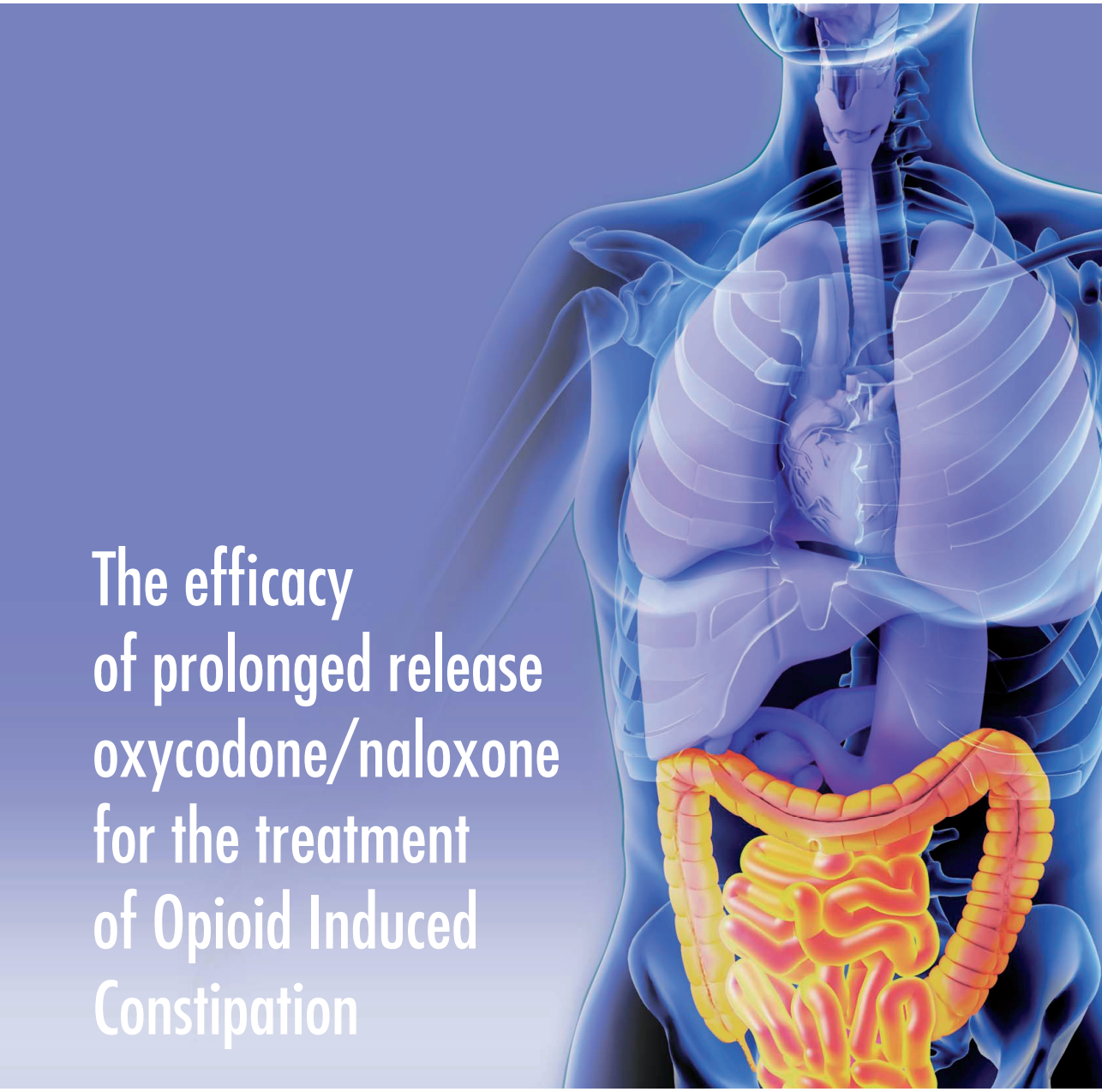
Gineke Koopmans-Klein



The efficacy of prolonged release oxycodone/naloxone for the treatment of Opioid Induced Constipation

From clinical trial to daily practice

Gineke Koopmans-Klein

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From clinical trial to daily practice

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From clinical trial to daily practice

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Thesis

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Voor André, Marit, Niels en Lieke

