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Observational study

Effects of prolonged-release oxycodone/naloxone on pain control, bowel function and quality of life: A prospective observational study

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HIGHLIGHTS

- Prospective observational study in patients with moderate/severe chronic pain.
- First data set to compare PR oxycodone/naloxone (OXN) with other strong opioids.
- Stronger reduction of pain intensity and interference with OXN vs. other opioids.
- OXN favourable over other opioids in bowel function, QoL and tolerability.
- Insights into pain management with strong opioids during routine clinical practice.

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ABSTRACT

Background and aim: Strong opioids including oxycodone are amongst the most effective analgesics to combat moderate to severe pain of various aetiologies, but opioid-induced bowel dysfunction (OIBD) represents a relevant problem. The rationale for development of a prolonged-release (PR) fixed combination of oxycodone and naloxone was to counteract OIBD. Due to its negligible oral bioavailability, the μ-opioid receptor antagonist naloxone is able to selectively displace opioids from local μ-receptors in the gastrointestinal tract without affecting central opioid binding sites. Pivotal trials of PR oxycodone/naloxone not only demonstrated improved bowel function but also equivalent analgesic efficacy compared to PR oxycodone alone. Controlled clinical trials comparing PR oxycodone/naloxone with strong opioids other than oxycodone are not available. The present study is the first data set aimed at comparing pain control, bowel function, and quality of life (QoL) in patients newly treated with or switched to PR oxycodone/naloxone or other strong opioids during routine clinical practice.

Methods: In this three-arm, prospective observational study, 588 patients with moderate to severe pain of varying aetiologies received either PR oxycodone/naloxone (OXN group and OXN 40/20 group with indicated use of the 40 mg/20 mg dose strength at baseline) or other strong opioids (control group), dosed according to pain severity, for 4–6 weeks. Data documented include pain intensity (NRS), bowel function (Bowel Function Index, BFI), pain-related functional impairment (BPI-SF), QoL (EuroQol EQ-5D-3L), and a global assessment of treatment.

Results: Patients receiving PR oxycodone/naloxone experienced a clinically important reduction in pain intensity and pain-related functional impairment of approximately 40%. The reductions of pain intensity (-2.9 ± 2.3) and pain-related functional impairment (-2.4 ± 2.3) in the OXN group were significantly more pronounced than in the control group (-2.1 ± 2.1 and -1.8 ± 1.7). In the control group, mean reductions in pain intensity did not reach the threshold of ≥30% for at least moderate clinically important differences, although patients were prescribed higher doses of morphine equivalents than OXN group patients. Improvements in bowel function (OXN: -16.0 ± 27.6; control: 3.1 ± 24.4) and QoL (OXN: 20.8 ± 24.2; control: 13.2 ± 23.1) were also significantly more pronounced in the OXN group, with BFI scores reduced to a level that reflects normal bowel function. Results for the OXN 40/20 group receiving higher doses of PR oxycodone/naloxone were in line with those for the OXN group. In the control group, more frequent gastrointestinal adverse events and less favourable ratings of tolerability resulted in a higher rate of treatment discontinuations due to adverse events.

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Conclusions: In patients receiving PR oxycodone/naloxone, more favourable outcomes compared with other strong opioids regarding pain control, bowel function, and QoL were observed.
Implications: The present findings underline the value of PR oxycodone/naloxone in the management of patients with moderate to severe chronic pain. The data set further adds to our understanding of the benefits and risks of opioid treatment in routine clinical practice.

