Global Journal of Anesthesiology

Michael A Ueberall[1]* and Gerhard HH Mueller-Schwefe[2]

[1]Institute for Neurological Sciences, Nordost Park 51, 90411 Nuernberg, Germany

[2]Interdisciplinary Center for Pain and Palliative Care Medicine, Schillerplatz 8/1, 73033 Goeppingen, Germany

Dates: **Received:** 16 July, 2015; **Accepted:** 07 September, 2015; **Published:** 10 September, 2015

***Corresponding author:** Michael A Ueberall, MD, Institute for Neurological Sciences, Nordostpark 51, 90411 Nuernberg, Germany, Tel: +49 (0)911-21773760; Fax: +49 (0)911-21773761; E-mail: michael.ueberall@ifnap.de

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Keywords: Chronic pain; Constipation; Bowel function; Quality-of-life; Oxycodone; Naloxone

Case Report

Differential Gastrointestinal Effects of Who-Step III Opioids in Low Back Pain Patients with vs. Without Constipation: Post-Hoc Analysis of Data from a 12-Week Prospective, Open-Label Blinded Endpoint Streamlined Study

Abstract

Objective: Opioid-induced constipation (OIC) is the most prevalent patient complaint associated with longer-term opioid use and interferes with analgesic efficacy, functionality, quality-of-life, and patient compliance. To compare effects of prolonged release (PR) oxycodone and PR naloxone (OXN), vs. PR oxycodone (OXY) vs. PR morphine (MOR) on bowel function under real-life conditions in chronic low back pain (LBP) patients with vs. those without pre-existent constipation.

Research design and methods: Post-hoc analysis of data from a prospective, randomized, open-label, blinded endpoint (PROBE) streamlined study, carried out in 88 centres 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. Bowel function was graded with respect to the bowel function index and characterized as normal (NCP; n=643) or constipated (COP; n=258). 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.

Main outcome measures: Primary endpoint was the proportion of patients experiencing a decrease of ≥1 complete spontaneous bowel movements (CSBMs) per week at end of observation vs. baseline. Secondary analyses addressed absolute/relative BFI changes, proportion of patients with ≤3 CSBMs per week, use of laxatives, treatment emergent adverse events (TEAEs), analgesic effects, and differences between initially non-constipated vs. constipated patient groups.

Results: CSBMs decreased 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). Overall, percentage of patients who met the primary endpoint was 10.3% (31/301) with OXN and significantly inferior to those seen with OXY (42.3%, 127/300; OR: 6.39, 95%-CI: 14.13-9.89; p<0.001) or MOR (42.0%, 126/300; OR: 6.31, 95%-CI: 4.08-9.77; p<0.001). CSBM changes varied with baseline BFI scores and were higher for COP vs. NCP. Primary endpoint for NCP/COP was met with MOR in 40.1/47.0%, with OXY in 39.6/48.9%, and with OXN in 6.5/19.5%. An absolute (relative) BFI deterioration of ≥12 mm VAS (≥50%) vs. baseline was seen for NCP with OXN/OXY/MOR in 40.7/67.5/72.8% (25.7/36.3/43.8%; p<0.001 for OXN vs. OXY and MOR), and for COP in 43.7/71.6/71.1% (21.8/53.4/54.2%; p<0.001 for OXN vs OXY and MOR). Pain intensity, pain-related functionality in daily life as well as quality-of-life improved significantly with all three opioids, however significantly superior with OXN vs. OXY vs. MOR independent of the constipation status at baseline. Overall 359 TEAEs (OXN: 78, OXY: 134, MOR: 147) in 204 patients (OXN: 41, OXY: 80, MOR: 83) occurred, most affecting the gastrointestinal (49.3%) and the nervous system (39.3%). With exception of constipation, related treatment TEAE contrasts between NCP vs. COP 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 OIC, superior tolerability and significantly better analgesic efficacy compared with OXY and MOR both in patients with and without a pre-existent constipation.

Introduction

With a median frequency of 30% among non-cancer patients (range 12%–52%), opioid-induced constipation (OIC) is among the spectrum of opioid-related side effects the most frequently reported adverse event associated with chronic opioid therapy [1,2] and one of the main reasons for dose reduction, treatment failure and premature treatment discontinuation [3].

Interaction of opioids with μ-opioid receptors of enteric neurons located in the myenteric and submucous plexus of the gut wall increase the absorption of fluids and electrolytes, impair the release of digestive enzymes and reduce the intestinal transit by stimulating nonpropulsive duodenojejunal phasic pressure contractions, and stimulating the pyloric and ileocolonic sphincters [4,5]. In total, these effects are associated with serious negative effects on patients' individual health-related quality of life (QoL) and on society in terms of health care resource use and work productivity loss [6]. Patients with opioid-related bowel dysfunction have more hospital admissions, emergency room visits, home health services, nursing home care, physician visits, and laboratory tests, as well as higher mean all-cause costs for emergency, physician visits, nursing facilities, home health care, and prescription drug services compared to patients without OIC [7-9].

Laxative regimens are recommended for clinical use, both to prevent and treat OIC. However, they are non-specific, associated

with several drawbacks (e.g. muscular bowel function damage, nutritional deficits, kidney stones, renal failure and/or interference with other drugs, etc.), and insufficiently effective in the majority of patients, as they do not specifically address the underlying opioid-receptor-mediated mechanisms of OIC [10,11].

More recently, few specific alternatives to prevent/treat OIC have been developed, which antagonize opioid-receptor activities in the gut wall without compromising pain control or drug safety of the opioid analgesics [12,13]. Of these options, 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 by such 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 prolonged-release in combination with an extensive hepatic first-pass metabolism and the subsequent low systemic bioavailability (~2%) ensures the lack of antagonistic effects on its central analgesic action [14,15]. In randomized controlled trials with patients suffering from OIC due to the use of strong-acting WHO-step III opioids, naloxone was able to reduce constipation as well as related comorbidities and few open-label trials present evidence that it is also able to prevent OIC if given first line [16-25].

However, with prevalence rates ranging from 2-28% of the whole population in the US and Europe constipation is a common gastrointestinal motility disorder among elsewhere healthy people [26], and a common, nevertheless rather complex and multifactorial side effect of chronic pain even in the absence of opioids. Reasons for that are pain-related mobility restrictions and a number of non-opioids, adjuvant agents (e.g. anticonvulsants, antidepressants) as well as concomitant drugs used for the pharmacological treatment of pain and pain-related health disturbances in these patients. In clinical practice pain patients with constipation usually suffer from multiple precipitants ranging from secondary causes (including medications, neuropathic or myopathic disorders, and endocrinopathies) to primary aetiologies such as irritable bowel syndrome, slow-transit, or evacuation disorders.

This heterogeneity in the pathogenesis of constipation in pain patients raises a number of questions with respect to OIC and chronic pain. From a clinical perspective, three questions are important. First: how develops OIC in chronic pain patients already suffering from a non-opioid-related constipation. Second: are there any differences with respect to OIC in these patients in comparison to initially non-constipated pain patients. And third: how effective are specific and/or unspecific countermeasures if given to chronic pain patients without vs. with a pre-existent non-opioid-related bowel dysfunction.

To gain further insight into this problem, the German Pain Association and the German Pain League commissioned a post-hoc analysis of data from a prospective randomized open-label blinded endpoint streamlined real-life study on the safety, tolerability and efficacy of morphine (MOR), oxycodone (OXY) and oxycodone/naloxone (OXN) in patients with chronic moderate-to-severe low-back-pain refractory to other analgesics [24,25], with a special focus on the gastrointestinal effects in patients without vs. with a pre-existent non-opioid-related constipation.

Patients and Methods

Overall study design

The underlying 12-week study followed a prospective, randomized, open-label, blinded endpoint (PROBE) design, developed to address some of the potential limitations of randomized controlled trials (RCTs) and observational studies. Main advantage of such a PROBE trial design is the assessment of clinical outcomes in studies that allow both, the enrolment of a broad patient population (in our case patients who require WHO-step III opioid analgesics owing to elsewhere refractory moderate-to-severe chronic low back pain) as well as open-label non-interventional dose adjustments and the discretionary use of concomitant laxatives etc. on an as needed basis, which better reflect clinical practice but with the advantage of randomization and a rigorous evaluation of study endpoints by blinded data analyses [27,28]. Opioid treatment followed medical requirements according to the decision of the participating physicians.

The study was performed by using electronic case report forms for all data obtained by the participating physicians as well as conventional paper-pencil pain questionnaires/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 amongst other parameters pain intensity, pain-related disabilities in daily life, quality-of-life, quality-of-life impairments by pain, bowel function, use of analgesics and adjuvant therapies, etc, [29,30].