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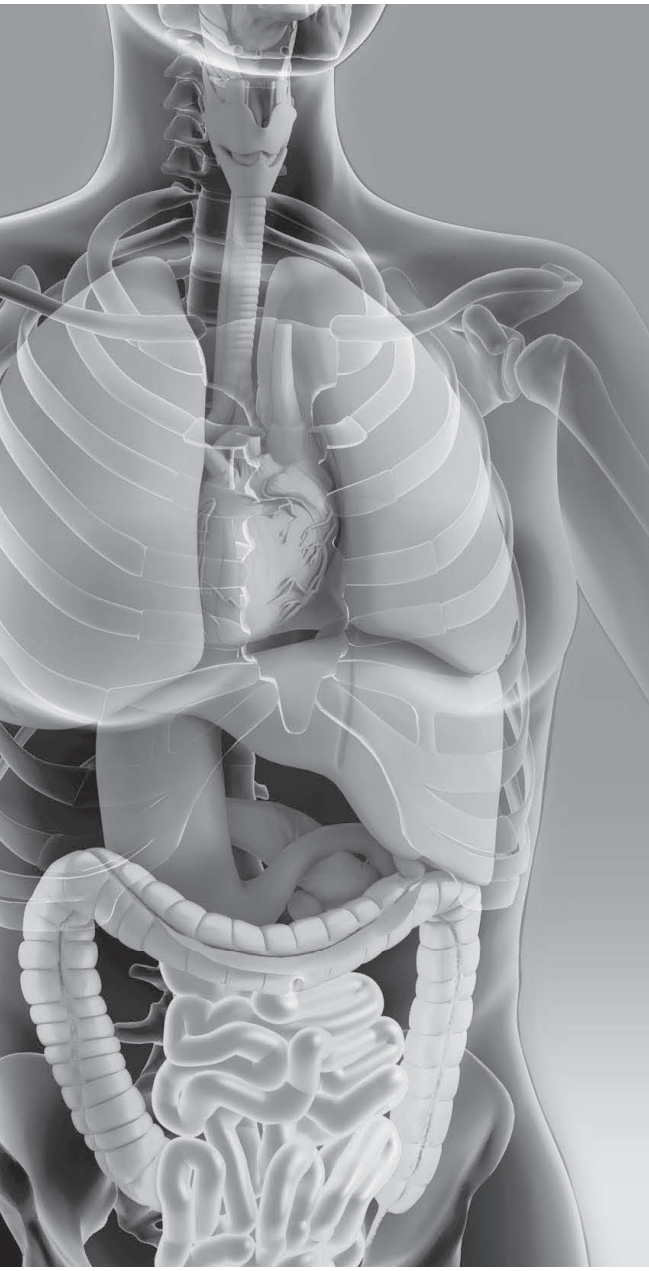

Chapter 1

Introduction

Binding of opioids to μ-receptors within the gastrointestinal (GI) tract can lead to impairment of motility and secretion and induce a variety of symptoms, including nausea, gastro-paresis, secondary pseudo-obstruction and constipation[1]. This complex of impairment and symptoms is called Opioid Induced Bowel Dysfunction (OIBD)[1-3]. OIC is the most common symptom of OIBD[2-7].

In 2014 a consensus definition for OIC was agreed upon and by consensus, OIC is defined as follows: "A change when initiating opioid therapy from baseline bowel habits that is characterized by any of the following: reduced bowel movement frequency, development or worsening of straining to pass bowel movements, a sense of incomplete rectal evacuation, or harder stool consistency"[1]. Other associated symptoms of OIC are: bloating, acid reflux, rectal pain and nausea[8,9]. OIC is a common side effect of opioid treatment and in contrast to other side effects of opioid treatment patients do not develop a tolerance to constipation[2-7]. In literature the incidence of OIC varies between 15-90% of patients on opioid treatment[3,10-13]. Besides opioid use also other factors can contribute to the development of constipation in patients on opioid treatment. Factors that have been identified are disease progression, dehydration, other medications (like chemotherapeutic agents), immobility and age[10,14,15].

Pathophysiology

The effects that opioids have on the physiological function of the GI tract have been extensively studied in animal models and humans[1,2,8-10]. OIC develops predominantly as a result of activation of enteric μ-opioid receptors which are distributed throughout the GI tract[1,2]. They mediate a number of effects that influence the function of the GI-tract when activated by opioids[1,2].

Activation of the enteric μ-opioid receptors by opioids for example: causes non-peristaltic contractions, decreases gastric motility and emptying, increases pyloric sphincter tone; decreases GI, biliary, and pancreatic secretions; inhibits peristalsis in the small and large intestines; increases the amplitude of non-propulsive segmental contractions in the small intestine; increases water absorption from bowel contents; increases anal sphincter tone; and constricts the sphincter of Oddi [2,16].

The combined action of opioids on inhibition of GI emptying, GI motility, GI transit, intestinal fluid secretion and the enhancement of absorption contribute to the constipating effect of opioids; as these effects are localized to the GI tract, it is called peripheral action[2].

Besides the physical burden of OIC and OIC associated symptoms, OIC has a major impact on patient's quality of life (QoL)[10,12,17-19]. Significant differences are detected in QoL between patients depending on the presence and severity of OIC[17,20]. Besides a direct

impact of OIC and associated symptoms on QoL, OIC also has an impact on the treatment of pain. Literature has described that OIC can be intolerable to patients. Nearly 2/3 of patients changed the opioid dose; either lowering the dose (10.2%) or skipping doses and/or irregular use (7.5%) or discontinued opioid treatment (5.4%) all at the expense of analgesic efficacy[2,12,18,20]. The interference of OIC with pain management also results in a decrease of QoL[20].

Pharmacological treatment of OIC

In current practice the advice for treatment and prevention of OIC is to treat patients on opioid analgesics prophylactically with a laxative regime in addition to lifestyle modifications, such as increased exercise, greater fluid intake, and dietary changes[1,2]. The pharmacological component of the laxative regimen may include stool softeners, bulking agents, osmotic agents, and stimulant-type laxatives[1,3,21]. In some cases, two or more laxatives with complementary mechanisms of action may be prescribed, such as a stool softener plus a stimulant. Rectal laxatives, including stimulant suppositories such as bisacodyl, lubricants such as glycerin, and enemas are sometimes used, although care should be taken with enemas to preserve the patient's electrolyte balance[1,3,21].

Despite this laxative regimen, literature describes that some patients still experience OIC and/or do not tolerate the adverse events of the laxative regime; i.e. patients with laxative-refractory OIC[12,19]. Also literature describes that laxatives are ineffective to treat OIC[1,2]. Moreover, treatment with laxatives causes side effects and complications[3,14].