1. Introduction

Oxycodone is a widely used, well characterised strong opioid with proven efficacy in cancer pain [1–3], musculoskeletal and neuropathic pain [1,3,4]. The most troublesome adverse effects of opioid therapy [5] are gastrointestinal (GI) problems including constipation, straining, abdominal pain, and nausea [6]. This symptom complex of opioid-induced bowel dysfunction (OIBD), primarily mediated by the stimulation of local μ-receptors in the GI tract [7], has a strong negative impact on quality of life (QoL) [5,6,8]. Approximately 30% of pain patients reduce or terminate opioid treatment due to OIBD [5]. Oral administration of opioid receptor antagonists with limited systemic availability has been suggested to counteract OIBD by selectively displacing opioids from local μ-receptors in the GI tract without affecting central opioid binding sites [6]. Due to its extensive first-pass metabolism and resulting negligible oral bioavailability (<3%) [9], the competitive opioid receptor antagonist naloxone is a potentially suitable agent for this approach [10]. Compared to oxycodone alone, a fixed 2:1 combination of prolonged-release oxycodone and -naloxone (PR oxycodone/naloxone), with matched kinetic properties of the two components, demonstrated comparable analgesic efficacy [11] and improved bowel function [12–14] in phase-III trials in patients with moderate to severe chronic non-cancer pain. It was approved in Germany and several other European countries in 2006 and 2008, respectively. A prospective observational study in 7836 patients with severe chronic pain of various aetiologies confirmed that PR oxycodone/naloxone provides analgesia with positive effects on pain-related functional impairment and bowel dysfunction under conditions of routine clinical practice [15]. At the time of that study, two tablet formulations of PR oxycodone/naloxone (10 mg/5 mg and 20 mg/10 mg) were available. Since then, two additional strengths (5 mg/2.5 mg and 40 mg/20 mg oxycodone/naloxone) have been introduced, allowing further adjustment of dose and potential improvement of treatment benefits. The present prospective observational study was designed to evaluate pain control, bowel function, and QoL in patients newly treated with or switched to PR oxycodone/naloxone or other strong (WHO step-III) opioids. As per recommendation of the European Association of Palliative Care, patients not achieving adequate analgesia and/or suffering from unmanageable side effects may benefit from switching to another opioid [16]. Patients with a more severe pain condition, who received the higher 40 mg/20 mg dose strength of PR oxycodone/naloxone, allowing for adequate analgesia with twice daily dosing, were documented as a separate cohort.

Our aim was to find out to what extent patients benefit from their individual therapy with PR oxycodone/naloxone compared to treatment with other strong opioids under routine practice conditions. As available clinical studies only compared PR oxycodone/naloxone to PR oxycodone alone, this represents the first data set to directly compare the fixed combination with other strong opioids and strengthens our understanding of the benefits and risks of PR oxycodone/naloxone in clinical practice.

2. Methods

2.1. Study design

This multicentre, prospective, observational study was performed from November 2009 through December 2010 by German non-hospital-based physicians. The primary objective was to document pain control and bowel function during four to six weeks of treatment with PR oxycodone/naloxone (Targin®, Mundipharma GmbH, Limburg, Germany) or other strong opioids during routine practice. Results for the secondary objective, the development of an opioid responsiveness and tolerability prediction model, will be reported separately.

Participating physicians were allowed to observe the treatment of ≤8 patients for the study and received an adequate reimbursement for documentation per patient.

Demographics, a detailed medical history including pain-causing underlying disease, data on analgesic and concomitant treatments in the previous 30 days, pain intensity, bowel function, QoL and a global assessment of analgesic treatment (effectiveness and tolerability) were collected at the initiation visit (V1). Data documented after four to six weeks of treatment (V3) and at an optional visit for patients requiring closer monitoring of their analgesic treatment after the first or second week (V2) included pain intensity, consumption of analgesic prolonged-release and rescue medication, concomitant treatment (including laxative use), bowel function, pain-related functional impairment, QoL, adverse events and a global assessment (V3 only). Data were gathered based on interviews and questionnaires.

2.2. Patients and treatment

Patients with moderate to severe pain of varying aetiologies could be enrolled, if the physician had decided to start or change treatment with PR oxycodone/naloxone or other strong opioids due to insufficient pain control and/or tolerability of the previous medication. Patients had to provide written informed consent before enrolment. Treatment followed recommendations for the respective opioid per marketing authorisation. The prescription of analgesic co-medication or rescue medication including immediate-release opioids and laxatives was at the discretion of the treating physician.

