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Are strong opioids equally effective and safe in the treatment of chronic cancer pain? A multicenter randomized phase IV 'real life' trial on the variability of response to opioids

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Background: Guidelines tend to consider morphine and morphine-like opioids comparable and interchangeable in the treatment of chronic cancer pain, but individual responses can vary. This study compared the analgesic efficacy, changes of therapy and safety profile over time of four strong opioids given for cancer pain.

Patient and methods: In this four-arm multicenter, randomized, comparative, of superiority, phase IV trial, oncological patients with moderate to severe pain requiring WHO step III opioids were randomly assigned to receive oral morphine or oxycodone or transdermal fentanyl or buprenorphine for 28 days. At each visit, pain intensity, modifications of therapy and adverse drug reactions (ADRs) were recorded. The primary efficacy end point was the proportion of nonresponders, meaning patients with worse or unchanged average pain intensity (API) between the first and last visit, measured on a 0–10 numerical rating scale. (NCT01809106).

Results: Forty-four centers participated in the trial and recruited 520 patients. Worst pain intensity and API decreased over 4 weeks with no significant differences between drugs. Nonresponders ranged from 11.5% (morphine) to 14.4% (buprenorphine). Appreciable changes were made in the treatment schedules over time. Each group required increases in the daily dose, from 32.7% (morphine) to 121.2% (transdermal fentanyl). Patients requiring adjuvant analgesics ranged from 68.9% (morphine) to 81.6% (oxycodone), switches varied from 22.1% (morphine) to 12% (oxycodone), discontinuation of treatment from 27% (morphine) to 14.5% (fentanyl). ADRs were similar except for effects on the nervous system, which significantly prevailed with morphine.

Conclusion: The main findings were the similarity in pain control, response rates and main adverse reactions among opioids. Changes in therapy schedules were notable over time. A considerable proportion of patients were nonresponders or poor responders.

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Clinical Trial Registration: NCT01809106 (https://clinicaltrials.gov/ct2/show/NCT01809106?term=cerp&rank=2).
Key words: opioids in cancer pain, variability of response, changes of therapy, neurotoxic effects

introduction

Opioids are the mainstay of treatment for cancer pain and their role has been regulated by several guidelines and scientific recommendations [1–3]. The WHO 'analgesic ladder' suggests treatment based on the intensity of pain, from no drug in case of no pain (step 0) to strong opioids (step III) for moderate to severe pain [2, 4]. Adjuvant analgesic drugs should be added according to the guidelines.

Strong opioids (morphine and morphine-like drugs) are often indicated as medications with comparable properties and somehow interchangeable [1, 2], but in fact, they have different pharmacokinetic and pharmacodynamic properties. Individual genetically determined variants have opened up new controversies about the impact of opioids in painful conditions [5–7]. Liver or renal failure can result in different responses [8, 9]. Co-treatments with other drugs can generate pharmacological interactions and alter the response to opioids [10]. The type of pain too can influence their efficacy, particularly neuropathic and breakthrough pain (BTP) [11, 12].

Several studies have compared the efficacy and safety of different opioids in cancer pain [13–19], usually comparing morphine head-to-head with another opioid. Despite differences in design and assessment methods, the analgesic efficacy appeared similar. The safety profile was also often reported as comparable.

In clinical practice, the achievement of overall pain reduction with limited side-effects is the main goal but some dynamic aspects over time, including dose changes, switching to other opioids and supplementary analgesics, are similarly important. We launched this study with the aim of comparing the analgesic efficacy of four strong opioids, morphine, oxycodone, buprenorphine and fentanyl, commonly used for the relief of cancer pain. In parallel, we recorded every change in therapeutic schedule over time and the safety profile.

methods

study design and patients

This is a multicenter, randomized, open-label, active-controlled, four-arm, of superiority, phase IV clinical trial. In each center, the study protocol had to be approved by the institutional review board and patients had to give written informed consent before any study-related activities were carried out.

