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ORIGINAL RESEARCH ARTICLE

Long-Term Efficacy of OROS® Hydromorphone Combined with Pregabalin for Chronic Non-Cancer Neuropathic Pain

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Abstract

Background and Objectives Treatment for chronic non-cancer neuropathic pain can be complicated by side effects and drug interactions. Combining opioid analgesics and calcium channel modulators may overcome these and improve efficacy. The objective of the present study was to evaluate the efficacy and safety of OROS® hydromorphone combined with pregabalin in patients with chronic non-cancer neuropathic pain.

Methods This retrospective observational study was conducted on clinical records from patients aged ≥18 years with chronic non-cancer neuropathic [>4 on the Douleur Neuropathique en 4 questions (DN4) scale] pain of ≥6 months duration, with severe intensity [>4 on the Numerical Rating Scale (NRS); range 0–10], who attended all visits and had ≥12 months of follow-up at the Tor Vergata University Polyclinic Hospital, from November 2008 to February 2011. Patients received an oral combination of OROS® hydromorphone and pregabalin. Pain was evaluated at each visit (months 1, 3, 6, 9, and 12) using the NRS and DN4 scale; Patients' Global Impression of Change (PGIC) was administered at months 1, 6, and 12. Dosage and side effects were recorded at each visit.

Results Of 1,292 patients (32 % men, mean ± SD age 67.6 ± 11.9 years), 1,126 attended all visits. Seventeen percent ($n = 224$) had purely neuropathic pain. Initial mean dosage was 6.06 ± 2.00 mg/day for OROS® hydromorphone, 113.02 ± 21.94 mg/day for pregabalin. Dosages increased up to month 6, and returned to near initial dosages at month 12 (range 4–120 mg/day for OROS® hydromorphone; 75–600 mg/day for pregabalin). NRS pain scores (mean ± standard deviation) were 7.25 ± 1.34 at baseline and 1.85 ± 1.36 at 12 months ($p < 0.0001$); DN4 scores were 6.19 ± 1.65 at baseline, reduced to 1.84 ± 1.25 at 12 months ($p < 0.0001$), reductions of 74.4 and 70.2 %, respectively. More than 90 % of patients had a ≥50 % score reduction on both scales after 12 months. The PGIC scale showed that >75 % of patients felt improvement at 1 month, increasing to 91 % and 93 % at 6 and 12 months. The incidence of side effects was similar between elderly (aged >65 years) and younger subjects; there were no cases of addiction.

Conclusions The OROS® hydromorphone and pregabalin combination was efficacious for chronic non-cancer neuropathic pain and well tolerated, providing significant pain reduction without the risk of addiction and with a good tolerability profile, regardless of age.

Key Points

Efficacy of pregabalin and hydromorphone combination for chronic non-cancer neuropathic pain.

Hydromorphone is also useful in older patients who are frequently treated with multiple medications.

Good tolerability profile and low risk of addiction to hydromorphone during the prolonged period of treatment.

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1 Background

It is estimated that about 20 % of the population, both in Europe and worldwide, suffer or has suffered from moderate to severe chronic non-cancer pain [1, 2]. Chronic non-cancer pain is defined as pain that persists for at least 3 months, or for longer than expected for resolution of the underlying tissue damage [3].

Chronic neuropathic pain is described as chronic "pain arising as a direct consequence of a lesion or disease affecting the somatosensory system" [4]. Approximately 6–8 % of the general population reports chronic pain with a neuropathic component [5].

A wide repertoire of analgesics is available today for the treatment of chronic pain. Drugs currently recommended for the management of chronic neuropathic pain include tricyclic antidepressants (amitriptyline, cyclobenzaprine, imipramine), selective serotonin and noradrenaline reuptake inhibitors (duloxetine, venlafaxine), anticonvulsants (gabapentin, pregabalin), opioids (tramadol, oxycodone, morphine), topical agents for localized pain (lidocaine, capsaicin), and carbamazepine for trigeminal neuralgia [6, 7]. However, a significant proportion of patients does not obtain satisfactory pain control with monotherapy [8]; therefore, in clinical practice, therapies that combine molecules with different mechanisms of action are often used [9–11].