Analyses were carried out for three cohorts defined by treatment initiated at V1: (1) indicated start of or switch to PR oxycodone/naloxone by using the 5 mg/2.5 mg, 10 mg/5 mg and/or 20 mg/10 mg dose strength of PR oxycodone/naloxone (OXN cohort); (2) other strong opioids (control cohort); (3) indicated use of the higher 40 mg/20 mg dose strength of PR oxycodone/naloxone in patients with a more severe pain condition, allowing for adequate analgesia with twice daily dosing (OXN 40/20 cohort).

2.3. Outcome measures

2.3.1. Pain

The average pain intensity in the last 24 h as reported by the patient and documented by the physician was assessed by an

11-point numeric rating scale (NRS). A validated German version of the Brief Pain Inventory Short Form (BPI-SF) [17,18] was used to evaluate worst, least and average pain during the preceding 24 h, and pain right now.

2.3.2. Bowel function

Patient-reported bowel function was assessed with the investigator-administered, validated Bowel Function Index (BFI) [19,20] which rates ease of defaecation, feeling of incomplete bowel evacuation, and a personal judgement of constipation on a NRS from 0 (no difficulty) to 100 (severe difficulty). The mean BFI is calculated as arithmetic means of these three individual items.

2.3.3. QoL

Pain-related functional impairment as reported by the patient and documented by the physician was measured by the 7-item composite pain interference included in the BPI-SF (general activity, walking ability, normal work, mood, enjoyment of life, sleep, relations with other people; 11-point NRS for each item, ranging from 0 = no impairment to 10 = most severe impairment) [17]. QoL was reported by the patient and documented by the physician using a validated German version of the European Quality of Life Questionnaire EuroQol EQ-5D-3L, consisting of five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression), each of which can take one of three responses with level 1 = no problems and level 3 = extreme problems; the current health state was evaluated by a visual analogue scale (VAS) from 0 (worst) to 100 (best imaginable health state) (EQ-5D VAS score) [21].

2.3.4. Global assessment

Effectiveness and tolerability of analgesic treatment were rated on a 5-point scale (1 = very good, 5 = very bad) by patients and physicians.

2.4. Statistics

Safety parameters were evaluated for all patients who received at least one dose of PR oxycodone/naloxone or other strong opioids. Other variables were analysed for patients with at least one dose of study medication and available data on pain intensity and bowel function at V1 and V3 (=completers population, CMP). Summary measures are reported as proportions or as mean ± standard deviation (SD). Exploratory p-values derived from analysis of covariance (ANCOVA) were calculated for comparisons between treatment and baseline using treatment as factor and baseline value as covariate. Morphine equivalents for average daily doses documented at V3 were calculated for treatment with oxycodone, buprenorphine, fentanyl (conversion ratio stated in the respective product information: in particular, oxycodone:morphine = 1:2) and hydromorphone [22].

2.5. Trial registration

The study was conducted in accordance with AMG (German Medicines Act) chapter 67, section 6. It was approved by an ethics committee and registered with the German Federal Institute for Drugs and Medical Devices (BfArM) with study code OXN9505.

3. Results

3.1. Patients and treatment

In this observational study, 588 patients were documented by 141 physicians, mainly general practitioners. Demographics and baseline characteristics for the 544 patients of the CMP population are summarised in Table 1.

Table 1
Patient demographics, disease characteristics and prior analgesic treatment per treatment initiated at visit V1.

