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Original article

Effectiveness and tolerability of low-dose oral oxycodone/naloxone added to anticonvulsant therapy for noncancer neuropathic pain: an observational analysis

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Abstract

Background:
Opioids may alleviate chronic neuropathic pain (NP), but are considered second/third-line analgesia due to their poor gastrointestinal (GI) tolerability. A fixed combination of prolonged-release oxycodone and naloxone (OXN) has been developed to overcome the GI effects. The aim of this analysis was to evaluate analgesic effectiveness and tolerability of low-dose OXN in patients with moderate-to-severe noncancer NP despite analgesia.

Methods:
This retrospective observation of consecutive adult patients, treated open-label for 8 weeks at a single Italian centre, evaluated effectiveness (pain intensity numerical rating scale [NRS], Patients' Global Impression of Change [PGIC], Douleur Neuropathique 4 inventory [DN4] and Chronic Pain Sleep Inventory [CPSI]), doses of daily OXN and adjuvant medication, rescue paracetamol use, bowel function index (BFI), laxative use, and safety.

Results:
Of 200 patients (mean age 65.9 years; 54% female) with NP included in the analysis; 97% completed 8 weeks' treatment. At the observation start, all patients were taking anticonvulsants and complained of constipation, and 60% were receiving opioids. Pain intensity and DN4 score decreased significantly by endpoint (NRS $p<0.0001$; DN4 $p<0.0001$) and need for rescue analgesics abated. Reduction in pain intensity throughout the observation was similar regardless of NP aetiology. According to PGIC, 87.8% of patients were much/extremely improved, CPSI ($p<0.0001$) and BFI were significantly improved ($p<0.0001$) and laxative use decreased. No differences were found between patients <65 years vs those ≥65 years. OXN was generally well tolerated.

Study limitations:
Study limitations including the retrospective observational design, the lack of a control group and the single-centre design may limit the generalizability of our findings.

Conclusions:
Low-dose OXN (25.0 ± 12.5 mg/day) added to anticonvulsants was highly effective in controlling noncancer NP of varied aetiology, with reduced need for rescue analgesia and improved quality of sleep, and was well tolerated, with improved bowel function and reduced laxative use. The efficacy and tolerability of OXN demonstrated in this real-world setting suggest its utility in this difficult to manage patient population.

Introduction

Neuropathic pain (NP) – "pain arising as a direct consequence of a lesion or disease affecting the somatosensory system" according to the Special Interest Group on Neuropathic Pain (NeuPSIG)[1] – may be related to cancer or of noncancer origin, can be continuous and/or episodic (paroxysmal) and is associated with dysaesthesia, hyperalgesia and allodynia[2–5]. Although treatments for NP may provide clinically meaningful reduction in pain and improvement on a broad spectrum of domains of health-related quality of life (QoL), including mood, sleep or enjoyment of life[6], it remains difficult to manage, poses diagnostic and therapeutic challenges and presents a significant burden to individuals and society[7,8].

Pharmacological treatment for NP includes antidepressants, anticonvulsants, topical anaesthetics, and opioids, accompanied by nonpharmacological interventions such as physical therapy, psychological and interventional approaches[7,8]. Current guidelines recommend that combinations of pharmacotherapies may be more effective than monotherapy[8,9].

There are a number of limitations of current treatment, the main one being that many patients do not receive adequate pain relief due either to a lack of willingness on the part of physicians to prescribe stronger analgesics, mainly because of the risk of abuse and addiction[10], or to other factors that prevent an efficacious dose being taken, e.g. intolerable side effects or contraindications to treatment[11–13]. Currently, opioids are considered a second or third line class of analgesics[9]. One of the causes of inadequate opioid treatment is the poor gastrointestinal (GI) tolerability of these powerful pain medications, termed opioid-induced bowel dysfunction (OIBD). Opioids exert their analgesic effects primarily by interacting with the μ-receptors in the central nervous system; however, activation of local μ-receptors in the GI tract causes bowel dysfunction, in particular constipation, one of the most frequent and persistent side effects of opioid therapy, known to cause considerable distress and reduced QoL in many patients[13–15].

An oral fixed combination of prolonged-release oxycodone and naloxone (OXN; Targin, Mundipharma*) has been developed as a novel analgesic to overcome the adverse GI effects associated with strong opioids. Oxycodone is a strong opioid agonist with a high oral bioavailability and when administered orally provides potent analgesic effects. Naloxone, a powerful μ-opioid receptor competitive antagonist, when administered orally, blocks opioid action at the intestinal receptor level, thus preventing opioid-induced bowel dysfunction. Because naloxone has a marked first-pass hepatic metabolism, its systemic bioavailability after oral administration is exceedingly low (<3%), and the systemic exposure is insufficient to inhibit the central, pain-relieving action of oxycodone[12]. The new OXN formulation has been documented, both in RCTs and in observational studies, as providing analgesic efficacy while improving OIBD and a consequent decrease in the use of rescue medications and laxatives[16–20]. OXN, licensed since 2006 in Germany for the treatment of severe pain, which can only be adequately managed with opioid analgesics, is currently marketed in several other European countries.