Especially for chronic neuropathic pain treatment, the combination of opioid analgesics and anti-epileptic calcium channel modulators is considered a valid therapeutic option as it is thought that the mechanisms of action of these classes of drugs may be synergistic. Moreover, clinical studies with different experimental designs [12–15] have shown that combination therapy is effective and has a favorable tolerability profile regardless of the molecules used.

Drugs such as gabapentin and pregabalin act by binding to the alpha-2-delta subunit of the voltage-dependent calcium channel complex, both in the brain and in the dorsal horn of the spinal cord, where they inhibit the release of excitatory neurotransmitters involved in the neuropathic pain process. For this mechanism they are considered the drugs of first choice for the treatment of neuropathic pain [6, 7].

Hydromorphone, a derivative of morphine used for many years, is also approved for use in patients with severe pain [16]. It is available in several formulations, including the osmotic controlled-release oral delivery system (OROS®), which provides analgesia for 24 h with minimal peak-trough fluctuations [17].

Unlike numerous drugs, the metabolism of hydromorphone does not occur via the cytochrome P450 (CYP) enzyme system but mainly in the liver by glucuronidation to the major metabolites hydromorphone-3-glucuronide, hydromorphone-3-glucoside, and dihydroisomorphine-6-glucuronide, followed by urinary excretion [18]. Hydromorphone-3-glucuronide has no analgesic activity, while the 6-glucuronide metabolite of morphine has both analgesic and depressant effects on the central nervous system, in particular, in elderly subjects [19].

As hydromorphone is not metabolized via the CYP system, it is less likely to be involved in pharmacokinetic alterations to concomitantly administered drugs. These characteristics make hydromorphone an opioid analgesic that can be used concomitantly with a relatively wide range of drugs. Hydromorphone may therefore be particularly useful in older patients who are frequently treated with multiple medications. Drugs that are contraindicated for use in conjunction with hydromorphone because of pharmacodynamic interactions include monoamine oxidase inhibitors, opioid receptor agonists/antagonists (e.g., buprenorphine), central nervous system depressants, and muscle relaxants [16]. However, hydromorphone does not interact with analgesic/neuromodulatory molecules that act on calcium channels, such as pregabalin.

Currently, no data are available on the combination of hydromorphone and pregabalin for the treatment of severe chronic non-cancer neuropathic pain. We have previously conducted clinical trials of combination therapy with calcium channel modulators (pregabalin) and opioid analgesics (controlled-release oxycodone). A randomized study [12] revealed that combination therapy is more efficacious than either drug alone, while a long-term observational study [13] has shown that this combination has good efficacy and tolerability profiles.

The present study is a long-term retrospective study with the objective of evaluating the efficacy and safety of combination therapy with OROS® hydromorphone and pregabalin in a large sample of patients with chronic non-cancer neuropathic pain treated in a real-world clinical setting.

2 Methods

2.1 Study Design and Setting

This retrospective observational study was conducted at the Pain Medicine Unit of the Polyclinic Tor Vergata (study center), University of Rome, from November 2008 to February 2011. The analysis was undertaken using clinical records of patients followed at the Ambulatory of Pain Medicine Unit. The study included patients with at least 12 months of evaluation who had attended all visits

that were normally expected after initiation or modification of analgesic therapy, according to the clinical practice at the study center. According to Italian laws, the Ethics Committee of Tor Vergata University Polyclinic Hospital was notified of the study (trial register protocol n. 157/12).

2.2 Eligibility Criteria

The study evaluated patients aged ≥18 years who were referred to the study center for the treatment of chronic non-cancer pain that was predominantly neuropathic [Douleur Neuropathique en 4 questions (DN4) >4], with a duration of ≥6 months and severe intensity [score >4 on a 11-point numerical scale (Numerical Rating Scale; NRS) where 0 = no pain; 10 = the worst pain imaginable].