	OXN (n = 320)	Control (n = 176)	OXN 40/20 (n = 48)
Age, years			
Mean ± SD	64.1 ± 14.3	65.3 ± 13.4	64.6 ± 14.0
Sex, %			
Female	64.4	64.2	64.6
Ethnic origin, %			
Caucasian	99.0	100.0	97.9
BMI, kg/m^2			
Mean ± SD	28.2 ± 5.6	27.7 ± 5.0	28.1 ± 5.3
Pain-causing underlying disease[a,b], %			
Musculoskeletal	93.4	89.2	91.7
Nervous system	23.1	15.3*	22.9
Neoplasm	13.8	13.6	16.7
Other	10.9	9.7	6.3
Median duration of pain, months	31.9	37.6	35.6
Prior analgesic treatment[a], %			
None	8.8	5.7	2.1
At least one prior analgesic	70.0	69.9	89.6#
Not specified	21.3	24.4	8.3
At least one prior			
Non-opioid analgesic, local anaesthetic or non-pharmacological analgesic treatment	34.4	35.2	12.5#
Opioid	51.9	41.5*	87.5#
Weak opioid (WHO step II)	32.2	30.1	0#
Strong opioid (WHO step III)	21.3	12.5*	87.5#
Co-analgesic	4.1	7.4	4.2

Statistically significant differences (p < 0.05) are indicated: control vs. OXN and vs. OXN + OXN 40/20 (*), OXN 40/20 vs. OXN (#).
BMI, body mass index.
[a] Multiple entries were possible.
[b] Classified according to ICD 10.

Baseline patient characteristics were mostly balanced between treatment cohorts. Slightly fewer control group patients were documented to have a pain-causing underlying disease of the nervous system. Furthermore, fewer control group patients than OXN patients were treated with strong opioids prior to study initiation.

Complaints regarding the previous analgesic treatment were more common in the OXN- and OXN 40/20 cohorts: 51.6% and 45.8% of patients reported at least one problem compared to 39.2% of the control group. Most patients of the OXN- and OXN 40/20 groups complained about GI problems (35.6% and 37.5%), with constipation as the most commonly reported condition at baseline (24.1% and 33.3%). Overall GI complaints and constipation were less frequent in the control group (19.3% and 10.2%, respectively). Laxative use in the previous 30 days was reported by OXN- and control group patients only (9.7% and 5.7%).

Across cohorts, insufficient pain control with the previous analgesic medication was the major reason for including patients in this study (75.0%, 78.4% and 97.9% of patients in the OXN-, control- and OXN 40/20 groups, respectively), and only around 10% of patients across all treatment cohorts rated its effectiveness as 'good' or 'very good'. Inadequate tolerability was stated less frequently (21.6%, 13.6%, and 10.4%). This was also reflected by 'good' or 'very good' ratings for the tolerability of the previous analgesic treatment by 46.5% and 53.6% of the OXN- and control group patients and 72.9% of the patients in the OXN 40/20 cohort.

Patients in the control group were initiated on fentanyl (29.5%), buprenorphine (26.7%), hydromorphone (23.3%), morphine (13.6%) or oxycodone (13.1%). Their median daily dose documented at V3 was 60.0 [1.9–480.0] mg morphine equivalents (mean: 69.2 ± 65.5 mg). The median daily oxycodone doses at V3 in the OXN- and OXN 40/20 cohorts were 40.0 [8.0–320.0] mg (mean:

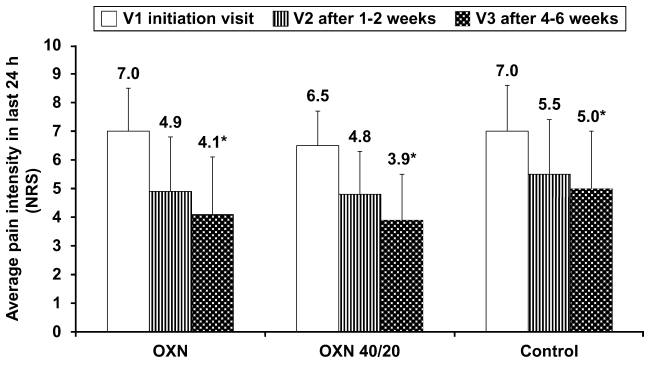

Fig. 1. Average pain intensity in the previous 24 h (NRS) at initiation visit V1 and follow-up visits V2, V3 (mean ± SD per treatment cohort). *$p < 0.0001$ vs. V1.

