adverse events due to opioids was influenced by several clinical factors, as in case of drowsiness and bone metastases. Existing literature reports a high prevalence of drowsiness [81.8%] in a population of patients with bone metastases (19). Another study (20) indicates that drowsiness intensity is on average equal to 3.7±2.9 in a 0 to 10 points NRS in these patients. Despite these data, the cause-effect relationship between bone metastases and drowsiness remains unclear: sometimes it could be related to frequent additional doses of short-acting opioids in patients with BTP.

Constipation is a common problem, occurring in 40% to 95% of patients treated with opioids (21). In our analysis, the risk of constipation was halved when using transdermal fentanyl and buprenorphine with respect of oral morphine and oxycodone. Also in two previous studies (22,23) transdermal fentanyl was associated with lower constipation compared with oral opioids.

The previous use of WHO-step II "weak" opioids doubled the risk of constipation, thus confirming the lack of tolerance over time related to this side effect.

Our analysis disclosed that the risk of severe dry mouth was higher in women. Dry mouth affects 25% of patients with chronic non-malignant pain treated with opioids (24) and about 50% in patients with chronic cancer pain (4). The increased risk of xerostomia in women could be related to the mean age that in our study is equal to 65.1 (SD 12.7). Independently from the opioid treatment, the symptom troubled 1% to 29% of the female population, mostly menopausal women (25,26).

Some drugs influenced opioid toxicity when co-administered. Interestingly, we found an increased risk of drowsiness when opioids were associated with either anticoagulants, antidiabetics or other central nervous system drugs, and confusion, when administered concurrently with antibiotics. It has been recognized that the simultaneous use of opioids and benzodiazepines reduces neuronal activity, exerts sedative effects, induces drowsiness and other more harmful consequences, as the increase of respiratory depressant effects (27). For this reason, recent literature tends to dissuade the parallel administration of opioids and benzodiazepines (28).

We did not find references to explain why anticoagulants increased the risk of drowsiness. Antibiotics increased more than 4 times the risk of confusion when associated with opioids. We wonder how much infection per se, or antibiotics or their combination could be correlated with this symptom.

We remind that methodologically, since concomitant diseases and relative therapy were generally correlated, if both disease and therapy were associated with endpoint at univariate analysis, only the therapy was included in the multivariate analysis.

Antidiabetic drugs increased the risk of drowsiness, confusion and dry mouth. Also in this case, it is difficult to discriminate whether these effects could be also due to drugs or to diabetes itself. Two studies documented the association between increased glucose concentration and xerostomia (29,30). Furthermore, hyperinsulinaemia was suggested to alter central opioid tone, up-regulating limbic μ-opioid receptors and increasing beta-endorphin levels (31) but the interactions between insulin, glycemia and endogenous or exogenous opioids are far from a clear explanation.

In conclusion, we found some clinical factors able to modulate the efficacy and safety outcomes of opioids therapy. These factors can be distinguished in several categories including tumor localizations and metastases, the intensity and characteristics of pain (mainly BTP), the opioids way of administration (transdermal vs. oral), the experience of a previous weak opioid treatment, demographic data (sex and age), and the polypharmacy. Quite unexpectedly, we did not find depression and the presence of neuropathic pain as influencing factors.

Within the identified factors, we acknowledge that a couple of points should be stressed:

1. the characteristics of pain especially alter the efficacy of opioids. In particular, the presence of BTP makes pain harder to treat while a high initial pain intensity fosters a good response.
2. patients with polypharmachological therapy due to concurrent diseases are more likely to experience severe opioid adverse effects.

This post-hoc analysis presents several limitations related both to its exploratory purpose and to the protocol of the original study. For instance, all the clinical conditions reported were based on the case history and clinical examinations. No laboratory tests were executed and the assessment on the organs functions and diseases severity were precluded. Nevertheless, the clinical use of opioids is a critical topic that requests efforts to optimize their use and avoid a number of hidden dangers. We hope that the emerged observations might contribute to a careful choice of the correct opioid for the treatment of cancer pain patients.

