

# Analgesic effectiveness and tolerability of oral oxycodone/naloxone and pregabalin in patients with lung cancer and neuropathic pain: an observational analysis

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**Introduction:** Cancer-related pain has a severe negative impact on quality of life. Combination analgesic therapy with oxycodone and pregabalin is effective for treating neuropathic cancer pain. We investigated the efficacy and tolerability of a dose-escalation combination therapy with prolonged-release oxycodone/naloxone (OXN-PR) and pregabalin in patients with non-small-cell lung cancer and severe neuropathic pain.

**Methods:** This was a 4-week, open-label, observational study. Patients were treated with OXN-PR and pregabalin. Average pain intensity ([API] measured on a 0–10 numerical rating scale) and neuropathic pain (Douleur Neuropathique 4) were assessed at study entry and at follow-up visits. The primary endpoint was response to treatment, defined as a reduction of API at T28  $\geq 30\%$  from baseline. Secondary endpoints included other efficacy measures, as well as patient satisfaction and quality of life (Brief Pain Inventory Short Form), Hospital Anxiety and Depression Scale, and Symptom Distress Scale; bowel function was also assessed.

**Results:** A total of 56 patients were enrolled. API at baseline was  $8.0 \pm 0.9$ , and decreased after 4 weeks by 48% ( $4.2 \pm 1.9$ ;  $P < 0.0001$  vs baseline); 46 (82.1%) patients responded to treatment. Significant improvements were also reported in number/severity of breakthrough cancer pain episodes ( $P = 0.001$ ), Brief Pain Inventory Short Form ( $P = 0.0002$ ), Symptom Distress Scale ( $P < 0.0001$ ), Hospital Anxiety and Depression Scale depression ( $P = 0.0006$ ) and anxiety ( $P < 0.0001$ ) subscales, and bowel function ( $P = 0.0003$ ). At study end, 37 (66.0%) patients were satisfied/very satisfied with the new analgesic treatment. Combination therapy had a good safety profile.

**Conclusion:** OXN-PR and pregabalin were safe and highly effective in a real-world setting of severe neuropathic cancer pain, with a high rate of satisfaction, without interference on bowel function.

**Keywords:** oxycodone/naloxone, opioids, pregabalin, neuropathic cancer pain, non-small-cell lung cancer, breakthrough cancer pain

## Introduction

Severe chronic pain affects most patients with advanced cancer; current guidelines recommend strong around-the-clock opioids as first-line therapy to achieve adequate control of moderate-to-severe chronic pain.<sup>1,2</sup>

Treatment of cancer-related neuropathic pain includes antidepressants, anticonvulsant agents, topical lidocaine, and oral opioids. Although alleviated by opioids, chronic neuropathic pain seems less responsive than nociceptive pain to opioids, and

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so these drugs are considered second- or third-line analgesics in this setting.<sup>3–5</sup> Given the multifactorial pathogenesis of neuropathic pain, current guidelines recommend combination pharmacotherapy in the management of this heterogeneous and complex condition.<sup>1,2</sup> The combination of gabapentin and alpha-lipoic acid has been shown to be effective in neuropathic pain.<sup>6</sup> The combination of controlled-release oxycodone and pregabalin was found as an effective long-term option for non-cancer pain treatment, and this combination significantly reduced oxycodone dosages.<sup>7</sup>

Nevertheless, many cancer patients still do not receive adequate pain control.<sup>8,9</sup> The poor gastrointestinal (GI) tolerability of opioids is one of the causes of their limited compliance and inadequate analgesia.<sup>10</sup> Opioids exert their analgesic effect primarily interacting with the  $\mu$ -receptors in the central nervous system; their activation of  $\mu$ -receptors in the GI tract also causes opioid-induced bowel dysfunction (OIBD), with constipation, abdominal cramps, nausea and vomiting: all these symptoms often interfere with the analgesic efficacy of opioids, causing substantial distress, impairing treatment adherence and quality of life (QoL).<sup>10,11</sup>

The oral prolonged-release oxycodone/naloxone (OXN-PR) combination in a fixed 1:2 ratio has been shown to be associated with superior GI tolerability.<sup>12,13</sup> The powerful  $\mu$ -opioid receptor antagonist naloxone is added to counteract OIBD by blocking the oxycodone action at opioid receptors locally in the gut; the extensive first-pass hepatic metabolism of naloxone and its low (<3%) systemic bioavailability after oral administration ensure the lack of antagonistic effects on oxycodone central analgesic action. The OXN-PR formulation has been found to be analgesically effective, while improving OIBD and decreasing the use of rescue medications and laxatives.<sup>12,14,15</sup> However, a few prospective studies on OXN-PR in cancer patients are available;<sup>14,16</sup> moreover, the value of OXN-PR in combination with pregabalin in the treatment of severe neuropathic cancer pain has never been tested.