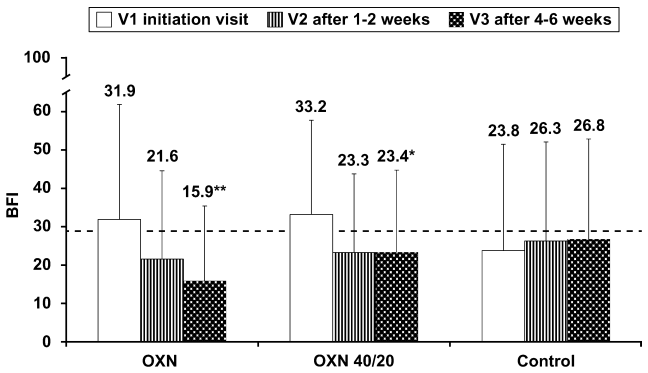

Fig. 2. Bowel Function Index (BFI) at initiation visit V1 and follow-up visits V2, V3 (mean ± SD per treatment cohort). The dashed line represents the upper limit of normal bowel function (=BFI 28.8). *$p = 0.0074$ and **$p < 0.0001$ vs. V1.

29.9 ± 21.9 mg) and 160.0 [30.0–320.0] mg (mean: 63.9 ± 25.8 mg), respectively. At least one concomitant additional analgesic (mostly dipyrone/metamizol, ibuprofen, or diclofenac) was used by 55.5% of patients with no major between-cohort differences. Treatment with at least one concomitant co-analgesic (mainly amitriptyline, pregabalin, gabapentin) tended to be more common in the control and OXN 40/20 groups (40.9% and 37.5%) than in the OXN group (30.0%). Throughout the observation period, the majority of patients reported not having taken rescue medication during the last seven days before the visit.

3.2. Effectiveness

3.2.1. Pain

Average pain intensity during the last 24 h before V1 was comparable in the treatment cohorts with a mean NRS of 7.0 ± 1.5. During treatment with study medication, pain decreased in all cohorts (Fig. 1). The reduction of pain intensity from V1 to V3 was significantly more pronounced in the OXN- and OXN 40/20 cohorts (−2.9 ± 2.3 and −2.6 ± 1.9) than in the control cohort (−2.1 ± 2.1; $p < 0.0001$ vs. OXN, $p = 0.0038$ vs. OXN 40/20).

Gradual reductions from V1 to V3 of the BPI-SF items of worst, least, and average pain in the preceding 24 h and pain right now were apparent across treatment cohorts. Mean changes of the composite pain severity were significantly larger in the OXN- and OXN 40/20 groups (−2.5 ± 2.1 and −2.3 ± 1.8) than in the control group (−1.9 ± 2.0, $p < 0.0001$).

3.2.2. Bowel function

Consistent with the greater frequency of GI complaints, the mean BFI at study initiation was higher in the two OXN groups than in the control group (Fig. 2). During treatment with PR oxycodone/naloxone, mean BFI decreased, while there was a slight increase in the control group. Accordingly, changes in mean BFI were significantly better in the OXN (−16.0 ± 27.6) and OXN 40/20 groups (−9.8 ± 21.7) than in the control group (3.1 ± 24.4; $p < 0.0001$ vs. OXN, and $p = 0.0251$ vs. OXN 40/20).

The mean number of days with laxative use in the preceding week decreased significantly in the OXN cohort from 1.8 at V1 to 1.1 at V3 ($p < 0.0001$) and remained nearly constant in the OXN 40/20 cohort (1.6 days at V1, 1.9 days at V3; $p = 0.2081$). In contrast, a significant increase of the mean number of days with laxative use from 0.8 to 1.9 days ($p < 0.0001$) was apparent in the control cohort.

3.2.3. QoL

Pain-related functional impairment as reflected by the BPI-SF composite pain interference score is presented in Fig. 3. Throughout the study, all seven individual items (data not shown) and the mean pain interference score decreased across treatment cohorts.