Conclusions

This analysis appears as a piece of puzzle in evaluating the response to opioids in cancer patients with pain. Deepening these findings will be useful to know in advance the clinical factors influencing the response to opioids and to help the clinicians in scheduling the therapeutic strategies. In an optimistic vision, it could be suitable to match the patient's main characteristics (age, gender, genetics, primary tumor and metastases, co-morbidities, co-treatments, organ function, type of pain, psychological profile, allergies) to opioid properties (pharmacokinetics, pharmakodynamics, toxicity, drug interactions) in order to customize the treatment and reach the best therapeutic outcome.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent

Informed consent was obtained from all individual participants included in the study.

Conflict of interest

The authors declare that they have no conflict of interest.

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None

Author contributions

All authors were involved in developing the design of the study. FG prepared and cleaned the data. FG did the statistical analysis in consultation with ER. OC, AR, FG and RA wrote the first draft. MIB and NC reviewed the manuscript. All authors also contributed by reviewing previous versions of the manuscript and improving the final version to be published.

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1 **Table 1. Patient's demographic and clinical characteristics at baseline.**

	ITT population N=498
Age (years) – Mean (SD)	66.9 (11.8)
Female	221 (44.4)
Primary site of tumor	
Lung/ Pleura	141 (28.3)
Digestive system	114 (22.9)
Genito/urinary/reproductive system	94 (18.9)
Breast	65 (13.1)
Head, neck	42 (8.4)
Other	42 (8.4)
Presence of metastasis	424 (85.1)
Metastasis localization	
Lymph nodes	235 (55.4)
Bone	185 (43.7)
Lung	123 (29.1)
Liver	119 (28.1)
Other	154 (36.4)
Missing	1
Karnofsky Performance Status – Mean (SD)	66.9 (17.0)
Pain characteristics	
Average pain intensity – Mean (SD)	6.0 (1.4)
Average pain intensity≥6	297 (59.6)
Worst pain intensity – Mean (SD)	8.0 (1.5)
Worst pain intensity≥8	321 (64.5)
~~Neuropathic pain~~	~~62 (12.4)~~
BTP in the 24h before baseline	223 (44.8)
At least 3 episodes of BTP in the 24h before baseline	99 (19.9)
Type of pain	
Only nociceptive	412 (83.7)
Neuropathic and mixed	80 (16.3)
Not evaluable	6
Psychological aspects	
Anxiety	375 (75.3)
Worry	428 (85.9)

Irritability	297 (59.6)
Depression	370 (74.3)
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)
Prior weak opioid exposure	323 (64.9)
Codeine	224 (69.4)
Tramadol	99 (30.6)
Co-analgesic therapy	
Steroids	134 (57.8)
Anticonvulsants	45 (19.4)
Antidepressants	32 (13.8)
Bisphosphonates	50 (21.6)
Other adjuvants	32 (13.8)
Total	266 (53.4)
Concomitant diseases	320 (64.3)
Metabolic/hormonal disease	95 (29.7)
Cardiovascular disease	237 (74.1)
Neurological/psychological disease	25 (7.8)
Digestive system disease	23 (7.2)
Respiratory disease	35 (10.9)
Other disease	83 (25.9)
Therapy for concomitant diseases	278 (86.9)
Cardiovascular drugs	213 (76.6)
Antidiabetic drugs	74 (26.6)
Gastrointestinal drugs	52 (18.7)
Antibiotics	11 (4.0)
Central nervous system drugs	26 (9.4)
Hormonal drugs	20 (7.2)
Respiratory drugs	16 (5.8)
Other drugs	78 (28.1)

Data are number (%) unless otherwise specified. SD: Standard Deviation.

BTP: Breakthrough cancer pain.

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Table 2. Effect of clinical factors on no response to opioid therapy. Univariate and multivariate logistic regression models.