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 (e.g. 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 non-pregnant, non-lactating females who were at least 18 years with a documented history of moderate to severe non-malignant chronic low back pain, 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. Exclusion criteria were those contraindications listed in the German prescribing information of the three opioid analgesics that address situations that would place the patient at risk upon exposure to the medication as well as 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, and 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 disease, significant structural abnormalities of the gastrointestinal tract, patients with known or suspected alcohol or drug dependence, patients 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 were seen as comparably effective and therefore – at least from a medical point of view – interchangeable for the 1st line treatment of opioid naïve patients suffering from elsewhere refractory low back pain [31]. Therefore, an electronic treatment allocation system recommended one of these three alternative opioid treatments on a randomized 1:1:1 ratio (block size 9), 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 basically non-interventional 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 vice versa implicate the exclusion of this patient from the per-protocol analysis of randomized treatment allocations. 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 prolonged release preparation twice daily. Any dose adjustments, prescriptions of analgesic co-medication, 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) [32,33], which calculates as the mean of three items recorded retrospectively by patients for the last seven days on the basis of an 100 mm horizontal visual analogue scale (VAS_{100}) 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´). BFI reference (i.e. ´normal´) range is 0-28.8 mm VAS and BFI changes ≥12 mm VAS 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 last seven days and the use of laxatives as well as other pharmacological and non-pharmacological 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 (at baseline) and the German Pain Diary (throughout the whole observation period) for pain intensity, pain-related disabilities in daily life activities/functionality and quality-of-life. Pain intensity measures based on the low back pain intensity index (LBPIX), which was calculated as arithmetic mean of the lowest, average and highest 24 hour LBP intensities on an 100mm visual analogue scale (VAS_{100}; 0 = 'no pain' and 100 = 'worst pain conceivable"). LBP-related disabilities were assessed with a modified version of the pain disability index (mPDI), which recorded the degree of LBP-related functional restrictions on the basis of an 11-point numerical rating scale (NRS_{11}; 0 = 'none' and 10 = 'worst conceivable") with respect to seven distinct domains of daily life. Quality-of-life was measured using the quality-of-life impairment by pain (QLIP) inventory, a seven question tool assessing different pain-related QoL restrictions resulting in an overall QoL-score (ranging from 40 = 'no impairment' to 0 = 'maximum impairment'). All parameters were recorded by patients retrospectively for the last seven 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 assessments consisted of monitoring all treatment-emergent adverse events (TEAEs), collected via spontaneous reports and patient visits. TEAEs were collected both through direct questioning by the physicians, as well as spontaneous patient reports and were recorded at each visit.

Statistical analysis

Aim of this post-hoc analysis was to evaluate the dynamics of bowel dysfunction as consequence of a treatment with three different WHO-step III opioids in patients without vs. with an already established non-opioid-related constipation under real-life conditions. Patients were categorized on the basis of their baseline BFI score as "non-constipated" (NCP; BFI ≤28.8 mm VAS) or as "constipated" (COP; BFI >28.8 mm VAS) and treatment effects were compared between both groups with respect to the end-of-study outcomes after 12 weeks. Primary criterion for this analysis was the treatment contrast for the frequency of patients with a ≥1 decline in the number of CSBMs per week (Table 1). Secondary bowel tolerability aspects were the percentages of patients (a) experiencing a clinically relevant BFI worsening (i.e. an increase ≥12 mm VAS) or (b) with a ≥50% BFI worsening vs. baseline, (c) with ≤3 CSBMs per week, and (d) with prescribed laxatives, each at the end of the 12-week observation period. Secondary efficacy analyses were performed with respect to (a) opioid-related changes in pain intensity, disability and quality-of-life. Safety analyses addressed the percentages of patients with (a) TEAEs, (b) TEAE-related study discontinuations, as well as (c) spectrum and (d) characteristics of TEAEs reported.

Data analyses were performed for all enrolled patients who took at least one dose of OXN, OXY or MOR and who had at least one post-baseline/post-dose measure. Due to the explorative post-hoc character

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Table 1: Primary endpoint analysis. Data show the absolute (relative) proportion of patients suffering from a ≥1 decline in complete spontaneous bowel movements (CSBMs) at the end of the 12-week observation period vs. baseline for all opioids evaluated as well as for non-constipated vs. constipated patient groups.

CSBM decrease ≥1 at week 12 vs. baseline	MOR N(%)	OXY N(%)	OXN N(%)	MOR vs. OXY OR (95%-CI) / significance	MOR vs. OXN OR (95%-CI) / significance	OXY vs. OXN OR (95%-CI) / significance
All	126/300 (42.0)	127/300 (42.0)	31/301 (10.3)	0.99 (0.71-1.36) p=0.934	6.31 (4.08-9.77) p<0.001	6.39 (4.13-9.89) p<0.001
Non-constipated patients (NCP; BFI at baseline ≤28.8)	87/217 (40.1)	84/212 (39.6)	14/214 (6.5)	1.02 (0.69-1.50) p=0.921	9.56 (5.22-17.53) p<0.001	9.38 (5.11-17.22) p<0.001
Constipated patients (COP; BFI at baseline >28.8)	39/83 (47.0)	43/88 (48.9)	17/87 (19.5)	1.08 (0.59-1.97) p=0.806	3.65 (1.84-7.23) p<0.001	3.93 (2.00-7.73) p<0.001

CSBM: complete spontaneous bowel movement; MOR: morphine; OXY: oxycodone; OXN: oxycodone/naloxone; OR: odds-ratio; 95%-CI: 95%-confidence interval.

of this analysis no formal sample size estimation has been performed. Linear interpolation was used to impute intermittent missing scores and the last observation carried forward (LOCF) method 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 intervals (95%-CI) of the mean, median, and range (minimum –maximum) values. For categorical and ordinal variables data were summarized by frequency number (n) and percentage (%) of participants in each category; where appropriate, 95% confidence intervals were added. For between groups comparisons of continuous/categorical variables, Student t / Pearson's chi-squared test were used. For within group (e.g. pre-post) comparisons paired samples t-tests were performed. All statistical tests were carried out using a 2-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 has been 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 registered in the German pain study registry (DGS: 2012-0012-05a). All patients provided written informed consent prior to study enrollment. The concept for this post-hoc analysis has been approved by the steering committees of the German Pain Association and the German Pain League and is registered in the ENCEPP database of the European Medicines Agency for non-interventional studies (ENCEPP/SDPP/11048).

Results

Patient disposition

Between April and August 2013, a total of 901 patients were enrolled, received treatment as assigned and reported at least one post-baseline measure (see patient disposition in Figure 1). With 71.4% (n=643), seven of ten study patients presented with normal BFI scores and were classified as "non-constipated" (NCP), whereas 28.6% (n=258) presented with BFI scores above the normal reference range of 28.8 mm VAS and were therefore classified as "constipated" (COP). Overall, a higher percentage of NCP (67.3%; 433/643) vs. COP (57.4%; 148/258) patients completed the study (OR: 1.53, 95%-CI: 1.14-2.06; p=0.005), however, in both groups, discontinuation rates were significantly less for OXN (22.4/32.2%) in comparison to MOR (41.0/48.2%; OR: 2.41/1.96; p<0.001/0.033) and OXY (34.4/47.7%; OR: 1.82/1.92; p=0.006/0.036). Main reason for premature discontinuation was insufficient tolerability reported by 251 patients (27.9%), followed by TEAEs (171/901, 19.0%) and insufficient analgesic efficacy (69/901, 7.7%). Between group analyses showed comparable TEAE-related discontinuation rates with MOR and OXY for NCP (25.8/25.0%) and COP (22.9/23.9%), which were – for all reasons evaluated – significantly worse than those observed with OXN in both BFI groups (7.0/8.0%; p<0.01 for each comparison).

Baseline characteristics

Baseline demographics were comparable between opioids and BFI groups and presented in Table 2. Overall, mean age (±SD) was 46.3±9.7 (median: 47, range: 19-77) years and 55.7% (502/901) were female. With 58.8% (530/901) 6 out of 10 LBP study patients suffered for longer than 6 months prior study enrolment, with 79.8% (710/901) 8 out of 10 reported a treatment by at least 5 different specialists (average 5.6±1.4, median: 6, range: 2-10), and with 94.0% (847/901) more than 9 out of 10 patients documented a pre-treatment with at least 4 analgesic medications (on average 6.3±1.9, median: 6, range: 1-12). Non-opioid analgesics were the most frequently used treatments reported by 99.0% (n=892/901) of patients prior study entry, followed by nonsteroidal anti-inflammatory drugs (NSAIDs; 95.3%, 859/901), WHO-step II opioids (69.4%, n=625/901), antidepressants (66.6%, 600/901), muscle relaxants (63.2%, 569/901) and anticonvulsive agents (37.1%, 334/901). With 37.7% (340(901), a third of patients presented with advanced pain chronification (stage III) according to the Mainz Pain Staging System (MPSS) [34], and 56.4% (n=508/901) suffered from a high disability with either moderate (grade III; n=352/901, 39.1%) or severe (grade IV; n=156/901, 17.3%) limitations according to the von Korff pain grading scale [35,36]. Baseline pain intensity as well as all other pain-related patient measures were comparable among treatment groups. Average LBP intensities, assessed on the basis of the LBPIX at baseline were 46.0±17.5 mm VAS_{100} for MOR, 45.7±17.2 mm VAS_{100} for OXY, and 45.5±13.6 mm VAS_{100} for OXN. Corresponding mPDI and QLIP scores for MOR / OXY / OXN were, 41.7±13.5 / 42.3±13.0 / 42.4±13.0 NRS_{70}, and 17.2±5.9 / 17.1±5.7 / 17.1±5.6 NRS_{40} respectively. 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. Average BFI at baseline was 19.8±19.4 (median: 16, range 0-76) mm VAS with insignificant differences among opioid treatment groups, however, significant differences between BFI groups: NCP: 9.2±9.9 vs. COP: 46.4±9.2 (p<0.001). Mean (±SD) number of CSBMs per week was 4.8±1.5 for NCP vs. 3.1±1.5 for COP (p<0.001).