In Dutch clinical practice a prophylactic laxative regime is advised consisting of treatment with at least one laxative in an adequate dosage (e.g. macrogol plus electrolytes or lactulose) and if needed addition of a second laxative of a different therapeutic class (e.g. bisacodyl)[22,23]. As the efficacy of this laxative regime for the treatment and prevention of OIC has not been established yet, a pilot study was conducted to explore the efficacy of the current Dutch prophylactic laxative regime under conditions of daily practice.

Over the last decade opioid receptor antagonists like methylnaltrexone, naloxegol and naloxone are increasingly being used for the pathophysiological treatment of OIC[24-26]. Currently described peripherally-acting μ-opioid receptor antagonists (PAMORA's) in literature are methylnaltrexone (MNTX), naloxegol, alvimopan and naldemedine[1,2]. Another agent described in literature is prolonged release combination of oxycodone and naloxone (PR OXN), although it acts on peripheral opioid receptors it is sometimes considered to be another agent as it relies on the drug combination[2]. PAMORA's and PR OXN block opioid actions at peripheral opioid receptors that mediate decreased intestinal secretion and propulsive colonic motility[1,2]. By blocking μ-opioid receptors in the

gut, there is restoration of the function of the enteric nervous system, and propulsive motility and secretory functions can be generated by local enteric neural circuits in response to physiologic stimuli such as meal ingestion, or sensation of a bolus to evoke normal peristalsis[1,2].

As the number of PAMORAs increase it is important to explore their efficacy not only in randomized controlled trials but also in real-life settings and when possible explore their efficacy in comparison to each other. A systematic review and meta-analysis was performed to obtain more insights in the efficacy of these opioid receptor antagonist for the treatment of OIC.

The aim of this thesis was to further elucidate the efficacy of PR OXN, specifically for patients with laxative-refractory OIC. PR OXN combines the opioid receptor agonist oxycodone and the opioid receptor antagonist naloxone. When administered orally, a reduction of constipation can be achieved due to a local action of naloxone in the gut without affecting pain relief by oxycodone[27-29]. PR OXN has proven equivalent analgesic efficacy to prolonged release oxycodone (PR OXY) with significant improvements in bowel function in chronic non-malignant pain[30-35] as well as in moderate/severe malignant pain[36-38].

In order to gain more insights in the efficacy of PR OXN in patients with laxative-refractory OIC a post-hoc analysis was designed to explore the efficacy of PR OXN in this specific population. Moreover, two additional observational studies were designed in which patients (with and without laxative-refractory OIC) were treated as in daily practice in Belgium with PR OXN, investigating the efficacy of treatment in a real-life situation.

As treatment with PR OXN is more expensive than treatment with PR OXY, it was also important to assess cost utility of PR OXN treatment for laxative-refractory patients, therefore also a cost-utility analysis was performed.

The results of the studies in this thesis add to the current knowledge of opioid antagonist treatments, especially PR OXN treatment, specifically in patients with laxative-refractory OIC. Moreover, the results may, hopefully, improve treatment of OIC in this specific patient population.

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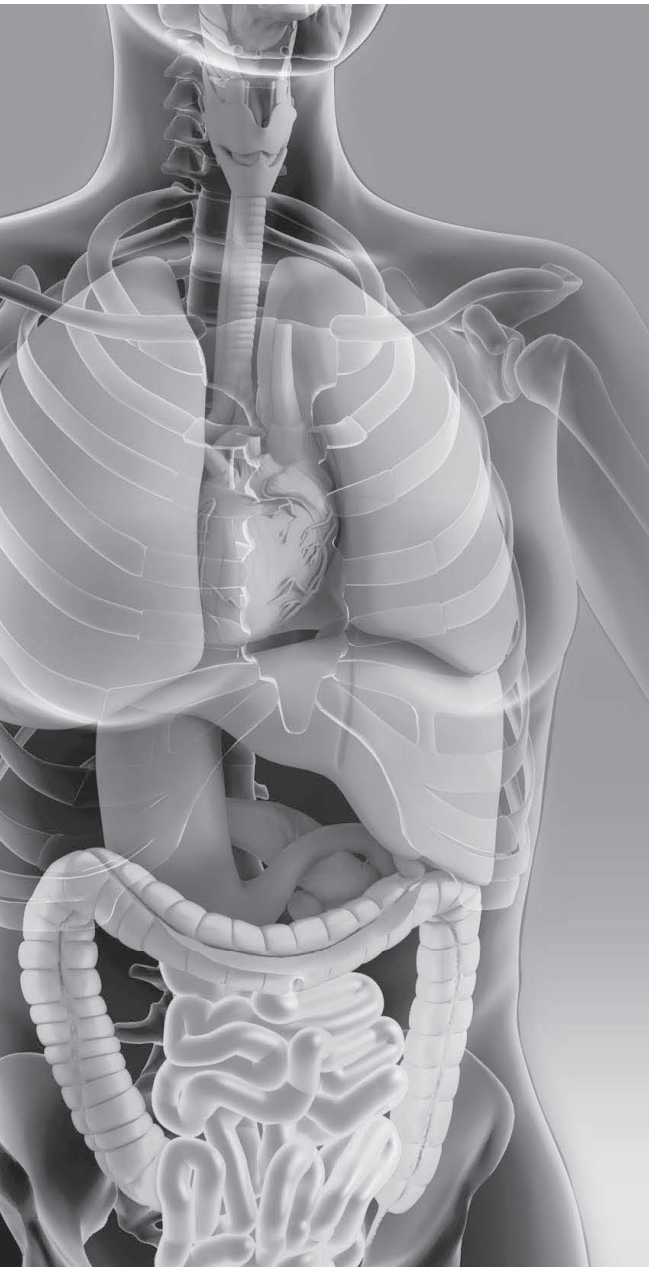

Chapter 2

The efficacy of standard laxative use for the prevention and treatment of opioid induced constipation during oxycodone use: a Dutch small observational pilot study.