Eligibility criteria were: 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 on a 0–10 Numerical Rating Scale (NRS)]; need for WHO step III strong opioids never previously given; age >18 years. Cerebral tumors and leukemia were excluded on account of their different pain mechanisms. Patients undergoing concurrent radiotherapy, first-line chemotherapy started 7 days before randomization, any nonpharmacological analgesic treatment and pre-existing renal failure were excluded.

randomization

Eligible patients were centrally randomized in a 1 : 1 : 1 : 1 ratio to receive oral controlled-release (CR) morphine (active comparator) or CR oxycodone or transdermal (TD) fentanyl or TD buprenorphine, taken around the clock (ATC) for pain relief.

procedures

The follow-up lasted 28 days with six visits on days 1, 3, 7, 14, 21 and 28. At baseline, the oncological medical history (primary tumor site, presence of metastases, previous and ongoing cancer treatments), concomitant diseases, and Karnofsky Performance Status index were assessed together with pain characteristics: API and worst pain intensity (WPI) experienced in the previous 24 h measured on the NRS, type of pain (nociceptive, neuropathic, mixed), presence of neuropathic pain according to the DN4 questionnaire [20] and BTP according to the Davies algorithm [21]. Overall therapy under way at the beginning of the study and any new therapy scheduled after randomization were recorded.

The initial dose of opioid was based on the recommendations of the European Association for Palliative Care/EAPC [2]. During the follow-up, any adjustment necessary for better control of pain was allowed for clinical and ethical reasons. Physicians could change the dose, add another opioid or an adjuvant drug or change the opioid (switch). In case of constantly unsatisfactory analgesia or severe toxicity, the opioid could be discontinued.

At each visit, API and WPI, changes of analgesic therapy (ATC daily dose, type(s) and dose(s) of extra opioids or adjuvant drugs), opioid switches or discontinuations and adverse drug reactions (ADRs) were recorded.

end points

On the basis of the differences in pain intensity between the first and last visit and according to Farrar criteria [22], patients were classified as nonresponders (NRs), i.e. those with no improvement or worsening, partial responders (PRs) with <30% pain reduction and responders (Rs) with >30% pain reduction. The primary efficacy end point was the proportion of NRs based on the API difference. The secondary end points included the proportion of (i) NRs based on the WPI difference; (ii) Rs based on the API difference; (iii) patients requiring a mean increase in the opioid daily dose >5% according to the Opioid Escalation Index % (OEI%) [23]; (iv) requiring a switch to another opioid; (v) needing supplementary doses of opioids; (vi) needing adjuvant analgesic drugs to optimize the ATC therapy; and (vii) discontinuing the opioid.

ADRs were measured using a questionnaire self-filled by the patient (presence and severity of symptoms measured with a 4-point verbal rating scale: no, light, moderate, severe), from the Therapy Impact Questionnaire [24].

statistical analysis

Due to the lack of specific literature, sample size was calculated using data from our observational study [25]. Assuming 35% of NRs to oral morphine, 214 patients were to be included in each arm to detect, with 80% power and 5% type 1 error for a bilateral test, a reduction of at least 40% in patients treated with the other opioids. Anticipating 15% of drop-outs, 1008 patients had to be randomized.

Efficacy analyses were done on the intention-to-treat (ITT) population, which included all randomized patients without major violations of the eligibility criteria and with at least one pain evaluation after baseline. Only patients who started on opioid were included in the safety analysis, which considered patients in the arm of the treatment they actually received. Each patient was considered until the end of the 28-day follow-up, or until a switch or premature discontinuation of the study for any reason. Only for

the pain intensity analysis, in case of premature discontinuation of the opioid, the last-observation-carried-forward method was applied for missing data handling. The χ^2 test (or Fisher's exact test, where appropriate) was used to assess differences between oral oxycodone, TD buprenorphine or TD fentanyl, compared with oral morphine.

results

Between May 2011 and July 2014, 520 patients were randomized by 44 Italian centers. Twenty (45.4%) were palliative care units, 17 (38.6%) oncology wards, 5 (11.4%) pain therapy centers, 1 (2.3%) an onco-hematology ward and 1 (2.3%) a supportive care center. In September 2014, in view of the disappointing recruitment, the Steering Committee decided to early stop enrollment, fully aware that the study could lose the power to test the planned differences between treatments.

The selection process is illustrated in Figure 1. Altogether 515 patients were included in the safety analysis and 498 in the ITT analysis. The demographic and clinical characteristics of patients at baseline are given in Table 1, with the pain features and the previous ATC therapy according to WHO guidelines.

