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Observational Study

Effect of a Fixed-Dose Opioid Agonist/ Antagonist on Constipation in Patients on Long-term Opioids for Non-Malignant Pain Unable to Tolerate Laxatives

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Background: Chronic pain affects a large number of patients throughout the world and impacts greatly on their quality of life, including the ability of a patient to sleep, go to work, and socialize. Guidance on the use of opioids in chronic pain patients is available from the British Pain Society; however, patients receiving opioid treatment for their pain often suffer from symptoms associated with opioid-induced bowel dysfunction (OIBD), including constipation. The usual treatment of constipation in these patients is laxatives; however, one study has shown that 54% of patients do not receive the desired results from this approach. Oxycodone/naloxone tablets have been shown to provide analgesia to chronic pain patients, while improving the symptoms of OIBD, as the naloxone component blocks the effects of oxycodone at opioid receptors in the gut.

Objectives: The objective of the present study was to assess improvements in quality of life and bowel function in patients receiving oxycodone/naloxone tablets for their chronic non-malignant pain.

Study Design: This was a 12-week observational follow-up study that included 28 outpatients with chronic non-malignant pain attending the Pain Clinic at St. Bartholomew's Hospital in London. All patients had recently been prescribed oxycodone/naloxone tablets as treatment for their pain.

Methods: Patients were assessed at baseline, week 1, week 4, and week 12 for functioning and well-being using the Patient Assessment of Constipation Quality of Life questionnaire (PAC-QOL), and for bowel function using the Bowel Function Index (BFI).

Results: Mean PAC-QOL scores, as well as scores for each of the subscales (worries and concerns, physical discomfort, psychosocial discomfort, and satisfaction) significantly improved from baseline to week 12. Mean BFI scores significantly decreased from baseline to all time-points during the study. Subscale analysis of the BFI scores showed that mean scores for ease of defecation and judgment regarding constipation had significantly decreased at week 12; however, mean scores for feeling of incomplete bowel evacuation had not.

Limitations: The results of the current study should be interpreted in relation to the study design. However, the results are consistent with previous studies that included a comparator group, had a longer duration of treatment, and included larger patient numbers.

Conclusions: The results of this study indicate that patients receiving oxycodone/naloxone tablets achieved statistically and clinically significant improvements in bowel function as well as quality of life after 12 weeks of treatment.

Key words: Non-malignant pain, opioid, opioid-induced constipation, laxatives, oxycodone, naloxone, audit

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Chronic pain has been shown to affect a large number of patients throughout the world, with approximately 7.8 million people in the UK and 60 million people in the US reportedly suffering from pain (1-3). Chronic pain patients often report that their pain has a serious impact on their quality of life, with pain affecting their ability to sleep, go to work, and to socialize (1-3). The treatment and management of chronic pain is th erefore an area that requires an increased focus, with one study reporting that very few patients were managed by pain specialists and almost half had their pain managed inadequately (2).

The British Pain Society has issued recommendations for the appropriate use of opioids for persistent non-malignant pain, which include advice on how opioids can be incorporated into a comprehensive treatment plan (4). Controlled release oxycodone has also been shown to significantly improve pain control and provide greater improvements in the ability to cope with pain in patients suffering from moderate to severe osteoarthritis (5,6) and back pain (7).

Treatment with opioid analgesics, however, activates peripheral mu opioid receptors in the gastrointestinal tract (8,9), leading to the development of opioid-induced bowel dysfunction (OIBD). Patients suffering from OIBD report a number of symptoms including constipation, abdominal cramping, bloating, and the formation of hard, dry stools (10). If left untreated, OIBD can lead to further complications such as fecal impaction and spurious diarrhea, pseudo-obstruction of the bowel, and interference with drug administration and absorption (11). Studies have suggested that patients may discontinue their treatment to avoid the side-effects of opioid treatment (10,11), and that severe OIBD can reduce the value of analgesia by greater than 30% (8).