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ABSTRACT

Objective

Dutch clinical guidelines recommend that a standard laxative treatment (SLT) should be prescribed concomitantly when starting opioid treatment to prevent opioid-induced constipation (OIC).

Clinical evidence for SLT in the treatment of OIC is lacking, therefore an observational pilot study was performed to explore the efficacy and tolerability of SLT on OIC in patients treated with the opioid oxycodone.

Results

Twenty-four patients (58% female, median (range) age 65 (39-92)) were included in this pilot study. The analysis showed that 9 out of 21 patients (43%) were non-responders to SLT. When also taking into consideration patients tending to develop diarrhea 75% of patients are non-responsive to SLT.

Conclusion

This pilot study indicates that optimal laxative therapy (SLT) might not be effective and feasible for the prevention and treatment of OIC.

INTRODUCTION

Opioids are an option for the pharmacological treatment of moderate to severe pain and are generally used when non-opioid treatments are ineffective or contra-indicated [1-3]. A significant disadvantage of all opioid use is opioid induced constipation (OIC). Although there might be variation in occurrence of OIC depending on the type of opioid used, OIC is a side effect of all opioids and has a negative impact on pain treatment, quality of life and daily activities [4-12].

Opioid induced constipation (OIC)

To date OIC is defined as: 'A change when initiating opioid therapy from baseline bowel habits that is characterized by any of the following: reduced bowel movement frequency, development or worsening of straining to pass bowel movements, a sense of incomplete rectal evacuation, or harder stool consistency'[12]. OIC is characterized by three major symptoms: hard and dry stools, impeded and painful defecation and significantly less frequent stools than normal for the patient (in general defined as less than 3 bowel movements per week). Other associated symptoms are flatulence, colic pain and pelvic pressure pain [4, 13-16]. OIC can lead to an increased morbidity and even mortality of patients. It can result in bleeding, pain, gastro-intestinal reflux, nausea, vomiting and rectal pain as well as hemorrhoids, diverticular disease and fecal impaction [4, 13-16]. Severe OIC can result in complications like fecal impaction with paradoxical diarrhea and incontinence, bowel obstruction, bowel rupture, pseudo-obstruction with anorexia, urine retention with overflow incontinence and delirium[6, 14]. Surveys in patients suffering from OIC have shown that OIC also has an impact on the treatment of pain. Almost 2/3 of patients change their opioid dosage; patients change to a lower dose (10.2%), skip dosages and/or are using opioids irregularly (7.5%) or stop using opioids for their pain management (5.4%) [6, 11]. Moreover, OIC can in itself also be a cause for pain; the majority of patients with OIC report pain caused by OIC. Pain caused by OIC results in more discomfort than pain caused by the underlying condition [6, 11, 17].

Current management of OIC in Dutch clinical practice

Management of OIC usually consists of non-pharmacological and pharmacological approaches. The international consensus is that treatment of OIC should be focused on the prevention of OIC rather than treatment of already manifest OIC [12, 18-22]. Pharmacologcial treatments include osmotically acting laxatives (e.g. magnesium oxide, lactulose and polyethylene glycol), stimulant laxatives (e.g. bisacodyl and sennosides), stool softener (e.g. liquid paraffin and sodium docusate), bulk forming laxatives (e.g. isphagula and methylcellulose) or enema's (e.g. sodium laurylsulfate and sodium phosphate). When these laxatives fail opioid antagonists like oxycodone/naloxone combina-

tion, methylnaltrexone or naloxegol can be considered. These treatment possibilities for OIC have already been reviewed in several recent publications by Nelson et al., Argoff et al. and Camilleri et al.[12, 21, 22]

In the Netherlands pharmacological treatment for constipation due to opioid therapy is described in Dutch clinical guidelines regarding treatment of cancer pain and for the treatment of constipation[23, 24]. These guidelines recommend that laxatives should be concomitantly prescribed when starting opioid treatment [23, 24]. As literature on treatment of OIC at time of guideline development was sparse and non-conclusive, the recommendations were predominantly based on expert opinion taking in consideration the high incidence of OIC in patients treated with opioids, the harm it can cause for patients and practical experience [23, 24].

First choice treatments in the Dutch guidelines were defined based on available studies at time of guideline development; treatments of first choice are the osmotically acting laxative lactulose and polyethylene glycol plus electrolytes (which is also considered to be bulk forming) of which PEG plus electrolytes is the most prescribed laxative. If these are not effective enough addition of a stimulant laxative like bisacodyl (orally or rectally) can be considered[23, 24].

Next to the recognition of OIC in the Dutch guidelines a quality indicator was set up within the Dutch Health Care Transparency Program ensuring that all patients with an opioid prescription also had a prescription of a laxative, in order to improve outpatient drug safety [25, 26]. The Institute for Rational Use of Medicines (IVM) published the 2013 results of this quality indicator in the Monitor Prescribing Behavior Practitioners. The calculation of the quality indicator was based on reimbursement data of community pharmacists and dispensing general practitioners collected by Vektis, a national data-center for healthcare insurers. These data showed that on average 49% (median 48%, range 33-64%) of patients on opioids were prescribed a laxative together with their opioid prescription[27]. Also data from the Dutch Foundation for Pharmaceutical statistic, gathering data from more than 95% of the community pharmacies in the Netherlands, show that in 90% of participating community pharmacies less than 60% of patients were prescribed a laxative together with their opioid prescription in 2013 [28]. These results show that, despite implementation of the quality indicator, physicians do not always follow guidelines. Moreover, the Dutch laxative guidelines can be interpreted in different ways.