Our study was aimed at evaluating the efficacy, tolerability, and effect on GI function of OXN-PR in association with pregabalin in patients with lung cancer and severe malignant pain in a real-world clinical setting.

## Methods

This 28-day, single-center, prospective observational study was conducted at the Palliative Care and Cancer Pain Service, San Camillo-Forlanini Hospital, Rome, Italy. The study was approved by the Ethics Committee of San Camillo-Forlanini Hospital, and all patients gave written informed consent for

the collection and analysis of their anonymous demographic and clinical data.

## Design of the study

From January 2013 to May 2014, males and females >18 years of age with non-small-cell lung cancer (NSCLC) referred to our specialist Pain Unit were screened and considered for this study if they had a history of debilitating pain that required continued around-the-clock opioid therapy. Patients previously untreated with pregabalin and with uncontrolled pain despite other opioid treatment, or with side effects contraindicating further dosage increase and requiring switch to another opioid, were also considered.

The inclusion criteria for our study were: 1) presence of severe pain at baseline, defined as average pain intensity (API) score  $\geq 7$  on a 0–10 numerical rating scale (NRS; where 0 indicates no pain and 10 the worst imaginable pain) that occurred within the 24 hours preceding the screening visit and requiring WHO step III analgesics (strong opioids) and 2) a clear neuropathic component of pain, caused either from primary or metastatic compression of nervous structures, or from invasive procedures or cancer treatments including surgery, radiation, and chemotherapy. The “definite” neuropathic component was established according to pain description (eg, shooting, burning, tingling sensation with numbness, painful cold, pins and needles, localization to specific dermatomes, or nerve distributions), physical evaluation, and a  $\geq 4$  score at the Douleur Neuropathique 4 (DN4) Inventory, a questionnaire used for the diagnosis of neuropathic pain based on pain descriptors and bedside sensory examination.<sup>17,18</sup> The inclusion criteria also included Eastern Cooperative Oncology Group Performance Status score <3 and an estimated survival expectancy  $\geq 2$  months.

Patients were excluded from the study if changes of chemotherapy occurred, or patients underwent radiotherapy on the lesion that caused the neuropathic pain in 3 weeks before enrollment or throughout the study; diagnosis of neuropathy prior to the diagnosis of cancer, as well as neuropathy considered unrelated to cancer; cognitive impairment or dementia not allowing correct pain assessment; symptomatic cerebral metastases or known psychiatric disease; severe respiratory disease with hypoxemia and/or hypercapnia; moderate or severe liver (total bilirubin  $\geq 1.5$  mg/dL) and/or renal insufficiency (glomerular filtration rate <30 mL/min); paralytic ileus; history of alcohol and drug abuse; inability to take oral medication; and known hypersensitivity to the study medications.

Regular visits were scheduled at baseline (prior to the start of the treatment, T0), after 14 days (T14) and 28 days

(T28), and the end of the observation. Additional visits were possible at all times according to individual patient needs (eg, if patients had inadequate pain control, difficult analgesics titration, and/or adverse events [AEs]).

## Study drugs

At the T0 visit, in the absence of contraindications, all patients were prescribed oral OXN-PR (Targin® tablets, Mundipharma Pharmaceuticals, Milan, Italy) and pregabalin (Lyrica® tablets, Pfizer Limited, Sandwich, UK), and were instructed to interrupt other analgesics and/or anticonvulsants. Ongoing acetaminophen and/or adjunctive therapy with steroids were confirmed with no further dose increase for the observation period. Other treatments for any other underlying medical condition were continued unchanged, including laxatives.

The starting OXN-PR dose was determined individually according to the age, health status, previous analgesic therapy, and patient's needs: in patients naïve to opioids, OXN-PR was started at 5/2.5 or 10/5 mg, twice daily (bid), and the first tablet was administered at 8 pm. In previously opioid-treated patients, starting OXN-PR doses were chosen equivalent to morphine dosage, according to traditional conversion tables. Patients not achieving acceptable pain control were instructed to increase their OXN-PR doses in the following week, with daily increments of 5/2.5–10/5 mg, until patient reported satisfied with pain relief, or emergence of poor tolerability, and/or a maximum daily dose of 60/30 mg (patients naïve to opioids) or 80/40 mg of OXN-PR (patients opioid-pretreated). After 7 days, the study investigator or a palliative care-certified nurse made telephone calls to the patients to ensure that the patients were taking proper doses of OXN-PR. At the subsequent T14 visit, the OXN-PR-titrated dose was confirmed or changed by the visiting pain clinician according to the patients' needs, side effects, or other inconveniences related to OXN-PR, and the daily OXN-PR dose for the following 2-week period was adjusted accordingly.