The aim of this retrospective observational analysis was to analyse data from patients with NP uncontrolled by other treatments and at high risk of opioid discontinuation due to OIBD treated with low-dose combination OXN in a real-world clinical setting. Subgroup analysis was performed according to age (<65 years vs ≥65 years).

*Targin is a registered trade name of Mundipharma Pharmaceuticals Srl, Milan, Italy.

Methods

Study design

This was an 8 week, single-centre retrospective observational analysis of data from patients treated from December 2011 to November 2012 at the Tor Vergata Policlinic Pain Unit in Rome, Italy – a major reference centre for the treatment of pain in Italy.

Data from consecutive adult patients with NP treated with OXN were included in this analysis. According to standard practice, patients were eligible for OXN treatment if they were aged >18 years, diagnosed with chronic NP of any noncancer aetiology pain, of moderate-to-severe intensity (numerical rating scale [NRS] score ≥4) despite anticonvulsant treatment and complaining of constipation, either spontaneous or drug-induced, judged as clinically significant (i.e., less than three complete spontaneous bowel movements with difficulty passing stools despite appropriate dietary changes and/or laxative use). Pregnant women were not eligible for OXN treatment. Patients with a history of alcohol and/or drug abuse, dementia or cognitive impairment were not included in the present data analysis.

The study was approved by the local Institutional Review Board.

Treatments

Patients were prescribed oral prolonged release (PR) OXN combination for pain control and were instructed to suspend other World Health Organization (WHO) Step I–IIII analgesics. The starting OXN dose (oxycodone/naloxone 5/2.5–30/15 mg/day) was determined individually by the treating pain physician according to patients' needs and previous analgesic therapy, and was administered twice a day. All patients were already

taking gamma-aminobutyric acid (GABA) analogues (gabapentin or pregabalin) for the treatment of NP: their adjuvant drugs were continued and dosages modified or left unchanged according to patients' needs. Paracetamol 1000 mg was allowed as rescue, on-demand analgesia. For the entire duration of the observation period, treatments aimed at the care of any other underlying medical condition were continued at the usual dosages.

Assessments

Patients were evaluated at baseline (T0) and after 2 weeks (T1), 30 days (T2 visit) and 60 days (T3 visit, end of the observation). Demographic information and details of clinical history, location and pathology of NP, and previous treatments for pain and constipation were recorded prior to starting OXN treatment.

Effectiveness

The following effectiveness variables were assessed at each time point:

(a) intensity of pain (on a numerical rating scale [NRS], from 0 – no pain, to 10 – worst imaginable pain);
(b) daily dose of adjuvants and OXN required to exert clinical effects;
(c) need for rescue paracetamol, expressed as number of doses per day;
(d) patients' perception of treatment effectiveness, evaluated by the Patients' Global Impression of Change (PGIC) 7 point response scale scored as: (1) 'extremely better', (2) 'much better', (3) 'a little better', (4) 'no change', (5) 'a little worse', (6) 'much worse', or (7) 'extremely worse'[21]; and
(e) bowel function in the last 7 days, assessed by the Bowel Function Index (BFI) questionnaire according to Rentz *et al.*[22].

The BFI is a measure of general bowel function recently validated as a reproducible tool that detects clinically meaningful changes in opioid-induced constipation, with scores ranging from 0 (free from symptoms) to 100 (most severe symptoms)[22]: in patients with chronic pain, normal bowel function is defined as a BFI value of $\leq$29, and a BFI value change of $\geq$12 points represents a clinically meaningful change in constipation severity[23]. The following effectiveness and tolerability variables were also assessed at T0 and T3:

(f) the NP DN4 score, assessed by the Douleur Neuropathique 4 inventory – a questionnaire used for the diagnosis of NP in daily clinical practice consisting of pain descriptors and items relating to bedside sensory examination[24,25];
(g) the presence and severity of sleep disturbances, evaluated by the Chronic Pain Sleep Inventory (CPSI) – a single index assessing overall sleep quality scored with a 100 mm VAS (where 0 = very poor and 100 = excellent) based on three items, all attributing sleep problems to pain (trouble falling asleep because of pain; awakened by pain during the night; and awakened by pain in the morning), according to Kosinski *et al.*[26]; and
(h) the laxative use and number of laxative doses per week.

Safety

Safety evaluations were also performed at each time point with the recording of treatment-related adverse events (AEs), defined as any new AE that occurred or worsened in intensity and/or frequency after the first intake of OXN treatment. Only AEs of moderate (i.e., those events requiring dose tapering or not permitting dose escalation when required) or severe intensity (i.e., those events that required treatment discontinuation) were considered. The potential correlation between the AE and OXN treatment was judged by the visiting pain physician.

