

# Development of opioid-induced constipation: post hoc analysis of data from a 12-week prospective, open-label, blinded-endpoint streamlined study in low-back pain patients treated with prolonged-release WHO step III opioids

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**Background:** Opioid-induced constipation is the most prevalent patient complaint associated with longer-term opioid use and interferes with analgesic efficacy, functionality, quality of life, and patient compliance.

**Objectives:** We aimed to compare the effects of prolonged-release (PR) oxycodone plus PR naloxone (OXN) vs PR oxycodone (OXY) vs PR morphine (MOR) on bowel function under real-life conditions in chronic low-back pain patients refractory to World Health Organization (WHO) step I and/or II analgesics.

**Research design and methods:** This was a post hoc analysis of the complete data set from a prospective, randomized, open-label, blinded endpoint (PROBE) streamlined study (German pain study registry: 2012-0012-05; European Union Drug Regulating Authorities Clinical Trials [EudraCT]: 2012-001317-16), carried out in 88 centers in Germany, where a total of 901 patients requiring WHO step III opioids to treat low-back pain were enrolled and prospectively observed for 3 months. Opioid allocation was based on either optional randomization (n=453) or physician decision (n=448). In both groups, treatment doses could be adjusted as per the German prescribing information, and physicians were free to address all side effects and tolerability issues as usual. The primary endpoint was the proportion of patients maintaining normal bowel function throughout the complete treatment period, assessed with the Bowel Function Index (BFI). Secondary analyses addressed absolute and relative BFI changes, complete spontaneous bowel movements, use of laxatives, treatment emergent adverse events, analgesic effects, and differences between randomized vs nonrandomized patient groups.

**Results:** BFI changed significantly with all three WHO step III treatments, however significantly less with OXN vs OXY and MOR despite a significantly higher use of laxatives with the latter ones ( $P < 0.001$ ). The percentage of patients who maintained normal BFI scores despite opioid treatment was 54.5% (164/301) with OXN and was significantly superior to those seen with OXY (32.8% [98/300]) (odds ratio [OR]: 2.47, 95% confidence interval [CI]: 1.77–3.44;  $P < 0.001$ ) or MOR (29.7% [89/300]) (OR: 2.84, 95% CI: 2.03–3.97;  $P < 0.001$ ). Absolute BFI changes of  $\geq 12$  mm 100 mm horizontal visual analog scale (VAS<sub>100</sub>) vs. baseline were seen for OXN in 41.4%, for OXY in 68.7%, and for MOR in 72.3%. Complete spontaneous bowel movements decreased at least by one per week in 10.3% with OXN vs 42.3% for OXY (OR: 6.39, 95% CI 4.13–9.89;  $P < 0.001$ ) and 42.0% for MOR (OR: 6.31, 95% CI: 4.08–9.76;  $P < 0.001$ ). Overall, 359 treatment emergent adverse events (78 [OXN], 134 [OXY], and 147 [MOR]) in 204 patients

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(41 [OXN], 80 [OXY], and 83 [MOR]) occurred, most affecting the gastrointestinal (49.3%) and the nervous system (39.3%). Treatment contrasts between randomized vs nonrandomized patients were insignificant.

**Conclusion:** In this post hoc analysis of data from a real-life 12-week study, OXN treatment was associated with a significantly lower risk of opioid-induced constipation, superior tolerability, and significantly better analgesic efficacy compared with OXY and MOR.

**Keywords:** chronic pain, bowel function, quality of life

## Introduction

Opioids are frequently used alternatives for the treatment of moderate to severe chronic nonmalignant pain in industrialized countries, second only to nonsteroidal anti-inflammatory agents in terms of prescription frequency.<sup>1–3</sup> Beside analgesia, opioid therapy is associated with a number of well-characterized side effects, including constipation, nausea, sedation, dysphoria, itching, respiratory depression, and hormonal changes as well as immunological problems, which frequently develop in competition with analgesic effects.<sup>4–9</sup>

Among the spectrum of opioid-related adverse events, opioid-induced constipation (OIC) is the most frequently reported troublesome adverse event associated with chronic opioid therapy.<sup>10–12</sup> Due to its persistence throughout opioid use, OIC is one of the main reasons for dose reduction, treatment failure, and premature treatment discontinuation, affecting approximately one-third of opioid-treated patients.<sup>12–15</sup>

Laxative regimens are recommended for clinical use, both to prevent and treat OIC. However, they are nonspecific, associated with several drawbacks (eg, bowel function muscle damage, nutritional deficits, kidney stones, renal failure, and/or interference with other drugs, etc), and are insufficiently effective in the majority of patients as they do not specifically address the underlying opioid receptor-mediated mechanisms of OIC.<sup>10,16</sup>

More recently, few specific alternatives to prevent/treat OIC were developed, of which only naloxone – an opioid receptor antagonist – became available as a fixed prolonged-release (PR) preparation with PR oxycodone (OXY) in a 1:2 ratio within one tablet (OXN), addressing the compliance and adherence problems of chronic pain patients with increasing tablet prescriptions. When administered orally, naloxone antagonizes the opioid-receptor activity of its counterpart, oxycodone, in the gut wall, while its PR formulation in combination with an extensive hepatic first-pass metabolism and subsequent low systemic bioavailability (~2%) ensures the lack of antagonistic effects on its central analgesic action.<sup>17,18</sup>

Several randomized controlled trials (RCTs) evaluated safety and efficacy of OXN in comparison with OXY, and reported a significant and clinically relevant improvement in OIC in various types of pain, even after long-term treatment,

without compromising pain control and drug safety in comparison with OXY.<sup>19–26</sup> However, despite these measures, the overall safety and efficacy balance of OXN versus a conventional opioid therapy with OXY or morphine (MOR) (each plus laxatives), as first-line alternative in patients naïve to World Health Organization (WHO) step III opioids remains unclear. Due to this, the German Pain Association and the German Pain League initiated, in 2012, a prospective randomized open-label, blinded endpoint (PROBE), streamlined real-life study to evaluate the safety, tolerability, and efficacy of OXN in comparison with OXY and MOR in patients with chronic moderate to severe low-back pain (LBP) refractory to other analgesics, published recently by Ueberall and Mueller-Schwefe.<sup>27</sup> In this study, half of the patients followed the randomized treatment allocation process, and their data – methodologically defined as those of the per-protocol population – was published, while the data of the remaining patients remained unconsidered and as such, free for further analyses.

## Patients and methods

### Study design

The underlying 12-week study followed a PROBE design, developed to address some of the potential limitations of RCTs and observational studies. The main advantage of the PROBE trial design is the assessment of clinical outcomes in studies that allow both the enrollment of a broad patient population (in our case patients who require WHO step III opioid analgesics owing to a few refractory moderate to severe chronic LBP) as well as open-label, noninterventional dose adjustments and the discretionary use of concomitant laxatives, etc on an as-needed basis, which better reflects clinical practice and which also has the advantage of randomization and a rigorous evaluation of study endpoints by blinded data analyses.<sup>28,29</sup> Opioid treatment followed medical requirements according to the decision of the participating physicians.

The study was performed using electronic case report forms for all data obtained by the participating physicians, as well as conventional paper-and-pencil pain questionnaires and diaries to obtain patient-reported data, throughout the whole 12-week observation period. Patient questionnaires/

diaries used were those recommended by the German Pain Association and the German Pain League, which cover a broad spectrum of validated instruments, addressing, among other parameters, pain intensity, pain-related disabilities in daily life, quality of life (QoL), QoL impairments from pain, bowel function, and use of analgesics and adjuvant therapies, etc.<sup>30,31</sup>

Regular study visits were scheduled at baseline (prior start of treatment), as well as after 4 (interim visit) and 12 weeks (end of observation visit). Optional, additional interim visits were possible at all times according to individual patient needs and established procedures (eg, if patients had to be closely monitored due to commencement of treatment, inadequate pain control, tolerability issues, and/or adverse events).

### Patients/study eligibility criteria

Patients eligible for the study were males and nonpregnant, nonlactating females who were at least 18 years, with a documented history of moderate to severe, nonmalignant chronic LBP, previously treated with WHO step I or II analgesics with or without adjuvant treatments, who experienced either insufficient pain relief and/or unacceptable side effects and who required an around-the-clock therapy with any of the three mentioned WHO step III opioids. The exclusion criteria were those contraindications listed in the German prescribing information of the three opioid analgesics,<sup>32–34</sup> addressing situations that would place the patient at risk upon exposure to the medication, and conditions that would confound the analysis and/or interpretation of the study results. Therefore, patients were excluded if they had previously shown hypersensitivity to any of the product constituents or if they had severe respiratory depression, chronic obstructive airway disease, pulmonary hypertension, severe bronchial asthma, paralytic ileus, moderate to severe hepatic impairment and/or renal impairment, or any other condition in which an opioid therapy is contraindicated. In addition, patients with irritable bowel syndrome, gastrointestinal (GI) disease, or significant structural abnormalities of the GI tract, who participated in a clinical research study involving a new chemical entity or an experimental drug within 30 days prior study entry, or in whom a surgery was planned during the scheduled observational period that would influence pain or bowel function, were excluded as well.