	Univariate analysis			Multivariate analysis		
	OR	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**
Arm (ref. oral morphine)			0.596			0.464
Transdermal buprenorphine	0.96	0.44 - 2.10	0.910	0.95	0.40 - 2.25	0.903
Oral oxycodone	1.30	0.61 - 2.74	0.495	1.30	0.57 - 2.96	0.526
Transdermal Fentanyl	0.75	0.33 - 1.73	0.500	0.64	0.25 - 1.61	0.343
Primary site of tumor (ref. Respiratory system)			0.126			0.095
Digestive system	2.09	0.99 - 4.42	0.052	2.16	0.94 - 4.93	0.069
Genito/urinary/reproductive system	1.17	0.49 - 2.80	0.720	1.50	0.58 - 3.87	0.402
Breast	0.48	0.13 - 1.73	0.261	0.37	0.09 - 1.46	0.156
Head/Neck	1.97	0.73 - 5.31	0.181	2.34	0.78 - 7.03	0.131
Other	1.04	0.32 - 3.37	0.953	1.12	0.31 - 4.02	0.866
Liver metastasis	2.22	1.25 - 3.97	0.007	2.16	1.08 - 4.29	**0.028**
Depression	1.97	0.94 - 4.14	0.073	1.98	0.87 - 4.51	0.105
Neuropathic pain	1.83	0.89 - 3.76	0.100	2.02	0.87 - 4.69	0.103
Baseline Average Pain Intensity $\geq$ 6	0.62	0.35 - 1.07	0.088	0.49	0.26 - 0.91	**0.024**
At least 3 episodes of BTP in the 24h before baseline	2.05	1.12 - 3.77	0.021	2.89	1.44 - 5.80	**0.003**

OR: odds ratio; 95%CI: 95% confidence interval.

BTP: Breakthrough cancer pain

Table 3. Effect of clinical factors on occurrence of severe adverse events. Univariate and multivariate logistic regression models.

	Univariate analysis			Multivariate analysis		
	OR	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**
CONSTIPATION						
Arm (ref. oral morphine)			0.195			0.036
Transdermal buprenorphine	0.64	0.38 - 1.08	0.092	0.51	0.29 - 0.90	**0.020**
Oral oxycodone	0.68	0.40 - 1.14	0.143	0.58	0.33 - 1.02	0.060
Transdermal Fentanyl	0.59	0.35 - 1.00	0.050	0.45	0.25 - 0.81	**0.008**
Age (10 years increase)	0.80	0.69 - 0.94	0.007	0.81	0.68 - 0.96	**0.018**
At least 3 episodes of BTP in the 24h before baseline	1.94	1.24 - 3.04	0.004	1.50	0.91 - 2.47	0.110
Previous weak opioid pain therapy	1.61	1.03 - 2.51	0.037	1.89	1.15 - 3.10	**0.012**
DROWSINESS						
Arm (ref. oral morphine)			0.221			0.259
Transdermal buprenorphine	1.02	0.59 - 1.74	0.953	0.97	0.55 - 1.72	0.920
Oral oxycodone	0.83	0.48 - 1.43	0.495	0.77	0.43 - 1.39	0.393
Transdermal Fentanyl	0.59	0.33 - 1.05	0.070	0.57	0.31 - 1.06	0.075
Bone metastasis	1.44	0.96 - 2.15	0.074	1.63	1.06 - 2.51	**0.026**
Antihypertensive drugs	1.52	1.02 - 2.27	0.039	1.09	0.69 - 1.71	0.723
Anticoagulants/blood thinning drugs	2.47	1.51 - 4.04	<.001	2.16	1.24 - 3.77	**0.007**
Cardiotonic drugs	3.35	0.89 - 12.65	0.075	1.48	0.33 - 6.52	0.607
Antianginal drugs	3.63	1.24 - 10.66	0.019	1.75	0.53 - 5.84	0.361
Antidiabetic drugs	2.57	1.56 - 4.25	<.001	2.26	1.31 - 3.89	**0.003**
Central nervous system drugs	2.77	1.25 - 6.15	0.012	2.73	1.18 - 6.32	**0.019**
DRY MOUTH						
Arm (ref. oral morphine)			0.919			0.942
Transdermal buprenorphine	0.91	0.51 - 1.62	0.743	0.88	0.47 - 1.65	0.683
Oral oxycodone	0.81	0.45 - 1.46	0.480	0.83	0.44 - 1.56	0.558
Transdermal Fentanyl	0.90	0.50 - 1.60	0.712	0.86	0.45 - 1.62	0.634
Female sex	1.65	1.09 - 2.50	0.019	2.00	1.25 - 3.18	**0.004**
Liver metastasis	1.53	0.96 - 2.43	0.074	1.51	0.91 - 2.51	0.113
Anticoagulants/blood thinning drugs	1.69	1.01 - 2.85	0.047	1.60	0.88 - 2.89	0.123
Antianginal drugs	2.52	0.86 - 7.42	0.093	2.13	0.62 - 7.32	0.229
Antidiabetic drugs	1.99	1.18 - 3.35	0.010	2.05	1.15 - 3.67	**0.015**
Gastrointestinal drugs	1.92	1.06 - 3.45	0.030	1.53	0.79 - 2.95	0.203