Some of the patients included in the study presented with mild liver disease (based on the Child–Pugh score) or mild renal impairment (based on the NKF-KDOQI classification), or were non-responders to other analgesic treatments. Previous analgesic treatments included paracetamol, non-steroidal anti-inflammatory drugs, and corticosteroids as rescue medication, and only 155 patients had received World Health Organization Step II–III analgesics, without satisfactory pain control.

According to standard practice, pregnant or breast-feeding patients, patients with known hypersensitivity to opioids, patients receiving treatment with antiepileptic drugs or monoamine oxidase inhibitors, or with a history of alcohol or opioid abuse, respiratory insufficiency, psychiatric disease, severe liver disease, and severe renal impairment were excluded. Patients with ongoing oncologic disease were also excluded.

2.3 Treatment and Assessments

Patients received an oral combination of OROS® hydromorphone (Jurnista®, Janssen-Cilag S.p.A., Cologno Monzese, Italy) and pregabalin (Lyrica®, Pfizer, Rome, Italy) for a total of 12 months. The two drugs were administered according to the manufacturers' prescribing information.

Initial dosage was in the therapeutic range recommended by international guidelines [7, 20], based on the underlying pathologic condition and intensity of the pain. Dosages were then titrated on subsequent visits at months 1, 3, 6, 9, and 12, to obtain optimum effectiveness and tolerability based on patient responses. Patients could also access the study center outside of the normal planned visits at any time during the treatment period.

In keeping with clinical practice at the study center, visits were always conducted by physicians specialized in pain therapy and patients were asked to report any side effects; when necessary, symptomatic treatment was administered for these problems. Patients were asked to describe their pain over the previous 7 days using the validated NRS and DN4 scale [21]. In addition, the Patients' Global Impression of Change (PGIC) scale [22, 23] was administered at months 1, 6, and 12 to assess the overall change in health status compared with baseline. The PGIC is a scale divided into 7 points: −3 = very much worse, −2 = much worse, −1 = slightly worse, 0 = unchanged, +1 = slightly improved, +2 = much improved, and +3 = very much improved.

Patients who failed to attend the planned visits were considered lost to follow-up. However, these patients and those withdrawn from treatment were contacted 1 week and again 1 month after the date of withdrawal to assess the occurrence of any side effects and to exclude the occurrence of abuse (addiction) of study drugs. No serious side effects were reported, according to the US Food and Drug Administration definition.

2.4 Analysis

Descriptive statistics were used to analyze NRS and DN4 scores, variations in OROS® hydromorphone and pregabalin dosage, and the incidence of side effects at each visit. We also evaluated the proportion of patients who achieved complete pain relief, and that of patients who discontinued the study because of side effects. Differences between NRS and DN4 values at different times were compared using the Wilcoxon signed-rank test for paired data. Possible relationships between withdrawal and sex, age, severity of pain at baseline, prior therapies, and underlying disease were assessed by constructing a contingency table that was analyzed by the Fisher exact test. Differences were considered statistically significant for values of $p < 0.05$.

3 Results

3.1 Patient Characteristics

We analyzed the clinical data of 1,292 patients (408 men, 884 women, mean age 67.6 ± 11.9 years, range 21–89 years). Of these, 1,126 subjects (87.2 %) had attended all planned visits. The baseline demographic and clinical characteristics of the patients are summarized in Table 1. The most common pathologies underlying the chronic neuropathic pain were radiculopathies (61.1 %), followed by failed back surgery syndrome (8.8 %).

Purely neuropathic pain (from diabetic neuropathy, trigeminal neuralgia, post-herpetic neuralgia) was found in 17 % of the total population (224 patients).