### Medication

Based on the recommendations of the German National Association of Statutory Health Insurance Physicians and

the Drug Commission of the German Medical Association, MOR, OXY, and OXN have been seen as comparably effective and therefore, at least from a medical point of view, interchangeable for the first-line treatment of opioid-naïve patients suffering from elsewhere refractory LBP.<sup>35</sup> Therefore, an electronic treatment allocation system recommended one of these three alternative opioid treatments in a randomized 1:1:1 ratio (block size nine) after completion of the baseline evaluation by the physician and confirmation of a general treatment indication for a WHO step III opioid. To account for the noninterventional character of the original study, physicians were generally allowed to follow this recommendation or to choose alternatively one of the two other opioid treatments, which would exclude the patient from the per-protocol analysis of the randomized treatment allocations. The initial starting dose, dose titration, and further dose adjustments followed the recommendations given in the marketing authorization in existence at the time of the study and documented in the German prescribing information for those WHO step III opioids considered to be evaluated in this study. For opioid-naïve patients, the recommended starting dose was 20 mg morphine equivalent (MEQ) of a PR preparation twice daily. Any dose adjustments, prescriptions of analgesic comedication, rescue medication, or laxatives were done at the discretion of the physician and due to the individual needs of the participating patients.

### Study assessments

#### Bowel function/opioid-induced constipation

OIC was assessed using the validated Bowel Function Index (BFI),<sup>36,37</sup> calculated as the mean of three items recorded retrospectively by patients for the previous 7 days, using a 100 mm horizontal visual analog scale (VAS<sub>100</sub>), at the end of each treatment week. Single BFI items were: ease of defecation (0= “easy/no difficulty” and 100= “severe difficulty”), feeling of incomplete bowel evacuation (0= “not at all” and 100= “very strong”), and personal judgment of constipation (0= “not at all” and 100= “very strong”). The BFI reference (ie, “normal”) range is 0–28.8 mm on the VAS<sub>100</sub>, and BFI changes of  $\geq 12$  mm on the VAS<sub>100</sub> were confirmed to be significant. In addition, the number of complete spontaneous bowel movements (CSBMs), defined as stools not induced by rescue medication or other external measures and associated with a sensation of complete evacuation, in the previous 7 days, and the use of laxatives as well as other pharmacological and nonpharmacological OIC counter measures, were documented to assess constipation.

## Efficacy measures

Efficacy assessments were performed on the basis of patient-reported information documented in the German Pain Questionnaire<sup>38</sup> (at baseline) and the German Pain Diary (throughout the whole observation period) for pain intensity, pain-related disabilities in daily life activities/functionality, and QoL. Pain-intensity measures based on the LBP intensity index, which was calculated as arithmetic mean of the lowest, average, and highest 24-hour LBP intensities on a VAS<sub>100</sub> (where 0= “no pain” and 100= “worst pain conceivable”). LBP-related disabilities were assessed with a modified version of the Pain Disability Index (modified PDI), which recorded the degree of LBP-related functional restrictions on the basis of an eleven-point numerical rating scale (NRS<sub>11</sub>) (where 0= “none” and 10= “worst conceivable”) with respect to seven distinct domains of daily life. QoL was measured using the quality of life impairment by pain (QoL impairment by pain) inventory, a seven-question tool assessing different pain-related QoL restrictions that provides an overall QoL-score (ranging from 40= “no impairment” to 0= “maximum impairment”). All parameters were recorded by patients retrospectively for the previous 7 days, starting at baseline (to assess the situation prior onset of the WHO step III opioids) and covering the whole observation period, with regular assessments at the end of each treatment week.

## Safety and tolerability measures

Safety assessment consisted of the monitoring of all treatment-emergent adverse events (TEAEs), collected as spontaneous reports and during patient visits. TEAEs were collected both through direct questioning by the physicians, as well as spontaneous patient reports and were recorded at each visit.

## Final assessment

Final assessments of overall treatment satisfaction and patient condition (vs baseline, for each patient) were performed at the end of the 12-week observation period for each patient, using a seven-point clinical global impression of change scale ranging from +3 (“very much improved”) to -3 (“very much worse”) scored by the treating physician.

## Statistical analysis

The aim of this post hoc analysis was to evaluate the dynamics, extent, and preventability of bowel dysfunction as consequence of a treatment with WHO step III opioids under real-life conditions, as well as to evaluate differences among those opioid analgesics used. The primary criterion for this

approach was the treatment contrast for the frequency of patients maintaining a normal BFI score ( $\leq 28.8$ ) over the whole 12-week observation period. Secondary bowel tolerability aspects were the percentage of patients: with a  $\geq 50\%$  BFI worsening at end of observation vs baseline; experiencing a clinically relevant BFI worsening vs baseline (ie, an increase  $\geq 12$  mm VAS<sub>100</sub>); with a  $\geq 1$  decline in the number of CSBMs per week; with  $\geq 4$  CSBMs per week; and with prescribed laxatives at the end of the 12-week observation period. Secondary efficacy analyses were performed with respect to opioid-related changes in pain intensity, disability, and QoL, as well as treatment allocation effects between randomized and nonrandomized patients. Safety analyses addressed the percentage of patients with TEAEs and TEAE-related study discontinuation, as well as the spectrum and characteristics of the reported TEAEs.

Data analyses were performed for all enrolled patients (irrespective of the mode of treatment allocation) who took at least one dose of OXN, OXY, or MOR and who had at least one postbaseline/postdose measure. Due to the explorative post hoc character of this analysis, no formal sample size estimation was performed. Linear interpolation was used to impute intermittent missing scores, and the last observation carried forward method was used to impute missing scores after early discontinuation. For continuous variables, descriptive statistics were summarized by the number of patients (n), the mean, standard deviation (SD), 95% confidence interval (CI), median, and range (minimum–maximum) values. For categorical and ordinal variables, data were summarized by the number (n) and percentage (%) of participants in each category; where appropriate, 95% CIs were added. For between-group comparisons of continuous/categorical variables, Student's *t*/Pearson's chi-squared test, respectfully, were used. For within-group (eg, pre–post) comparisons, paired sample *t*-tests were performed. All statistical tests were carried out using a two-sided significance level of 0.05. Test procedures were only used to evaluate the biometrical significance of differences found, not to confirm any a priori defined hypotheses.

## Ethics

The original study was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practices, conformed to relevant national and local ethical as well as regulatory requirements, and was registered in the German pain study registry (Deutsche Gesellschaft für Schmerzmedizin [DGS]: 2012-0012-05) and the European Union Drug Regulating Authorities Clinical Trials (EudraCT) data base (EudraCT: 2012-001317-16). All patients provided

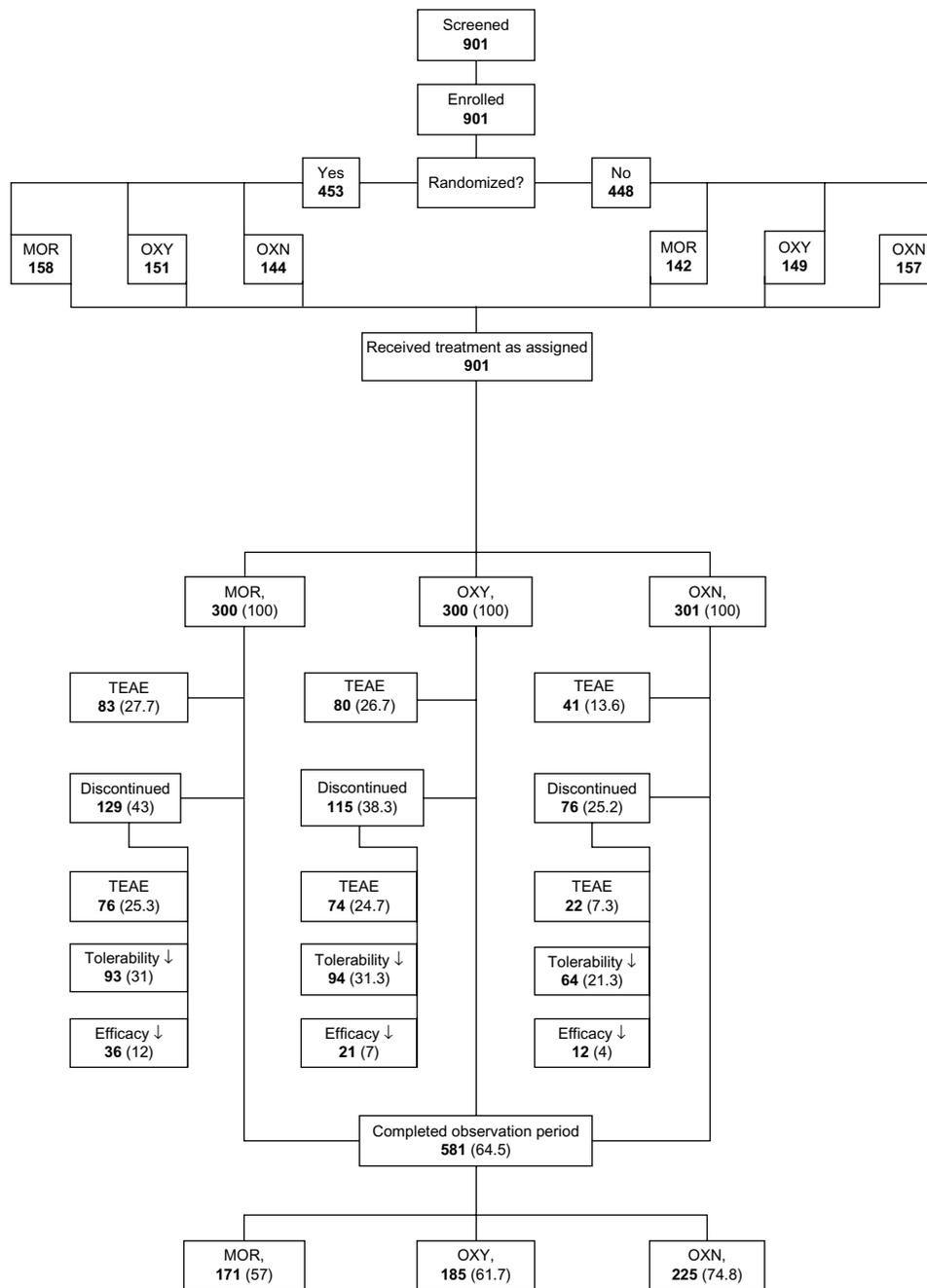
written informed consent prior to study enrollment. The concept for this post hoc analysis was approved by the steering committees of the German Pain Association and the German Pain League.