The usual treatments for the symptoms of OIBD are laxatives (9), including a stool softener and a stimulant laxative (10); however, these symptoms can often be refractory to even an aggressive regimen of laxative treatment (9). One study has estimated that 54% of patients receiving treatment for OIBD do not achieve the desired results with their medication even half the time (10). The ineffectiveness of laxatives to target the underlying cause (i.e., activation of μ-opioid receptors in the gut leading to opioid-induced inhibition of gastric motility as well as alterations in fluid balance) (10) and so to treat the symptoms of OIBD, has led to the development of treatments containing opioid receptor antagonists, such as naloxone, to help prevent the negative effects of opioids on receptors in the gut (9). As well as being ineffective at treating the symptoms of OIBD, laxatives themselves have the potential to cause adverse effects. Stool softeners often have a bitter taste and can cause nausea in some patients, while stimulant laxatives can cause dermatitis and electrolyte imbalances (9).

Objectives

Oxycodone/naloxone tablets (Targinact® tablets, Napp Pharmaceuticals Limited, UK) are indicated for the treatment of severe pain, which can be adequately managed only with opioid analgesics, and have been shown to provide effective analgesia as well as improving constipation in OIBD patients (12-14). The opioid antagonist naloxone is added to counteract opioid-induced constipation by blocking the action of oxycodone at opioid receptors locally in the gut. Oxycodone/naloxone tablets are licensed for use in the UK, Europe, Israel, Malaysia, Hong Kong, the Philippines, Singapore, South Korea, Australia, New Zealand, and Canada; they are not licensed for use in the US. The tablets contain prolonged-release oxycodone and prolonged-release naloxone in a 2:1 ratio (14). Naloxone, given orally, has negligible bioavailability (< 3%) (15) and is added to counteract opioid-induced constipation by blocking the action of oxycodone at opioid receptors locally in the gut. Naloxone has a much higher affinity for opioid receptors than oxycodone, so binds preferentially to these receptors. Naloxone is able to antagonize the binding of oxycodone to the opioid receptors in the gastrointestinal tract, but is almost completely metabolized by the healthy liver before it can reach the central nervous system (CNS). At the doses given in this clinical practice audit, the central effects of the oral naloxone component are minimal; however, it can have a full local inhibitory effect at opioid receptors in the gut (16). One study has shown that 10 mg naloxone can lessen the effects of 20 mg oxycodone on colon transit time, and it is believed that the principal effect of naloxone occurs in the small intestine (17). One study has presented the pharmacokinetic properties of oxycodone/naloxone tablets, and has found that these fixed-dose combination tablets are bioequivalent to single components and similar to oxycodone prolonged release and oxycodone prolonged release tablets given as separate formulations. In addition, the pharmacokinetic properties of oxycodone are not significantly influenced by the naloxone in the fixed-dose combination (18). A number of studies have shown that oxycodone/naloxone tablets can improve bowel function while maintaining

analgesic efficacy (12,14,19,20). Studies have also shown that the naloxone component of oxycodone/naloxone tablets can reduce abuse potential when compared to oxycodone tablets when given through intranasal sufflation (21), i.v. {sp} injection (22), and when given orally intact or chewed (23). Oxycodone/naloxone tablets have also been shown to be the least attractive of the oxycodone products to abuse by recreational drug users (24).

The aim of this study was to assess improvements in bowel function in patients with OIBD, who had not tolerated laxatives for their symptoms, and were now receiving oxycodone/naloxone tablets for their non-malignant pain.

Methods

This was a 12-week, observational follow-up study that took place at the Pain Clinic at St Bartholomew's Hospital, London, UK. The study was initiated on April 21, 2011, and completed on December 26, 2011.

The objective of the study was to determine if patients with chronic non-malignant pain taking a fixed dose of oxycodone/naloxone showed an improvement in symptoms of constipation as measured by the Patient Assessment of Constipation Quality of Life questionnaire (25) (PAC-QOL, Johnson and Johnson) and Bowel Function Index (26) (BFI, Mundipharma Research Limited).

Patients

Patients who were routinely attending their appointments in the outpatient Pain Clinic at St Bartholomew's Hospital in London, who were taking long-term opioids for chronic non-malignant pain were included in the study. All patients had recently been prescribed an opioid-equivalent fixed dose of oxycodone/naloxone combination tablets in response to symptoms of opioid-induced constipation, and they had either not tolerated or not responded to a laxative regimen. The diagnosis of opioid-induced constipation was based on the number of bowel movements the patient reported.

Procedure

All patients included in this clinical practice audit were started on 10 mg prolonged release oxycodone hydrochloride, 5 mg prolonged release naloxone hydrochloride tablets. Patients were then titrated to analgesic effect.