WPI and API at each visit are illustrated in Table 2. Mean WPI at baseline was homogeneously distributed from 8.2 [fentanyl (F)] to 7.8 [morphine (M)] and fell to final values of 4.5 [oxycodone (O),F] to 4 (M). Mean API at baseline dropped from 2.9 (O) to 2.6 (M). Consequently, the pain intensity differences were very close among opioids, with WPI mean reductions of 3.9 (B), 3.8 (M), 3.7 (F) and 3.4 (O), and API reductions of 3.4 (M, F) and 3.1 (O, B). No significant differences were observed between M and the other opioids.

The proportions of NRs based on API are provided in Table 3. There were no significant differences from M.

The secondary end points are described in Table 4. Each group needed an increase in the ATC daily dose over time to maintain the analgesic effect. The suggested initial daily dose was 60 mg of oral M for patients with previous WHO step II treatment or half of this (30 mg/day) for opioid-naïve patients. The doses of the other opioids were regulated on the basis of the oral M equivalent dose ratio [2]. The proportion of patients requiring additional opioids, generally oral immediate-release or intravenous morphine, did not significantly differ among groups. The proportions of patients requiring adjuvant drugs ranged from 68.9% to 81.6%, opioid switches from 22.1% to 12.0%.

Discontinuation from the randomly given opioid mainly included unsuccessful pain relief or severe unmanageable toxicity; this occurred from 27% to 14.5%.

The addition of NSAIDs, which can be considered as co-analgesics in patients receiving strong opioids, is shown in Figure 2. The number of patients receiving NSAIDs increased over time with M, was steady with F and decreased with O and B.

Patients who presented at least one ADR during the study, of whatever severity, are listed in Table 5. Drowsiness, constipation and dry mouth occurred in more than half the cases. ADRs judged as 'moderate' and 'severe' by the patients occurred in 60% (B), 58.9% (M), 50.4% (F) and 48.8% (O). Some ADRs were reported equally in the arms, particularly those regarding the digestive system (dry mouth, gastralgia, nausea, vomiting, constipation). Important differences were observed for those involving the nervous system (confusion, hallucinations, myoclonus). Hallucinations were typically related to M, occurring in 13.2% of patients but only 6.2% with O and B and 2.4% with F ($P = 0.001$). Severe myoclonus was not seen with O but occurred in 4.7% of cases with M ($P = 0.029$). High levels of confusion were less frequent with F (6.3%) than with M (15.5%), ($P = 0.018$).

discussion

This study was primarily designed to compare the analgesic properties of oral morphine with three other commonly used strong opioids. Morphine-like opioids are often considered interchangeable. The recently published EAPC recommendations [2] indicate 'no important differences between morphine, oxycodone, and hydromorphone given orally, permitting a weak recommendation that any one of these drugs can be used as