## Results

### Patient disposition

Between April and August 2013, a total of 901 patients were enrolled, received treatment as assigned, and reported at least

one postbaseline measure (Figure 1). Among 453 (50.3%) patients, half were randomized to one of the three WHO step III opioids (144 [OXN], 151 [OXY], 158 [MOR]), whereas in 448 (49.7%), treatment was assigned by the physician (157 [OXN], 149 [OXY], 142 [MOR]). Overall, significantly more OXN patients completed the study (225/301 [74.8%]) compared with OXY (185/300 [61.7%]) and MOR (171/300 [57.0%]) (OR: 2.23, 95% CI: 1.58–3.16;



**Figure 1** Patient disposition. Data is presented as n(%) of patients. The arrows indicate insufficient numbers. **Abbreviations:** %, percentage of patients; MOR, morphine; n, number of patients; OXN, oxycodone/naloxone; OXY, oxycodone; TEAE, treatment emergent adverse event.

$P=0.005$ ). The main reason for premature discontinuation was insufficient tolerability, reported by 251 patients (27.9%), followed by TEAEs (172/901 [19.1%]) and insufficient analgesic efficacy (69/901 [7.7%]). Between-group analyses showed comparable discontinuation rates for MOR (129/300 [43.0%]) and OXY (115/300 [38.3%]), which were – for all reasons evaluated – significantly worse than those observed with OXN (76/301 [25.2%]) ( $P<0.001$ ). Corresponding comparisons of randomized vs nonrandomized patient groups were without any significant result.

### Baseline characteristics

Baseline demographics were comparable between opioids and treatment allocation groups and are presented in Table 1.

Overall, the mean age ( $\pm$  SD) was 46.3 $\pm$ 9.7 (median 47, range 19–77) years, and 55.7% (502/901) were female. A total of 58.8% (530/901) of study patients suffered for longer than 6 months prior study enrollment, 79.8% (710/901) reported a treatment by at least five different specialists (average 5.6 $\pm$ 1.4 [median 6, range 2–10]) and 94.0% (847/901) of patients documented at least four analgesic medications (on average 6.3 $\pm$ 1.9 [median 6, range 1–12]) at pretreatment. Nonopioid analgesics were the most frequently used treatments, reported by 99.0% (892/901) of patients prior study entry, followed by nonsteroidal anti-inflammatory drugs (NSAIDs) (95.3% [859/901]), WHO-step II opioids (69.4% [625/901]), antidepressants (66.6% [600/901]), muscle relaxants (63.2% [569/901]), and antiepileptic agents (37.1% [334/901]).

**Table 1** Patient demographics and baseline characteristics

	Opioid treatment groups			Treatment allocation groups	
	MOR (n=300)	OXY (n=300)	OXN (n=301)	RND (n=453)	nRND (n=448)
Age (years); mean (SD)	46.5 (9.3)	46.7 (9.9)	46.1 (9.9)	46.3 (9.7)	46.6 (9.7)
Proportion >55 years; n (%)	56 (18.7)	57 (19.0)	56 (18.6)	76 (16.8)	93 (20.8)
Sex: female; n (%)	168 (56.0)	166 (55.3)	168 (55.8)	255 (56.3)	247 (55.1)
Height (cm); mean (SD)	170.4 (8.6)	171.4 (9.2)	171.2 (9.1)	171.1 (9.1)	170.9 (8.8)
Weight (kg); mean (SD)	79.4 (17.7)	79.5 (15.8)	80.2 (15.5)	79.6 (16.3)	79.8 (16.5)
BMI (kg/m <sup>2</sup> ); mean (SD)	27.3 (5.9)	27.0 (4.5)	27.4 (5.0)	27.1 (4.7)	27.3 (5.5)
Obesity (BMI >30.0); n (%)	63 (21.0)	62 (20.7)	65 (21.6)	91 (20.9)	99 (22.1)
Low-back pain duration >6 months; n (%)	179 (59.7)	173 (57.7)	178 (59.1)	268 (59.2)	262 (58.5)
Number of physicians involved; median (range)	6 (2–9)	6 (3–10)	6 (2–10)	6 (2–10)	6 (2–10)
Number of analgesics prior enrollment; median (range)	6 (1–12)	6 (1–12)	6 (1–12)	6 (1–12)	6 (1–12)
Nonopioid analgesics; n (%)	296 (98.7)	298 (99.3)	298 (99.0)	449 (99.1)	443 (98.9)
NSAIDs; n (%)	285 (95.0)	288 (96.0)	286 (95.0)	453 (95.8)	425 (94.9)
Low-potent opioid analgesics; n (%)	207 (69.0)	208 (69.3)	210 (69.8)	311 (68.7)	314 (70.1)
Antidepressants; n (%)	206 (64.3)	203 (67.7)	191 (63.5)	301 (66.4)	299 (66.7)
Anticonvulsants; n (%)	113 (37.7)	109 (36.3)	112 (37.2)	178 (39.3)	156 (34.8)
Muscle relaxants; n (%)	193 (64.3)	180 (60.0)	196 (65.1)	292 (64.5)	277 (61.8)
Switch from WHO step I; n (%)	87 (29.0)	87 (29.0)	87 (28.9)	135 (29.8)	126 (28.1)
WHO step II; n (%)	207 (69.0)	208 (69.3)	210 (69.8)	311 (68.7)	314 (70.1)
Others; n (%)	6 (2.0)	5 (1.7)	4 (1.3)	7 (1.5)	8 (1.8)
MPS I; n (%)	34 (11.3)	37 (12.3)	35 (11.6)	54 (11.9)	52 (11.6)
II; n (%)	153 (51.0)	151 (50.3)	151 (50.2)	238 (52.5)	217 (48.4)
III; n (%)	113 (37.7)	112 (37.3)	115 (38.2)	161 (35.5)	179 (40.0)
von Korff I; n (%)	23 (7.7)	25 (8.3)	22 (7.3)	31 (6.8)	39 (8.7)
2; n (%)	105 (35.0)	110 (36.7)	108 (35.9)	179 (39.5)	144 (32.1)
3; n (%)	121 (40.3)	113 (37.7)	118 (39.2)	166 (36.6)	186 (41.5)
4; n (%)	51 (17.0)	52 (17.3)	53 (17.6)	77 (17.0)	79 (17.6)
Neuropathic pain; n (%)	52 (17.3)	51 (17.0)	47 (15.6)	74 (16.3)	76 (17.0)
Tailored treatment target (VAS <sub>100</sub> ); mean (SD)	20.6 (14.4)	20.5 (12.3)	21.8 (13.1)	21.5 (13.6)	20.5 (12.9)
LBPIX (VAS <sub>100</sub> ); mean (SD)	46.0 (17.5)	45.7 (17.2)	45.5 (13.6)	44.6 (16.2)	46.8 (16.2)
modified PDI (NRS <sub>70</sub> ); mean (SD)	41.7 (13.5)	42.3 (13.0)	42.4 (13.0)	41.8 (12.9)	42.5 (13.4)
QoL impairment by pain (NRS <sub>40</sub> ); mean (SD)	17.2 (5.9)	17.1 (5.7)	17.1 (5.6)	17.5 (5.8)	16.8 (5.7)
BFI (VAS <sub>00</sub> ); mean (SD)	19.6 (19.6)	19.9 (19.4)	19.9 (19.3)	20.3 (19.9)	19.3 (19.0)
Proportion with normal BFI ( $\leq 28.8$ mm VAS <sub>00</sub> ); n (%)	217 (72.3)	212 (70.7)	214 (71.1)	319 (70.4)	324 (72.3)

**Abbreviations:** BFI, bowel function index; BMI, body mass index; LBPIX, low back pain intensity index; mPDI, modified Pain Disability Index; MPS, Mainz Pain Staging System; nRND, nonrandomized treatment group; NRS<sub>70</sub>, 70 point numerical rating scale; NRS<sub>40</sub>, 40 point numerical rating scale; NSAID, nonsteroidal anti-inflammatory drug; QoL impairment by pain, quality of life impairment by pain; RND, randomized treatment group; SD, standard deviation; VAS<sub>100</sub>, 100 mm horizontal visual analog scale; WHO, World Health Organization. OXY, oxycodone; OXN, oxycodone/naloxone; MOR, morphine.