Patient data were recorded at baseline, week 1, week 4, and week 12. Data were recorded for 2 scales associated with constipation: the PAC-QOL and the BFI.

The PAC-QOL questionnaire is a standardized, validated, patient-reported outcomes measure evaluating the burden of constipation on patients' functioning and well-being. It consists of 28 items that are associated with 4 scales: worries and concerns (11 items); physical discomfort (4 items); psychosocial discomfort (8 items); and satisfaction (5 items). The PAC-QOL questionnaire has been shown to be responsive to improvements over time (25).

The BFI is a validated 3-item, clinician administered questionnaire (26). The following 3 items are rated on a numerical analogue scale (NAS): ease of defecation during the last 7 days (0 = easy/no difficulty, 100 = severe difficulty); feeling of incomplete bowel evacuation during the last 7 days (0 = not at all, 100 = very strong); and personal judgment of patient regarding constipation during the last 7 days (0 = not at all, 100 = very strong). The index is calculated as the mean of the 3 items on the questionnaire and total scores range from 0 to 100. Higher BFI scores indicate worse bowel function. A reduction of 12 points or more represents a clinically significant improvement (27).

The Brief Pain Inventory (BPI) was used to measure patients' pain at all time points during the study. This BPI is a short questionnaire containing a number of visual analogue scales from 0 to 10, measuring different aspects of pain (e.g., worst pain in the last 24 hours and pain right now) where 0 = no pain, and 10 = pain as bad as you can imagine. In addition, the BPI measures the amount of interference the patients' pain has on day-to-day life (e.g., general activity and sleep) where 0 = does not interfere, and 10 = completely interferes (28).

Statistical Analysis

Both the total and mean (range 0 – 4) scores from the items within each of the 4 scales on the PAC-QOL questionnaire, as well as the overall PAC-QOL score were calculated. The scores for the 4 scales were calculated using the following items: worries and concerns (pacq13 to pacq23); physical discomfort (pacq1 to pacq4); psychosocial discomfort (pacq5 to pacq12); and satisfaction (pacq24 to pacq28). The overall PAQ-QOL score was calculated using scores from all 28 items. The mean value from all 3 items on the BFI was calculated to give the BFI score.

A total score was calculated for the BPI, as well as sub-scores for Question 8 on the BPI questionnaire ("In the past 24 hours, how much relief have pain treatments or medication provided? Please circle the one percentage that most shows how much relief you have received").

The change from baseline to week 1, week 4, and week 12 was also calculated for all PAC-QOL, BFI, and BPI assessments. The overall scores and changes from baseline at each time-point were analyzed using a paired t-test. The null hypothesis was that the mean change was not significantly different from baseline (change = 0). Paired t-tests were performed at the 5% significance level. All statistical analyses were conducted using SAS® version 9.2.

Results

Patients

Twenty-eight patients were recruited and 16 patients (57.1%) completed the study. Of the 12 patients (42.9%) who discontinued, 5 patients (17.9%) discontinued treatment at the end of week 1, and 7 patients (25%) discontinued treatment at the end of week 4. With regards to the patients that discontinued treatment, 9 patients were lost to follow-up and 3 patients discontinued due to side-effects (diarrhea and lack of efficacy). Sixteen patients completed the week 12 assessment.

Over 70% of patients included in the study were female (Table 1). At baseline, mean age was 55.79 years and mean BPI Score was 83.71. The mean (SD) BFI score at baseline was 79.29 (19.976), indicating that patients were severely constipated at the start of the audit.

Efficacy

Mean PAC-QOL scores significantly improved from baseline to all time-points during the study (Table 2 and Fig. 1). Subscale analyses also reported a significant improvement from baseline to week 12 for worries and concerns, physical discomfort, psychosocial discomfort, and satisfaction (P = 0.002, P = 0.007, P = 0.002, and P = 0.002, respectively; Table 2 and Fig. 2).