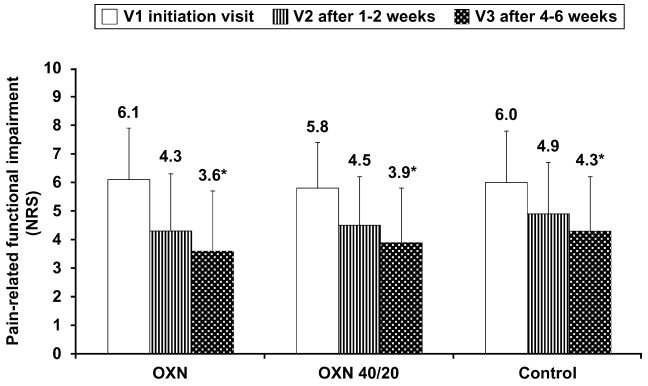

Fig. 3. Pain-related functional impairment (BPI-SF pain interference) at initiation visit V1 and follow-up visits V2, V3 (mean ± SD per treatment cohort). *$p < 0.0001$ vs. V1.

The reduction in pain interference from V1 to V3 was significantly larger in the OXN group (−2.4 ± 2.3) compared to control patients (−1.8 ± 1.7; $p = 0.0005$) and patients in the OXN 40/20 group (−1.9 ± 1.9; $p < 0.0001$).

Patients' ratings of their current health state by EQ-5D VAS significantly improved during treatment (Fig. 4). The extent of improvement was significantly greater in the OXN group (20.8 ± 24.2) than in OXN 40/20 (15.4 ± 21.5; $p < 0.0001$) and control patients (13.2 ± 23.1; $p < 0.0001$), with OXN patients reporting the best health state at V3. Percentages of patients reporting improvements in individual dimensions of the EQ-5D during the observational period were highest in the OXN- or OXN 40/20 groups and smallest in the control group. Proportions of patients reporting

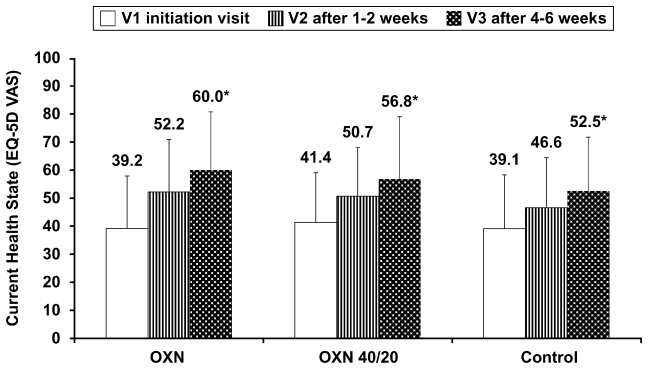

Fig. 4. Patient-reported health state (EQ-5D VAS) at initiation visit V1 and follow-up visits V2, V3 (mean ± SD per treatment cohort). *$p < 0.0001$ vs. V1.

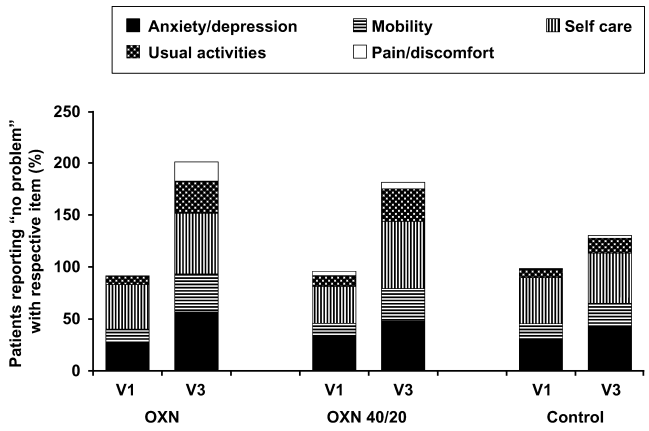

Fig. 5. Patient-reported quality of life (EQ-5D) at initiation visit V1 and follow-up visit V3. Percentages of patients reporting to have no problems (=level 1) with regard to the five dimensions are displayed according to treatment cohort.

no problems (=level 1) with regard to mobility, self care, usual activities, pain/discomfort, and anxiety/depression at V1 and V3 are presented in Fig. 5.