Previous weak opioid pain therapy	1.75	1.05 - 2.93	0.032	1.94	1.11 - 3.39	**0.020**
NAUSEA						
Arm (ref. oral morphine)			0.758			0.644
Transdermal buprenorphine	0.90	0.45 - 1.80	0.756	0.81	0.39 - 1.68	0.567
Oral oxycodone	1.16	0.59 - 2.27	0.669	0.95	0.46 - 1.94	0.878
Transdermal Fentanyl	0.80	0.39 - 1.65	0.549	0.63	0.29 - 1.36	0.242
Female sex	1.73	1.06 - 2.85	0.029	1.47	0.81 - 2.66	0.205
Primary tumor site (ref. Respiratory system)			0.058			0.309
Digestive system	1.20	0.59 - 2.45	0.621	0.87	0.40 - 1.89	0.730
Genito/urinary/reproductive system	1.00	0.46 - 2.19	1.000	0.93	0.41 - 2.10	0.852
Breast	2.23	1.05 - 4.73	0.036	1.45	0.60 - 3.49	0.405
Head/neck	0.34	0.08 - 1.54	0.162	0.29	0.06 - 1.36	0.117
Other	2.14	0.90 - 5.07	0.086	1.70	0.67 - 4.30	0.260
Liver metastasis	1.62	0.95 - 2.77	0.078	1.69	0.92 - 3.10	0.089
Antihypertensive drugs	0.58	0.34 - 0.99	0.047	0.59	0.33 - 1.04	0.067
Karnofski PS index (10% increase)	1.17	1.01 - 1.36	0.040	1.23	1.05 - 1.45	**0.012**
CONFUSION						
Arm (ref. oral morphine)			0.083			0.094
Transdermal buprenorphine	0.53	0.25 - 1.14	0.105	0.51	0.22 - 1.18	0.114
Oral oxycodone	0.54	0.25 - 1.16	0.116	0.55	0.24 - 1.28	0.164
Transdermal Fentanyl	0.35	0.15 - 0.83	0.018	0.31	0.12 - 0.81	**0.017**
Primary tumor site (ref. Respiratory system)			0.407			0.830
Digestive system	0.40	0.16 - 0.97	0.043	0.53	0.20 - 1.44	0.215
Genito/urinary/reproductive system	0.64	0.28 - 1.48	0.295	0.63	0.25 - 1.60	0.333
Breast	0.85	0.35 - 2.04	0.715	0.92	0.34 - 2.48	0.876
Head/neck	0.47	0.13 - 1.65	0.236	0.67	0.17 - 2.59	0.558
Other	0.82	0.29 - 2.33	0.706	0.79	0.24 - 2.61	0.695
Bone metastasis	1.65	0.93 - 2.94	0.089	1.77	0.89 - 3.52	0.101
Anticoagulants/blood thinning drugs	2.61	1.37 - 4.97	0.004	1.85	0.85 - 4.04	0.121
Cardiotonic drugs	4.49	1.09 - 18.52	0.038	1.43	0.27 - 7.69	0.678
Antianginal drugs	3.64	1.10 - 12.03	0.035	1.07	0.27 - 4.27	0.925
Antidiabetic drugs	2.81	1.47 - 5.36	0.002	2.82	1.34 - 5.96	**0.006**
Gastrointestinal drugs	2.67	1.31 - 5.47	0.007	1.68	0.73 - 3.89	0.223
Antibiotics	4.05	1.20 - 13.64	0.024	4.34	1.03 - 18.25	**0.045**

Previous weak opioid pain therapy	2.50	1.10 - 5.70	0.029	2.59	1.06 - 6.34	**0.038**

OR: odds ratio; 95%CI: 95% confidence interval.

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