BFI scores significantly decreased from baseline to all time-points (Table 3 and Fig. 3). Analysis of 2 items on the BFI (ease of defecation and judgment regarding constipation) also showed a significant decrease from baseline to week 12 (P = 0.002 and P = 0.003, respectively). The mean change in BFI score from baseline to week 12 for feeling of incomplete

Table 1. *Patient disposition and baseline characteristics.*

Parameter	Baseline
Gender (n[%])	
Female	20 (71.4)
Male	8 (28.6)
Age (years)	
Mean (SD)	55.79 (15.478)
Median	54.5
Range	–27 – 83
BPI Score	
n	28
Mean (SD)	83.71 (14.644)
95% CI	58.00, 107.0
BPI Q8	
n	28
Mean (SD)	32.50 (21.538)
95% CI	0.00, 70.00

Table 2. *Mean change from baseline in PAC-QOL scores.*

Parameter	Baseline	Change from baseline		
		Week 1	Week 4	Week 12
PAC_QOL				
n	28	28	23	16
Mean (SD)	2.09 (0.751)	0.41 (0.704)	0.48 (0.563)	0.48 (0.588)
95% CI	1.07, 3.04	-0.82, 1.64	-0.46, 1.32	-0.64, 1.71
P-value		0.005	< 0.001	0.005
Worries and concerns				
n	28	28	23	16
Mean (SD)	2.27 (0.954)	0.55 (0.939)	0.60 (0.801)	0.79 (0.836)
95% CI	0.64, 3.55	-1.00, 2.18	-0.36, 2.00	-0.82, 2.45
P-value		0.004	0.002	0.002
Physical discomfort				
n	28	28	23	16
Mean (SD)	2.63 (1.051)	0.73 (1.209)	0.77 (0.991)	0.91 (1.151)
95% CI	1.00, 3.75	-1.50, 3.00	-0.50, 2.25	-1.25, 2.50
P-value		0.003	0.001	0.007
Psychosocial discomfort				
n	28	28	23	16
Mean (SD)	2.11 (1.175)	0.50 (1.019)	0.68 (0.898)	0.69 (0.754)
95% CI	0.38, 3.75	-0.88, 2.13	-1.00, 1.63	-0.25, 2.88
P-value		0.015	0.001	0.002
Satisfaction				
n	28	28	23	16
Mean (SD)	1.24 (0.500)	-0.30 (0.709)	-0.32 (0.844)	-0.85 (0.902)
95% CI	0.60, 2.00	-1.20, 1.00	-1.40, 1.00	-3.00, 0.60
P-value		0.034	0.081	0.002