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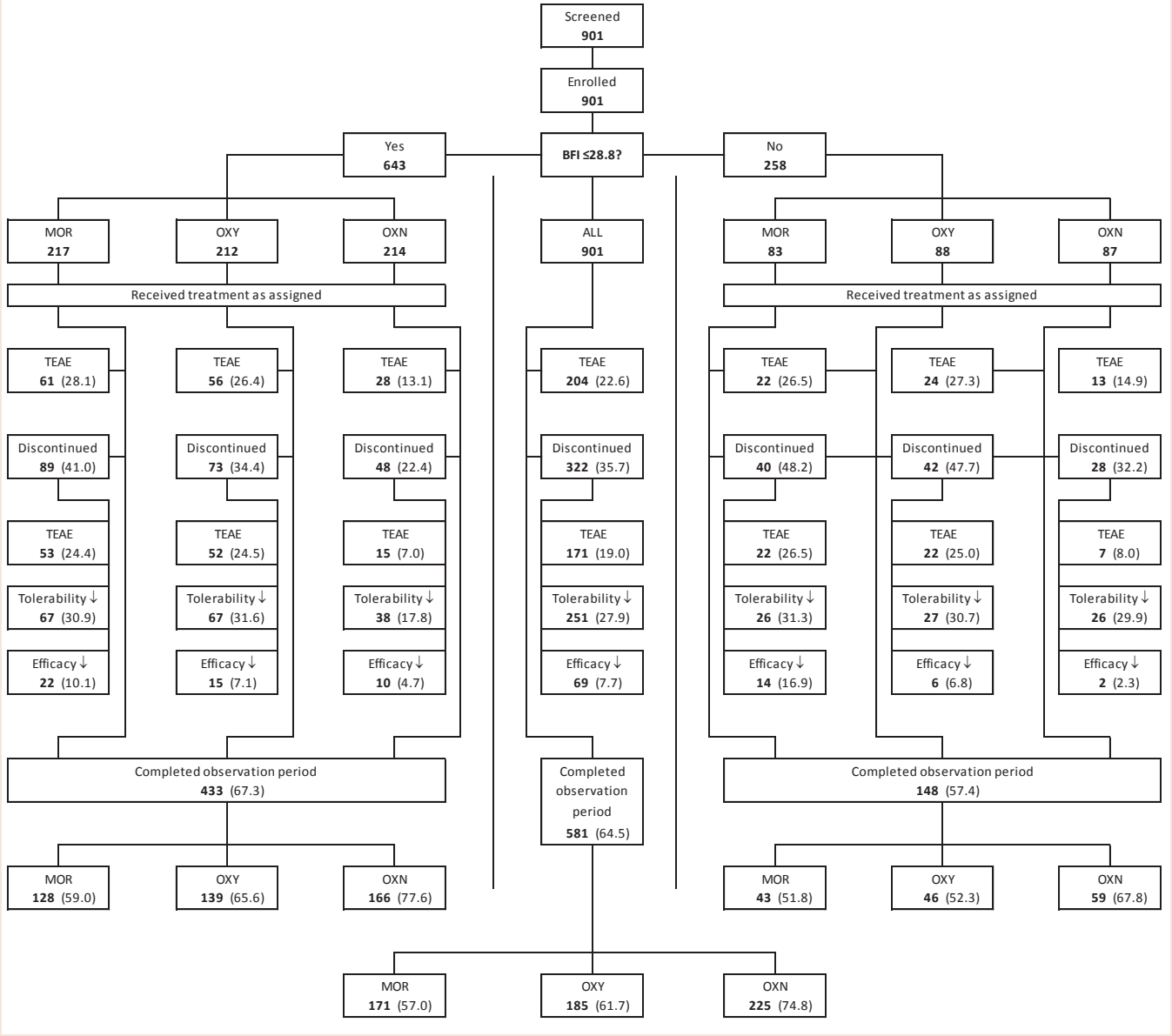

Figure 1: Patient disposition.
BFI: bowel function index; MOR: morphine; OXY: oxycodone; OXN: oxycodone/naloxone; n: number of patients; %: percentage of patients; TEAE: treatment emergent adverse event.

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, average initial starting doses were comparable among treatment and BFI groups (NOC: 28.6±10.8, COP: 28.9±10.7), as well as dose titration and the maintenance dose. At study end patients treated with MOR received on average 103.8±39.3 (median: 100, range 15-200), those with OXY 106.6±37.4 (median: 120, range: 20-180), and those with OXN 112.9±34.2 (median: 120, range: 10-200) mg MEQ. Corresponding end-of-study opioid doses for NCP vs. COP patients were 108.4±36.8 vs. 106.2±38.2 mg MEQ. Dosing frequency was comparable among opioid treatment and BFI patient groups. Most patients took their WHO-step III opioids twice daily (MOR: 267/300, 89.0%; OXY: 274/300, 91.3%; OXN: 275/301, 91.4%; NCP: 579/643, 90.0%; COP: 237/258, 91.9%), 7.7% (69/901) three times a day, and 1.8% (16/901) once daily.

Bowel function / opioid induced constipation

As expected with the introduction of WHO-step III opioids, the bowel function worsened significantly from baseline to end-

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Table 2: Patient demographic and baseline characteristics.

	Opioid treatment groups			BFI at baseline	
	MOR	OXY	OXN	≤28.8 (NCP)	>28.8 (COP)
	(n=300)	(n=300)	(n=301)	(n=643)	(n=258)
Age (years); mean (SD)	46.5 (9.3)	46.7 (9.9)	46.1 (9.9)	46.6 (9.8)	46.0 (9.6)
Proportion >55 years; n (%)	56 (18.7)	57 (19.0)	56 (18.6)	125 (19.4)	44 (17.1)
Gender: female; n (%)	168 (56.0)	166 (55.3)	168 (55.8)	360 (56.0)	142 (55.0)
Height (cm); mean (SD)	170.4 (8.6)	171.4 (9.2)	171.2 (9.1)	170.5 (9.1)	172.2 (8.5)
Weight (kg); mean (SD)	79.4 (17.7)	79.5 (15.8)	80.2 (15.5)	79.8 (16.9)	79.3 (15.1)
Body Mass index (kg/m2); mean (SD)	27.3 (5.9)	27.0 (4.5)	27.4 (5.0)	27.4 (5.4)	26.7 (4.3)
Obesity (BMI: >30.0); n (%)	63 (21.0)	62 (20.7)	65 (21.6)	136 (21.2)	54 (20.9)
Low back pain duration >6 months; n (%)	179 (59.7)	173 (57.7)	178 (59.1)	378 (54.8)	152 (58.9)
No. of. physicians involved; median (range)	6 (2-9)	6 (3-10)	6 (2-10)	6 (2-10)	6 (2-10)
No. of analgesics prior enrollment; median (range)	6 (1-12)	6 (1-12)	6 (1-12)	6 (1-12)	6 (1-11)
Non-opioid analgesics; n (%)	296 (98.7)	298 (99.3)	298 (99.0)	635 (98.8)	257 (99.6)
NSAIDs; n (%)	285 (95.0)	288 (96.0)	286 (95.0)	607 (94.4)	252 (97.7)
Low-potent opioid analgesics; n (%)	207 (69.0)	208 (69.3)	210 (69.8)	441 (68.6)	184 (71.3)
Antidepressants; n (%)	206 (64.3)	203 (67.7)	191 (63.5)	437 (68.0)	163 (63.2)
Antikonvulsants; n (%)	113 (37.7)	109 (36.3)	112 (37.2)	255 (39.7)	79 (30.6)
Muscle relaxants; n (%)	193 (64.3)	180 (60.0)	196 (65.1)	397 (61.7)	172 (66.7)
Switch from: WHO-step I; n (%)	87 (29.0)	87 (29.0)	87 (28.9)	190 (29.5)	71 (27.5)
WHO-step II; n (%)	207 (69.0)	208 (69.3)	210 (69.8)	441 (68.6)	184 (71.3)
Others; n (%)	6 (2.0)	5 (1.7)	4 (1.3)	12 (1.9)	3 (1.2)
MPSS I; n (%)	34 (11.3)	37 (12.3)	35 (11.6)	82 (12.8)	24 (9.3)
II; n (%)	153 (51.0)	151 (50.3)	151 (50.2)	308 (47.9)	147 (57.0)
III; n (%)	113 (37.7)	112 (37.3)	115 (38.2)	253 (39.3)	87 (33.7)
von Korff 1; n (%)	23 (7.7)	25 (8.3)	22 (7.3)	53 (8.2)	17 (6.6)
2; n (%)	105 (35.0)	110 (36.7)	108 (35.9)	222 (34.5)	101 (39.1)
3; n (%)	121 (40.3)	113 (37.7)	118 (39.2)	257 (40.0)	95 (36.8)
4; n (%)	51 (17.0)	52 (17.3)	53 (17.6)	111 (17.3)	45 (17.4)
Neuropathic pain; n (%)	52 (17.3)	51 (17.0)	47 (15.6)	105 (16.3)	45 (17.4)
Tailored treatment target (VAS100); mean (SD)	20.6 (14.4)	20.5 (12.3)	21.8 (13.1)	20.9 (13.3)	21.3 (13.3)
LBPIX (VAS100); mean (SD)	46.0 (17.5)	45.7 (17.2)	45.5 (13.6)	45.5 (15.9)	46.5 (17.0)
mPDI (NRS70); mean (SD)	41.7 (13.5)	42.3 (13.0)	42.4 (13.0)	42.0 (13.2)	42.4 (13.1)
QLIP (NRS40); mean (SD)	17.2 (5.9)	17.1 (5.7)	17.1 (5.6)	17.3 (5.7)	16.8 (5.9)
BFI (VAS100); mean (SD)	19.6 (19.6)	19.9 (19.4)	19.9 (19.3)	9.2 (9.9)	46.4 (9.2)
Number of CSBMs per week; mean (SD)	4.4 (1.7)	4.4 (1.7)	4.3 (1.6)	4.8 (1.5)	3.1 (1.5)
Use of laxatives; n (%)	69 (23.0)	69 (23.0)	68 (22.6)	113 (17.6)	
Proportion with normal BFI (≤28.8 mm VAS); n (%)	217 (72.3)	212 (70.7)	214 (71.1)	643 (100.0)	- (-)