However, to date two main interpretations of the Dutch laxative guidelines are used with respect to laxative treatment schedules: 1. Provide a laxative prescription together with the opioid prescription and use laxative on an as needed basis and 2. Standard laxative treatment (SLT) consisting of intake of laxative together with the opioid on a daily basis, starting at day one. Laxative use is reduced in case of development of diarrhea and increased when not effective or on increase of opioid dose . The effect of "as

needed" intake of laxatives was already clearly visible in clinical trials investigating the efficacy of prolonged-release oxycodone/naloxone where laxative use in the control arm was "as needed" [29-35]. Interestingly, the impact of the SLT for laxative intake has not been investigated yet. Moreover, there are no unambiguous incidence- and/or prevalence rates for failure of laxatives in OIC. In this report a descriptive analysis of an observational pilot study is described investigating the efficacy of laxative treatment according to SLT in the Netherlands with respect to bowel function and tolerability as well as patient handling of laxatives.

PATIENTS AND METHODS

A prospective observational study was performed investigating a standard laxative treatment regime (SLT) consisting of prophylactic daily intake of polyethylene glycol (PEG) with electrolytes and bisacodyl as needed. This SLT was started together with opioid-intake at day 1. Nine centers in the Netherlands, in which the laxative regimen PEG with electrolytes and bisacodyl was standard of care, participated. Since patients were treated as they would have been treated in daily practice and were not subject to additional procedures the study did not fall under the scope of the Medical Research Involving Human Subjects Act. The Agreement on Medical Treatment Act and the Personal Data Protection act did apply. All patients who were prescribed at least 2x10 mg oxycodone Slow Release (SR) and the SLT regime were followed for 28 days by their physician. No other in- and exclusion criteria were applied.

Bowel function was measured with the Bowel Function Index (BFI), a measure which is specific and validated for OIC (BFI[36]; Copyright for the BFI is owned by Mundipharma Laboratories GmbH, Switzerland 2002; the BFI is subject of European Patent Application Publication No. EP 1 860 988 and corresponding patents and applications in other countries). A BFI below 28.8 is considered normal (not constipated) in opioid-treated patients and a decrease of at least 12 points in BFI is considered clinically relevant [36-39].

In addition, the Bristol Stool Form Scale (BSFS) was used to assess bowel function. BSFS gives an indication of the type of stool from watery stools (diarrhea) to dry and hard lumps (constipation). Type 1 and 2 indicate constipation, type 3 and 4 represent normal stools, type 5 represents a stool tending towards diarrhea and type 6 and 7 represent diarrhea [40]. Analgesia was measured with a numerical pain score (Numerical Rating Scale (NRS), 0-100). Laxative use (daily dosage and treatment duration) as well as adverse events were also registered.

Descriptive analyses of the results are presented. To evaluate the efficacy of the SLT regime a responder analysis was performed.

Responder analysis: A responder to laxative treatment was defined as:

1. a patient with a clinically relevant improvement of already present constipation (decrease of BFI with 12 points or more) or as a patient who did not develop constipation as measured with the BFI (BFI remains below 30 points throughout the observation) **AND**
2. a patient without development of diarrhea (type 6 or 7 of the Bristol Stool Form Scale) **AND**
3. a patient without early discontinuation due to adverse events of laxative treatment.

RESULTS

Of the nine centers asked to participate six included a total of 24 patients in the period July 2012 until October 2013. The majority of patients were female (58%), which is consistent with the patient population with chronic pain, median (range) age of patients was 65 (39-92) years, and all but one patient had non-malignant pain. At the start of the study 22 of 24 patients had severe pain (pain NRS score ≥60). Table 1 describes the demographics of the included patient population. The average (sd) pain score decreased from 74.2 (14.5) (median(range) 80 (30-90)to 53.0 (26.2) (median(range) 53 (5-90)) after 4 weeks of treatment.

Table 1: Demographics of included patients

Gender	
male, n (%)	10 (42%)
female, n (%)	14 (58%)
Median (range) age (yrs)	65 (39-92)
Previous medication, n(%)	
WHO-step I	5 (21%)
WHO-step II	11 (46%)
WHO-step III	6 (25%)
adjuvantia	2 (8%)
Painscore (NRS) at start of observation	
average (sd)	74 (14)
median (range)	80 (30-90)
Origin of pain, n (%)	
malignant	1 (4%)
non-malignant	23 (96%)
BFI at start of observation	
average (sd)	26.6 (27.3)
median(range)	21.8 (0-77)
Patients with BFI>28.8 at start of observation, n (%)	9 (37.5%)

Table 2 lists the BFI at study start, at the final visit and the delta BFI, as well as the highest value of the Bristol Stool Form Scale and the three criteria of the responder analysis. For three patients data were insufficient to perform a responder analysis.