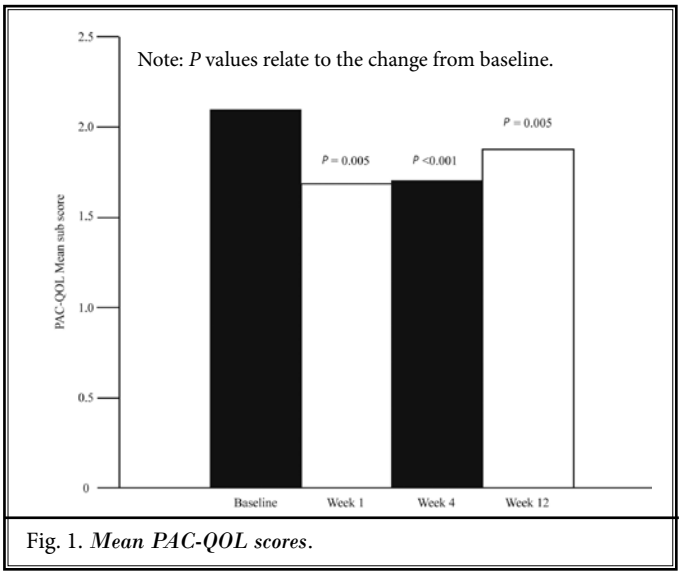

Fig. 1. ***Mean PAC-QOL scores.***

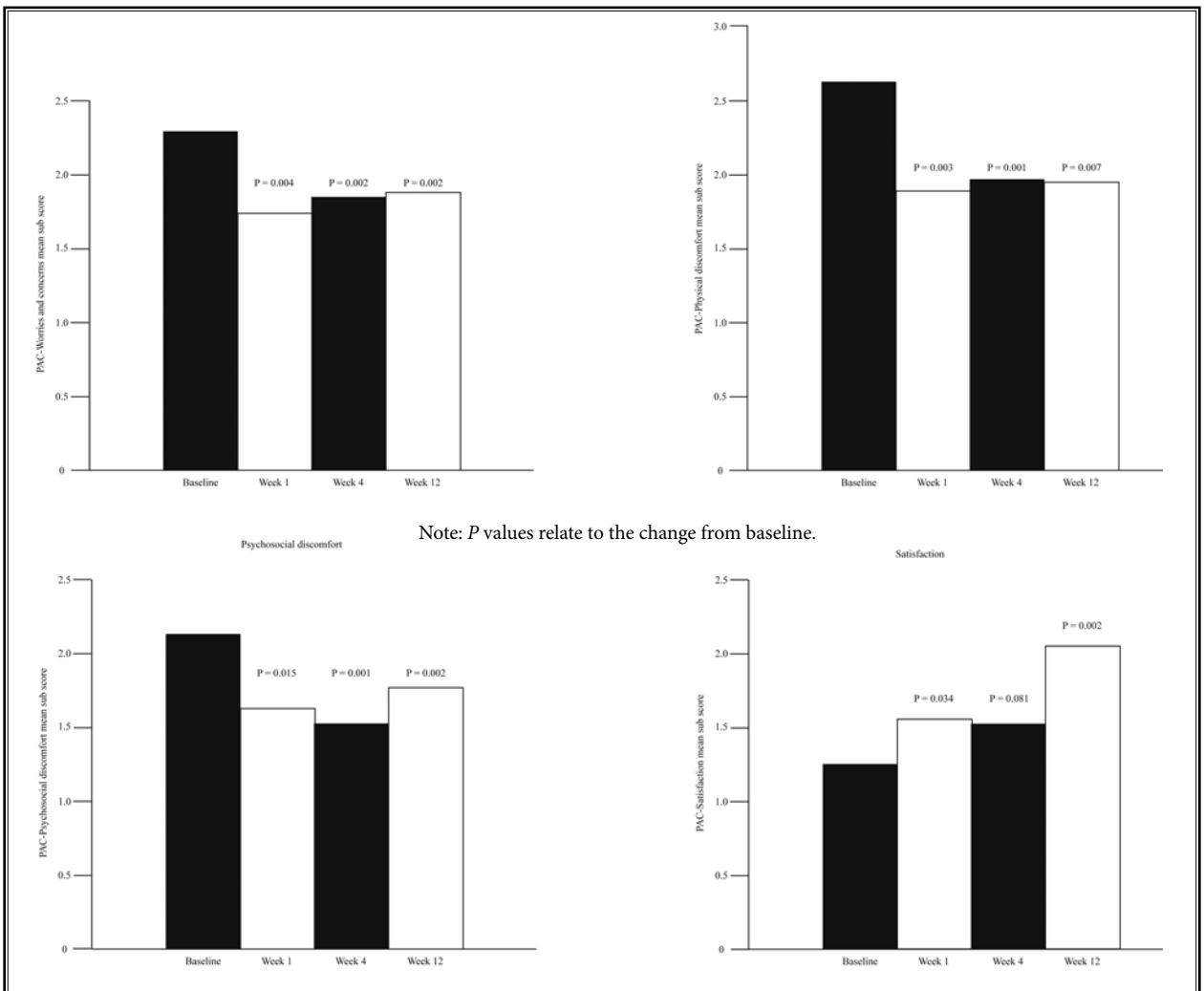

Fig. 2. ***Mean PAC-QOL scores with analytical scores.***

Table 3. *Mean change from baseline in BFI scores.*

Parameter	Baseline	Change from baseline		
		Week 1	Week 4	Week 12
BFI Score				
n	28	28	23	16
Mean (SD)	79.29 (19.976)	23.81 (35.367)	24.20 (31.216)	26.04 (30.110)
95% CI	41.67, 100.0	-45.0, 90.00	-10.0, 83.33	-21.7, 70.00
P-value		$P = 0.001$	$P = 0.001$	$P = 0.004$
Ease of defecation				
n	28	28	23	16
Mean (SD)	80.18 (18.781)	24.11 (33.639)	22.61 (30.891)	28.13 (29.262)
95% CI	50.0, 100.0	-40.0, 90.0	-30.0, 80.0	-30.0, 70.0
P-value		$P < 0.001$	$P = 0.002$	$P = 0.002$
Feeling of incomplete bowel evacuation				
n	28	28	23	16
Mean (SD)	75.71 (22.637)	20.00 (37.093)	19.78 (37.794)	16.88 (34.345)
95% CI	45.00, 100.0	-35.00, 90.00	-25.00, 90.00	-55.0, 60.00
P-value		$P = 0.008$	$P = 0.020$	$P = 0.068$
Judgment regarding constipation				
n	28	28	23	16
Mean (SD)	81.96 (24.050)	27.32 (37.577)	30.22 (30.840)	33.13 (36.873)
95% CI	30.00, 100.0	-50.0, 90.00	0.00, 80.00	-50.0, 90.00
P-value		$P < 0.001$	$P < 0.001$	$P = 0.003$

bowel evacuation was not statistically significant; however, as the change from baseline was greater than 12 points, this was clinically significant (Table 3).