A total of 37.7% (340/901) patients presented with advanced pain “chronification” (stage III) according to the Mainz Pain Staging System (MPSS),<sup>39</sup> and 56.4% (508/901) suffered from a high disability with either moderate (grade III) (352/901 [39.1%]) or severe (grade IV) (156/901 [17.3%]) limitations according to the von Korff pain grading scale.<sup>40</sup> Baseline pain intensity as well as all other pain-related patient measures were comparable among the treatment groups. The tailored treatment target was defined at baseline as 20.6±14.4 for MOR, 20.5±12.3 for OXY, and 21.8±13.1 for OXN. Average LBP intensities, assessed on the basis of the LBP intensity index at baseline were 46.0±17.5 mm on the VAS<sub>100</sub> for MOR, 45.7±17.2 mm on the VAS<sub>100</sub> for OXY, and 45.5±13.6 mm on the VAS<sub>100</sub> for OXN. Corresponding modified PDI and QoL impairment by pain scores for MOR, OXY, and OXN were 41.7±13.5, 42.3±13.0, and 42.4±13.0 (NRS<sub>70</sub>), and 17.2±5.9, 17.1±5.7, and 17.1±5.6 (NRS<sub>40</sub>), respectively. The proportion of patients presenting with a neuropathic LBP symptomatology was 17.3% (52/300) for MOR, 17.0% (51/300) for OXY, and 15.6% (47/301) for OXN. The average BFI at baseline was 19.8±19.4 (median 16, range 0–76) mm on the VAS<sub>100</sub>, with insignificant differences among the treatment and treatment allocation groups. The proportion of patients with normal BFI scores was 71.4% (643/901).

## Opioid treatment

With 28.7±11.8 (median 30, range 5–50) mg MEQ for MOR, 28.7±10.2 (median 30, range 10–60) mg MEQ for OXY, and 28.8±10.3 (median 30, range 10–60) mg MEQ for OXN, the average initial starting doses were comparable among treatment and treatment allocation groups, as were the dose titration and the maintenance doses. At study end patients treated with MOR had received on average 103.8±39.3 (median 100, range 15–200) mg MEQ, while those with OXY received 106.6±37.4 (median 120, range 20–180) mg MEQ, and those with OXN received 112.9±34.2 (median 120, range 10–200) mg MEQ.

## Bowel function/opioid-induced constipation

As expected, with the introduction of WHO step III opioids, the bowel function worsened significantly from baseline to end of study. The percentage of patients who maintained normal BFI scores (ie, ≤28.8) throughout the 12-week treatment period was 54.5% (164/301) for OXN and hence significantly higher/better than that of OXY (32.8% [98/300]) (OR: 2.47, 95% CI: 1.77–3.44; *P*<0.001) or MOR (29.7% [89/300]) (OR: 2.84, 95% CI: 2.03–3.97; *P*<0.001) (Table 2).

**Table 2** Primary endpoint analysis

Proportion of patients with a normal BFI (≤28.8) throughout the complete treatment period	MOR		OXY		OXN		MOR vs. OXY		MOR vs. OXN		OXY vs. OXN	
	RND	nRND	RND	nRND	RND	nRND	OR (95%-CI) / significance					
	89/300 (29.7)		98/300 (32.8)		164/301 (54.5)							
	43/158 (27.2)	46/142 (32.4)	47/151 (31.1)	51/149 (34.2)	82/144 (56.9)	82/157 (52.2)	1.15 (0.82–1.63) <i>P</i> =0.428	2.84 (2.03–3.97) <i>P</i> <0.001	2.47 (1.77–3.44) <i>P</i> <0.001	2.84 (2.03–3.97) <i>P</i> <0.001	2.47 (1.77–3.44) <i>P</i> <0.001	1.09 (0.83–1.42) <i>P</i> =0.685
		RND vs. nRND: <i>P</i> =0.327		RND vs. nRND: <i>P</i> =0.567		RND vs. nRND: <i>P</i> =0.412						

**Note:** Data show the absolute (relative) proportion of patients maintaining normal bowel function (defined as a BFI score of ≤28.8) throughout the complete 12-week treatment period, for all opioids evaluated as well as for randomized vs nonrandomized treatment groups.

**Abbreviations:** BFI, bowel function index; CI, confidence interval; MOR, morphine; nRND, nonrandomized treatment group; OR, odds ratio; OXN, oxycodone/naloxone; OXY, oxycodone; RND, randomized treatment group.

BFI scores increased from baseline to study end for MOR, from 19.6±19.6 to 53.6±33.1 mm VAS<sub>100</sub> ( $P<0.001$ ), for OXY, from 19.9±19.4 to 48.2±32.3 mm VAS<sub>100</sub> ( $P<0.001$ ), and for OXN, from 19.9±19.3 to 30.0±26.2 mm VAS<sub>100</sub> ( $P<0.001$ ) (Figure 2). Between-group analyses showed significantly different BFI changes, with lowest absolute (relative) BFI increments at end of week 12 vs baseline for OXN (10.1 mm VAS<sub>100</sub> [50.8%]) vs OXY (28.3 mm VAS<sub>100</sub> [142.2%]) vs MOR (34.0 mm VAS<sub>100</sub> [173.5%]).

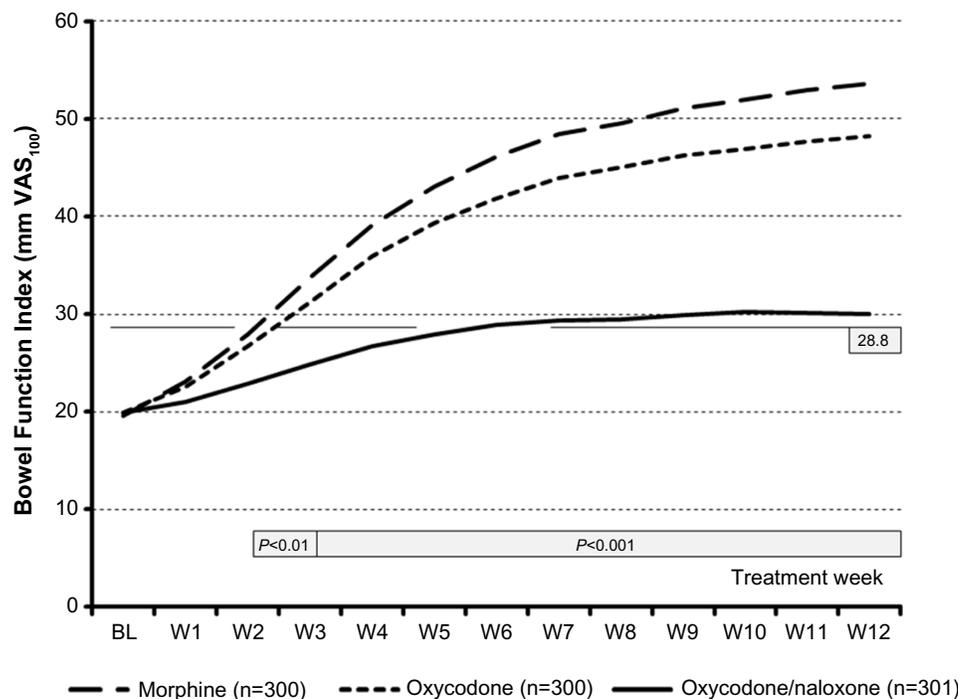
With 24.6% (74/301), major relative BFI worsening (ie, ≥50% vs baseline) was found significantly less with OXN vs OXY (41.3% [124/300]) (OR: 2.16, 95% CI: 1.53–3.06;  $P<0.001$ ) and vs MOR (46.7% [140/300]) (OR: 2.68, 95% CI: 1.90–3.80;  $P<0.001$ ) (Figure 3 and Table 3). Significantly more patients reported a clinically relevant absolute BFI increase (≥12 mm VAS<sub>100</sub>) with MOR (72.3% [217/300]) (OR: 3.68, 95% CI: 2.62–5.18;  $P<0.001$ ) and OXY (68.7% [206/300]) (OR: 3.09, 95% CI: 2.21–4.31;  $P<0.001$ ) compared with OXN (41.5% [125/301]).

CSBMs decreased at least by one per week in 31/301 patients with OXN (10.3%) vs 127/300 (42.3%) for OXY (OR: 6.39, 95% CI: 4.13–9.89;  $P<0.001$ ) vs 126/300 (42.0%) for MOR (OR: 6.31, 95% CI: 4.08–9.76;  $P<0.001$ ). The average number of CSBMs per week dropped, for MOR

from 4.4±1.7 to 2.8±1.9 ( $P<0.001$ ), for OXY from 4.4±1.7 to 2.8±2.0 ( $P<0.001$ ), and for OXN from 4.3±1.6 to 3.9±1.8 ( $P<0.001$ ). The percentage of patients with four or more CSBMs per week at study end was 62.1% (187/301) for OXN vs 36.7% (110/300) for OXY (OR: 2.83, 95% CI: 2.04–3.94;  $P<0.001$ ) vs 32.7% (98/300) for MOR (OR: 3.38, 95% CI: 2.42–4.73;  $P<0.001$ ).