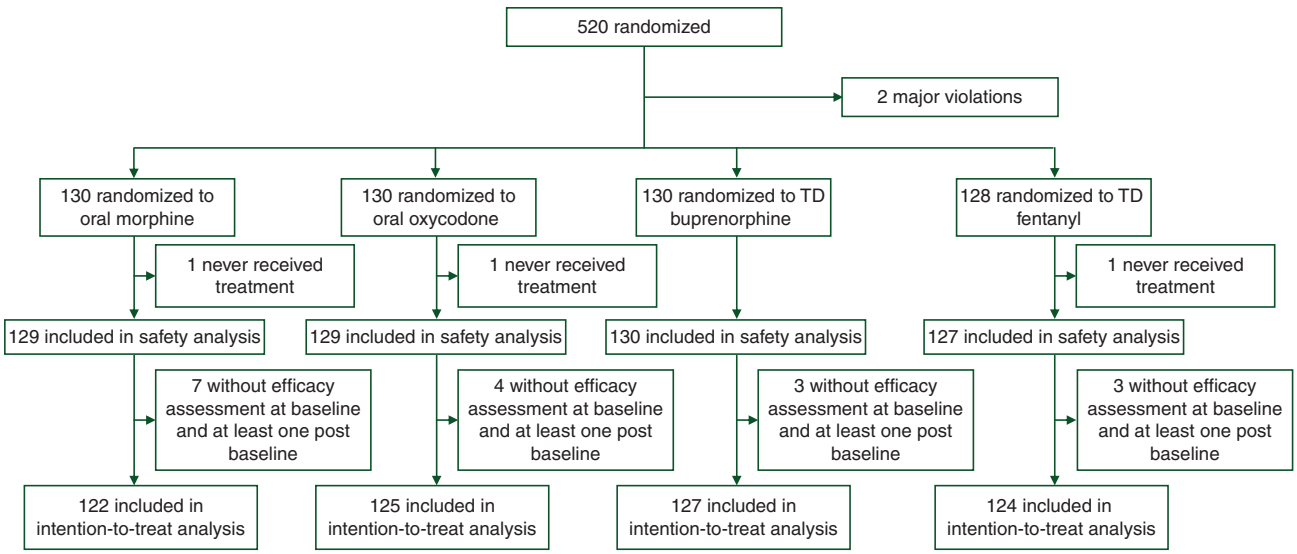


Figure 1. CERP study flow chart.

Table 1. Main demographic and clinical characteristics of the patients at baseline

	Oral morphine (*N* = 122)	Oral oxycodone (*N* = 125)	Transdermal buprenorphine (*N* = 127)	Transdermal fentanyl (*N* = 124)
Age (years), mean (SD)	67.5 (11.7)	66.9 (11.1)	65.2 (13.5)	68 (10.6)
Female	55 (45.1)	53 (42.4)	59 (46.5)	54 (43.5)
Primary site of tumor				
Lung, pleura	34 (27.9)	31 (24.8)	39 (30.7)	37 (29.8)
Colon, rectum	11 (9)	14 (11.2)	15 (11.8)	17 (13.7)
Breast	17 (13.9)	16 (12.8)	22 (17.3)	10 (8.1)
Prostate	6 (4.9)	13 (10.4)	4 (3.1)	6 (4.8)
Pancreas	14 (11.5)	8 (6.4)	13 (10.2)	4 (3.2)
Genitourinary	10 (8.2)	8 (6.4)	3 (2.4)	10 (8.1)
Esophagus, stomach, duodenum	3 (2.5)	8 (6.4)	1 (0.8)	6 (4.8)
Head, neck	9 (7.4)	8 (6.4)	13 (10.2)	12 (9.7)
Gynecologic	11 (9)	6 (4.8)	8 (6.3)	9 (7.3)
Myeloma	1 (0.8)	4 (3.2)	2 (1.6)	5 (4)
Sarcoma	–	2 (1.6)	3 (2.4)	3 (2.4)
Others	6 (4.9)	7 (5.6)	4 (3.1)	5 (4)
Presence of metastases	101 (82.8)	112 (89.6)	107 (84.3)	104 (83.9)
Previous cancer therapies	94 (77.0)	101 (80.8)	102 (80.3)	95 (76.6)
Surgery	53 (56.4)	60 (59.4)	61 (59.8)	56 (58.9)
Chemotherapy	67 (71.3)	83 (82.2)	79 (77.5)	73 (76.8)
Biological therapy	13 (13.8)	17 (16.8)	18 (17.6)	17 (17.9)
Hormone therapy	19 (20.2)	28 (27.7)	16 (15.7)	13 (13.7)
Radiotherapy	40 (42.6)	44 (43.6)	44 (43.1)	37 (38.9)
Other	7 (7.4)	7 (6.9)	4 (3.9)	4 (4.2)
Concomitant diseases	80 (65.6)	76 (60.8)	81 (63.8)	83 (66.9)
Karnofsky performance status	65.7 (17.6)	67.4 (16.4)	67.5 (17.1)	67.0 (17.2)
Previous background pain therapy				
No therapy (WHO step 0)	8 (6.6)	15 (12)	12 (9.4)	13 (10.5)
Nonopioids (WHO step I)	26 (21.3)	29 (23.2)	26 (20.5)	26 (21)
Weak opioids (WHO step II)	88 (72.1)	81 (64.8)	89 (70.1)	85 (68.5)
Other adjuvant therapies for pain				
None	66 (54.1)	60 (48)	73 (57.5)	67 (54)
Steroids	32 (27.1)	36 (29.5)	32 (25.4)	34 (28.1)
Anticonvulsants	14 (11.9)	13 (10.7)	8 (6.3)	10 (8.3)
Antidepressants	10 (8.5)	10 (8.2)	6 (4.8)	6 (5)
Bisphosphonates	13 (11)	18 (14.8)	11 (8.7)	8 (6.6)
Other	7 (5.9)	8 (6.6)	9 (7.1)	8 (6.6)
Missing	4	3	1	3
Ongoing anticancer therapy	53 (43.4)	48 (38.4)	48 (37.8)	42 (33.9)
Ongoing therapies for concomitant diseases	77 (63.1)	71 (56.8)	76 (59.8)	70 (56.5)
Ongoing therapies for other symptoms	49 (40.2)	46 (36.8)	51 (40.2)	41 (33.1)
Pain duration (months)	2.8 (3.4)	3.7 (4.9)	3.5 (5.2)	3.2 (4.5)
Breakthrough pain	42 (34.4)	62 (49.6)	60 (47.2)	59 (47.6)
Type of pain				
Only nociceptive	98 (80.3)	106 (84.8)	102 (80.3)	106 (86.2)
Only neuropathic	–	–	1 (0.8)	–
Nociceptive and neuropathic	23 (18.9)	18 (14.4)	23 (18.1)	15 (12.2)
Insufficient information to classify	1 (0.8)	1 (0.8)	1 (0.8)	2 (1.6)
Missing	–	–	–	1