The starting pregabalin dose was 25 mg bid, or 75 mg bid if patients were pretreated with gabapentin. If API was still >4 after the first 7-day treatment, and no side effects were reported, patients uptitrated their pregabalin daily dose every 3 days by 50 mg increments, up to a maximum dose of 300 mg daily until the achievement of appropriate pain relief and in the absence of side effects.<sup>19</sup>

At the T0 visit, oral immediate-release morphine sulfate 10 mg was also prescribed as rescue medication, up to a maximum of three doses per day; patients were also instructed to contact our center in advance of their scheduled control

in case of rescue morphine daily dosing more than twice. Sublingual or transmucosal fentanyl as rapid onset opioid was prescribed for the management of episodes of breakthrough cancer pain (BTCP), ie, the transitory exacerbation of pain, with a rapid onset and severe in intensity, with a specific unpredictable or predictable trigger or occurring spontaneously, despite an adequately controlled background pain.<sup>2</sup>

## Assessment

At the T0 visit, demographic and clinical data were recorded, as well as details on pain, ongoing treatments, and constipation. At every visit, API related to the preceding 24 hours was rated on an 11-point NRS. Patients were also required to record the daily number of BTCP, the intensity of this later on an 11-point NRS, as well as the use of rescue analgesics for its treatment.

T0 and T28 evaluation also included the following:

1. Interference of pain in the patient's life, evaluated by a validated Brief Pain Inventory Short Form (BPI-SF) national version;<sup>20</sup> BPI-SF 7-item composite pain interference includes general activity, walking ability, normal work, mood, enjoyment of life, sleep, and relations with other people, with a 11-point scale for each item, ranging from 0=no impairment to 10= most severe impairment.
2. Symptoms of anxiety and depression, assessed using a validated Hospital Anxiety and Depression Scale (HADS) questionnaire for outpatients: it detect states of anxiety and depression on two 7-item scales, one for anxiety and one for depression, each ranging from 0= absent or normal to 3= most severe impairment (sum score 1–7= normal, 8–10= mildly affected, 11–21= moderately to severely affected).<sup>21,22</sup>
3. Health-related QoL, assessed using the four items on emotional functioning of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30).<sup>23</sup> EORTC QLQ-C30 is a cancer-specific questionnaire composed of both multi-item scales and single-item measures. Patients reported their symptom extent based on the descriptors: 1 (not at all), 2 (a little), 3 (quite a bit), and 4 (very much), thus higher scores indicating a worse level of functioning.<sup>24</sup>
4. Distress due to cancer-related symptoms assessed with the Symptom Distress Scale (SDS):<sup>25,26</sup> patients scaled the intensity and frequency of nausea, anorexia, insomnia, bowel pattern, respiration, coughing, fatigue, concentration, appearance, and mood from 1 to 5, with items rated 3

or higher indicating serious distress (a summed score  $\geq 25$  indicates moderate distress, scores  $\geq 33$  indicate severe distress).<sup>27</sup>

5. Bowel function, in particular symptoms of constipation, which was considered as clinically significant if patients reported less than three complete spontaneous bowel movements, with difficulty passing stools despite laxatives and/or appropriate dietary modifications. Bowel function in the last 7 days was also evaluated by the Bowel Function Index (BFI): scores range from 0 (free from symptoms) to 100 (most severe symptoms); in patients with chronic pain, a BFI value of 29 is set as upper normal limit.<sup>28</sup>

At the T28 visit, patients' satisfaction with the efficacy and tolerability of the new analgesic treatment was rated as very satisfied, satisfied, moderately satisfied, or dissatisfied.

## Safety

At each time point, any new AE that occurred or worsened in intensity and/or frequency after the intake of OXN-PR and pregabalin was recorded; the potential correlation between the AE and the new analgesic treatment was judged by the pain therapist. This safety evaluation considered only AEs of severe intensity (ie, those persistent despite treatment and requiring discontinuation of the treatment) and/or moderate AEs (ie, those requiring treatment and/or not permitting a dose escalation of the treatment, or requiring its down-tapering).

## Statistical analysis

As in other studies assessing analgesic efficacy in cancer patients, the primary endpoint of the trial was the proportion of patients who achieved a substantial reduction in their pain intensity after the new analgesic combination: "Responders" were those patients who achieved at T28 a reduction of API  $\geq 30\%$  from baseline.<sup>29–31</sup>

Secondary endpoints were: mean percentage change in API from baseline; the percentage of patients achieving an API  $< 5$ , as well as the percentage reporting satisfaction with pain relief; changes in the number and intensity of BTCP episodes from baseline; changes in neuropathic pain from baseline (DN4 evaluation); and interference of pain in the patient's life (BPI), distress (SDS), anxiety and depression (HADS), QoL (EORTC QLQ-C30 evaluation), and bowel function (BFI).