MOR: morphine; OXY: oxycodone; OXN: oxycodone/naloxone; BFI: bowel function index; NCP: non-constipated patient group; COP: constipated patient group.

of-study (Figure 2). Average BFI scores for NCP/COP patients increased with MOR from 9.0±9.7/47.4±8.9 to 45.5±32.5/74.7±24.2 mm VAS_{100} ($p<0.001$ for each), for OXY from 9.2±10.3/45.8±9.1 to 37.3±29.2/74.6±22.8 mm VAS_{100} ($p<0.001$ for each), and for OXN from 9.3±9.8/46.0±9.5 to 19.1±20.0/56.7±19.6 mm VAS_{100} ($p<0.001$ for each). Between group analyses showed significantly different BFI changes for NCP/COP with lowest absolute and relative BFI increments at end of week 12 vs. baseline for OXN (9.9/10.7 mm VAS_{100}, 11.2/20.5%) vs. OXY (28.1/28.8 mm VAS_{100}, 31.1/51.7%; $p<0.001$ for each comparison to OXN) vs. MOR (36.5/27.3 mm

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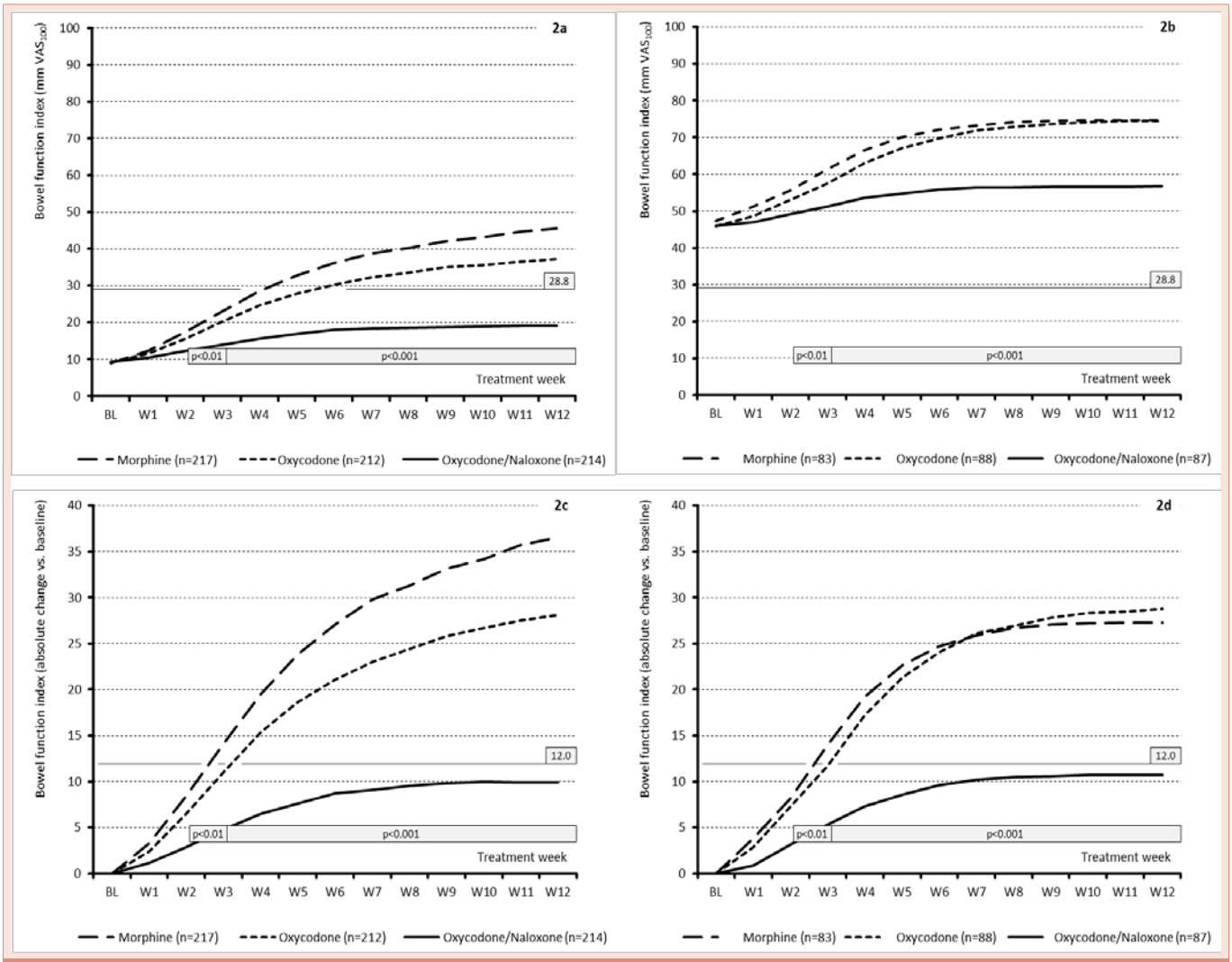

Figure 2: Treatment-related change of the bowel function index (BFI) during the course of the 12-week study for all opioids evaluated as well as for non-constipated (left Figures: 2a, 2c) vs. constipated patient groups (right Figures: 2b, 2d).Figures show the overall course of the BFI (Figures 2a, 2b) and the absolute BFI change (Figures 2c, 2d) over the whole 12 week observation period. BFI changed significantly for all three treatment groups vs. baseline, but significantly less for oxycodone/naloxone vs. oxycodone vs. morphine.

Horizontal lines in 2a and 2b marked with "28.8" indicate the upper normal reference range of the BFI; horizontal lines in 2c and 2d marked with "12.0"indicate the absolute threshold for significant BFI changes vs. baseline; horizontal bars indicate the significance level with respect to treatment comparisons between oxycodone/naloxone vs. oxycodone and morphine; VAS100: 100mm visual analogue scale (0: no bowel dysfunction, 100: worst bowel dysfunction conceivable); BL: baseline; W1-W12: treatment week 1-12

VAS_{100}, 40.7/53.2%; p<0.001 for each comparison to OXN). With 40.7 vs. 43.7% (87/214 vs. 38/87), clinically relevant absolute BFI worsening's (i.e. ≥12mm VAS_{100} vs. baseline) have been found with OXN significantly less for NCP/COP in comparison to OXY (67.5 vs. 71.6%; 143/212 vs. 63/88; OR: 3.03/3.25, p<0.001) and MOR (72.8 vs. 71.1%; 158/217 vs. 59/83; OR: 3.91/3.17, p<0.001; Figures 3a,b, (Table 3).

In parallel significantly more patients reported a clinically significant relative BFI increase (≥50% vs baseline) at end of the study for NCP vs. COP with MOR (43.8 vs. 54.2%; 95/217 vs. 45/83; OR: 2.25/4.24; p<0.001) and OXY (36.3 vs. 53.4%, 77/212 vs. 47/88; OR: 1.65/4.10; p<0.001), compared to OXN (25.7 vs. 21.8%, 55/214 vs. 19/87). Percentage of NCP patients who maintained normal BFI scores (i.e. ≤28.8) throughout the 12-week treatment period was 76.2% (163/214) for OXN and hence significantly higher/better than those seen for OXY (46.2%, 98/212; OR: 3.72, 95%-CI: 2.46-5.63; p<0.001) and MOR (40.1%, 87/217; OR: 4.78, 95%-CI: 3.15-7.24; p<0.001).