Data are number (%) unless otherwise specified.
SD, standard deviation.

the first choice opioid for moderate to severe cancer pain' and, further, that 'transdermal fentanyl and buprenorphine are alternatives to oral opioids.' These recommendations come from studies usually comparing newer drugs or preparations with morphine as the standard comparator in patients already exposed to opioids and sometimes already responsive to morphine.

The opioids share a common mechanism of action [26, 27], not without some distinctions [28]—but the pharmacokinetics

Table 2. Average and worst pain intensity at each visit

	Baseline	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	P^a
Oral morphine							
API	6.0 (1.3)	3.1 (1.9)	2.8 (2)	2.7 (1.9)	2.6 (2.1)	2.6 (2.1)	–
WPI	7.8 (1.5)	4.6 (2.5)	4.3 (2.6)	4.0 (2.5)	3.8 (2.8)	4.0 (2.7)	–
Oral oxycodone							
API	6.0 (1.5)	3.3 (2)	2.9 (1.9)	3.0 (2)	2.9 (2)	2.9 (2.1)	0.344
WPI	7.9 (1.6)	5.2 (2.6)	4.7 (2.7)	4.5 (2.6)	4.6 (2.6)	4.5 (2.7)	0.223
Transdermal buprenorphine							
API	5.9 (1.2)	3.4 (1.9)	2.9 (2)	2.6 (1.9)	2.6 (1.9)	2.7 (1.9)	0.518
WPI	8.0 (1.4)	5.1 (2.6)	4.5 (2.6)	4.1 (2.5)	4.0 (2.6)	4.2 (2.6)	0.971
Transdermal fentanyl							
API	6.2 (1.5)	3.5 (1.9)	3.1 (2)	3.2 (2.1)	2.8 (2.1)	2.8 (2.2)	0.972
WPI	8.2 (1.5)	5.2 (2.7)	4.8 (2.6)	4.7 (2.7)	4.4 (2.7)	4.5 (2.8)	0.681

Data are mean (SD).
[a]Wilcoxon test for pain intensity difference between visit 6 and baseline. Oral morphine is the active comparator.
API, average pain intensity; WPI, worst pain intensity.