Statistical analysis

Statistical comparisons over time and between subgroups were performed. In the event of early discontinuation or missing values, the last observation carried forward (LOCF) approach was used to impute missing data concerning pain intensity, adjuvant and OXN doses, and DN4, CPSI and BFI assessments. Normal data distributions of continuous variables were assessed by the Shapiro–Wilk test. The significance of differences between pairs of continuous variables were evaluated by Student's *t* test or the Wilcoxon–Mann–Whitney test, as appropriate; changes in continuous variables over time as well as inter-group comparisons were evaluated by analysis of variance (ANOVA test, using Bonferroni's correction to adjust for multiple comparisons), or by Kruskal–Wallis analysis, as appropriate. Categorical variables were compared using Fisher's exact test. Correlation between changes in pain NRS between T0 and T3 (end of the observation) and corresponding changes in anti-epileptic dose were assessed by liner regression. Effectiveness and safety data are presented separately for the overall population and for the age subgroups analyses (<65 years vs $\geq$65 years). A p-value <0.05 was considered statistically significant (STATISTICA software, version 8.0, StatSoft Inc., Tulsa, OK, USA).

Results

Cohort characteristics at the start of observation

This retrospective assessment evaluated 200 consecutive patients selected according to the above-mentioned criteria. Six patients (3.0%) withdrew from treatment during the observation (all due to side effects, see below): 4 patients (two aged <65 years) discontinued the

Table 1. Cohort demographics and clinical characteristics for overall population and age-stratified subgroups.

Parameter	All	Subgroups by age	
		<65 years	65 years or older
N (%)	200 (100)	81 (40.5)	119 (59.5)
Age, mean ± SD	65.9 ± 12.9	53.1 ± 8.4	74.6 ± 6.5*
Women, *n* (%)	109 (54.5)	41 (50.6)	68 (57.1)
Causes of pain, *n* (%)			
Post-traumatic	8 (4.0)	6 (7.4)	2 (1.7)
Post-surgery	34 (17.0)	13 (16.0)	21 (17.6)
Radiculopathy	42 (21.0)	17 (21.0)	25 (21.0)
Post-herpetic neuralgia	57 (28.5)	21 (25.9)	36 (30.3)
Diabetic	39 (19.5)	14 (17.3)	25 (21.0)
Post-stroke	6 (3.0)	2 (2.5)	4 (3.4)
Trigeminal	11 (11.5)	8 (9.9)	3 (2.5)
Other	3 (1.5)	0	3 (2.5)
Previous analgesic Tx, *n* (%)			
None	35 (17.5)	13 (16.0)	22 (18.5)
Step I WHO drugs[a]	45 (22.5)	18 (22.2)	27 (22.7)
Step II WHO opioids	17 (8.5)	6 (7.4)	11 (9.2)
Step III WHO opioids	103 (51.5)	44 (54.3)	59 (49.6)
Adjuvant pain medications, *n* (%)			
Gabapentin	55 (27.5)	22 (28.4)	32 (26.8)
Pregabalin	145 (72.5)	58 (71.6)	87 (73.1)
Rescue paracetamol, *n* (%)	102 (51)	41 (50.6)	61 (51.3)
Pain intensity, NRS, mean ± SD	7.0 ± 1.4	6.9 ± 1.6	7.1 ± 1.3
DN4 inventory, mean ± SD	6.1 ± 1.2	6.0 ± 1.2	6.2 ± 1.1
Chronic Pain Sleep Inventory, mean ± SD	35.2 ± 9.6	36.7 ± 10.4	34.2 ± 8.8
Bowel Function Index, mean ± SD	73.7 ± 20.0	76.5 ± 19.3	71.8 ± 20.4
Laxative use, *n* (%)	193 (96.5)	78 (96.3)	115 (96.6)

Values are expressed as mean ± standard deviation (SD) or *n* (%).
The sum of percentages may not be equal 100 due to rounding.
DN4, Douleur Neuropathique 4 inventory; NRS, numerical rating scale; Tx, therapy.
[a]WHO Step I includes non-steroidal anti-inflammatory drug ($n = 42$), acetaminophen ($n = 2$) and prednisone ($n = 1$).
*$p < 0.0001$ versus <65 years old.

PR OXN combination after the T1 visit but before T2; another two patients (both aged >65 years) discontinued between the T2 and T3 time points. The remaining 194 patients (97%) continued the new analgesic treatment to the end of the observation period. Characteristics of the overall population and age-stratified subgroups are shown in Table 1 (median age 68 years; 54% female). The most common NP aetiology was post-herpetic neuralgia (28.5%). At entry visit, all patients were already receiving pregabalin or gabapentin, nearly two-thirds of patients were taking regular opiates (oxycodone in 50 patients [25%], hydromorphone in 31 [15.3%], tramadol in 14 [7%], fentanyl patches in 12 [6%], tapentadol in 8 [4%] and other opioids in 5 [2.5%]), and half were taking NSAIDs or paracetamol. Despite this, severe pain (NRS score >6) was reported by 65% of patients at the start of the observation, and overall median NRS and DN4 scores were high. Most (89.5%) patients reported sleep of poor quality (CPSI score >50) and 70.0% complained of severe constipation (BFI >60); this was despite regular laxative use in 87% of the cohort. As expected, worse bowel dysfunction was noted in opioid-pretreated versus opioid-naïve patients, (BFI 79.6 ± 14.9 vs 64.9 ± 23.4, respectively, $p < 0.001$). The number of subjects on laxatives at the start of the observation was similar in pre-treated and opioid-naïve patients (99.0% in pre-treated patients versus 92.5% in opioid-naive patients; p = NS), although the mean weekly number of laxative doses was significantly different (5.5 ± 1.3 vs 4.7 ± 1.7, respectively; $p < 0.001$). Demographic and clinical characteristics prior to treatment were similar between patients aged <65 years (40.5%) and ≥65 years (59.5%) (Table 1).