Table 2: Patient-level data of constipation at start of study (based on BFI≥28.8), BFI at start of study, BFI at study completion, highest BSFS value during the study, individual responder parameters and responder analysis

						Responder analysis			
Patient	**Constipated at start (Y/N)**	**BFI start**	**BFI end**	**ΔBFI**	**BSFS: Highest type during study**	**patient achieved a decrease in BFI ≥12 or had a BFI<28.8 during observation (Y/N)**	**patient did not experience diarrhea (type 6 or 7) during the observation (Y/N)**	**patient did not experience adverse events due to laxative use (Y/N)**	**responder (Y/N)**
1	N	7	6.7	-0.3	6	Y	N	Y	N
2	N	6.7	3.3	-3.4	5	Y	Y	Y	Y
3	N	0	0	0	5	Y	Y	Y	Y
4	N	1.7	3.3	1.6	5	Y	Y	Y	Y
5	N	20	20	0	4	Y	Y	Y	Y
6	N	23.6	20	-3.6	5	Y	Y	Y	Y
7	N	16	12	-4	4	Y	Y	Y	Y
8	Y	77	43	-34	7	Y	N	Y	N
9	Y	60			4		Y	Y	
10	Y	50	43	-7	6	N	N	Y	N
11	Y	50	23	-27	6	Y	N	Y	N
12	Y	56	30	-26	4	Y	Y	Y	Y
13	N	0	23	23	5	Y	Y	Y	Y
14	N	16.6	46.7	30.1	5	N	Y	Y	N
15	Y	50	43.3	-6.7	5	N	Y	Y	N
16	N	0	13.3	13.3	6	Y	N	Y	N
17	Y	53	50	-3	3	N	Y	N	N
18	N	20	20	0	5	Y	Y	Y	Y
19	N	0	0	0	5	Y	Y	Y	Y
20	N	0	0	0	5	Y	Y	Y	Y
21	N	0	10	10	6	Y	N	Y	N
22	Y	53			2		Y	Y	
23	N	0			3		Y	Y	
24	Y	77	50	-27	5	Y	Y	Y	Y

At the start of the observational study 38% (9/24) of patients already suffered from constipation (BFI>30), constipation could even be rated as severe OIC (BFI>50). Five of these 9 patients were using WHO-step 3 medication, 3 were using WHO-step 2 medication and one patient was using WHO-step 1 medication only (diclofenac+paracetamol). Despite the observed constipation (based on BFI) none of the patients were using laxatives on a regular (daily) basis as recommended in the Dutch guidelines. At study start all patients (constipated and non-constipated) were switched to standard laxative treatment regime with daily intake of PEG+electrolytes and as needed bisacodyl (orally).

The responder analysis showed that 9 out of 21 patients (43%) were non-responders to SLT. Of the 7 patients with severe OIC at start of the study (BFI>50) completing the observation, 5 were non-responders (71%).

Non-responsiveness was primarily due to constipation (BFI) and the development of diarrhea. Only one patient experienced adverse events that were clearly related to the laxative use according to the investigator. Based on BFI-results laxative use was not effective in 4 patients, i.e. 1 non-constipated patient developed constipation despite the use of laxatives and 3 constipated patients did not reach a clinically relevant improvement of BFI. Another problem of laxative use appeared to be the development of diarrhea (a BSFS type 6 or 7) in 6 patients.

Further investigation of laxative use could be performed for 20 out of 24 patients (83%); these patients returned patient diaries with information on laxative use (data missing for patient 7, 9, 22 and 23). From the returned patient diaries it could be derived that less than half of the patients took daily laxative intake as defined in SLT, 9 out of 20 patients (45%) switched to laxative intake on an ''as needed basis" (patient 6, 8, 11, 12, 16, 17, 18, 21 and 24). In 5 out of 9 cases this switch from "intake on a daily basis starting at day 1 with the opioid" to ''as needed" laxative intake' was due to problems with daily laxative intake, like the development of diarrhea (4 out of 9) or adverse events caused by laxatives (1 out of 9). For the other 4 patients no reason for the switch to "as needed" laxative intake could be identified from the patient diaries. The switch to an "as needed" laxative intake by the patients resulted in a daily dose of PEG+electrolytes which varied per patient and even within patients between 0-3 sachets per day (according to the SmPC of PEG+electrolytes daily dose is 1-2 sachets). For the 5 patients using additional biacodyl the daily dose of bisacodyl varied between 5-20 mg.

DISCUSSION

OIC is a common opioid-related side effect, which may vary between opioids, and it is known to have a major impact on opioid treatment, pain and quality of life, justifying a strong need for clear guidance. Unfortunately, the current Dutch guidelines on

prophylactic laxative treatment are not helpful in this respect. The two main interpretations of the recommendations in the guidelines are: 1. Prophylactic daily intake of a concomitant standard laxative regime (SLT) starting together with first opioid-intake at day 1 and 2. Intake of laxatives together with the opioid on an ''as needed basis".

This pilot study was designed to explore the impact of SLT on OIC during treatment with the opioid oxycodone. Only patients on oxycodone were enrolled, to avoid variation in results due to differences within opioids, moreover oxycodone is the most prescribed opioid in the Netherlands.

This pilot study shows that the efficacy of laxatives is highly variable. 43% of patients did not respond to the treatment with laxatives in a defined SLT regime. The percentage of non-responders was much higher for patients who had severe OIC (BFI>50) at study entry; 71% of these patients did not respond to SLT. These results are reflected in the literature in which 40-70% of all opioid treated patients eventually develop OIC [19, 41]. This suggests that SLT might not be effective for the prevention and treatment of OIC, however the results need to be confirmed in a clinical study with a larger number of patients.

It is well-known that laxatives do not address the actual cause of OIC [37]. Laxatives stimulate bowel-motility in the colon, while OIC is predominantly caused by inhibition of the motility of the small intestine[42, 43]. This might be an explanation why, in daily practice, laxatives are not always effective in the prevention and treatment of OIC [18, 41, 44, 45].