Table 3. Nonresponders (NRs) in each arm and other responses on the basis of API

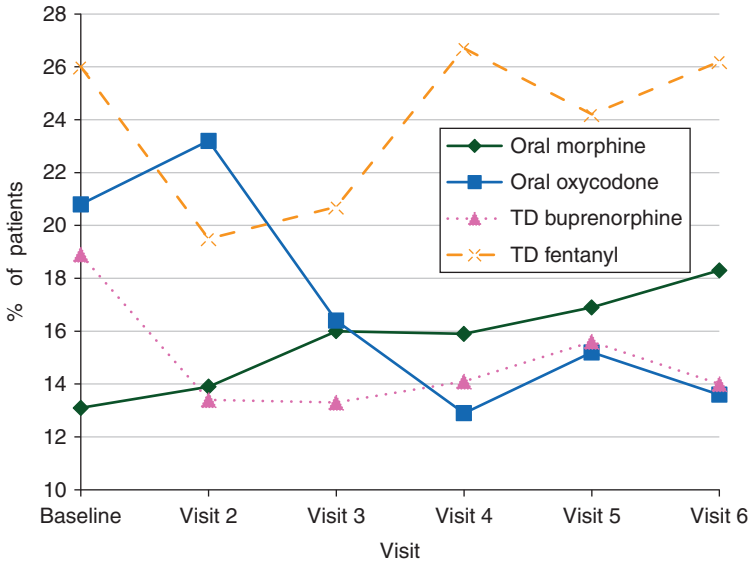
	Oral morphine ($N = 122$)	Oral oxycodone ($N = 125$)	P^a	Transdermal buprenorphine ($N = 127$)	P^a	Transdermal fentanyl ($N = 124$)	P^a
API–NRs	14 (11.5)	18 (14.4)	0.494	14 (11)	0.910	11 (8.9)	0.499
API–PRs	16 (13.1)	15 (12)		14 (11)		19 (15.3)	
API–Rs	92 (75.4)	92 (73.6)		99 (78)		94 (75.8)	

Data are number (%).
[a]Chi-square test for comparison of proportion of NRs (PRs and Rs were pooled). Oral morphine is the active comparator.
API, average pain intensity; NRs, nonresponders; PRs, partially responders; Rs, responders.

Table 4. Secondary end points

	Oral morphine ($N = 122$)	Oral oxycodone ($N = 125$)	P	Transdermal buprenorphine ($N = 127$)	P	Transdermal fentanyl ($N = 124$)	P
WPI–NRs	17 (13.9)	22 (17.6)	0.430	12 (9.4)	0.270	17 (13.7)	0.959
API–Rs[a]	92 (75.4)	92 (73.6)	0.744	99 (78)	0.635	94 (75.8)	0.942
Baseline dose[b] (mg/day)	45.7 (16.2)	44.6 (16)		53.7 (12.5)		53.4 (14.2)	
Final dose[b] (mg/day)	58.9 (38.6)	71.1 (60.8)		80.1 (40.4)		111.4 (74.9)	
Mean dose[b] increase	32.7%	70.9%		56.4%		121.2%	
OEI >5%	13 (10.7)	24 (19.2)	*0.060*	18 (14.2)	*0.401*	45 (36.3)	*<0.001*
Patients requiring additional opioids	36 (29.5)	33 (26.4)	*0.586*	48 (37.8)	*0.167*	46 (37.1)	*0.207*
Patients requiring adjuvant drugs	84 (68.9)	102 (81.6)	*0.020*	100 (78.7)	*0.076*	100 (80.6)	*0.033*
Switches	27 (22.1)	15 (12)	*0.034*	21 (16.5)	*0.263*	16 (12.9)	*0.057*
Premature discontinuations for pain treatment-related reasons	33 (27)	19 (15.2)	*0.051*	26 (20.5)	*0.222*	18 (14.5)	*0.015*

Data are number (%) or mean (SD).
[a]Chi-square test for comparison of proportion of Rs (PRs and NRs were pooled).
[b]ATC daily doses (as oral morphine equivalent daily dose).
[c]Chi-square test. Oral morphine is the active comparator.
WPI, worst pain intensity; API, average pain intensity; NRs, nonresponders; Rs, responders; OEI, Opioid Escalation Index; ATC, around the clock; OMEDD, oral morphine equivalent daily dose.



Oral morphine	122	122	106	88	77	71
Oral oxycodone	125	125	111	101	92	88
TD buprenorphine	127	127	113	99	96	93
TD fentanyl	124	124	116	101	91	84

Figure 2. Patients receiving NSAIDs as co-analgesics at each visit.

(bioavailability, plasma protein binding, blood/brain barrier crossing ability and metabolic pathways) and pharmacodynamics (receptor affinity, receptor subtypes occupied, pharmacological potency) are different. As a result, different opioids are likely to differ in some respects.