3.3. Safety

Overall, 16.2% of patients experienced at least one drug-related adverse effect, mostly mild (6.6%) or moderate (8.8%) in nature. There were no serious adverse drug reactions. Most commonly reported adverse drug reactions and premature discontinuations per treatment group are summarised in Table 2. Discontinuations due to adverse events were more frequent in the control group (8.3%) than in the OXN- and OXN 40/20 groups (5.5% and 0%).

3.4. Global assessment

At the end of the observation period, 73.0% and 74.4% of OXN- and OXN 40/20 patients, respectively, rated the overall effectiveness of their study medication as 'very good' or 'good', compared to 55.4% of control patients. Tolerability ratings of 'very good'/'good' were also more frequent for OXN and OXN 40/20 (84.1% and 83.3%) than for other strong opioids (68.9%).

4. Discussion

The present observational 4–6 week study in patients with moderate to severe pain of varying aetiologies (e.g., ca. 90% musculoskeletal pain, ca. 15% due to neoplasm) is the first data set to explore effects on pain intensity, bowel function and QoL in patients newly treated with or switched to PR oxycodone/naloxone or other strong opioids. It adds to available controlled clinical trials in non-cancer and cancer pain in which PR oxycodone/naloxone was compared to PR oxycodone alone. These demonstrated that PR oxycodone/naloxone was superior to PR oxycodone in bowel function [12–14,23] while analgesic efficacy was comparable [11,23]. Long-term efficacy and safety of PR oxycodone/naloxone were proven in a 12-month open-label extension study [24].

Patients treated with PR oxycodone/naloxone achieved reductions in average pain intensity and pain interference of approximately 40%, comparable to effects in a previous observational study [15,25] and equivalent to at least moderate clinically important differences [26]. Stronger improvement of analgesia in the OXN groups compared to the control group may be due to paradoxical analgesia caused by very low doses of naloxone that enter the systemic circulation after oral application of PR oxycodone/naloxone [27]. Baseline complaints and improvements in bowel function in the OXN cohort were less pronounced than in previous controlled clinical trials which enrolled only patients with opioid-induced constipation [13]. Nevertheless, mean changes were clinically relevant [19] and mean BFI scores were reduced to levels well below 28.8, the upper limit describing normal bowel function [28]. In parallel, PR oxycodone/naloxone treatment resulted in significantly improved patient-reported QoL and very positive ratings for effectiveness and tolerability. Comparable to a previous observational trial [15,25], the incidence of drug-related adverse events documented in the present study was generally low and the reactions were as anticipated for treatment with a strong opioid analgesic. The lower prevalence of nausea and vomiting in patients treated with PR oxycodone/naloxone compared to control group patients may be explained by the opioid antagonistic effect of naloxone in the GI tract: blockade of μ-opioid receptors by naloxone can reverse the opioid-mediated gastric retention that has been associated with nausea and vomiting [29]. Results for the OXN 40/20 group were in line with those for the OXN group and confirmed the value of the additional higher dose strength allowing for adequate analgesia with twice daily administration in patients with a more severe pain condition.

In the control group, mean reductions in pain intensity did not reach the threshold of ≥30% for at least moderate clinically important differences, although patients were prescribed higher doses of morphine equivalents than OXN group patients. Improvements in pain interference and QoL were also less pronounced than for both PR oxycodone/naloxone cohorts. In spite of less frequent GI complaints and lower mean BFI scores at the initiation visit, control group patients had higher BFI scores, required more laxatives and reported more frequent constipation and nausea/vomiting at study end than both PR oxycodone/naloxone cohorts. With more frequent, predominantly GI adverse events and less favourable

Table 2
Most common[a] adverse drug reactions (ADR) per system organ class and study discontinuations in the safety population.