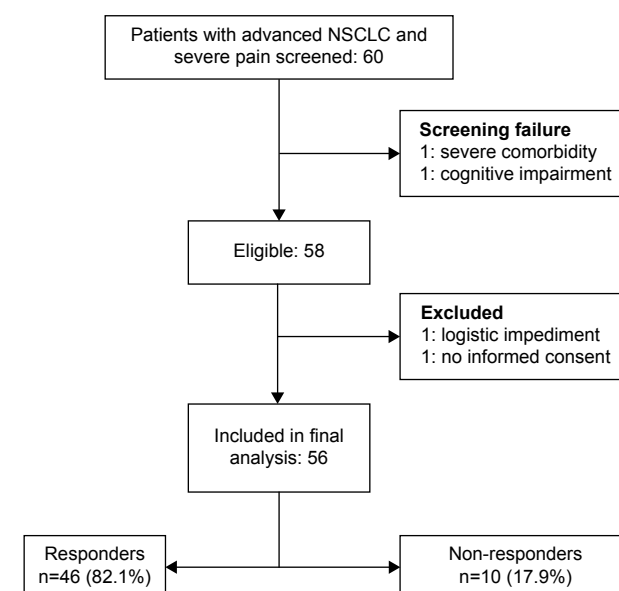
According to the given definition, based on a Fleming design with 80% power and 5% type 1 error, the study design required 39 patients to test the null hypothesis that the true

confirmed response rate was at most 50%, versus the alternative hypothesis that it was  $> 70\%$ . Considering the short duration planned for this observation, to allow for dropouts and incomplete data ( $\sim 25\%$ ), at least 49 patients were required. Missing data were treated with the "last observation carried forward" method.

Data are reported as mean  $\pm$  standard deviation or median and range. Changes over time in categorical variables were compared using the Cochran's Q test, and differences between pairs of continuous variables were evaluated by Student's *t*-test or Wilcoxon test. Continuous variables over time were assessed by analysis of variance or Kruskal–Wallis analysis. Normality distribution of continuous variables was assessed by the Shapiro–Wilk test. A *P*-value  $< 0.05$  was considered statistically significant (STATISTICA software, version 8.0, StatSoft® Inc., Tulsa, OK, USA).

## Results

From January 2013 to May 2014, 60 patients with advanced NSCLC and severe pain despite analgesic treatment were screened: two patients were not included (terminal illness; cognitive limitation), two others were excluded (logistic impediments to completing the 4-week observation; no informed consent). The remaining 56 patients (93.3% of the screened population) were included in the final analysis (mean age  $64 \pm 10$ , 77% males). Patient flow throughout the study is shown in Figure 1. Their demographic and baseline clinical characteristics are shown in Table 1. All the patients



**Figure 1** Patient disposition and response rate after oxycodone/naloxone and pregabalin.

**Note:** Response,  $> 30\%$  pain intensity reduction between the first visit and the last visit.

**Abbreviation:** NSCLC, non-small-cell lung cancer.



**Table 1** Demographic and clinical characteristics of patients at baseline

Age, years (range)	64±10 (37–83)
Male sex, n (%)	43 (76.8)
Presence of bone metastases, n (%)	40 (71.2)
Karnofsky performance status, n (%)	
50–59	5 (8.9)
60–79	43 (76.8)
80–90	8 (14.3)
Pain, NRS	8.0±0.9
Pain duration, days	47±36
Previous analgesic treatment, n (%)	
Step I WHO drugs	45 (80.4)
Step II WHO opioids	18 (32.1)
Step III WHO opioids	18 (32.1)
Adjuvant pain medications, n (%)	
Steroids	39 (69.6)
Anticonvulsants	13 (23.2)
Antidepressants	3 (5.4)
Bisphosphonates	16 (29.1)
Alpha-lipoic acid	46 (82.1)
Patients reporting BTCP, n (%)	51 (91.1)
Number of daily BTCP episodes	3.2±3.0
Patients reporting constipation, n (%)	20 (35.7)
Bowel Function Index	44.6±15.3

**Note:** Values are mean (± standard deviation).

**Abbreviations:** NRS, numerical rating scale; BTCP, breakthrough cancer pain; WHO, World Health Organization.

were at tumor, node, metastasis classification (TNM, seventh edition) stage IV; mean Karnofsky Performance Scale Index was 66±10. In more than two-thirds of the patients, bone metastases were present. Chemotherapy was the main cancer treatment in 38/56 (67.9%) of the patients, and 30/56 (53.6%) received also radiation therapy.