In this trial, CR morphine, CR oxycodone, TD fentanyl and TD buprenorphine seemed to achieve similar levels of pain relief and rates of response. At the end of the study, 8.9%–14.4% of patients were classifiable as NRs and 11%–15.3% as PRs, meaning that 22%–26.4% had poor responses with <30% reduction of pain intensity. Therefore, three quarters of responses were positively addressed to reducing pain, and one quarter was negative: this substantially limits the consolidated efficacy appraisal of the opioids in the treatment of cancer pain and highlights personal variability in response [29]. Even patients reaching a good response needed frequent adjustments of the therapy schedule.

This is the key point of the study: equal pain relief achieved, dissimilar changes of the therapeutic schedules appear, corresponding to the majority of secondary end points. Dose escalation was greater with fentanyl, and switches and discontinuations were more frequent with morphine. Our previous publication [30] indicated no significant differences between opioids on analgesic effects, but there were more switches with morphine and the dose increases with fentanyl, over time. The present study confirms these observations, under more controlled conditions. The variability in the response to opioids does not concern the actual analgesia as such, but the changes of therapy needed to maintain it.

The continued interaction between outcome and changes of process partially changed *a posteriori* the primary intention of this study of comparing four opioids head-to-head, into a more general evaluation of strategies starting from a randomly given drug, but spreading into numerous therapeutic variables. This combines the pragmatic method of a clinical trial with the patterns of clinical practice. The main objective of physicians for cancer patients with pain is to relieve the pain over time. To do this, they adapt the therapy whenever pain tends to increase. They can change the dosage, add extra opioids or adjuvant drugs, switch to another molecule or discontinue opioids and use other analgesic techniques. For instance, 22% of patients receiving morphine switched to another opioid compared with 12% of those on oxycodone. With morphine, there was low-dose escalation, scant use of adjuvants, but frequent switches and discontinuations and the highest prevalence of neurotoxic effects. Oxycodone had an intermediate efficacy profile, often needing adjuvants but limited supplementary opioids, and low rates of switching and discontinuation. Buprenorphine was midway in many variables except for the particularly high need for extra opioids. Fentanyl required the most dose escalation and extra adjuvants. Fentanyl seemed the most difficult for maintaining analgesia, requiring constant adjustment of therapy. However, it had low percentages of switching and discontinuation. The differences between opioids tended to vary.

Side-effects are often indicated as substantially similar in the literature and this study confirmed the absence of difference in the main ADRs except for neurotoxic effects which were more frequent with morphine. In this study, all the outcomes, in terms of analgesic efficacy, dose escalation, opioid rotation, use of adjuvant analgesics and side-effects, are related to 28 days of observation. Longer periods might cause different effects not investigated here. The study has its limits and weak points. In particular, the early interruption because of the slow recruitment made the trial underpowered and significantly limited the findings on the primary end point. Quite possibly, the lack of differences should be interpreted in the light of this limit.