3.2 Pain Assessment

The mean [± standard deviation (SD)] baseline NRS score was 7.25 ± 1.34 (range 4–10) and was significantly reduced during the study (1.85 ± 1.36 at 12 months, $p < 0.0001$) with a progressive trend at each visit (Table 2).

Thirty-three patients (2 % of total) reported complete resolution of pain symptoms (i.e., NRS = 0) over the course of treatment, which led to interruption of treatment in 12 subjects at month 9 and 21 subjects at month 12.

The mean DN4 score was reduced in a similar manner over the course of treatment (6.19 ± 1.65 at baseline, range 3–10; 1.84 ± 1.25 at 12 months, $p < 0.0001$), with differences detectable at all visits (Table 2). Compared with baseline, the mean NRS score was reduced by 74.4 % at the end of treatment (12 months), while the mean DN4 score was reduced by 70.2 %. In addition, after 12 months more than 90 % of patients had a score reduction of at least 50 % on both the NRS and the DN4. The number of patients who experienced reduction of 30 % and 50 % in terms of pain intensity and neuropathic components at the various visits is presented in Table 3.

PGIC scores revealed that more than 75 % of patients reported an improvement already at the 1-month visit. This percentage increased further at 6 months (91 %) and 12 months (93 %). The percentage of patients whose pain worsened was 6 % at 1 month, about 1 % at 6 months, and 0.2 % at 12 months. None of the patients ever reported their condition as "very much worse" (score −3).

Comparing patients with purely neuropathic pain ($n = 224$) with patients with mixed (i.e., nociceptive-neuropathic) pain ($n = 1{,}068$) did not reveal differences in NRS or DN4 scores at baseline or on subsequent visits (Table 4). Withdrawal rates were also similar between groups (14.7 % for neuropathic pain, 12.4 % for mixed forms).

Table 1 Patient characteristics

Characteristic	*N*	%
Male	408	31.6
Female	884	68.4
Age >65 years	453	35.0
Underlying disease		
Radiculopathy	789	61.1
Failed back surgery syndrome	114	8.8
Diabetic neuropathy	108	8.4
Post-herpetic neuralgia	66	5.1
Trigeminal neuralgia	50	3.9
Post-surgical neuropathic pain	45	3.5
Post-traumatic neuropathic pain	23	1.8
Other[a]	97	7.4

[a] Other underlying diseases included complex regional pain syndrome types I and II, fibromyalgia, polymyalgia rheumatica, post-stroke pain, alcoholic neuropathy, HIV-associated neuropathy, metabolic neuropathy, multiple sclerosis neuropathy, and vascular neuropathy

Table 2 NRS and DN4 scores at each visit over the course of treatment

Visit	NRS score		DN4 score	
	Mean ± SD	Range	Mean ± SD	Range
Baseline	7.25 ± 1.34	4–10	6.19 ± 1.65	3–10
Month 1	5.54 ± 1.31	3–10	5.16 ± 1.66	2–9
Month 3	4.60 ± 1.36	1–10	4.14 ± 1.65	1–8
Month 6	2.11 ± 1.71	0–9	3.14 ± 1.63	0–7
Month 9	1.88 ± 1.48	0–8	2.13 ± 1.60	0–6
Month 12	1.85 ± 1.36	0–8	1.84 ± 1.25	0–5

SD standard deviation, *NRS* Numerical Rating Scale, *DN4* Douleur Neuropathique en 4 questions

3.3 Dosage of the Drugs Evaluated

The initial mean OROS® hydromorphone dosage was 6.06 ± 2.00 mg/day (range 4–8 mg), while that of pregabalin was 113.02 ± 21.94 mg/day (range 75–150 mg). During the first 6 months, the dosages of both OROS® hydromorphone and pregabalin were increased, reaching 15.16 ± 2.97 mg/day (mean value ± SD; range 4–20) and 309.54 ± 43.40 (range 175–375), respectively (Table 5). Starting from month 9, the dosages of both drugs could be progressively decreased (Table 5). Of note, this trend was particularly significant for OROS® hydromorphone, for which the mean dosage at 12 months was similar to the baseline dosage.