Before enrollment, 45 patients (80.4%) were taking nonsteroidal anti-inflammatory drugs, and 36 (64.2%) were already on opioids (WHO step III drugs in 50% of patients). At baseline, all the patients were taking some adjuvant therapy; the majority of the patients were taking alpha-lipoic acid, two-thirds were treated with steroids, one-third with bisphosphonates, and one-fifth were on anticonvulsants (gabapentin in all cases).

According to the reported API value at baseline (median 8, range 7–10), the enrolled population was suffering from very severe pain. At enrollment, pain duration was >30 days in 29 (51.8%) patients.

At enrollment, the majority of the patients reported BTCP episodes (n=51, 91.1%; median, three episodes daily); this was of severe intensity (mean NRS, 8.3±2.7). All the patients completed the 28-day study observation.

The mean OXN-PR starting dose was 22.1±8.9 mg daily (range 10–60 mg). Subsequently, OXN-PR daily dose increased to 36.3±15.7 mg at the T28 visit ( $P<0.0001$ ).

Mean pregabalin starting dose was 70.5±39.6 mg daily (range 25–150); at the T28 visit, all the patients were still on pregabalin, with a mean daily dose slightly increased versus baseline (115.0±69.6 mg, range 25–300 mg;  $P<0.0001$ ).

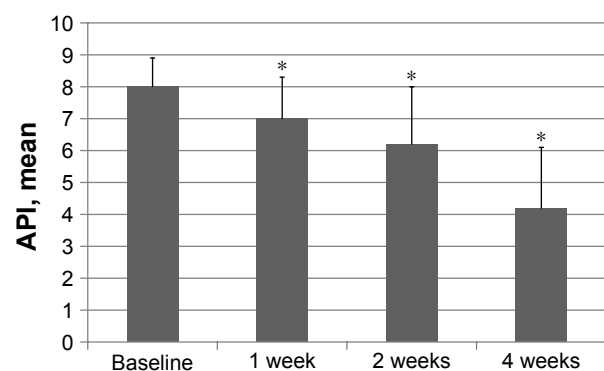
## Analgesic response

A substantial decrease in reported pain intensity was documented with the OXN-PR and pregabalin combination (API at T28=4.2±1.9,  $P<0.0001$  vs baseline); a significant reduction in pain severity was already reported after 14 days (Figure 2). Mean pain intensity decrease at T28 was 47.6%±24.3%, and the “waterfall” graph in Figure 3 shows the individual changes of pain intensity from baseline to T28. At T28, there were 46 (82.1%) responders (ie, those with a reduction in daily pain intensity ≥30% of the corresponding baseline value). Among the remaining ten (17.9%) patients with unsatisfactory analgesic response at T28 visit, six patients (10.7%) were still complaining of severe pain (API ≥7). On the contrary, 16 patients (28.5%) reported a complete or near-complete analgesic benefit (API 0–3) at T28 (Figure 4). Likewise, the DN4 score was markedly reduced at T28 visit (4.5±1.8 vs 6.75±0.86,  $P<0.001$ ).

At the end of the observation, fewer patients still reported episodes of BTCP (n=39, 69.6%;  $P<0.005$  vs baseline). The number of daily episodes also decreased at T28 (2.1±2.3; median 2, range 2–12;  $P=0.001$ ), also of reduced severity (NRS 5.7±3.9,  $P<0.001$  vs baseline).