Another more common problem with laxative use is the development of laxative-related side effects[46]. Diarrhea, one of the common side effects of laxative use, was also noted in this pilot study. 6 patients developed diarrhea (type 6 and 7 of the BSFS). When looking more closely at patients with type 5 of the BSFS, we found that 11 patients tended to develop diarrhea and only 6 patients had an ideal stool consistency (type 3 and 4 of the BSFS). Using a BSFS of 5 as cut-off value for diarrhea would result in 18 out of 24 patients (75%) being classified as non-responders to laxative treatment.

Moreover, in this pilot study 45% of patients switched from daily laxative intake in the SLT to " as needed" laxative intake. In half of the patients switching from ''daily intake" to an ''as needed intake" the development of diarrhea and other adverse events were responsible for this switch. Interestingly, the development of diarrhea was already anticipated in the guidelines; laxative treatment could potentially result in the development of diarrhea resulting in lowering or skipping of laxative dosages[19].

Although evidence is limited for laxatives in the treatment and prevention of OIC, laxatives are still considered a first-line treatment for OIC because of their accessibility, safety and low costs[12, 21]. This pilot study adds to already present data that laxatives might not be adequate for the prevention and treatment of OIC[47]. A more pharmacological treatment approach targeting the opioid receptors with opioid antagonists (e.g.

oxycodone/naloxone, methylnaltrexone and naloxegol) might be a good alternative for the treatment and prevention of OIC[12, 21, 22].

A limitation of this pilot study is the exploratory nature of the study. In order to design a clinical trial investigating prevention of OIC with a defined SLT taken concomitantly with opioid intake from day 1 some information is required concerning efficacy of this SLT regime. However, existing clinical trials are sparse and inconclusive necessitating a pilot study investigating the efficacy of SLT.

Another limitation of this pilot study was the impeded recruitment of patients. This might be caused by a resistance of physicians to treat patients with SLT. For most patients an ''as needed'' laxative treatment was expected to be more appropriate to treat and prevent OIC. Slow patient inclusion has been described before in studies addressing laxative regimens. In 2009 de Graeff et al. started a project to assess the efficacy of two laxatives (polyethylene glycol (PEG) with electrolytes versus magnesium(hydr) oxide) on the prevention of OIC. This project was terminated early due to insufficient patient recruitment (5 patients in 1.5 years) (source: http://www.zonmw.nl/nl/projecten/project-detail/preventie-van-obstipatie-bij-gebruik-van-opioiden-magnesiumhydroxide-versus-macrogolelektrolyte/voortgang/). This illustrates that patient recruitment is a problem in studies investigating the efficacy of defined SLT for the prevention of OIC.

CONCLUSION

In conclusion, this pilot study indicates that optimal laxative therapy (SLT), as defined by intake of laxatives starting on day 1 together with the opioid, might not be effective and feasible for the prevention and treatment of OIC. The responder analysis showed that 43% of patients were non-responders to SLT and results suggested that responder rate was even lower (71%) in patients with severe OIC (BFI>50). When taking into consideration patients tending to develop diarrhea 75% of patients are non-responsive to SLT. These results show that a larger clinical study is warranted investigating the efficacy and tolerability of SLT for the prevention and treatment of OIC.

TRANSPARANCY

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authors were involved in the development, writing, critical reviewing and approval of this manuscript.

Declaration of financial/other relationships

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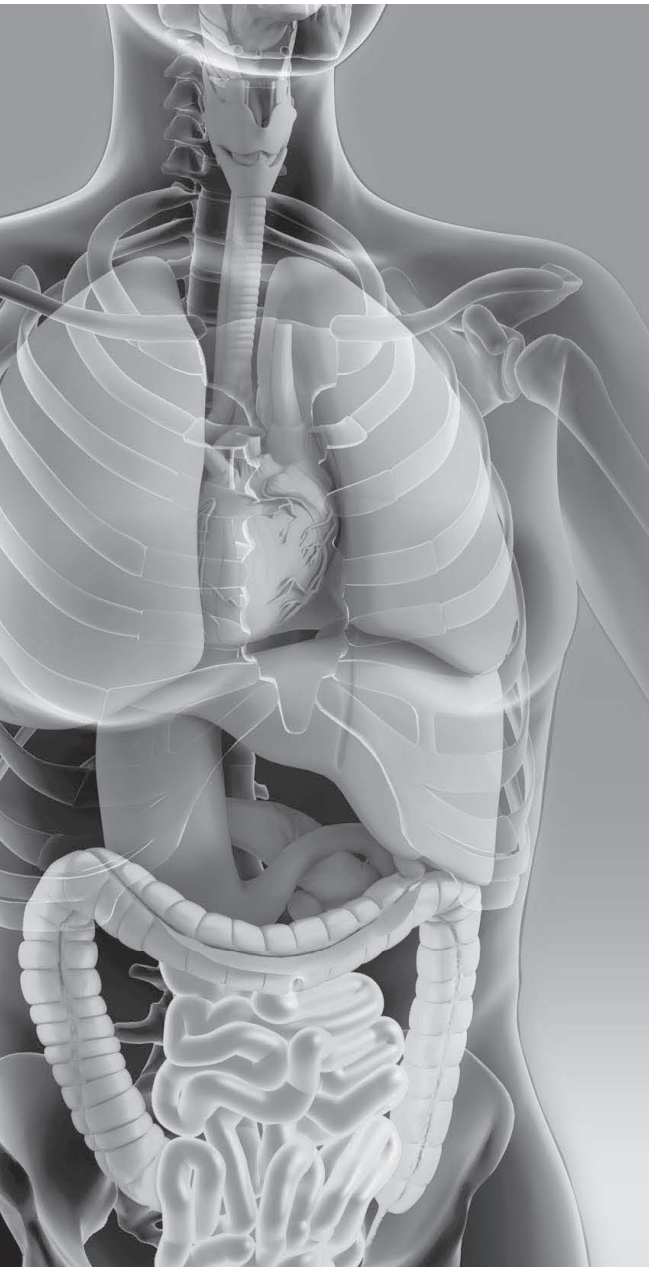