Patient BPI scores decreased over the course of the study from baseline to all time-points; however, these decreases were not statistically significant (Table 4). There was however, a significant increase from baseline to week 12 in the percentage of pain relief patients received from pain treatments/medication provided to them throughout the course of the study (Table 4).

Discussion

Patients receiving opioid treatment for their chronic non-malignant pain often report symptoms of OIBD, including constipation, abdominal cramping, and bloating (10). These symptoms are often inadequately treated with laxatives (9,10) and if left untreated could lead to further complications (11). The 28 outpatients participating in this study received oxycodone/naloxone tablets as treatment for their non-malignant pain for a total of 12 weeks. In this formulation, the opioid antagonist naloxone counteracts OIBD at the source by blocking the action of oxycodone at opioid receptors in the gut, to help prevent symptoms of OIBD.

Results for both the PAC-QOL and BFI questionnaires indicate that patients receiving oxycodone/naloxone tablets for their non-malignant pain who have not tolerated a laxative regimen showed significant improvements in bowel function and quality of life after 12 weeks of treatment.

The results of this clinical practice audit should be interpreted in relation to the study design and the patient population. The audit included patients that presented to the clinic with opioid-induced constipation, and so no formal sample size calculation was done. No control group was included with which to compare the results from the treatment group, and the study completed after 12 weeks of treatment. Although the majority of patients included in the study were receiving at least one laxative treatment, the exact medications taken and doses received are unknown. However, the results are in line with findings already published for patients receiving oxycodone/naloxone tablets for chronic non-malignant pain. Studies have shown that patients receiving oxycodone/naloxone tablets report a significant improvement in BFI scores when compared