The percentage of patients who used prescription laxatives prior to study participation was 23.0% both for MOR and OXY (69/300), and 22.6% (68/301) for OXN, hence comparable between the treatment groups at baseline. The proportion of patients who were forced to use laxatives to prevent/treat OIC increased from baseline to study end, with MOR up to 57.3% (172/300), with OXY to 56.7 (170/300), and with OXN to 29.2% (88/301). Vice versa, the percentage of patients without any need for laxatives at baseline but who needed any at study end was significantly lower for OXN (8.6% [20/233]) in comparison with OXY (43.7% [101/231]) (OR: 8.27, 95% CI: 4.89–14.02;  $P<0.001$ ) and MOR (44.6% [103/231]) (OR: 8.60, 95% CI: 5.06–14.51;  $P<0.001$ ).

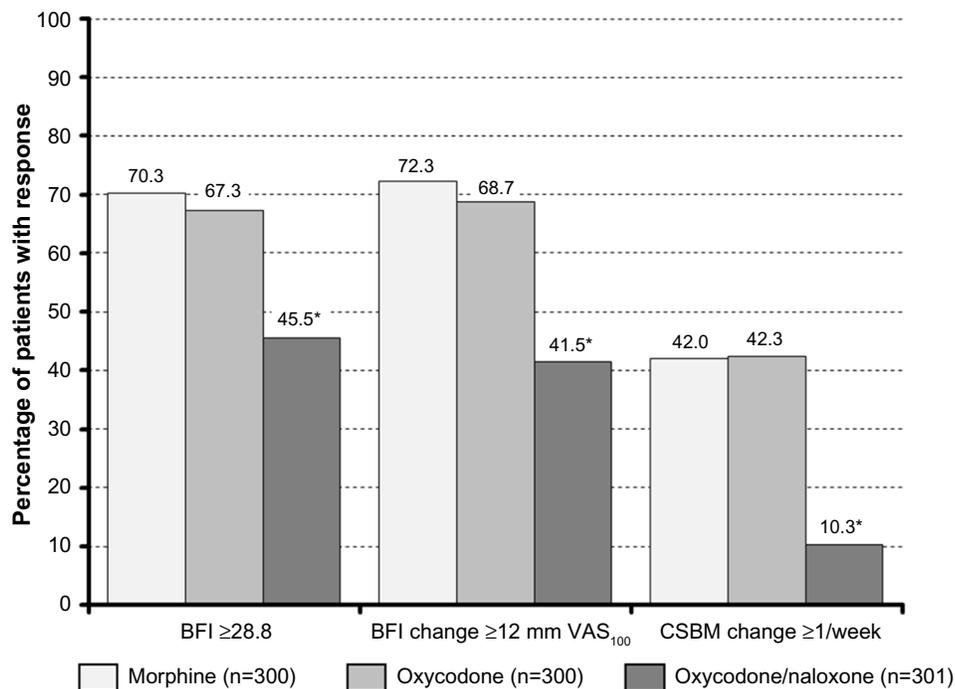
With increasing constipation problems, the proportion of patients who started – in addition to their prescribed laxatives – nonprescription laxatives as well as dietary measures and/or exercise changes increased as well. The percentages



**Figure 2** Change in mean BFI score during the course of the 12-week study.

**Notes:** BFI changed significantly for all three treatment groups vs baseline but significantly less for oxycodone/naloxone vs oxycodone vs morphine. The horizontal line marked with “28.8” indicates the upper normal reference range of the BFI; the horizontal bars indicate significance level with respect to treatment comparisons between oxycodone/naloxone vs oxycodone and morphine. The VAS<sub>100</sub> was scored as 0= no bowel dysfunction and 100= worst bowel dysfunction conceivable.

**Abbreviations:** BFI, Bowel Function Index; BL, baseline; VAS<sub>100</sub>, 100 mm horizontal visual analog scale; W, treatment week.



**Figure 3** Proportion of patients who recorded a Bowel Function Index score above the normal range ( $\geq 28.8$ ) (left), a significant worsening vs baseline ( $\geq 12$  mm) (middle), and a CSBM  $\geq 1$  decrease vs baseline (right) at the end of a 12-week treatment with morphine (light grey), oxycodone (grey), and oxycodone/naloxone (dark grey).  
**Note:** \*Significant difference ( $P < 0.001$ ) for oxycodone/naloxone vs morphine and vs oxycodone.

**Abbreviations:** BFI, Bowel Function Index; CSBM, complete spontaneous bowel movement; VAS<sub>100</sub>, 100 mm horizontal visual analog scale.

of patients who took none of these measures at baseline and who started to use any due to side effects of the opioid treatment increased with OXN significantly less (27.1% [58/214]) than with OXY (83.2% [168/202]) (OR: 13.29, 95% CI: 8.26–21.40;  $P < 0.001$ ) or MOR (89.4% [178/199]) (OR: 22.80, 95% CI: 13.30–39.26;  $P < 0.001$ ).

## Efficacy analyses

Opioid treatment was followed by a significant relief in pain and pain-related complaints for all three treatment groups, however, with superior effects for OXN in comparison with OXY and MOR (Figure 4). LBP intensity index decreased with OXN, OXY, and MOR, from  $45.5 \pm 13.6$ ,  $45.7 \pm 17.2$ , and  $46.0 \pm 17.5$  mm VAS<sub>100</sub>, respectively, at baseline to  $17.8 \pm 16.9$ ,  $24.0 \pm 19.8$ , and  $24.8 \pm 19.4$  mm VAS<sub>100</sub>, respectively, at study end. Corresponding absolute (relative) (ie, mm VAS<sub>100</sub> [%]) changes at study end vs baseline were for OXN, with  $-27.7 \pm 15.9$  ( $-62.5 \pm 32.7$ ), significantly greater than those reported for OXY ( $-21.7 \pm 18.7$  [ $-48.1 \pm 39.6$ ]) ( $P < 0.001$ ) or MOR ( $-21.1 \pm 18.0$  [ $-45.2 \pm 42.4$ ]) ( $P < 0.001$ ). The end of study percentage of patients who presented with at least 50% pain relief vs baseline was significantly higher for OXN (69.4% [209/301]) than for OXY (59.3% [178/300]) (OR: 1.56, 95% CI: 1.11–2.18;  $P < 0.001$ ) or MOR (51.3% [154/300]) (OR: 2.15, 95% CI: 1.54–3.01;  $P < 0.001$ ).

In parallel, pain-related restrictions of daily life activities and QoL improved as well. The percentages of patients who finally reported a  $\geq 50\%$  improvement in pain-related disabilities with respect to daily life activities, assessed via modified PDI, were 59.5% (179/301) for OXN vs 48.0% (144/300) for OXY (OR: 1.59, 95% CI: 1.15–2.20;  $P < 0.001$ ) vs 44.3% (133/300) for MOR (OR: 1.84, 95% CI: 1.33–2.55;  $P < 0.001$ ). The proportion of patients who presented with a  $\geq 50\%$  QoL improvement as assessed via QoL impairment by pain was 72.8% (219/301) for OXN vs 46.0% (138/300) for OXY (OR: 3.14, 95% CI: 2.23–4.41;  $P < 0.001$ ) vs 40.0% (120/300) for MOR (OR: 4.01, 95% CI: 2.84–5.65;  $P < 0.001$ ).

## Treatment satisfaction

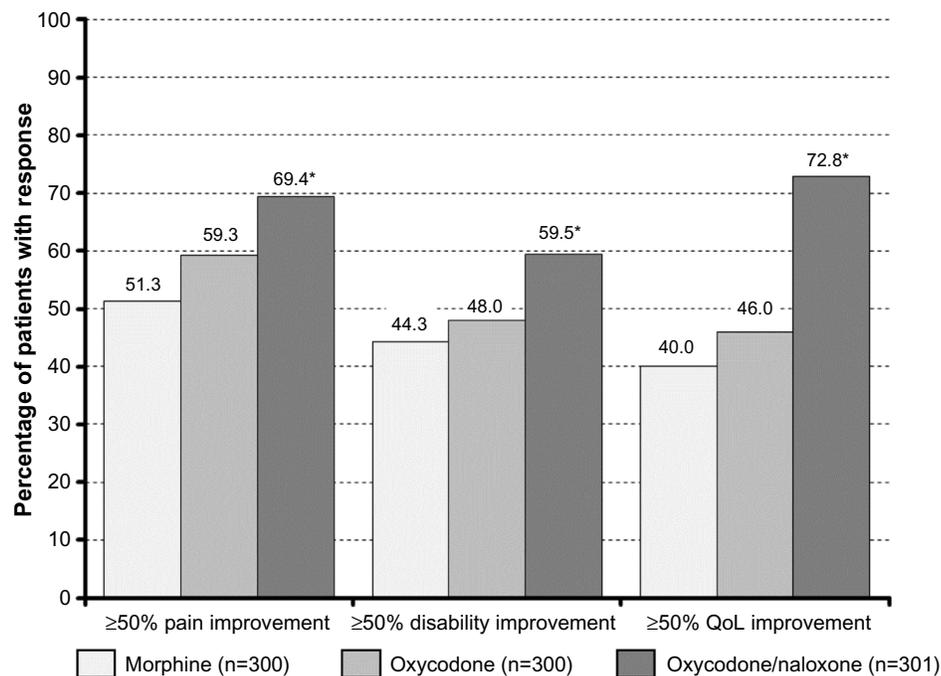
Overall, physician satisfaction with the WHO step III opioids was good. On a patient basis, physicians recorded for OXN a significantly higher treatment satisfaction vs baseline (90.7% [273/301]) in comparison with OXY (64.7% [194/300]) (OR: 5.33, 95% CI: 3.38–8.40;  $P < 0.001$ ) and MOR (59.3% [178/300]) (OR: 6.68, 95% CI: 4.25–10.50;  $P < 0.001$ ). Patient condition improved “very much” or “much” vs prior treatments in 88.0% (265/301) with OXN vs 50.3% (151/300) with OXY (OR: 7.26, 95% CI: 4.80–11.00;  $P < 0.001$ ) vs 47.3% (142/300) with MOR (OR: 8.19, 95% CI: 5.41–12.41;  $P < 0.001$ ).