The proportion of NCP/COP patients who reported a ≥1 decline in CSBMs at the end of the study vs. baseline (the primary endpoint of this post-hoc analysis) was 6.5/19.5% for OXN and therefore significantly lower than those seen with OXY (39.6/48.9%; OR: 9.38/3.93; p<0.001 for each) and MOR (40.1/47.0%; OR: 9.56/3.65; p<0.001 for each; (Table 1 and Figures 3a,b), which induced comparable CSBM

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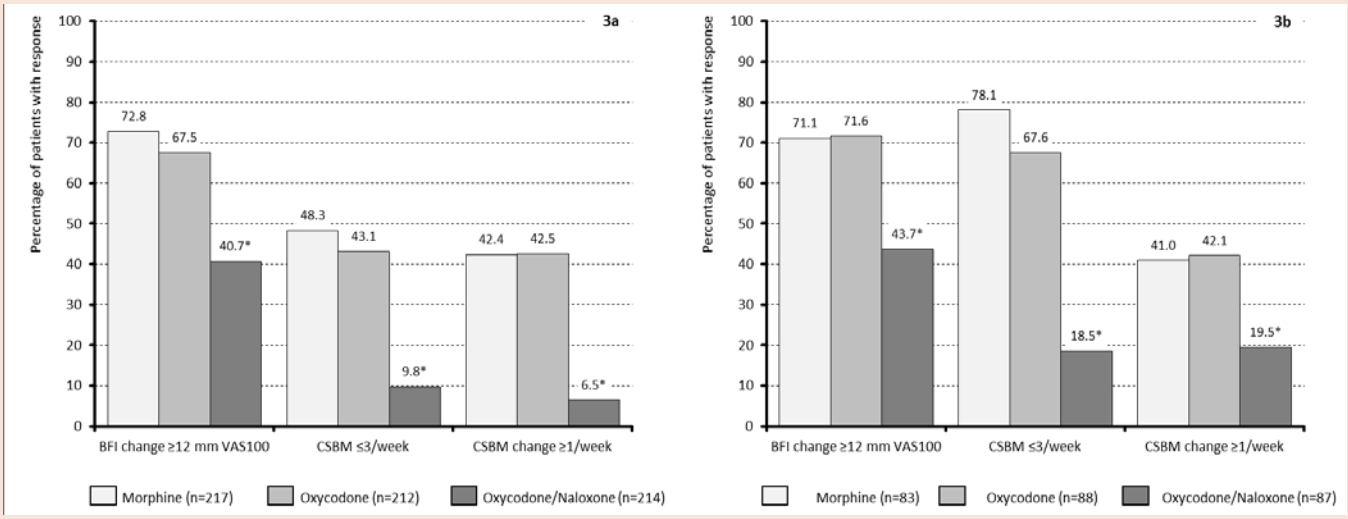

Figure 3: Proportion of non-constipated (Figure 3a, left panel) vs. constipated patients (Figure 3b, right panel) who reported (a) a significant absolute BFI worsening (i.e. ≥12 mm; left), (b) 3≤ CSBMs per week, and (c) a CSBM ≥1-decrease (right) each at the end of a 12-week treatment vs. baseline with morphine (light grey), oxycodone (grey), and oxycodone/naloxone (dark grey).

BFI: bowel function index, CSBM: complete spontaneous bowel movement.

* indicates a significant difference (p<0.001) for oxycodone/naloxone vs. morphine and vs. oxycodone.

Table 3: Secondary tolerability analysis. 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 non-constipated vs. constipated patient groups.

BFI increase ≥12 mm VAS at week 12 vs. baseline	**MOR N (%)**	**OXY N (%)**	**OXN N (%)**	**MOR vs. OXY OR (95%-CI) / significance**	**MOR vs. OXN OR (95%-CI) / significance**	**OXY vs. OXN OR (95%-CI) / significance**
All	217/300 (72.3)	206/300 (68.7)	125/301 (41.5)	1.19 (0.84-1.70) p=0.325	3.68 (2.62-5.18) p<0.001	3.09 (2.21-4.31) p<0.001
Non-constipated patients (NCP; BFI at baseline ≤28.8)	158/217 (72.8)	143/212 (67.5)	87/214 (40.7)	1.29 (0.85-1.96) p=0.225	3.91 (2.61-5.86) p<0.001	3.03 (2.04-4.50) p<0.001
Constipated patients (COP; BFI at baseline >28.8)	59/83 (71.1)	63/88 (71.6)	38/87 (43.7)	0.98 /0.50-1.89) p=0.942	3.17 (1.68-5.99) p<0.001	3.25 (1.74-6.09) p<0.001
BFI increase ≥50% at week 12 vs. baseline	**MOR N (%)**	**OXY N (%)**	**OXN N (%)**	**MOR vs. OXY OR (95%-CI) / significance**	**MOR vs. OXN OR (95%-CI) / significance**	**Y vs. OXN OR (95%-CI) / significance**
All	140/300 (46.7)	124/300 (41.3)	74/301 (24.6)	1.29 (0.94-1.79) p=0.188	2.79 (1.98-3.95) p<0.001	2.16 (1.52-3.06) p<0.001
Non-constipated patients (NCP; BFI at baseline ≤28.8)	95/217 (43.8)	77/212 (36.3)	55/214 (25.7)	1.48 (1.00-2.19) p=0.047	2.25 (1.50-3.38) p<0.001	1.65 (1.09-2.50) p=.018
Constipated patients (COP; BFI at baseline >28.8)	45/83 (54.2)	47/88 (53.4)	19/87 (21.8)	1.03 (0.57-1.89) p=0.623	4.24 (2.18-8.26) p<0.001	4.10 (2.12-7.93) p<0.001
CSBM ≤3 at week 12	**MOR N (%)**	**OXY N (%)**	**OXN N (%)**	**MOR vs. OXY OR (95%-CI) / significance**	**MOR vs. OXN OR (95%-CI) / significance**	**OXY vs. OXN OR (95%-CI) / significance**
All	202/300 (67.3)	190/300 (63.3)	114/301 (37.9)	1.19 (0.85-1.67) p=0.303	3.38 (2.42-4.73) p<0.001	2.83 (2.04-3.94) p<0.001
Non-constipated patients (NCP; BFI at baseline ≤28.8)	126/217 (58.1)	113/212 (53.3)	56/214 (26.2)	1.21 (0.83-1.78) p=0.321	3.91 (2.60-5.87) p<0.001	3.22 (2.14-4.84) p<0.001
Constipated patients (COP; BFI at baseline >28.8)	76/83 (91.6)	77/88 (87.5)	58/87 (66.7)	1.55 (0.57-4.21) p=0.387	5.43 (2.22-13.26) p<0.001	3.50 (1.62-7.58) p<0.001

BFI: bowel function index; MOR: morphine; OXY: oxycodone; OXN: oxycodone/naloxone; OR: odds-ratio; 95%-CI: 95%-confidence interval; NCP: non-constipated patient group; COP: constipated patient group; CSBM: complete spontaneous bowel movement.

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changes. Average number of CSBMs per week dropped for NCP/COP with MOR from 4.9±1.5/3.1±1.5 to 3.2±2.0/1.8±1.2 (p<0.001), for OXY from 4.8±1.5/3.2±1.3 to 3.2±2.1/1.8±1.5 (p<0.001), and for OXN from 4.8±1.3/3.0±1.6 to 4.5±1.5/2.6±1.6 (p<0.001). Percentages of NCP/COP patients with three or even less CSBMs per week at study end were with 26.2/66.7% for OXN significantly less than those reported for OXY (53.3/87.5%; OR: 3.22/3.50; p<0.001 for both) or MOR (58.1/91.6/%; OR: 3.91/5.43; p<0.001 for both; Table 3).

Use of laxatives

Treatment with any of the evaluated WHO-step III opioids was followed by an increased prescription of laxatives, irrespective of the bowel (dys-)function at baseline (Figures 4a,b). For MOR as well as OXY the proportion of NCP/COP patients increased significantly between baseline to end-of-study (p<0.001 for each), whereas for OXN only numerical increments occurred. Overall, percentage of OXN patients who used prescription laxatives to prevent or to treat OIC at study end was 8.6% (20/233) and hence significantly less than those 43.7% seen with OXY (101/231; OR: 8.27, 95%-CI: 4.89-14.02; p<0.001) or those 44.6% with MOR (103/231; OR: 8.57, 95%-CI: 5.06-14.51; p<0.001; Table 4). Percentages of NCP/COP patients who took no laxatives at baseline and who started to use any due to side effects of the opioid treatment increased with OXN significantly less (4.4/36.7%) than those reported for OXY (37.4/89.3%; OR: 12.90/14.39; p<0.001 for each) or MOR (39.1/91.7%; OR: 13.86/19.00; p<0.001 for each).

Pain relief, functionality and quality-of-life

Opioid treatment was followed by a significant relief in pain and pain-related complaints for all three treatment groups and in both BFI groups, however with superior effects for OXN in comparison to OXY and MOR. Overall, LBPIX decreased with OXN / OXY / MOR from 45.5±13.6 / 45.7±17.2 / 46.0±17.5 mm VAS at baseline to 17.8±16.9 / 24.0±19.8 / 24.8±19.4 mm VAS at study end. Corresponding absolute (mm VAS) / relative (%) changes at study end vs. baseline were for OXN with -27.7±15.9 / -62.5±32.7 significantly greater than those reported for OXY (-21.7±18.7 / -48.1±39.6; p<0.001) or MOR (-21.1±18.0 / -45.2±42.4; p<0.001). Between groups comparisons revealed only minor and biometrical insignificant differences of opioid-related analgesic effects for NCP/COP patients (Figures 5a,b). Relative improvements seen at week 12 vs baseline for NCP/COP were comparable with MOR (-45.9/-46.3%) and OXY (-47.2/-48.8%), but significantly better with OXN (-60.5/-61.5%; p<0.001 for each comparison; Figure 5a,b).