Patients, *n* (%)	OXN (*n* = 347)	Control (*n* = 192)	OXN 40/20 (*n* = 49)
Median morphine equivalents (range)[b]	40.0 (8.0–320.0)	60.0 (1.9–480.0)	160.0 (30.0–320.0)
At least one ADR	56 (16.1)	37 (19.3)	2 (4.1)
At least one severe ADR	9 (2.6)	13 (6.8)	2 (4.1)
Discontinuation due to ADR	19 (5.5)	16 (8.3)	0
Gastrointestinal ADR	39 (11.2)	29 (15.1)	2 (4.1)
Constipation	18 (5.2)	17 (8.9)	0
Nausea/vomiting	18 (5.2)	20 (10.4)	1 (2.0)
Nervous system ADR	18 (5.2)	13 (6.8)	1 (2.0)
Dizziness	13 (3.7)	9 (4.7)	1 (2.0)

[a] ≥3.5% in any cohort.
[b] Morphine equivalents for average daily doses documented at Visit 3 were calculated for treatment with oxycodone, buprenorphine, fentanyl (conversion ratio stated in the respective product information) and hydromorphone [22].

evaluations of tolerability, more patients in the control group, compared to both PR oxycodone/naloxone cohorts, discontinued treatment due to adverse events.

Most limitations of the present study are directly related to the nature of an observational trial. Without randomisation, assignment of patients to the treatment cohorts was not balanced. One patient (2.1%) in the OXN 40/20 group and approximately 9% and 6% of patients in the OXN- and control group, respectively, had not received prior analgesic treatment before initiation of a strong opioid. This practised approach may reflect a guideline-driven decision in favour of opioid analgesics in the case of patient-specific contraindications to the use of non-opioid analgesics [30] and/or the ongoing controversy on the usefulness of the second step of the analgesic ladder in non-malignant pain [31]. For a number of patients in each group, previous analgesic treatment, if any, was not specified. As expected, more patients treated with a higher dose of PR oxycodone/naloxone (OXN 40/20 group) than other patients had received strong opioids prior to study initiation. Exposure to strong opioids prior to study initiation and GI complaints were generally more common in both OXN groups than in control group patients. Such between-group differences at baseline must be considered when interpreting the data. They do, however, reflect clinical practice with physicians selecting patients with GI complaints for treatment with PR oxycodone/naloxone. Owing to the study design, it cannot be ruled out that the treating physicians may have influenced the patients' perception of the drug's effectiveness and tolerability. Despite these limitations, the present prospective observational study adds to our understanding of the benefits and risks of opioid treatment in routine clinical practice.

In summary, the results of the present prospective observational study confirmed that PR oxycodone/naloxone provides effective analgesia with the added benefit of improving bowel function and QoL. The low fraction of naloxone that enters the systemic circulation may contribute to the improved analgesia seen in the OXN groups. The mechanism by which naloxone reduces OIBD is clearly due to a local μ-opioid receptor antagonist effect in the intestinal walls and mucosa of the lower GI tract, most evident by less constipation. The beneficial effects of naloxone on the upper GI tract – improving gastric emptying in particular – may be the mechanism by which nausea is reduced in patients treated with PR oxycodone/naloxone. With the demonstrated favourable outcomes in comparison to other strong opioids PR oxycodone/naloxone represents a valuable therapeutic option in the management of patients with moderate to severe chronic pain of different aetiologies.

Conflict of interest

SH has received payments for consultancy from Mundipharma, Grünenthal, Janssen-Cilag, CT-AWD, Nycomed; she has also received payments for lectures from Mundipharma and Grünenthal.

OL declares receiving payments for consultancy from Mundipharma, Grünenthal, and Eisai; he has also received payments for lectures from Janssen-Cilag, CT-AWB, Nycomed, and MSD.

TC declares receiving payments for consultancy from Astellas, AWD, Teva, Medtronic, and Eisai; he has also received payments for lectures from Astellas, AWD, Teva, Medtronic, Eisai, Pfizer, Grünenthal, and Mundipharma.

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