The dosage ranges during the entire treatment period were 4–120 mg/day for OROS® hydromorphone and 75–600 mg/day for pregabalin.

3.4 Treatment Retention and Safety Analysis

Of the 166 patients who did not complete the 12 weeks of observation, 121 (9.4 % of total) withdrew because of adverse effects, while the remaining 45 were lost to follow-up for reasons not related to side effects, or because they no longer required analgesic therapy (Table 6).

Most of the patients who withdrew because of adverse effects (92 %, 112/121) did so before month 6: 35 at month 1, 45 at month 3, and 32 at month 6, followed by a total of 11 subjects after month 9. The most frequent causes of withdrawal were constipation, drowsiness, nausea, dizziness, and fluid retention (Table 6).

Table 3 Patients who experienced a score reduction of 30 or 50 % according to visit

	Baseline to month 1, *n* (%)	Months 1–3, *n* (%)	Months 3–6, *n* (%)	Months 6–9, *n* (%)	Months 9–12, *n* (%)	Baseline to month 12, *n* (%)
NRS score						
Patients in treatment, *n*	1,257	1,212	1,164	1,142	1,126	1,126
≥30 % reduction	414 (32.9)	300 (24.8)	917 (78.8)	294 (25.7)	14 (1.2)	1,085 (96.4)
≥50 % reduction	55 (4.4)	168 (13.9)	732 (62.9)	261 (22.9)	4 (0.4)	1,042 (92.5)
DN4 scale						
≥30 % reduction	28 (2.2)	200 (16.5)	501 (43.0)	793 (69.4)	132 (11.7)	1,126 (100)
≥50 % reduction	3 (0.2)	25 (2.1)	175 (15.0)	474 (41.5)	50 (4.4)	1,108 (98.4)

NRS Numerical Rating Scale, *DN4* Douleur Neuropathique en 4 questions

Table 4 DN4 and NRS scores for patients with purely neuropathic pain and those with mixed pain

Type of pain	DN4 baseline[a]	DN4 at 12 months[a]	NRS baseline[a]	NRS at 12 months[a]
Neuropathic	6.19 ± 1.64	1.84 ± 1.23	7.24 ± 1.35	1.84 ± 1.36
Mixed	6.16 ± 1.73	1.80 ± 1.32	7.28 ± 1.29	1.89 ± 1.35

NRS Numerical Rating Scale, *DN4* Douleur Neuropathique en 4 questions

[a] Values are expressed as mean ± standard deviation

Table 5 Dosages of OROS® hydromorphone and pregabalin over the course of treatment

Visit	OROS® hydromorphone (mg)		Pregabalin (mg)	
	Mean ± SD	Range	Mean ± SD	Range
Baseline	6.06 ± 2.00	4–8	113.02 ± 21.94	75–150
Month 1	8.79 ± 2.35	4–12	180.15 ± 34.30	100–225
Month 3	12.74 ± 2.34	8–16	254.56 ± 34.50	175–300
Month 6	15.16 ± 2.97	4–20	309.54 ± 43.40	175–375
Month 9	10.01 ± 5.66	0–120	301.66 ± 73.96	100–475
Month 12	6.33 ± 5.10	0–28	205.96 ± 134.40	0–600

SD standard deviation

There was no difference between those who dropped out and those who completed treatment regarding sex, age, underlying disease, pain severity (e.g., baseline NRS or DN4), or previous treatment (Fisher exact test; data not shown).

Most side effects were mild or moderate in severity (Table 7); no serious side effects were reported.

The incidence of side effects was similar between elderly subjects (aged >65 years) and younger subjects. In particular, at each visit except month 1, the cumulative incidence of side effects reported by the elderly was less than 5 %, which was comparable to or slightly lower than that of younger subjects (elderly vs. young: 6.9 vs. 9.0 % at month 1, 4.9 vs. 5.5 % at month 3, 3.5 vs. 4 % at month 6, 1 vs. 1 % at month 9, 0.7 vs. 0.5 % at month 12). In addition, there were no cases of addiction.