The mean starting dose of OXN at T0 was 16.0 ± 10.4 mg/day (range 10–60): it increased slightly from T0 to T2 (22.0 ± 12.4 mg at T1 and 24.5 ± 13.4 mg at T2 visit; $p < 0.0001$ between all time points) and then remained stable (25.0 ± 12.5 mg/day at final T3, range 10–80 mg/day; p = NS vs T2). The mean OXN starting dose was comparable in younger and older patients (16.2 ± 11.4 vs 16.0 ± 9.9, p = NS); no significant differences were found between age subgroups in terms of mean daily dose increases during the observation.

Clinical outcomes in the total cohort and in the age subgroups during the observation

Effectiveness

Between the first and final visit, there was a marked decrease in pain severity in the overall population: the

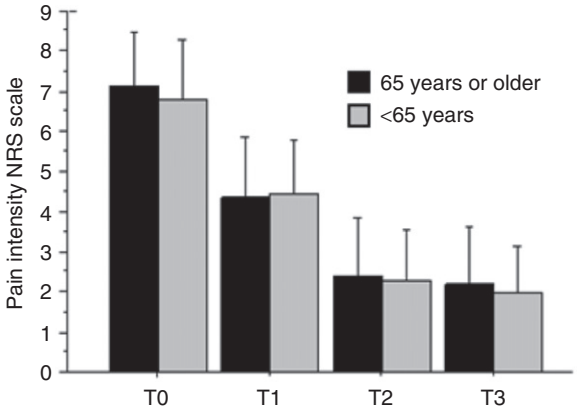

Figure 1. Mean pain intensity score (11 point numerical rating scale [NRS]) during OXN treatment in the two age subgroups (<65 years, ≥65 years); NRS changes significant versus T0 at all time-points ($p<0.0001$) in both subgroups; T3 vs T2: p value NS. Differences between subgroups not significantly different at post-hoc analysis. T0 = entry visit; T1 = 15 days after T0; T2 = 30 days after T0; T3 = 60 days after T0.

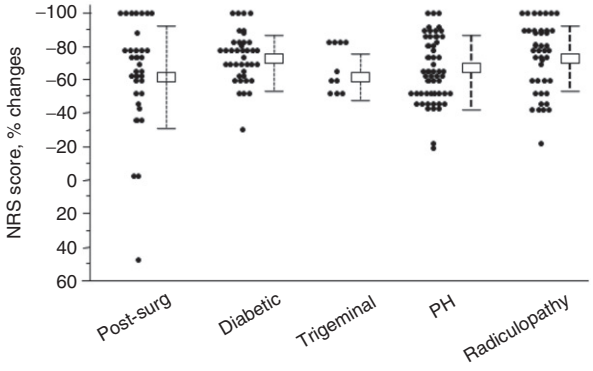

Figure 2. Mean percentage variation in numerical rating scale (NRS) pain intensity from baseline at T3 in different NP conditions (negative values indicate decrease in pain intensity). All variations not significantly different between different NP conditions. Boxes indicate mean values (±SD). Post-surg = post-surgery; PH = post-herpetic neuralgia.

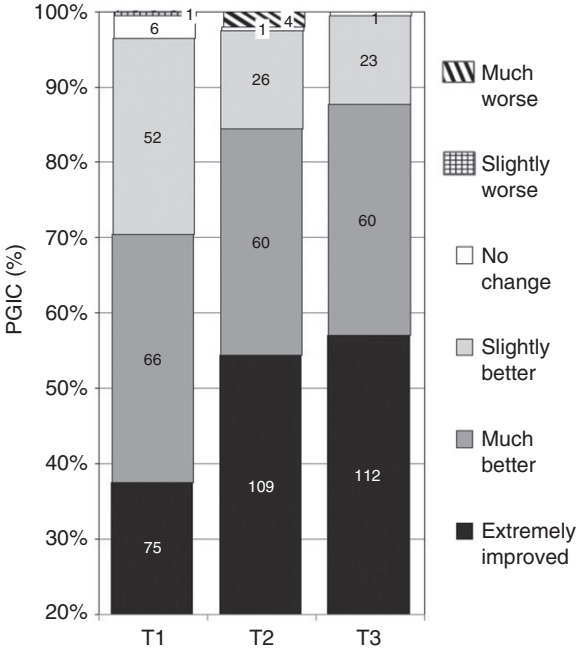

Figure 3. Patients' Global Impression of Change (PGIC) scale at different time points during OXN treatment in the overall cohort. T1 = after 15 days of treatment; T2 = after 30 days; T3 = after 60 days. T2 vs T1, $p<0.0001$; T3 vs T2, p = NS.