End of study percentages of patients who presented with at least 50% pain relief vs. baseline were with 69.4% (209/301) for OXN significantly higher than those reported 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 quality of life improved as well. Percentages of patients who finally reported a ≥50% improvement in pain-related disabilities with respect to daily life activities assessed via mPDI where 59.5% (179/301) for OXN vs. 48.0% (144/300; OR: 1.59, 95%-CI: 1.15-2.20; p<0.001) for OXY vs. 44.3% (133/300; OR: 1.84, 95%-CI: 1.33-2.55; p<0.001) for MOR. Proportion of patients who presented with a ≥50% QoL improvement assessed via QLIP were 72.8% (219/301) for OXN vs. 46.0% (138/300; OR: 3.14, 95%-CI: 2.23-4.41; p<0.001) vs. 40.0% (120/300; OR: 4.01, 95%-CI: 2.84-5.65; p<0.001) for MOR. Once again between BFI group comparisons showed only minor differences of opioid-related analgesic effects for NCP/COP patients (Figure 6). For pain, 50% response rates for NCP/COP patients were with MOR 52.5/48.2%, for OXY 59.9/57.6%, and for OXN 69.9/69.0%. For functionality, 50% response rates were with MOR 43.8/45.8%, with OXY 46.7/51.1%, and with OXN 57.5/64.4% and for quality-of-life corresponding 50% response rates were with MOR 40.1/39.8%, with OXY 46.2/49.5%, and with OXN 75.2/66.7%.

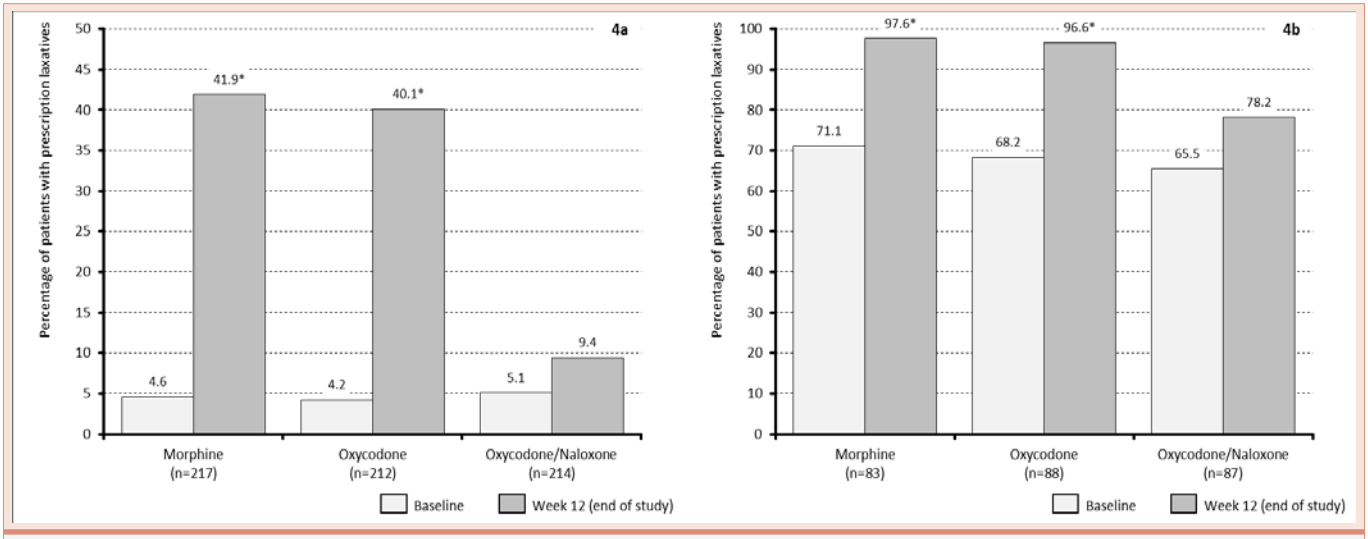

Figure 4: Proportion of non-constipated (Figure 4a, left panel) vs. constipated patients (Figure 4b, right panel) who used prescription laxatives at baseline (light grey) vs end of week 12 with morphine (left), oxycodone (middle), and oxycodone/naloxone (right).

* indicates a significant difference (p<0.001) between percentages observed at baseline vs. week 12.

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Table 4: Necessity for the prescription of laxatives due to the development of an opioid-related constipation. Data show the absolute (relative) proportion of patients who received prescription laxatives for all opioids evaluated as well as for non-constipated vs. constipated patient groups.

OIC-related extra prescription of laxatives at week 12 (only laxative naive patients at baseline)	MOR N (%)	OXY N (%)	OXN N (%)	MOR vs. OXY OR (95%-CI) / significance	MOR vs. OXN OR (95%-CI) / significance	OXY vs. OXN OR (95%-CI) / significance
All	103/231 (44.6)	101/231 (43.7)	20/233 (8.6)	1.04 (0.72-1.50) p=0.851	8.57 (5.06-14.51) p<0.001	8.27 (4.89-14.02) p<0.001
Non-constipated patients (NCP; BFI at baseline ≤28.8)	81/207 (39.1)	76/203 (37.4)	9/203 (4.4)	1.07 (0.72-1.60) p=0.725	13.86 (6.72-28.59) p<0.001	12.90 (6.24-26.67) p<0.001
Constipated patients (COP; BFI at baseline >28.8)	22/24 (91.7)	25/28 (89.3)	11/30 (36.7)	1.32 (0.20-8.64) p=0.772	19.00 (3.73-96.67) p<0.001	14.39 (3.52-58.90) p<0.001

OIC: opioid-related constipation; MOR: morphine; OXY: oxycodone; OXN: oxycodone/naloxone; OR: odds-ratio; 95%-CI: 95%-confidence interval; NCP: non-constipated patient group; COP: constipated patient group.

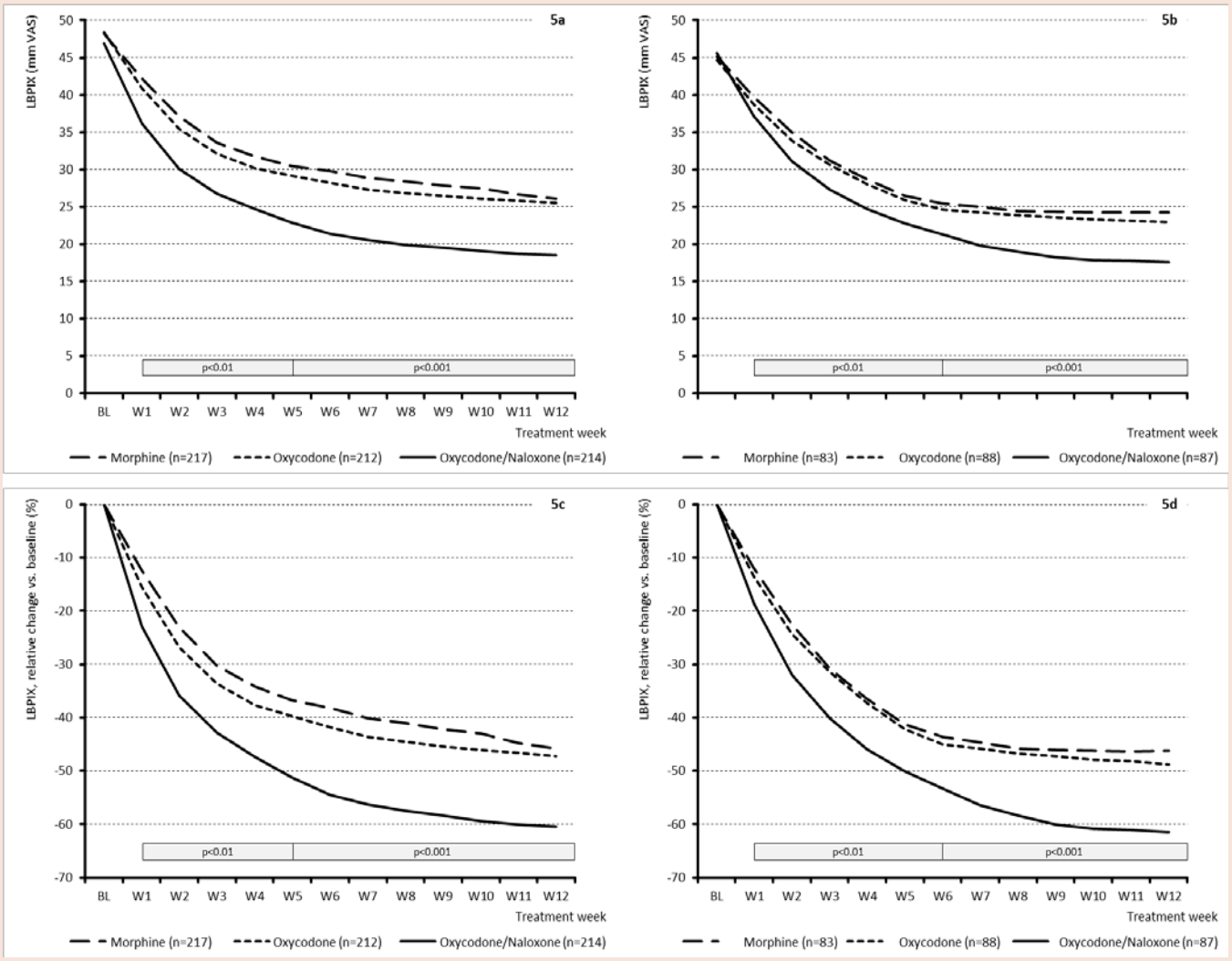

Figure 5: Absolute (5a and 5b) vs. relative change of the low back pain intensity index (LBPIX; % vs. baseline) for non-constipated (Figures 5a/c, left panel) vs. constipated patients (Figures 5b/d, right panel). LBPIX changed significantly with for all three opioid treatments in both groups vs. baseline, but significantly better with oxycodone/naloxone vs. oxycodone vs. morphine.