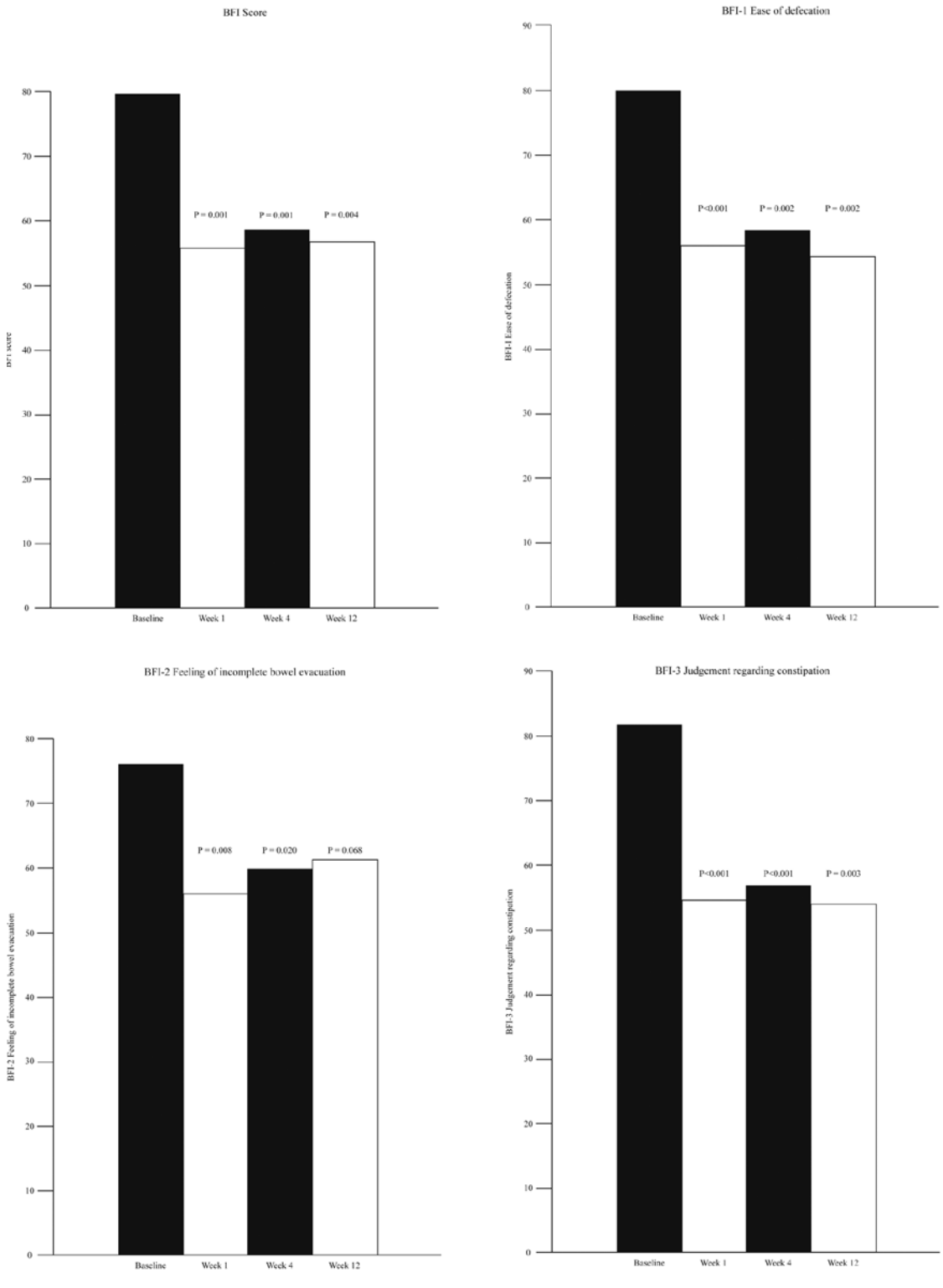

Fig. 3. *Mean BFI scores.*

Table 4. *Mean change from baseline in BPI scores.*

Parameter	Week 12	Change from baseline
BPI Score		
n	16	16
Mean (SD)	81.13 (16.484)	5.06 (10.711)
95% CI	38.00, 102.0	-15.0, 20.00
P-value*		0.078
BPI Q8		
n	16	16
Mean (SD)	51.56 (18.048)	-14.06 (22.302)
95% CI	20.00, 80.00	-50.0, 30.00
P-value†		0.023

*The changes from baseline to week 1 and week 4 were also not significant ($P = 0.341$ and $P = 0.167$, respectively).
†The changes from baseline to week 1 and week 4 were also not significant ($P = 0.468$ and $P = 0.260$, respectively).

to patients receiving oxycodone tablets after 12 weeks of treatment (12,14). Patients also reported a higher number of spontaneous bowel movements and reduced laxative use (12,14). These benefits were achieved without any loss of analgesic efficacy. An additional study reported that patients receiving oxycodone/naloxone tablets had an average 15-point reduction in BFI score after 12 months (13). In addition, the fact that these studies, which randomized larger numbers of patients (12,13,14), also reported similar improvements in bowel function with patients receiving oxycodone/naloxone tablets, indicates that the results in the 28 outpatients included in this study are reliable.

Conclusion

The results of this study indicate that patients receiving oxycodone/naloxone tablets showed statistically and clinically significant improvements in bowel function as well as quality of life after 12 weeks of treatment, as measured by the PAC-QOL and BFI questionnaires. Therefore, chronic non-malignant pain patients experiencing OIBD symptoms as a result of their opioid treatment, and who have had inadequate relief from laxatives, could benefit from treatment with oxycodone/naloxone tablets.

Acknowledgments

Author contributions

Drs. V Mehta (FRCA MD FFPMRCA), S Alawad (FRCA MD FFPMRCA), S Kuravinakop (MBBS DA FRCA), and S Nikolic (FRCA FFPMRCA) had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Drs. V Mehta, S Alawad, S Kuravinakop, and S Nikolic designed the study protocol. Dr. Nicola Berg wrote the first draft of the manuscript. Drs. V Mehta, S Alawad, S Kuravinakop, and S Nikolic provided revision for intellectual content and final approval of the manuscript.

Conflict of interest

The authors have not received any reimbursement or honorarium in any other manner. Dr V Mehta and Dr S Nikolic have acted as consultants for Napp Pharmaceuticals for educational meetings and received honorarium.

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