**Table 3** Secondary tolerability analysis

Proportion of patients with ...	MOR		OXY		OXN		MOR vs OXY		MOR vs OXN		OXY vs OXN		RND vs nRND	
	RND	nRND	RND	nRND	RND	nRND	OR (95%CI)/ significance							
... a BFI increase	140/300 (46.7)		124/300 (41.3)		74/301 (24.6)		1.24 (0.90–1.72)	2.68 (1.90–3.80)	2.16 (1.53–3.06)	1.06 (0.81–1.39)				
≥50% at study end vs baseline	71/158 (44.9) RND vs nRND: P=0.526	69/142 (48.6)	63/151 (41.7) RND vs nRND: P=0.891	61/149 (40.9)	33/144 (22.9) RND vs nRND: P=0.520	41/157 (26.1)	P=0.118	P<0.001	P<0.001	P<0.001				P=0.686
... a BFI increase	217/300 (72.3)		206/300 (68.7)		125/301 (41.5)		1.19 (0.84–1.70)	3.68 (2.62–5.20)	3.09 (2.21–4.31)	1.05 (0.80–1.37)				
≥12 mm VAS <sub>100</sub> at study end vs baseline	111/158 (70.3) RND vs nRND: P=0.396	106/142 (74.6)	103/151 (68.2) RND vs nRND: P=0.864	103/149 (69.1)	64/144 (44.4) RND vs nRND: P=0.325	61/157 (38.9)	P=0.325	P<0.001	P<0.001	P=0.735				
... a CSBM decrease	126/300 (42.0)		127/300 (42.3)		31/301 (10.3)		1.01 (0.73–1.40)	6.31 (4.08–9.76)	6.39 (4.13–9.89)	1.00 (0.76–1.33)				
≥1/week at study end vs baseline	69/158 (43.7) RND vs nRND: P=0.536	57/142 (40.1)	61/151 (40.4) RND vs nRND: P=0.494	66/149 (44.3)	13/144 (9.0) RND vs nRND: P=0.487	18/157 (11.5)	P=0.934	P<0.001	P<0.001	P=1.000				
... ≥4 CSBMs/week at study end	98/300 (32.7)		110/300 (36.7)		187/301 (62.1)		1.19 (0.85–1.67)	3.38 (2.42–4.73)	2.83 (2.04–3.94)	1.17 (0.90–1.52)				
... use of prescription laxatives at study end	48/158 (30.4) RND vs nRND: P=0.373	50/142 (35.2)	53/151 (35.1) RND vs nRND: P=0.571	57/149 (38.3)	89/144 (6.18) RND vs nRND: P=0.913	98/157 (62.4)	P=0.303	P<0.001	P<0.001	P=0.248				
... use of prescription laxatives at study end	172/300 (57.3)		170/300 (56.7)		88/301 (29.2)		1.03 (0.74–1.42)	3.25 (2.32–4.56)	3.17 (2.26–4.44)	1.09 (0.84–1.41)				
... use of prescription laxatives at study end	95/158 (60.1) RND vs nRND: P=0.302	77/142 (54.2)	83/151 (55.0) RND vs nRND: P=0.550	87/149 (58.4)	43/144 (29.9) RND vs nRND: P=0.819	45/157 (28.7)	P=0.869	P<0.001	P<0.001	P=0.521				

**Note:** Data show the absolute (relative) proportion of patients presenting with parameters characterizing treatment-related changes of bowel function, for all opioids evaluated as well as for randomized vs nonrandomized treatment groups.

**Abbreviations:** BFI, bowel function index; CI, confidence interval; CSBM, complete spontaneous bowel movement; MOR, morphine; OXY, oxycodone; nRND, nonrandomized treatment group; OR, odds ratio; OXN, oxycodone/naloxone; RND, randomized treatment group; VAS<sub>100</sub>, 100 mm horizontal visual analog scale.



**Figure 4** Proportion of patients who recorded a  $\geq 50\%$  improvement (vs baseline) with respect to pain intensity (left), pain-related disabilities in daily life (middle), and quality of life (right) at the end of a 12-week treatment with morphine (light grey), oxycodone (grey), and oxycodone/naloxone (dark grey).

**Note:** \*Significant difference ( $P < 0.001$ ) for oxycodone/naloxone vs morphine and vs oxycodone.

**Abbreviation:** QoL, quality of life.

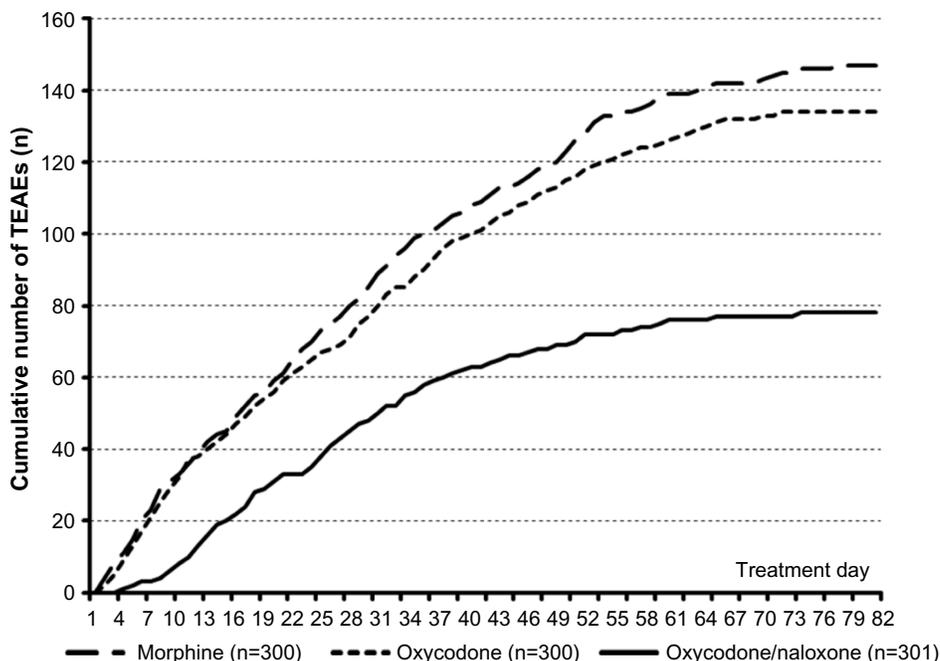
## Safety evaluation

As shown in Figures 5 and 6, 13.6% (41/301) of OXN patients reported at least one TEAE in comparison with 26.7% (80/300) for OXY (OR: 2.31, 95% CI: 1.51–3.50;  $P < 0.001$ ) and 27.7% (83/300) for MOR (OR: 2.43, 95% CI: 1.60–3.67;  $P < 0.001$ ). Two or more TEAEs were reported with OXN by 8.3% (25/301), with OXY by 13.7% (41/300), and with MOR by 14.7% (44/300) of patients. TEAE-related treatment discontinuations were seen in 7.3% (22/301) of patients treated with OXN vs 24.7% (74/300) with OXY (OR: 4.15, 95% CI: 2.50–6.90;  $P < 0.001$ ) vs 25.3% (76/300) with MOR (OR: 4.30, 95% CI: 2.59–7.14;  $P < 0.001$ ). Overall, 359 TEAEs were observed throughout the conduct of this study, 78 in relation with OXN, 134 with OXY, and 147 with MOR. A detailed TEAE analysis (Table 4) revealed that among the 177 events (49.3%), the majority of those TEAEs affected the GI tract, followed by 141 events (39.3%) affecting the central nervous system (CNS), 22 events (6.1%) affecting metabolism, 18 events (5.0%) affecting the skin, and one event (0.3%) classified as psychiatric. Constipation as a reportable TEAE was the most frequently documented drug-related adverse event, noted with OXN, OXY, and MOR, respectively, in 5.0%, 12.7%, and 12.7%, followed by nausea (4.3%, 8.7%, and 11.0%) and somnolence (6.3%, 9.3%, and 9.7%). With 17.0% (61/359) and 51.8% (186/359),

respectively, most TEAEs were classified as mild or moderate intense, and in 31.2% (112/359) these were severe. In all cases, TEAEs recovered completely, either without any counter measures (7.0% [25/359]), after treatment discontinuation (88.6% [318/359]), or with supportive drug treatment (4.5% [16/359]). Safety analyses performed for randomized vs non-randomized patients revealed only minor and insignificant differences between treatment allocation groups.