NRS score decreased from 7.0 ± 1.4 at T0 to 4.4 ± 1.4 at T1 ($p<0.0001$), and further NRS score reductions were found both at T2 (2.3 ± 1.3; $p<0.0001$ vs T1) and T3 (2.1 ± 1.3; NS vs T2). Likewise, DN4 score was markedly reduced at T3 visit (3.1 ± 1.3 vs 6.1 ± 1.2, $p<0.0001$). Analgesic effectiveness was similar in younger and older patients (Figure 1), and the magnitude of the decrease in DN4 scores throughout the observation were similar between age subgroups (p = NS).

At the end of observation a high proportion of patients reported no pain (15%) or pain of only mild intensity (NRS ≥ 1 – <4, 70.7%); no patients reported severe pain (NRS ≥ 7). Overall, 75% of patients had >50% improvement in NRS score from T0 to T3: subjects whose pain severity improved >50% by T3 had higher NRS scores at T0 (7.2 ± 1.3 vs 6.3 ± 1.4 in those who did not, respectively $p<0.001$).

Other demographics, clinical characteristics and treatments did not significantly differ between those who achieved a >50% decrease in NRS at T3 and those who did not; multivariate analysis found no variable to be significantly related to a >50% improvement in NRS score at T3 from T0.

Of interest, the magnitude of the decrease in pain intensity throughout the observation was comparable between different NP conditions (p = NS) (Figure 2).

According to PGIC, at T3, 87.8% of patients were much or extremely improved from T0 (Figure 3); a similar pattern was seen in young and older patients: in particular, 49 (60.4%) patients aged <65 years and 69 (57.9%) of those aged ≥65 years felt much or extremely improved already by the T1 visit (p = NS).

Overall, sleep quality markedly improved during the observation, with a striking decrease in CPSI values at T3 (from 35.2 ± 9.6 at T0 to 69.8 ± 8.4 at T3; $p<0.0001$) without significant differences between age subgroups (final CPSI values: 71.3 ± 8.0 in younger vs 68.9 ± 8.6 in older subjects; p = NS).

The proportion of patients taking rescue paracetamol abated from T0 to T3 (from 51% to 3%; $p<0.001$), without significant differences between age subgroups. The daily doses at T0 was 1.8 ± 0.7; at T3 there were only 6 patients (3.0%) still taking rescue paracetamol (once a day in all, $p<0.0001$).

Anticonvulsant doses and baseline characteristics, treatments and clinical outcomes

Anticonvulsant daily doses at the start of the observation are reported in Table 1; they were similar in young and older patients (p = NS). At T0, anticonvulsant daily doses were increased in 169 (84.5%) subjects, and left unchanged in the other 31 patients (15.5%); subsequently, anticonvulsant doses remained unchanged, or slightly decreased from T0 to T3 (Figure 4). Demographics, clinical characteristics and treatments between patients in whom anticonvulsant doses stayed the same or were augmented at T0 are reported in Table 2: as expected, those in whom the anticonvulsant prescription was left unchanged were already receiving higher doses, their pain was less severe, were taking fewer doses of rescue analgesics, and their sleep was less disturbed (all $p<0.001$); other characteristics were not significantly different.

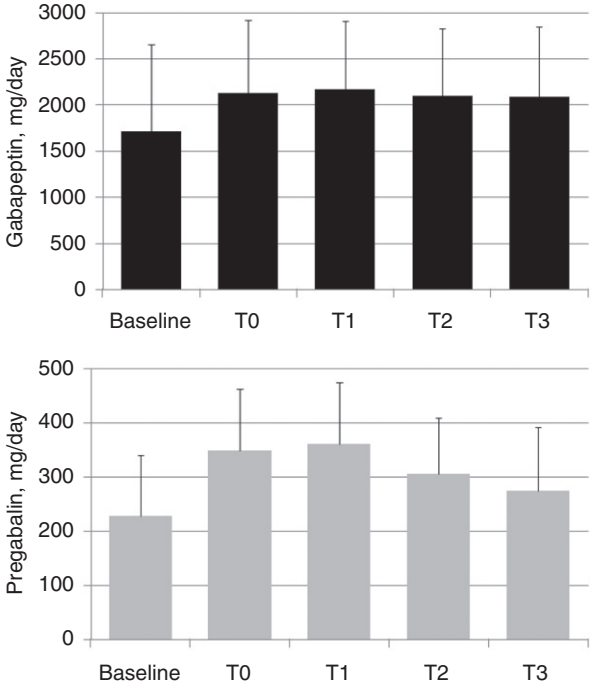

Figure 4. Dose of gabapentin (above) and pregabalin (below) in mg/day at baseline, as prescribed at entry visit (T0), and during the observation (T1 = 15 days, T2 = 30 days, and T3 = 60 days after T0).

No correlations could be found between the magnitude of changes in pain severity (NRS) during the observation and variations in anticonvulsant daily dose at entry visit (squared correlation coefficient 0.010; p = NS) (Figure 5) or between patients' perception of treatment effectiveness (PGIC scores) at T3 and changes in anticonvulsant dose during the observation (chi-squared 6.0, $p = 0.11$).