## Other efficacy results

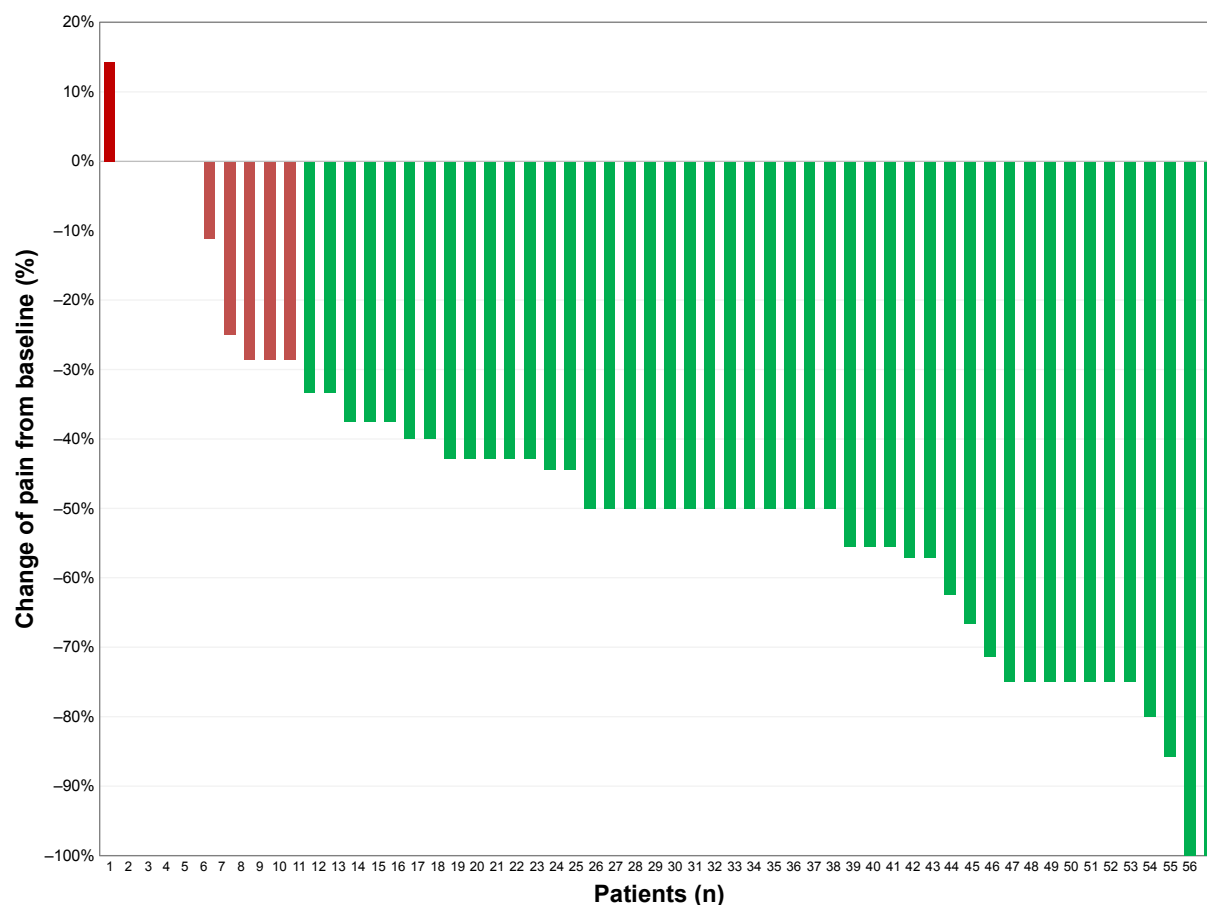
At study end, all secondary efficacy measures showed substantial improvement. Daily need of additional acetaminophen decreased from 86.8% to 40.4% at T28 ( $P<0.001$ ). Pain-related functional impairment also declined (BPI-SF composite pain interference score: from 6.9±1.6 to 5.5±1.8;  $P=0.0002$ ). All individual domain scores except quality of



**Figure 2** API score (11-point NRS) throughout the observation.

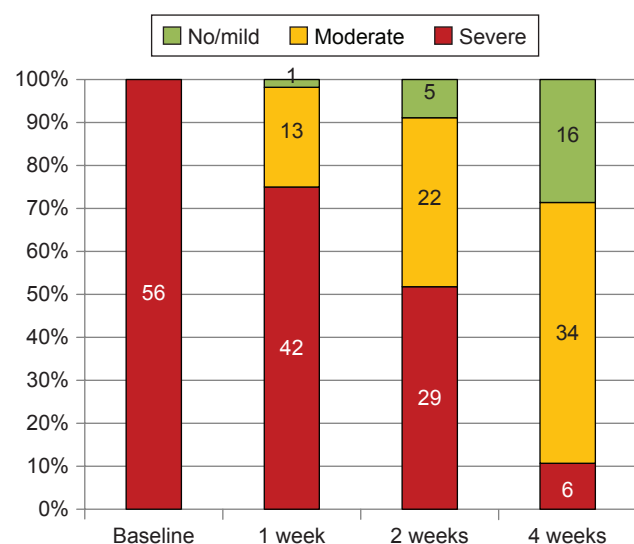
**Note:** \* $P<0.001$  versus result at previous time point.

**Abbreviations:** API, average pain intensity; NRS, numerical rating scale.



**Figure 3** Waterfall image of individual percentage changes from baseline in pain intensity score (numeric rating scale) among the 56 patients who completed the observation.

**Notes:** Mean pain intensity decrease at study end was  $47.6\% \pm 24.3\%$  (median  $-50\%$ , range  $+14\%$ ,  $-100\%$ ). Green bars indicate responders.



**Figure 4** Proportions and numbers of patients with severe (NRS 7–10), moderate (NRS 4–6), or mild (NRS 1–3) average pain intensity, or no pain at all (NRS 0) during the 28-day observation with OXN-PR and pregabalin.