4 Discussion

The overall results of this long-term observational study, conducted on data collected from the records of a very large sample of patients with chronic non-cancer neuropathic pain, show for the first time that combination therapy with OROS® hydromorphone and pregabalin can be considered a valid option for the treatment of chronic neuropathic pain. This combination therapy was well tolerated and effective, regardless of the source of pain or the age of the patient.

Our data reveal a continuous reduction in terms of pain intensity and neuropathic components, as measured respectively with NRS and DN4 scales, throughout the treatment period. This was already evident after 1 month of therapy and gradually increased until the month 9 visit. The reduction in pain was less evident between months 9 and 12, but it should be noted that by month 9 the mean scores for NRS and DN4 were already 1.88 and 2.13, respectively, which is compatible with a substantial resolution of pain. These data are particularly significant if we consider that the mean baseline values (NRS = 7.25, DN4 = 6.19) were indicative of severe chronic neuropathic pain.

The subjective evaluation provided by the PGIC of change from baseline in overall health was consistent with trends in the DN4 and NRS scores. At the 1-, 6-, and 12-month visits, the percentage of patients who reported an improvement was always >75 %. On the contrary, only 6 % of patients reported worsening of pain at month 1, followed by 1 % at month 6, and nearly 0 % at month 12.

Table 6 Reasons for withdrawal from the study

	Month 1, *n* (%)	Month 3, *n* (%)	Month 6, *n* (%)	Month 9, *n* (%)	Month 12, *n* (%)
Total withdrawals	35	45	48	22	16
Dizziness	7 (4.0)	10 (6.0)	6 (3.6)	2 (1.2)	1 (0.6)
Nausea	8 (4.8)	9 (5.4)	5 (3.0)	0	0
Constipation	14 (8.4)	20 (12.0)	18 (10.8)	4 (2.4)	2 (1.2)
Drowsiness	13 (7.8)	11 (6.6)	11 (6.6)	2 (1.2)	0
Water retention	2 (1.2)	6 (3.6)	6 (3.6)	2 (1.2)	1 (0.6)
Poor adherence	0	0	16 (9.6)	7 (4.0)	5 (3.0)
Personal problems	0	0	0	8 (4.8)	9 (5.4)

Individual patients may have discontinued treatment for combinations of more than one side effect

Table 7 Mild or moderate side effects reported during treatment

Adverse events not leading to discontinuation	Month 1, *n* (%)	Month 3, *n* (%)	Month 6, *n* (%)	Month 9, *n* (%)	Month 12, *n* (%)
Dizziness	7 (0.56)	10 (0.83)	6 (0.52)	2 (0.18)	1 (0.08)
Nausea	18 (1.43)	12 (0.99)	5 (0.43)	2 (0.18)	0
Constipation	45 (3.58)	30 (2.48)	27 (2.32)	7 (0.61)	5 (0.44)
Drowsiness	36 (2.86)	17 (1.40)	13 (1.12)	4 (0.35)	2 (0.17)
Water retention	2 (0.16)	6 (0.50)	6 (0.52)	0	1 (0.08)
Headache	0	0	1 (0.09)	0	0

Individual patients may have reported more than one side effect

These results are in line with our findings in two previous studies. The first study, an open-label, multicenter comparison of pregabalin alone and in combination with oxycodone, demonstrated that the combination therapy was more efficacious and resulted in more rapid resolution of pain [12]. The second was an observational study (very similar in design to the present study) conducted on clinical data of 1,051 patients with chronic non-cancer neuropathic pain that confirmed the long-term (12 months) effectiveness of combination therapy with oxycodone and pregabalin [13]. On the contrary, results from a randomized, placebo-controlled, double-blind study have documented the non-superiority of combination therapy with pregabalin and oxycodone compared with pregabalin monotherapy [24]. However, this study was conducted on a group of 62 patients and observation was limited to a period of only 4 weeks. Independent of the results, one benefit of combination therapy is the possibility of using a lower dose of each drug, compared with monotherapy, with ascertainable effects on safety and tolerability profiles [12].