Tolerability and safety

Overall, bowel function improved remarkably during the observation: the BFI decreased from 73.7 ± 20.0 at T0 to 48.8 ± 20.2 at T1 ($p<0.0001$), and further NRS score reductions were found both at T2 (32.2 ± 20.3; $p<0.0001$ vs T1) and T3 (31.9 ± 20.0 at T3 (NS vs T2). The reduction in BFI values during the observation was remarkable in both age subgroups and of comparable magnitude (Figure 6). Of note, the proportion of patients taking laxatives markedly decreased from T0 to T3 (from 96.5% to 60.3%, $p<0.0001$) and the mean weekly number of administrations decreased significantly (from 5.2 to 2.3, $p<0.0001$). As expected, bowel dysfunction improved more by T3 in opioid-experienced patients (−52.2 BFI points vs. −25.5 in opioid-naive, $p<0.0001$), although the reduction in BFI was clinically meaningful in both subsets.

Table 2. Cohort demographics and clinical characteristics of patients who did and did not increase their anticonvulsant therapy at entry visit.

Parameter	Increased anticonvulsant therapy	No increase in anticonvulsant therapy	p Value
N (%)	169 (84.5)	31(15.5)	
Women, *n* (%)	90 (53.2)	19 (61.2)	NS
Age, years ± SD	66.6 ± 12.5	62.1 ± 14.4	NS
Opioid-naïve, *n* (%)	70 (41.4)	10 (32.2)	NS
NRS ± SD	7.1 ± 1.3	6.3 ± 1.5	<0.01
DN4 ± SD	6.1 ± 1.1	5.7 ± 1.3	NS
CPSI ± SD	65.7 ± 8.7	59.7 ± 12.2	<0.01
BFI ± SD	72.7 ± 19.9	79.4 ± 20.3	NS
Antiepileptic therapy			
Gabapentin *n* (%)	43 (25.4)	12 (38.7)	NS
Gabapentin dose per day (mg) ± SD	1287 ± 350	3400 ± 693	<0.001
Pregabalin, *n* (%)	126 (74.6)	19 (61.3)	NS
Pregabalin dose per day (mg) ± SD	201 ± 72	432 ± 67	<0.001
Rescue paracetamol, *n* (%)	94 (55.6)	8 (25.8)	<0.05
Oxycodone/naloxone starting dose per day (mg) ± SD	16.1 ± 10.7	15.8 ± 9.0	NS

Values are expressed as mean ± standard deviation (SD) or *n* (%). The sum of percentages may not be equal 100 due to rounding.
BFI, Bowel Function Index; CPSI, Chronic Pain Sleep Inventory; DN4, Douleur Neuropathique 4 inventory; NRS, numerical rating scale.

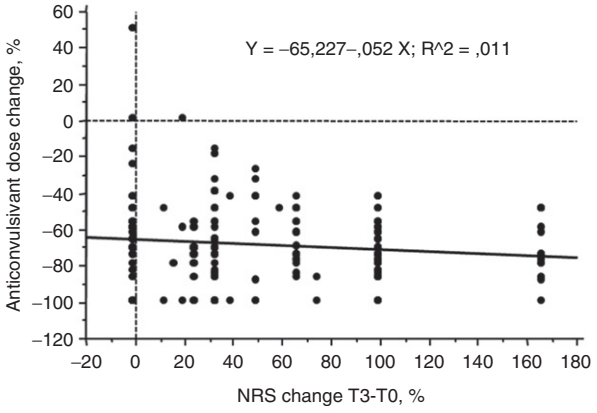

Figure 5. Correlation between variations in daily anticonvulsant dose and magnitude of pain severity (NRS score) reduction throughout the study (values expressed as a percentage of corresponding values at T0). No significant correlation was found (squared correlation coefficient = 0.01; p = NS).

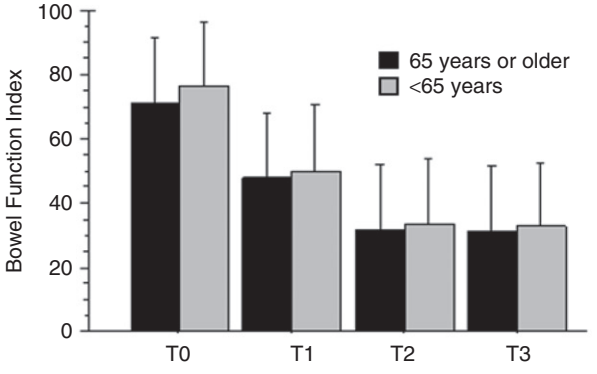

Figure 6. Bowel Function Index (BFI) throughout the study in the two age subgroups (<65 years, ≥65 years): BFI changes significant versus T0 at all time-points ($p < 0.0001$) in both subgroups; T3 vs T2: p = NS. Differences between subgroups: p = NS at post-hoc analysis. T0 = entry visit; T1 = 15 days after T0; T2 = 30 days after T0; T3 = 60 days after T0.