Table 5. Frequency of patients with ADRs in each treatment arm

	Oral morphine ($N = 129$)	Oral oxycodone ($N = 129$)	P^a	Transdermal buprenorphine ($N = 130$)	P^a	Transdermal fentanyl ($N = 127$)	P^a
Drowsiness							
Any degree	79 (61.2)	74 (57.4)	0.526	81 (62.3)	0.860	70 (55.1)	0.321
Severe	38 (29.5)	34 (26.4)	0.579	40 (30.8)	0.818	26 (20.5)	0.097
Confusion							
Any degree	59 (45.7)	55 (42.6)	0.616	61 (46.9)	0.848	46 (36.2)	0.122
Severe	20 (15.5)	12 (9.3)	0.131	12 (9.2)	0.125	8 (6.3)	0.018
Nausea							
Any degree	64 (49.6)	63 (48.8)	0.901	59 (45.4)	0.496	57 (44.9)	0.449
Severe	19 (14.7)	22 (17.1)	0.609	18 (13.8)	0.839	16 (12.6)	0.620
Vomiting							
Any degree	35 (27.1)	29 (22.5)	0.387	30 (23.1)	0.452	29 (22.8)	0.427
Severe	12 (9.3)	12 (9.3)	1.000	5 (3.8)	0.076	10 (7.9)	0.684
Constipation							
Any degree	82 (63.6)	75 (58.1)	0.372	87 (66.9)	0.571	77 (60.6)	0.628
Severe	50 (38.8)	40 (31)	0.192	39 (30)	0.138	36 (28.3)	0.078
Dry mouth							
Any degree	66 (51.2)	66 (51.2)	1.000	73 (56.2)	0.421	67 (52.8)	0.799
Severe	31 (24.0)	27 (20.9)	0.551	30 (23.1)	0.856	29 (22.8)	0.821
hallucinations							
Any degree	17 (13.2)	8 (6.2)	0.058	8 (6.2)	0.056	3 (2.4)	0.001
Severe	6 (4.7)	1 (0.8)	0.120[b]	2 (1.5)	0.172[b]	–	0.023[b]
Muscle spasm myoclonus							
Any degree	14 (10.9)	23 (17.8)	0.110	24 (18.5)	0.084	15 (11.8)	0.809
Severe	6 (4.7)	–	0.029[b]	1 (0.8)	0.066[b]	5 (3.9)	0.778
Gastralgia							
Any degree	24 (18.6)	21 (16.3)	0.623	21 (16.2)	0.603	26 (20.5)	0.706
Severe	3 (2.3)	6 (4.7)	0.500[b]	1 (0.8)	0.370[b]	4 (3.1)	0.721[b]
dysuria							
Any degree	22 (17.1)	17 (13.2)	0.385	16 (12.3)	0.280	13 (10.2)	0.112
Severe	2 (1.6)	4 (3.1)	0.684[b]	4 (3.1)	0.684[b]	4 (3.2)	0.445[b]
Breathlessness							
Any degree	17 (13.2)	12 (9.3)	0.324	30 (23.1)	0.039	22 (17.3)	0.356
Severe	4 (3.1)	3 (2.3)	1.000[b]	6 (4.6)	0.749[b]	5 (3.9)	0.748[b]
Itching							
Any degree	24 (18.6)	16 (12.4)	0.169	21 (16.2)	0.603	14 (11)	0.088
Severe	3 (2.3)	2 (1.6)	1.000[b]	1 (0.8)	0.370[b]	3 (2.4)	1.000[b]

Data are number (%).
[a]Chi-square test.
[b]Fisher's exact test.
ADRs, adverse drug reactions.

A second limit concerns the evaluation of the ADRs. The large number of comparisons could increase the possibility of false positives. Nevertheless, no correction has been made in the statistical analysis to avoid the risk that potential differences in safety events were not detected, particularly given the underpowered analysis.

A third critical point is that we originally calculated the sample size without any specific indications in the literature, assuming 35% of NRs to morphine and a hypothesis of detecting a relative decrease of 40% in patients treated with the other opioids. In fact, the proportion of NRs to morphine was much lower (11.5%) with the decrease in the power of the study. Nevertheless, to our knowledge, this is the biggest randomized trial on opioid treatment in cancer pain. The results, especially the secondary end points, can contribute to spark the debate on this controversial matter.

conclusion

Pain intensity, positive and negative responses and the general safety profile were comparable among the four groups examined in this study. Nevertheless, the old belief that strong opioids are identically effective and interchangeable in the treatment of chronic cancer pain may be not completely true as there were marked differences in the management of the opioid therapy over time.

These changes quite likely play a role in achieving an equivalent analgesic effect.

Moreover, there were many non- or partial responders even though opioids are still widely considered the most effective tools for relieving cancer pain.

The poor analgesic effect is a primary problem in clinical practice and calls for full attention. It can depend on the drugs used, on the patient's clinical conditions and on other variables. Understanding the interactions among these aspects could improve the approach and customization of the therapy. The characteristics of each opioid (pharmacokinetics, pharmacodynamics, toxicity, drug interactions) will have to be matched with the patient's characteristics (age, sex, genetics, primary tumor and metastases, co-morbidities, simultaneous treatments, organ function, types of pain, psychological structure, allergies). Combining all these variables could be the basis for a classification system to identify the best treatment for each patient.

Finally, other sources of variability such as therapeutic habits, doctors' and patients' preferences or compliance, favoring one drug or route of administration over another, still need to be tested in controlled trials with specifically designed end points.

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appendix

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