More generally, the potential of combining an opioid and a calcium channel modulator had already been suggested by the results of at least two previous studies, both randomized and placebo controlled, that evaluated therapy combining gabapentin with either oxycodone [25] or with morphine [15].

The tolerability profile and the risk of addiction are critical factors for any therapy with opioids, especially when administered for prolonged periods. The results of our study show that, after an increase in dosage up to month 6, there was a tendency to gradually reduce the OROS® hydromorphone dosage (−37 % at month 9, −45 % at month 12) and, although less pronounced, also the pregabalin dosage (−3.8 % at month 9 and −38 % at month 12). At month 12, dosages were similar to those administered at baseline, with a more pronounced effect for OROS® hydromorphone. This dose reduction probably contributed to reducing the incidence of side effects, which in fact were reported only sporadically at the month 9 and month 12 visits. While reducing the dosage of both drugs, pain relief was continuous, without signs suggestive of withdrawal symptoms or physical or psychologic opioid dependence during treatment.

The favorable tolerability profile was also confirmed by the fact that only 9.4 % of patients had side effects that affected adherence to therapy, requiring interruption. In agreement with the known adverse-event profile of opioids, the event most frequently leading to study interruption was constipation.

Another very significant element that emerges from this study is the similarity in the tolerability of the combination between elderly (aged >65 years) and younger subjects.

This important finding for clinical practice can be interpreted considering that hydromorphone has no analgesically active metabolites and does not interact with CYP450 [18, 19]; it is metabolized in the liver through a process of glucuronidation. Another practical advantage related to the use of OROS® hydromorphone in the elderly (who often receive drug polytherapy for co-morbidities) is the ability of once-daily administration to facilitate compliance to therapy.

There was also a decreasing trend in side effects over time, with a parallel reduction in patients who discontinued the study because of tolerability problems. Indeed, most opioid-related adverse events tend to resolve with time because of the development of tolerance. This may explain the decreasing trend in the frequency of adverse events over time, and the fact that the majority of patients (87.2 %) could be treated for a relatively extended period of time (12 months).

In addition, the kinetics of release of once-daily OROS® hydromorphone reduces the peak-to-trough fluctuations of plasma concentrations of the opioid and thus limits the occurrence of end-of-dose pain spikes, which are observed more frequently with formulations requiring repeated doses over 24 h. In this way, the synergistic effect with pregabalin is optimized, facilitating more accurate titration of this drug and limiting the occurrence of the side effects of each drug when administered individually.

The present study has some limitations related to the open nature of the study, the fact that it was a monocentric study and that it lacked a control arm. In particular, a placebo comparison arm could have provided information about the possibility that some patients had spontaneous improvement in pain.

No information was collected on changes in the sleep quality and this certainly represents another limitation. However, the large number of patients considered, the length of the observation period, and the use of multiple scales for pain assessment confer robustness to our results, offsetting the limitations reported above. In this regard, it is also significant that there is no evidence that efficacy is overestimated in observational studies compared with randomized controlled studies [26], and that observational studies have inherent advantages in that they better reflect the normal living conditions of patients and have longer observation periods [27].

5 Conclusions

This study provides useful information for the first time about the efficacy and tolerability of combination therapy with OROS® hydromorphone and pregabalin in the treatment of chronic non-cancer neuropathic pain. Based on our results, such a therapeutic strategy provides significant pain reduction without the risk of addiction and with a good tolerability profile, regardless of age. Combination therapy with OROS® hydromorphone and pregabalin can therefore be considered a valid therapeutic option for the treatment of chronic non-cancer pain that has a predominantly neuropathic component.

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