**Note:** Six patients still complained of severe pain (NRS  $>6$ ) after 28 days.

**Abbreviations:** NRS, numeric rating scale; OXN-PR, prolonged-release oxycodone/naloxone.

sleep decreased from baseline to T28, suggesting less interference of pain in daily life (Table 2).

In agreement with the favorable BPI-SF finding, health-related QoL substantially improved at T28 ( $P < 0.001$ , Table 2); conversely, distress due to cancer-related symptoms

**Table 2** Changes in selected data during the 28-day observation

	Baseline	Day 28 visit	P-value
<b>HADS</b>			
Symptoms of anxiety	$8.7 \pm 4.0$	$6.7 \pm 2.7$	$<0.0001$
Symptoms of depression	$7.3 \pm 3.8$	$6.1 \pm 3.3$	0.0006
<b>EORTC QLQ-C30 items</b>			
Tense	$3.7 \pm 2.1$	$3.1 \pm 2.3$	0.008
Worried	$4.8 \pm 1.7$	$3.8 \pm 1.8$	0.002
Irritable	$3.7 \pm 2.8$	$2.9 \pm 2.5$	0.01
Depressed	$3.9 \pm 1.7$	$3.0 \pm 2.2$	0.005
Symptom Distress Scale	$35.8 \pm 7.7$	$28.1 \pm 7.9$	$<0.0001$

**Note:** Values are mean  $\pm$  standard deviation.

**Abbreviations:** HADS, Hospital Anxiety and Depression Scale; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30.

decreased substantially over the observation (Table 2): both physical and emotional dimensions of SDS scales were significantly reduced ( $P<0.0001$ ).

After the new analgesic treatment, a substantial improvement in anxiety and depression symptoms was also recorded, as reflected by the significant decrease of HADS subscales scores ( $P<0.05$  for both) (Table 2).

## Tolerability and safety

Although at baseline only one-third (35.7%) of the patients reported constipation (Table 1), almost all (83.3%) showed abnormal BFI values (ie,  $>29$ ); indeed, the median baseline BFI value recorded at T0 (48) indicates that half of the patients suffered moderate-to severe bowel dysfunction at baseline. After OXN-PR and pregabalin, of relevance, none reported subjective worsening of their constipation symptoms, or constipation of new occurrence. The number of patients still complaining of constipation at the end of the study nearly reduced to half ( $n=13$ , 23.2%;  $P<0.01$  in Cochran's Q test). In fact, a significant reduction in the BFI value was found after the administration of OXN-PR and pregabalin, thus indicating an improvement in bowel function (mean value at T28,  $28.9\pm 21.7$ ,  $P<0.001$  vs baseline).

At the end of the study, 37 (66.0%) patients rated the new analgesic treatment positively; 14 (25.0%) and 23 (41.0%) said they were either very satisfied or satisfied, respectively. Only four patients (7.1%) rated themselves as dissatisfied after the administration of the OXN-PR and pregabalin combination.

Overall, the OXN-PR and pregabalin combination therapy was well tolerated in the 28-day observation. Side effects were documented in 26 patients. The most common AEs are summarized in Table 3. No severe AEs leading to

premature discontinuation were recorded. Most AEs were mild, without new or unexpected safety signals. The most frequent treatment-related AEs were somnolence, confusion, asthenia, loss of appetite, and nausea.

## Discussion

In cancer patients, pain is often associated with exacerbation of other symptoms, and affects mood, job performance, personal relationships, and the overall QoL.<sup>32</sup> In the last two decades, despite the improvements in quality of pharmacologic treatment, one-third of cancer patients are still not receiving adequate pain management.<sup>9</sup> The integration of early palliative intervention with anticancer treatment can reduce anxiety and depression, improving the QoL and prolonging survival.<sup>33</sup> According to a recent statement of the American Society of Clinical Oncology, "combined standard oncology care and palliative care should be considered early in the course of illness for any patient with metastatic cancer and/or high symptom burden".<sup>34</sup>

Pain may be the first sign of lung cancer, and its prevalence in patients with lung cancer is one of the highest ( $>85\%$ ) among different cancer types.<sup>8</sup> Extremely few data, however, are available on pain management in patients with lung cancer; in a small trial conducted in patients with NSCLC, subjects randomly assigned to an oral pain treatment protocol encompassing recommendations from existing cancer pain guidelines performed significantly better than patients managed according to physician preference.<sup>35</sup>

A neuropathic pain component of pain is present in 30% to 50% of patients with lung cancer.<sup>36-38</sup> Chemotherapy or radiotherapy, combined with general comorbidities and impaired functional status, makes neuropathic pain difficult to correct, and often adjuvants are added to target specific pathways of neuropathic pain.<sup>39</sup> Oxycodone plus pregabalin has been found to be effective in controlling neuropathic pain both in non-cancer and cancer patients.<sup>7,40</sup> However, response to opioids is often inadequate, requiring higher dosages;<sup>19</sup> and side effects of opioids are common: OIBD, in particular constipation, is common and persists, causing considerable distress and reduced QoL.<sup>11,41</sup>