## Discussion

OIC, the most prevalent and persistent side effect of long-term treatment with WHO step III opioids, develops gradually and frequently despite prophylactic and therapeutic countermeasures. This was a post hoc analysis of so far unpublished data derived from a 12-week, real-life study designed to evaluate the GI tolerability of three different oral PR WHO step III opioids in a typical clinical practice setting. The findings were that treatment with OXN was characterized by a significantly higher proportion of patients who were able to maintain normal bowel function in comparison with OXY and MOR, as assessed via BFI and CSBM analyses. Reported differences were not related to differences in dosing (as daily morphine equivalents were comparable among treatment groups) or to a different use of laxatives or related countermeasures between the treatment

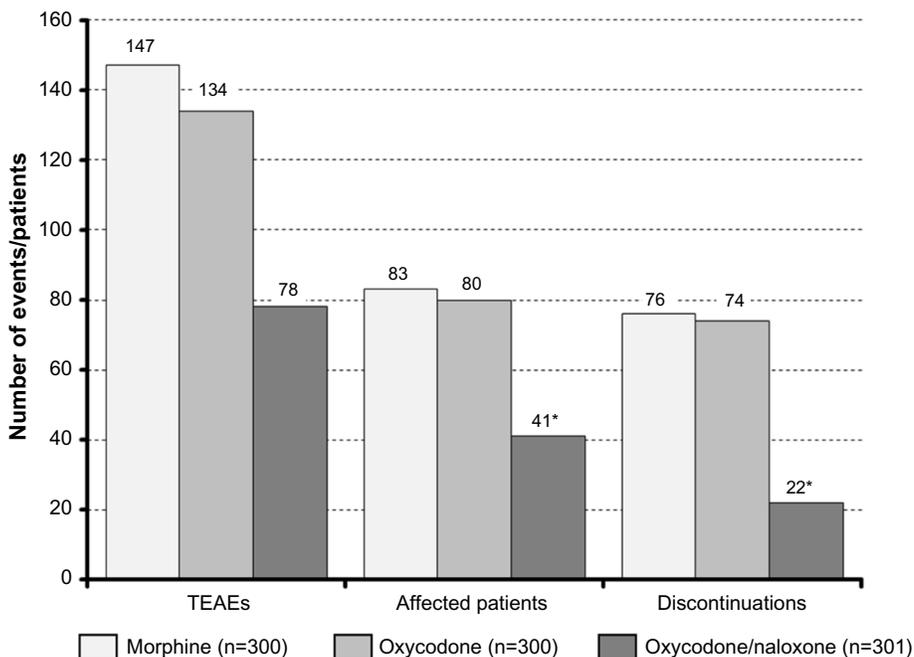


**Figure 5** Distribution of time to onset of TEAEs reported for morphine (dashed line), oxycodone (dotted line), and oxycodone/naloxone (solid line) during a 12-week treatment period.  
**Abbreviation:** TEAE, treatment-emergent adverse event.

groups (as the proportion of patients receiving these agents by prescription or over the counter were significantly lower for OXN compared with OXY and MOR), supporting, not only the rationale that OXN counteracts OIC via naloxone through mechanisms specifically addressing the underlying

processes but also, highlighting the limited efficacy of laxative regimens in OIC.

The importance of OIC (respective its prevention by adequate countermeasures) for patients suffering from chronic pain is highlighted by the reported differences for MOR,



**Figure 6** Number of TEAEs (left), patients affected by TEAEs (middle), and patients forced to discontinue treatment due to a TEAE (right), recorded during a 12-week treatment with morphine (light grey), oxycodone (grey), and oxycodone/naloxone (dark grey).  
**Note:** \*Significant difference ( $P < 0.001$ ) for oxycodone/naloxone vs morphine and vs oxycodone.  
**Abbreviation:** TEAEs, treatment-emergent adverse events.

**Table 4** Overall TEAE experience

	MOR (n=300)	OXY (n=300)	OXN (n=301)	RND (n=453)	nRND (n=448)
Number of TEAEs	147	134	78	189	170
Number of serious TEAEs	–	–	–	–	–
Subjects with TEAEs	83 (27.7)	80 (26.7)	41 (13.6)	102 (22.5)	102 (22.8)
Subjects with ≥2 TEAEs	45 (15.0)	41 (13.7)	25 (8.3)	59 (13.0)	52 (11.6)
Most common TEAEs					
Constipation	38 (12.7)	38 (12.7)	15 (5.0)	55 (12.1)	36 (8.0)
Nausea	33 (11.0)	26 (8.7)	13 (4.3)	35 (7.7)	37 (8.3)
Somnolence	29 (9.7)	28 (9.3)	19 (6.3)	40 (8.8)	36 (8.0)
Dizziness	15 (5.0)	14 (4.7)	9 (3.0)	15 (3.3)	23 (5.1)
Vomiting	10 (3.3)	7 (2.3)	5 (1.7)	13 (2.9)	9 (2.0)
Sleep problems	6 (2.0)	6 (2.0)	5 (1.7)	11 (2.4)	6 (1.3)
Sweating	4 (1.3)	3 (1.0)	3 (1.0)	5 (1.1)	5 (1.1)
Headache	2 (0.7)	3 (1.0)	3 (1.0)	4 (0.9)	4 (0.9)
Abdominal pain	4 (1.3)	3 (1.0)	1 (0.3)	4 (0.9)	4 (0.9)
Others	6 (2.0)	6 (2.0)	5 (1.7)	7 (1.5)	10 (2.2)
Affected organ classes					
Gastrointestinal system	77 (25.7)	69 (23.0)	31 (10.3)	96 (21.2)	81 (18.1)
Nervous system	53 (17.7)	52 (17.3)	36 (12.0)	72 (15.9)	69 (15.4)
Metabolic system	10 (3.3)	7 (2.3)	5 (1.7)	11 (2.4)	11 (2.5)
Skin	7 (2.3)	6 (2.0)	5 (1.7)	9 (2.0)	9 (2.0)
Psychiatric system	– (–)	– (–)	1 (0.3)	1 (0.2)	– (–)
Intensity					
Mild	24 (16.3)	21 (15.7)	16 (20.5)	32 (7.1)	29 (6.5)
Moderate	77 (52.4)	71 (53.0)	38 (48.7)	105 (23.2)	81 (18.1)
Severe	46 (31.3)	42 (31.3)	24 (30.8)	52 (11.5)	60 (13.4)
Counter measures					
None	8 (5.4)	2 (1.5)	15 (19.2)	6 (1.3)	19 (4.2)
Pharmacotherapy	4 (2.7)	4 (3.0)	8 (10.3)	9 (2.0)	7 (1.6)
Treatment discontinuation (TEAEs)	135 (91.8)	128 (95.5)	55 (70.5)	174 (38.4)	144 (32.1)
Treatment discontinuation (patients)	75 (25.0)	74 (24.7)	22 (7.3)	90 (19.9)	81 (8.1)
Treatment discontinuations for any reason (patients)	129 (43.0)	115 (38.3)	76 (25.2)	167 (36.9)	153 (34.2)

**Note:** Data is presented as n(%).

**Abbreviations:** MOR, morphine; n, number of patients; nRND, nonrandomized patients; OXN, oxycodone/naloxone; OXY, oxycodone; RND, randomized patients; TEAEs, treatment emergent adverse events.

OXY, and OXN with respect to pain relief as well as overall treatment satisfaction. As reported, treatment with OXN was associated, not only with significantly less bowel dysfunction and a superior tolerability in comparison with OXY and MOR but also, with a biometrically and clinically relevant superior analgesic efficacy, which was associated with significantly superior improvements of pain-related disabilities in daily life as well as QoL. Consequently, the proportion of patients whose overall condition improved with the opioid treatment was significantly superior for OXN vs OXY and MOR, and the corresponding ORs of 7.3 and 8.2 underline the clinical relevance of the combined opioid agonist/antagonist combination and its importance for patients.