LBPIX: low back pain intensity index; %: percent change vs. baseline; BL: baseline; W1-W12: treatment week 1-12.

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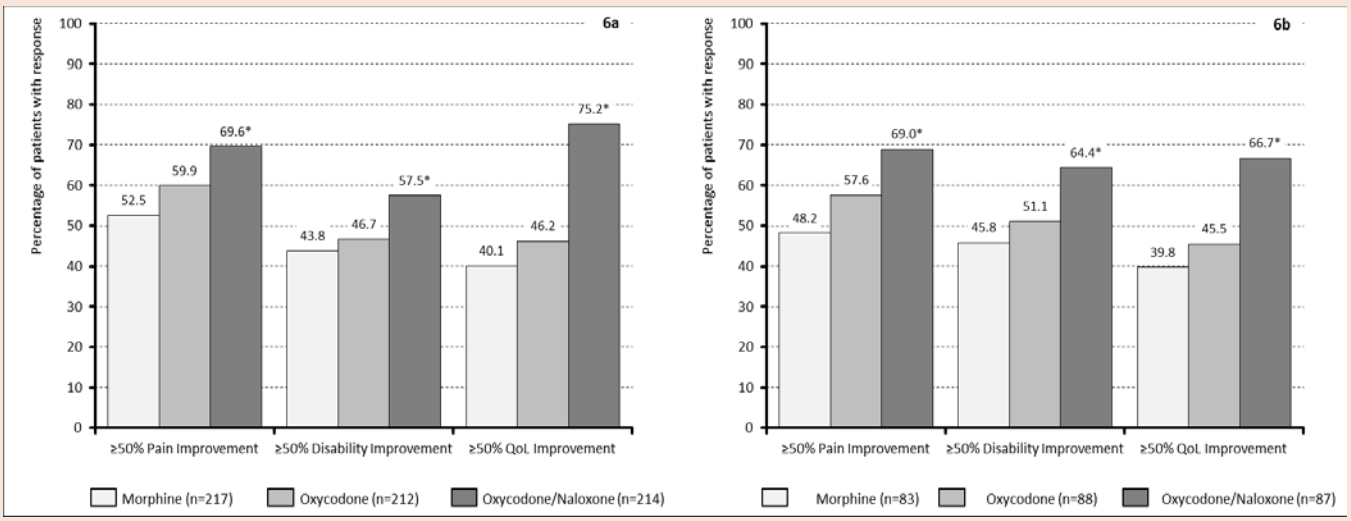

Figure 6: Proportion of non-constipated (Figure 6a, left panel) vs. constipated patients (Figure 6b, right panel) who recorded a ≥50% improvement (vs. baseline) with respect to pain intensity (left), pain-related disabilities in daily life (middle), and quality-of-life (right) at the end of a 12-week treatment with morphine (light grey), oxycodone (grey), and oxycodone/naloxone (dark grey).

* indicates a significant difference ($p<0.001$) for oxycodone/naloxone vs. morphine and vs. oxycodone.

Safety evaluation

As shown in Figures 7a, 7b, TEAEs occurred within NCP as well as COP patient groups significantly less with OXN in comparison to OXY and MOR. Overall, 13.6% of OXN patients (41/301) reported at least one TEAE in comparison to 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 15.0% (45/300) of patients. TEAE-related treatment discontinuations were seen in 7.3% of patients treated with OXN (22/301) vs. 24.7% with OXY (74/300; OR: 4.15, 95%-CI: 2.50-6.90; $p<0.001$) vs. 25.0% with MOR (75/300; 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 5) revealed that with 177 events (49.3%) the majority of those TEAEs affected the gastrointestinal tract, followed by 141 events (39.3%) affecting the central nervous system, 22 events (6.1%) affecting the metabolic system, 18 events (5.0%) affecting the skin, and 1 event classified as psychiatric

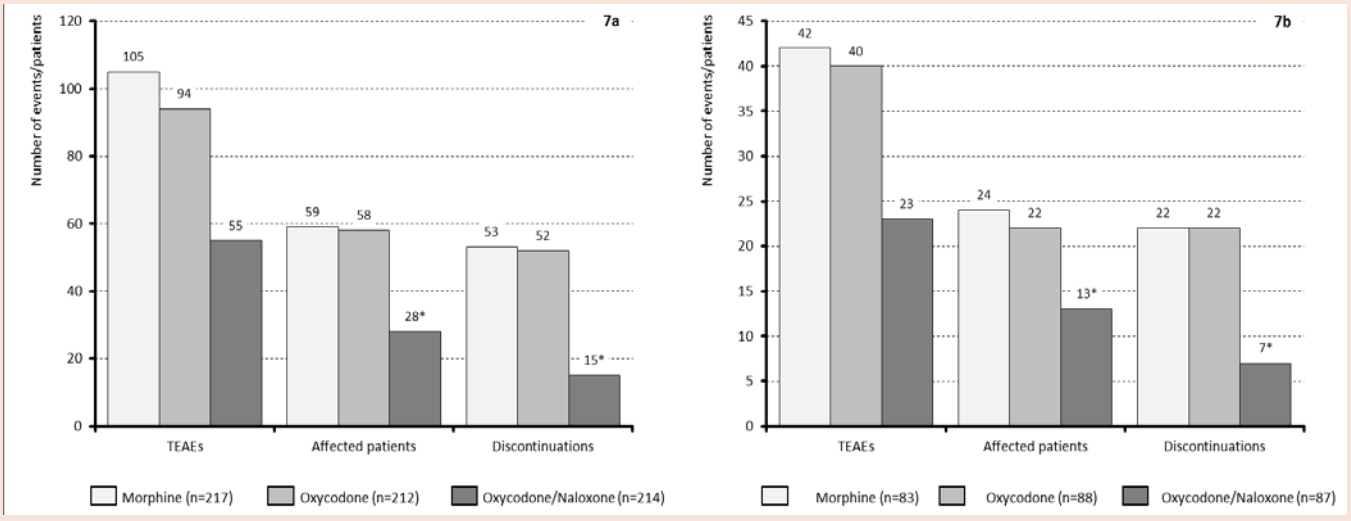

Figure 7: Number of treatment emergent adverse events (TEAEs; left), patients affected by TEAEs (middle), and patients forced to discontinue treatment due to a TEAE (right), recorded during a 12-week treatment with morphine (light grey), oxycodone (grey), and oxycodone/naloxone (dark grey) for non-constipated patients (Figure 7a, left panel) vs. constipated patients (Figure 7b, right panel).

* indicates a significant difference ($p<0.001$) for oxycodone/naloxone vs. morphine and vs. oxycodone.

Table 5: Overall treatment-emergent adverse event (TEAE) experience.

	Opioid treatment groups						BFI at baseline			
	MOR		OXY		OXN		≤28.8		>28.8	
	(n=300)		(n=300)		(n=301)		(n=643)		(n=258)	
No. of TEAEs	147		134		78		254		105	
No. of serious TEAEs	-		-		-				-	
Subjects with TEAEs	83	(27.7)	80	(26.7)	41	(13.6)	145	(22.6)	59	(22.9)
Subjects with ≥2 TEAES	45	(15.0)	41	(13.7)	25	(8.3)	79	(12.3)	32	(12.4)
Most common TEAES										
Constipation	38	(12.7)	38	(12.7)	15	(5.0)	38	(5.9)	53	(20.5)
Nausea	33	(11.0)	26	(8.7)	13	(4.3)	51	(7.9)	21	(8.1)
Somnolence	29	(9.7)	28	(9.3)	19	(6.3)	54	(8.4)	22	(8.5)
Dizziness	15	(5.0)	14	(4.7)	9	(3.0)	27	(4.2)	11	(4.3)
Vomiting	10	(3.3)	7	(2.3)	5	(1.7)	15	(2.3)	7	(2.7)
Sleep problems	6	(2.0)	6	(2.0)	5	(1.7)	12	(1.9)	5	(1.9)
Sweating	4	(1.3)	3	(1.0)	3	(1.0)	7	(1.1)	3	(1.2)
Headache	2	(0.7)	3	(1.0)	3	(1.0)	6	(0.9)	2	(0.8)
Abdominal pain	4	(1.3)	3	(1.0)	1	(0.3)	3	(0.5)	5	(1.9)
Others	6	(2.0)	6	(2.0)	5	(1.7)	12	(1.9)	5	(1.9)
Affected organ classes										
Gastrointestinal system	77	(25.7)	69	(23.0)	31	(10.3)	99	(15.4)	78	(30.2)
Nervous system	53	(17.7)	52	(17.3)	36	(12.0)	101	(15.7)	40	(15.5)
Metabolic system	10	(3.3)	7	(2.3)	5	(1.7)	15	(2.3)	7	(2.7)
Skin	7	(2.3)	6	(2.0)	5	(1.7)	13	(2.0)	5	(1.9)
Psychiatric system	-	(-)	-	(-)	1	(0.3)	-	(-)	1	(0.4)
Intensity										
Mild	24	(16.3)	21	(15.7)	16	(20.5)	43	(16.9)	18	(17.1)
Moderate	77	(52.4)	71	(53.0)	38	(48.7)	132	(52.0)	54	(51.4)
Severe	46	(31.3)	42	(31.3)	24	(30.8)	79	(31.1)	33	(31.4)
Counter measures										
None	8	(5.4)	2	(1.5)	15	(19.2)	21	(8.3)	4	(3.8)
Pharmacotherapy	4	(2.7)	4	(3.0)	8	(10.3)	7	(2.8)	9	(8.6)
Treatment discontinuation (TEAEs)	135	(91.8)	128	(95.5)	55	(70.5)	226	(89.0)	92	(87.6)
Treatment discontinuation (patients)	75	(25.0)	74	(24.7)	22	(7.3)	120	(18.7)	51	(19.8)
Treatment discontinuations for any reasons (pats.)	129	(43.0)	115	(38.3)	76	(25.2)	219	(34.1)	101	(39.1)

MOR: morphine; OXY: oxycodone; OXN: oxycodone/naloxone; BFI: bowel function index; %: percentage of patients; TEAEs: treatment emergent adverse events; pats: patients.