The oral fixed-dose OXN-PR combination has been shown to provide analgesic efficacy while improving OIBD in cancer patients.<sup>14-16,42</sup> A small, open-label study showed relevant improvement in pain and bowel function after OXN-PR.<sup>16</sup> In a randomized controlled trial comparing efficacy and safety of oxycodone PR and OXN-PR in opioid-pretreated patients with controlled pain and constipation at baseline, the switch to OXN was associated with a similar

**Table 3** Major side effects reported during the treatment

Adverse event <sup>a</sup>	Patients, n (%)
Any	26 (46.4)
Somnolence	18 (32.1)
Confusion	8 (14.3)
Nausea	5 (8.9)
Vomiting	1 (1.8)
Dry mouth	3 (5.3)
Abdominal cramps	1 (1.8)
Stomach pain	1 (1.8)
Dysuria	1 (1.8)
Anorexia	4 (7.1)
Asthenia	9 (16.1)

**Notes:** <sup>a</sup>Adverse events of moderate severity (ie, those events requiring dose tapering or not permitting dose escalation when required). No patient experienced a severe side effect leading to premature discontinuation of the analgesic combination. Numbers do not add up, since several patients reported more than one side effect.

analgesic effect compared to oxycodone PR, however, with a clinically relevant improvement in bowel function.<sup>14</sup> A retrospective study in 206 patients with uncontrolled pain showed OXN to be highly effective and well tolerated in both opioid-naïve and -pretreated patients, as well as in younger and older patients, without adverse effects on bowel function;<sup>42</sup> patients previously treated with OXY were not included in that study. Kang et al reported pain exacerbation and opioid withdrawal symptoms in a patient with gastric cancer and portal vein thrombosis after receiving OXN-PR; hepatic and renal function data were not described in the case report.<sup>43</sup> In a recent study comparing OXN-PR and oxycodone-PR in cancer patients naïve to strong opioids, the analgesic efficacy was found to be comparable, with an overall incidence of drug-related AEs remarkably lower after OXN-PR: nausea and vomiting were significantly less frequent, with greater improvement in QoL following OXN-PR.<sup>15</sup>

Different from the aforementioned studies, our study is the first prospective clinical trial to evaluate the efficacy and safety of OXN-PR and pregabalin in cancer patients with neuropathic pain. The target population had severe pain despite other non-opioid and opioid analgesic treatment. The majority of patients (82%) achieved the primary endpoint after 4 weeks of OXN-PR and pregabalin treatment. Pain relief was achieved even in patients previously treated with WHO step III opioids; the severity of neuropathic pain also declined after 28 days, as indicated by the significantly reduced DN4 values. All secondary efficacy measures improved substantially, with less interference of pain in the patient's life, less distress due to cancer-related symptoms, and improved QoL. The reduced bowel discomfort likely improved the adherence to the new treatment, contributing to the observed superior analgesic effects of the new treatment in comparison with previous painkillers. More recently, in a large randomized trial, OXN-PR was associated with a significantly better analgesic efficacy, lower risk of OIBD, and superior tolerability compared with oxycodone or morphine.<sup>44</sup> Of note, ultra-low dosages of naloxone could enhance, rather than attenuate, the analgesic effects of oxycodone within the central nervous system.<sup>45,46</sup> The improved QoL and GI tolerability of OXN-PR explain its lower cost-utility estimates compared with oxycodone.<sup>47</sup>

In the present study, the OXN-PR and pregabalin combination was well tolerated, and there were no serious drug-related AEs. Of note, central nervous system side effects, and in particular dizziness and drowsiness, were limited. The observed improvement in QoL and patient's satisfaction is in agreement with previous results, showing

that attenuation of neuropathic pain after opioids improves mood and sleep.<sup>48,49</sup>

This study had several limitations, including the open-label observational design, short treatment duration, small sample size, and lack of a control group. However, the results of the present study provide a solid basis for the design of a larger investigation to further assess the efficacy and tolerability of the OXN-PR and pregabalin combination for the management of severe neuropathic pain in patients with lung cancer.

## Conclusion

The opioid agonist–antagonist OXN-PR combination in conjunction with pregabalin effectively controlled severe neuropathic pain in patients with lung cancer. This drug combination did not worsen the bowel function, and also resulted in a significant improvement in QoL and patient's satisfaction. Thus, it could represent a valuable option in daily clinical practice for the management of severe neuropathic cancer pain.

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## Disclosure

The authors report no conflicts of interest in this work.

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