Attempts to explain the origin of these efficacy differences focus primarily on OIC-related issues, such as the reduction of OIC-related painful symptoms (eg, bloating/flatulence, abdominal pain/colic, painful defecation, etc) by the naloxone compound; this in turn, vice versa, may have

led to an overall reduced burden of pain and hence, to lower pain intensity reported by patients treated with OXN vs OXY and/or MOR. In addition, the naloxone-related improvement of bowel function might have been followed by an improved GI resorption of the agonist compound of OXN and as such, by a higher systemic bioavailability, which subsequently may have resulted in a stronger activation of opioid-receptors within the nervous system. Alternative explanations relate to observations that naloxone per se seems to exhibit analgesic effects via opioid receptor-independent pathways within the CNS, which – if applied in ultralow dosages (~1–2 µg/kg body weight) and during chronic exposure – might add to the opioid receptor-mediated activities of opioid analgesics.<sup>41–46</sup> This hypothesis is contradictory to usual beliefs of naloxone as a potent opioid receptor antagonist; however, the effects of naloxone on the nociceptive system are somewhat more complex than they first appeared. The administration of the naloxone compound within OXN differs pharmacologically

from conventional naloxone (eg, given intravenously as immediate release preparation to antagonize opioid-related side effects or overdose) predominantly by its a) use as an oral tablet developed for enteral absorption, b) slow absorption caused by a special PR formulation, c) predominantly preheated (local) interaction with opioid receptors in the submucosal and mesenteric plexuses of the gut, and d) very low (1%–2%) systemic bioavailability, due to an extensive first pass metabolism by the liver. All in all, these factors lead to the occurrence of very low but continuously available amounts of naloxone in the bloodstream (in our study  $0.610 \pm 0.223$  [median 0.605, range 0.057–1.225]  $\mu\text{g}/\text{kg}/\text{hr}$ ), which were exactly within the range previously defined as prerequisite to exhibit analgesic effects.<sup>41,46</sup> Additionally, this hypothesis is supported by the fact that in our study, OXN was also more effective (vs OXY vs MOR) in those patients, who presented without any opioid-related bowel dysfunction during the course of the 12-week treatment period.

As shown by those 9.3% (28/301) of OXN-treated patients who experienced a CSBM decrease  $\geq 1/\text{week}$  despite additional laxatives, naloxone was not able to prevent OIC. Despite the fact that this proportion of patients is significantly less than that was seen with OXY (33.3% [100/300]) (OR: 4.88, 95% CI: 3.09–7.70;  $P < 0.001$ ) or MOR (33.0% [99/300]) (OR: 4.80, 95% CI: 3.04–7.59;  $P < 0.001$ ), this is more than expected if OIC is assumed to be purely peripherally mediated, raising a few questions about the underlying pathophysiology. Usually, OIC is seen as a consequence of opioid interaction with  $\mu$ -opioid receptors located within the neuronal systems of the plexus myentericus and plexus submucosus of the GI tract, followed by reduced GI motility and a reduced secretion of digestive enzymes, increased fluid absorption, and increased sphincter tone. However, experimental studies were able to verify clinically relevant, centrally mediated opioid effects on the GI tract after intracerebroventricular administration of morphine as well, which could be reversed either by CNS coadministration of naloxone or vagotomy,<sup>47–49</sup> supporting the hypothesis that peripheral as well as central opioid effects are responsible for OIC.<sup>50,51</sup> Further, if at all, indirect evidence for this hypothesis can be taken from the fact that methylnaltrexone – a purely peripherally acting  $\mu$ -opioid receptor antagonist – improves OIC-related GI dysfunction only in 50%–60% of patients, providing some indication of the relevance of peripherally mediated mechanisms for OIC.<sup>52,53</sup>

To our surprise, OIC was obviously not an inevitable consequence of opioid treatment, as not all patients treated with OXY or MOR experienced a significant increase in related

parameters, such as the BFI, or reported relevant CSBM changes. Overall, 31.2% (187/600) patients treated either with MOR or OXY presented with “normal” BFI scores at study end, 29.5% (177/600) experienced only minor and neither statistically significant nor clinically relevant BFI changes in response to these opioids, and 16.0% (96/600) did so without any prescribed laxatives or other documented countermeasures. Even though corresponding percentages for OXN were, with 54.5% (164/301), 58.5% (176/301), and 47.5% (143/301) (OR: 2.64, 3.37, and 4.75, respectively;  $P < 0.001$  for each comparison), significantly greater, these data as well as those for CNS effects described earlier clearly show that the level of our understanding of the pathophysiological mechanisms underlying OIC in pain patients treated with WHO step III opioids is incomplete.

Irrespective of this, treatment with OXN induced significantly less OIC and OIC-related health problems than did treatment with OXY and MOR. Assuming that those patients who presented at baseline with BFI scores  $\geq 28.8$  suffered from nonopioid-related constipation (27.7% in the MOR group, 29.3% for OXY and 28.9% for OXN), only the differences to the corresponding percentages at study end or the percentages of patients with normal BFI scores at baseline, who presented with abnormal BFI scores at study end could be taken as truly WHO step III related and by such preventable by an opioid receptor antagonist like naloxone. Following this hypothesis, the percentage of patients who developed OIC beyond baseline was for OXN (23.4% [50/214]) significantly lower than that seen for OXY (53.8% [114/212]) (OR: 3.82, 95% CI: 2.52–5.79;  $P < 0.001$ ) and MOR (59.0% [128/217]) (OR: 4.72, 95% CI: 3.11–7.15;  $P < 0.001$ ). This four- to fivefold decreased risk for OIC highlights – especially in combination with the significantly lower use of laxatives and related measures – the superior GI tolerability profile of OXN in comparison with OXY and MOR, and its practical advantage for daily life treatments.

Overall, treatment with any of the three WHO step III opioids was safe. None of the study patients died nor showed any serious or unexpected TEAEs or persistent adverse effects after treatment discontinuation. The drug treatments differed significantly with respect to the number of patients affected by TEAEs, the overall number of TEAEs observed, and the percentage of patients forced to discontinue opioid treatment in favor of OXN vs OXY and MOR. The spectrum of TEAEs reported was comparable with those mentioned in the current Summary of Product Characteristics (SPCs). The number of OXN patients with TEAEs was close to those reported in previous studies;<sup>20–26</sup> however, discontinuation rates were

somewhat higher, which may reflect minor differences with respect to study design and/or conduct of study.

The patients who received one of the opioids evaluated in the original study by chance (ie, due to a randomization process) or by preference of their physician (ie, nonrandomized) were comparable with respect to their demographic as well as baseline characteristics. Obviously, the data set obtained and evaluated within the original study was insufficient to explain the possible reasons that physicians chose to follow or to reject the randomized opioid selection. In addition, treatment allocation effects on tolerability, efficacy, and safety were only minor, and as well, were clinically insignificant. The main explanation for this might be the open-label design that allowed physicians and patients to tailor opioid treatments to the individual needs of participating patients and to address requested effects as well as untoward treatment reactions on an as-needed basis.

## Study limitations

This study has certain limitations. PROBE-designed studies such as the one underlying the present post hoc analysis suffer several limitations in comparison with RCTs.<sup>54</sup> Most of these limitations are inherent to the open-label design, which comes along with a significant risk of bias. That is, patients or investigators may add concomitant treatments to address lack of efficacy, to improve tolerability, or to manage symptoms or risk based on their knowledge and beliefs of treatment allocation. However, although opioid medications were open label, the determination of endpoints in the original study was blinded, and the use of combined endpoints addressing safety, tolerability, and efficacy parameters (which were, as such, not reported to study participants) guaranteed valid results, invaluable for real-life treatment decisions. The results of the combined evaluation of randomized and nonrandomized patients expands current knowledge on differential opioid effects with respect to OIC and related health problems. Between-group comparisons revealed only minor and neither biometrically nor clinically relevant differences with respect to any parameters evaluated.

## Conclusion

OIC is the most frequently reported adverse event experienced by patients receiving long-term opioid therapy, and interferes significantly with opioid treatment effects, such as pain relief, and improvement in functionality and/or QoL. This post hoc analysis of data from a PROBE study provides valuable GI safety, tolerability, and efficacy data for MOR, OXY, and OXN, three WHO step III opioids frequently used

to treat patients with elsewhere refractory LBP. Patient-reported data revealed significant differences between these opioid analgesics with respect to the development of OIC and the occurrence of opioid-related adverse events, with superior effects of OXN vs OXY and MOR. Additionally, patients reported superior analgesic effects for OXN with respect to pain relief, as well as related improvements for daily life activities and QoL. Overall, this data provides evidence that the fixed agonist/antagonist combination of OXN is a safe, better tolerated, and more effective alternative to conventional opioid agonists, such as OXY and MOR.

## Author contributions

All authors contributed toward data analysis, drafting and revising the paper and agree to be accountable for all aspects of the work.

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Data of the PROBE study were presented at the World Pain Congress of the International Association for the Study of Pain, October 6–11, 2014, Buenos Aires, Argentina. Data of this post hoc analysis will be presented at the Ninth Congress of the European Pain Federation, September 2–5, 2015, Vienna, Austria.

## Disclosure

The concept for the original PROBE study as well as this post hoc analysis was developed by the Institute for Neurological Sciences on behalf of the German Pain Association (Deutsche Gesellschaft für Schmerzmedizin) and the German Pain League (Deutsche Schmerzliga). The original study was realized by an independent contract research organization (CRO) and partly (<49%) sponsored by an unrestricted scientific grant from Mundipharma, Germany. Neither the study sponsor, nor any of its employees exerted any influence on the conduct of the study, or on analyses, interpretation, or publication of the results. The current post hoc analysis was done independently of any financial and/or intellectual influence by the authors. MAU and GHHM-S are physicians with no significant/relevant financial or other relationship to the sponsor, except for minor reimbursements for occasional lectures or consultations.

The authors report no other conflicts of interest in this work.

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