(0.3%). Constipation as reportable TEAE was the most frequently documented drug-related adverse event, noted with OXN / OXY / MOR in 5.0 / 12.7 / 12.7%, followed by nausea (4.3 / 8.7 / 11.0%) and somnolence (6.3 / 9.3 / 9.7%). With 17.0 and 51.8% (61/359 and 186/359) most TEAEs were classified as mild or moderate intense, and in 31.2% (112/359) as 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).

With exception of constipation (as single TEAE) and the gastrointestinal tract (as affected organ system) which were both significantly more reported by COP vs NCP patients [20.5 vs. 5.9% (53/258 vs. 38/643) for constipation (OR: 4.12, 95%-CI: 2.64-6.43; p<0.001), 30.2 vs. 15.4% (78/258 vs. 99/643) for gastrointestinal system (OR: 2.38, 95%-CI: 1.69-3.35; p<0.001)], safety analyses revealed only minor and insignificant differences between BFI groups. Reportable numerical differences between NCP/COP groups were only found for the percentages of patients requiring no specific treatment (which were with 8.3 vs. 3.8% higher for NCP vs. COP) and for those receiving a pharmacological TEAE treatment (which were with 2.8 vs. 8.6% lower for NCP vs. COP).

Discussion

OIC, the most prevalent and persistent side effect of long-term treatment with WHO-step III opioids, develops gradually and in many patients despite recommended countermeasures. Currently

Citation: *Ueberall MA, Mueller-Schwefe GHH (2015) Differential Gastrointestinal Effects of Who-Step III Opioids in Low Back Pain Patients with vs. Without Constipation: Post-Hoc Analysis of Data from a 12-Week Prospective, Open-Label Blinded Endpoint Streamlined Study. Glob J Anesthesiol 2(2): 037-051.*

available strong opioids vary significantly in their propensity to cause constipation and among those WHO-step III opioids evaluated in this study, OXN was characterized by a superior gastrointestinal tolerability and significantly less OIC compared with OXY and/or MOR, both in patients with and without a pre-existent constipation at baseline.

Likewise, individuals vary in terms of opioid-independent bowel dysfunction and consequently also with respect to their liability for distinct opioid-related side effects – such as OIC. As shown by this analysis, OIC affects not only pain patients with initially normal bowel function, but especially those with already established opioid-independent constipation. Despite comparable opioid-related BFI changes vs. baseline (24.8 vs. 22.2 mm VAS), the dimension of the finally obtained average BFI deterioration for all three opioid treatment groups differed significantly between initially non-constipated (NCP) vs. constipated pain patients (COP; 34.0 vs. 68.6 mm VAS; $p<0.001$), as in the latter ones the opioid-related effects did obviously not replace but augment the pre-existent bowel dysfunction at baseline. Not surprisingly, related changes such CSBMs or use of prescription laxatives at the end of the 12-week treatment period differed in both groups and resulted in a two-fold higher prevalence of COP vs. NCP patients with three or even less CSBMs per week (84.5 vs. 44.8%; OR: 6.72, 95%-CI: 4.63-9.74; $p<0.001$) and a comparably higher rate of laxatives users as well (79.5 vs. 34.9%; OR: 7.19, 95%-CI: 5.10-10.12; $p<0.001$).

Differential effects of the WHO-step III opioids evaluated, were comparable in both patient groups evaluated in this post-hoc analysis. Independent of the baseline BFI and the stratification of patients based upon this parameter, treatment with OXN was characterized by significantly minor BFI and CSBM changes in comparison with OXY and/or MOR. Absolute BFI changes to baseline with OXN were 9.9/10.7 mm VAS for NCP/COP at the end of the 12-week treatment course and hence not only significantly less ($p<0.001$ for each comparison) than those observed for MOR (36.5/27.3 mm VAS) or OXY (28.1/28.8) but on average also clearly below the validated threshold for a clinically relevant BFI deterioration (12 mm VAS) reported by Rentz et al. [32]. In parallel OIC-related changes in bowel function parameters (such as the percentages of individuals presenting with a BFI deterioration of at least 12 mm VAS, three or even less CSBMs per week or a decrease in CSBMs of one or more – each at week 12 vs. baseline) were significantly less with OXN vs. OXY and/or MOR. These discrepancies were neither related to differences in dosing (as daily morphine equivalents were comparable among treatment groups), nor to a different use of laxatives or related countermeasures between the treatment 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 conventional laxative regimens in OIC.

OIC is obviously not an inevitable consequence of classical WHO-step III opioids, as not all patients treated with the pure μ-receptor agonists OXY or MOR experienced a significant increase in related parameters such as the BFI or reported relevant CSBM changes. Overall, 43.1% (185/429) of NCP patients treated either with MOR or OXY presented with ´normal´ BFI scores at study end, 29.8% (128/429) experienced only minor and neither statistically significant nor clinically relevant BFI changes in response to these opioids, and 18.4% (76/429) of patients did so without any prescribed laxatives or other documented countermeasures. Although corresponding percentages for OXN were with 76.2 / 59.3 / 59.3% (163/127/127 of 214; OR: 4.22 / 3.43 / 6.78; $p<0.001$ for each comparison) significantly greater than those rates found for MOR and OXY, the percentages reported for latter ones underline that the level of our understanding of the pathophysiological mechanisms of OIC in pain patients treated with WHO-step III opioids is still insufficient.

The importance of OIC, respective its prevention by adequate countermeasures for patients suffering from chronic pain with/without an opioid-independent bowel dysfunction is highlighted by the reported differences for MOR, OXY and OXN with respect to pain relief as well as related effects on disability in daily life and overall quality-of-life. As reported, treatment with OXN was – independent of the BFI-status at baseline – not only associated with significantly less bowel dysfunction and a superior tolerability in comparison to OXY and MOR, but also with a biometrical and clinically relevant superior analgesic efficacy, which was associated with significantly superior improvements of pain-related disabilities in daily life as well as quality-of-life. Consequently, the proportion of NCP/COP patients whose overall condition improved with the opioid treatment was significantly superior for OXN vs. OXY/MOR and corresponding odds ratios of 7.2/5.8 for NCP and 6.5/6.4 for COP underline the clinical relevance of the combined opioid agonist/antagonist combination and its importance for chronic pain patients.

Overall and irrespective of the pre-existent BFI-status, 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. 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 favour of OXN vs. OXY and MOR. Spectrum of TEAEs reported was comparable to those mentioned in the current SPCs. The number of OXN patients with TEAEs was close to those reported in previous studies, however, discontinuation rates were somewhat higher, which may reflect minor differences with respect to study design and/or conduct of study.

Study limitations

This study has certain limitations. PROBE-designed studies such as those underlying the present post-hoc analysis suffer several limitations in comparison to randomized controlled trials[50]. 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, determination of endpoints in the original study was blinded. The results of the differential evaluation of

patients who presented at baseline with vs without a clinical relevant bowel dysfunction allows further insight on differential opioid-effects with respect to OIC and related health problems and expands our current knowledge how to use these agents in chronic pain patients.

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, improvement in functionality and/or quality-of-life. This post-hoc analysis of data from a prospective randomized open-label blinded endpoint 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 in patients with vs. without a pre-existent bowel dysfunction. 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 both vs. OXY and MOR – irrespective of the BFI status at baseline. Overall, this data provides evidence that the fixed agonist/antagonist combination of OXN is a safe, superior tolerated and effective alternative to conventional opioid agonists such as OXY and MOR and worth to be used first line for pain patients with and/or without opioid-independent bowel problems.

Transparency

Declaration of financial/other relationships

The concept for the original PROBE study as well as this post-hoc analysis was developed by the Institute for Neurological Sciences (IFNAP) on behalf of the German Pain Association (Deutsche Gesellschaft für Schmerzmedizin, DGS) and the German Pain League (Deutsche Schmerzliga, DSL). The original study was realized by an independent 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 and publication of the results. The current post-hoc analysis was done independently from any financial and/or intellectual influences by the authors. M.A.U and G.H.H.M-S. Are physicians and independent of any significant/relevant financial or other relationship to the sponsor, except for minor reimbursements for occasional lecture or consulting fees.

Acknowledgements

Data of the PROBE study have been presented at the World Pain Congress of the International Association for the Study of Pain (IASP), October 6-11, 2014, Buenos Aires, Argentina. Data of this post-hoc analysis will be presented at the 9th Congress of the European Pain Federation (EFIC), September 2-5, 2015, Vienna, Austria.

Authors´ contribution

All authors were equally involved in developing the conceptual framework, in the organization of the paper, in the analysis and interpretation of data presented, and in the critical revision and review of the paper. All authors have seen and approved the final paper.

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