OXN was generally well tolerated, with an exceedingly low rate of AEs ($n = 11$), reported by 10 (5.0%) patients during the observation. There were 6 patients reporting 7 severe AEs (hallucinations, $n = 2$; confusion, $n = 2$; somnolence, nausea and visual disturbances, $n = 1$) causing discontinuation of OXN either after the first month of administration ($n = 4$) or after the second month ($n = 2$). One subject complained of confusion of moderate severity, limiting further drug escalation; two additional subjects reported abdominal distension and diarrhoea of mild severity and neither precluded nor limited treatment maintenance. AEs were equally distributed in younger ($n = 5$, 6.1%) and older subjects ($n = 5$, 4.2%; p = NS).

Discussion

In the present observation, low-dose PR OXN combination in addition to concomitant anticonvulsants was effective in patients with moderate-to-severe NP pain despite previous medications providing a marked reduction in pain severity and DN4 score over 8 weeks. In terms of subjective global assessment, the majority of patients reported that they were much or extremely improved; similarly, sleep quality markedly improved during the observation. Of relevance, the beneficial effects of OXN were similar in younger and older patients, and even patients previously treated with a WHO step III opioid achieved improved pain relief when switched to the PR OXN combination. Reduced bowel discomfort with OXN in our patients may have contributed to this improvement, directly or indirectly increasing patient's adherence to the new treatment.

The clinical utility of combination therapy for NP is specifically mentioned in the EFNS guidelines[9]. In particular, combination therapy with gabapentin and opioids (level A evidence) is recommended for patients who show partial response to drugs administered alone. A randomized controlled trial (RCT) of combination gabapentin and morphine vs monotherapy in patients with painful diabetic neuropathy or post-herpetic neuralgia showed that a significantly greater reduction in mean daily pain intensity was achieved with combination therapy but constipation was cited as a common adverse event[27]. Oxycodone, an established WHO step II/III opioid analgesic (depending on the dose used)[28], has been investigated in NP as monotherapy and in combination with pregabalin, and was found to be effective[29–35]. In a study comparing combination of PR oxycodone plus pregabalin versus either drug as monotherapy in patients with NP, we observed that combination therapy and oxycodone monotherapy were both more effective for alleviating NP than pregabalin monotherapy ($p = 0.003$), and a greater improvement in QoL was achieved with combination therapy versus monotherapy ($p = 0.0009$)[31]. Like other opioids, oxycodone causes OIBD[36].

Because of OIBD, a high proportion of patients require one or more laxative treatments[14,15,17], which are often ineffective as they do not address the underlying cause of bowel dysfunction. OIBD and related symptoms, including constipation, nausea, abdominal pain or even dizziness, persist over time or can even become worse; OIBD is frequently dose limiting and impacts badly patients' QoL, reducing patients' compliance with their therapy and leading to inadequate analgesia[13,15]. Combining an opioid agonist (i.e., oxycodone) and an opioid receptor antagonist (i.e., naloxone) has emerged as a successful approach to target the underlying mechanisms of opioid action in the GI tract and to overcome OIBD[37]. Naloxone, following oral administration, acts almost exclusively on opioid receptors in the GI tract; due to the extensive first-pass hepatic metabolism, its systemic bioavailability is however very low, without affecting the central analgesic activity of oxycodone. There is robust evidence that PR OXN is

effective in reducing OIBD, while maintaining analgesia in patients with chronic pain of noncancer and cancer aetiology – RCTs and post-marketing observations have documented the efficacy and safety of PR OXN combination, with an improvement in bowel function and a substantial reduction in the use of laxatives[16–19]. Improved QoL and reduced GI events with PR OXN combination may lead to better cost effectiveness compared with oxycodone monotherapy[38].

In the present study, all patients complained of constipation (spontaneous or drug-induced) at baseline. Similar to other post-marketing observations[18,39], an improved bowel function was documented after PR OXN in both opioid-pre-treated and naïve subjects. In these latter subjects, the improvement in bowel function cannot be attributed to laxatives, given that their use markedly decreased over the course of the study, thus suggesting an added benefit of PR OXN combination on bowel function. Potential explanations include reduced use of non-opioid analgesics and adjuvants throughout the observation (drugs that can also cause constipation); moreover, chronic pain *per se* can impair bowel function, due to inadequate activity or exercise, increased stress or disruption of regular diet.

Although direct evidence of the additional benefit of the PR OXN combination compared with a strong opioid on its own or with a laxative is still lacking, the cost effectiveness of the PR OXN combination has been recently documented in patients with non-cancer pain by comparing the cost of analgesic agents, laxatives and other resources, and benefits obtained with different treatments[38]: patients treated with PR OXN experienced a quality of life gain, with an incremental cost-effectiveness ratio well below the commonly applied thresholds. In fact, in our observation, PR OXN was associated with a marked reduction in the number of patients taking laxatives, as well as a reduction in their weekly dose (from T0 to T3: −37% and −55%, respectively).

Contrary to RCTs that examined the effect of PR OXN on pain and bowel function in unselected patients with non-cancer pain of different aetiologies and various treatments, our open-label observation was focused on patients with well defined neuropathic pain despite anticonvulsant therapy; moreover, we assessed the efficacy and tolerability of low dose OXN added to anticonvulsant therapy. The potential benefit of combining low doses of oxycodone and anticonvulsants to reduce the opioid dosage used was acknowledged recently in the Guidelines for Opioid Prescribing in Chronic Non-Cancer Pain[40], and our findings that low-dose OXN was effective in controlling pain when added to anticonvulsant drugs confirm previous observations[31]. The improvement in PGIC and sleep scores is also in agreement with previous data indicating that reductions of NP intensity with opioids are associated with improvements in mood and sleep[39,41]. In interventional studies on patients with NP, the EFNS recently recommended the inclusion of QoL measures, such as sleep, mood, or functional capacity, in addition to overall pain, in the evaluation of the effectiveness of new therapeutic strategies[9]. It is likely that in our patients better pain control and improved bowel discomfort at night achieved with the new PR OXN combination contributed to the observed improvement in sleep. Although very favourable, our preliminary uncontrolled findings need to be confirmed by further ad hoc evaluation.

In addition to the excellent effectiveness, low-dose OXN was very well tolerated, and provided substantial improvements in bowel function and reduced laxative consumption; only six patients (3%) discontinued the new treatment due to AEs. These favourable efficacy and tolerability findings are in agreement with those from a 4 week multicentre observational study of OXN treatment in 1488 patients with severe chronic NP, in which pain severity, bowel function and QoL improved with this treatment[42]. In contrast to our single-centre observation, this multicentre study did not focus on patients with bowel dysfunction, had a limited collection of data and a shorter follow-up period.

In our study, nausea and vomiting – other common side effects of opioid use – were exceedingly rare after OXN; of note, a marked decrease in these symptoms after OXN has been reported in another large observational study initiated immediately after drug licensing in Germany and which prospectively enrolled more than 7000 patients with severe pain of different aetiologies: the incidence of nausea and vomiting from the beginning to the end of the observation period decreased from 43.4% to 19.6%, and from 12.0% to 3.8%, respectively[18]. These findings indicate that the benefits provided by co-administration of naloxone may not be limited to constipation. Oral naloxone blocks activation of μ-opioid receptors in the submucosal and mesenteric plexuses, thus reducing the likelihood of decreased gastric emptying, intestinal peristalsis, and reduced secretion of digestive enzymes. In the upper gastrointestinal tract, prevention of these effects of μ-opioid receptor activation prevents nausea, vomiting, and loss of appetite.

Studies in patients with severe NP have demonstrated that morphine or oxycodone enhance the effectiveness of existing gabapentin or pregabalin[27,31,43–46]. In the present observation, all patients were pretreated with anticonvulsants, dosages of which were increased slightly in many patients at the entry visit. It is possible that the increase in anticonvulsant dose at the start of the observation in the majority of patients could lead to the effects of OXN being overestimated. However, our analysis of relationships between anticonvulsant doses (at start and changes during the observation) and clinical outcome (pain intensity and patients' perception of treatment effectiveness) showed no correlation, and multivariable analysis did

not find significant correlations between doses variations and the amount of benefit. Thus, the analgesic effectiveness documented in our observation is unlikely to be ascribed to anticonvulsant dose escalation. This issue however remains highly speculative and deserves further study.

Current guidelines on the pharmacological treatment of NP recommend strong opioids as second/third-line therapy in noncancer NP, because of their partial efficacy and potential risk for abuse, addiction, tolerance, and withdrawal effects on long-term use; many physicians have concerns relating to use of strong opioids in NP – particularly in pain of noncancer aetiology[47]. While acknowledging the very real risks and high medical and societal costs associated with prescription opioid abuse[47–49], there are initiatives to support the safe use of prescription opioid medications for patients with chronic pain[50]. Some experimental and clinical findings suggest that the positive reinforcing effects that lead to opioid abuse are diminished or even absent in individuals with severe chronic pain, making opioid addiction less likely[51,52]. Of note, withdrawal effects have never been documented in RCTs evaluating OXN PR[16,19,20,53]. Additional long-term studies with PR OXN combination in patients with NP are required to better understand the benefits and risk of this treatment.

This study has several limitations: the retrospective observational design (source of potential selection bias), the lack of a control group (no control for placebo effects) and the fact that this was a single-centre study may limit the generalizability of our findings. Nevertheless, in our opinion this study is of interest in view of the large number of participants, the long follow-up period, the careful data collection and observational nature of the study, which allowed the effectiveness of the drug to be tested in 'real' patients seen in normal clinical practice.

Conclusions

The PR OXN combination was found to be highly effective at low doses when added to anticonvulsant agents in controlling NP, and was well tolerated. This association resulted in a significant reduction in rescue pain medications, and improved analgesia was associated with improved quality of sleep. Despite the powerful analgesic effectiveness, no further worsening of bowel dysfunction was noted; in fact, bowel function improved and laxative use decreased considerably during OXN treatment. In this observational analysis, similar OXN effectiveness was found in young and older patients with NP of many different aetiologies. The efficacy and tolerability of OXN suggest it to be a valid treatment option in this difficult to manage patient population.

Transparency

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