Chapter 3

Systematic review and meta-analysis of peripherally acting opioid receptor antagonists (oxycodone/naloxone combinations, methylnaltrexone, naloxegol and other PAMORA's) for opioid induced constipation during opioid treatment in patients with chronic pain

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ABSTRACT

Background

Opioid-induced constipation (OIC) is a common and dominant adverse effect of opioid treatment. Current treatment standards of OIC advice general non-pharmacological measures, like dietary advices and exercise, and the treatment with non-specific laxatives like bisacodyl, poly ethylene glycol with electrolytes and lactulose. Over the last decade peripherally acting mu-opioid receptor antagonists (PAMORAs) and other agents have been developed for the treatment and prevention of OIC. Currently approved agents by the European Medicines Agency (EMA) for OIC are methylnaltrexone (MNTX), naloxegol, alvimopan, naldemedine and prolonged release oxycodone/naloxone (PR OXN).

Objectives

As the number of PAMORAs increase it is important to explore their efficacy not only in randomized controlled trials but also in real-life settings and when possible explore their efficacy in comparison to each other. Therefore we performed a systematic literature review to describe the current evidence for the efficacy of opioid receptor antagonists in the treatment of opioid induced constipation caused by opioid treatment in patients with chronic pain.

Methods

A systematic review and analysis in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines was performed. Medline, the Cochrane Central Register of Controlled Trials, Embase, Web of Science and Google Scholar were searched, without language restrictions. Included studies were randomized controlled trials as well as prospective observational studies, we excluded animal studies, review studies and retrospective analyses.

Selection criteria

The studied population was adult patients on opioids for treatment of pain. The interventions used should be peripherally acting (locally or non-systemically acting) opioid receptor antagonists (like oxycodone/naloxone combinations, methylnaltrexone, naloxegol, alvimopan and other PAMORA's). Exclusion criteria were studies including subjects treated for addiction in methadone maintenance programs or with buprenorphine/naloxone combinations, studies on healthy volunteers with opiate- or opioid-related constipation as a model to mimic the condition of patients on opioids, animal studies and basic laboratory-based research.

Data collection and analysis

For the data synthesis and the statistical analysis Review Manager (RevMan) and the GRADEpro Guideline Development Tool were used.

Main results

We included 57 articles in the meta-analysis clustered them based on unique studies, as for some studies multiple papers appeared. This resulted in the identification of 38 unique studies (13 RCTs and 25 observational studies). For all unique studies outcomes were extracted. The proportion of patients obtaining normal bowel function (according to ROME-3 criteria) was evaluated in 12 RCTs (2 naloxegol, 2 PR OXN, 2 MNTX, 3 alvimopan and 3 naldemedine RCTs). In these trials, 2812 patients received a drug and 2042 received control treatment. Treatment with opioid antagonists resulted in a statistically significant improvement of bowel function compared with rescue laxative use when looking at the proportion of patients with normal bowel movements according to ROME 3-criteria (RR:1.56; 95% CI 1.37-1.76; P<0.00001), although there was significant heterogeneity between the RCTs. The quality of the evidence varied from low too high, overall the risk difference of the proportion of patients with normal bowel function on opioid antagonist treatment was 206 (136 to 280) more per 1,000 treated patients. Besides the proportion of patients with normal bowel function all other assessed parameters were in favor of opioid antagonist treatment.

Analysis of observational study data showed that the vast majority of observational study data were generated for PR OXN. For PR OXN 15 studies were identified that included patients with OIC at study start (n=17085). The studies mainly differed in the included pain population (e.g. non-malignant pain, malignant pain, elderly, neuropathic pain and laxative refractory pain patients), resulting in considerable heterogeneity. Despite the heterogeneity the mean weighted improvement in BFI was -29.22 95 % CI [-35.22, -23.22] (p<0.00001) similar to the improvement seen in the RCTs -27.4 95%CI [-19.1 to -35.7]. Another 10 studies with PR OXN were identified that included patients without OIC at study start (n=4693). The mean weighted improvement was -3.38 95% CI [-10.37, 3.61]. The studies differed substantially, mainly in the included pain population (e.g. non-malignant pain, malignant pain, elderly, neuropathic pain and laxative refractory pain patients), resulting in considerable heterogeneity (I2=96%, Chi2=215.39, df=9).

Conclusion

Opioid antagonists, have been approved for the treatment of opioid induced constipation for a decade (first approval in EU dating from 2008 for PR OXN and MNTX). Despite approval and growing consensus with regard to using these agents in clinical practice the uptake in formal guidelines is still minimal. Together with the study by Nee et al. 2018

(describing the safety and efficacy with regard to non-responders on opioid antagonists) this study provides further evidence on the efficacy with respect to bowel function and pain of opioid antagonists, like naloxegol, alvimopan, naldemedine, PR OXN and MNTX, in the treatment of OIC in patients with opioid treatment for chronic pain.

BACKGROUND

Opioid-induced constipation (OIC) is a common and dominant adverse effect of opioid treatment affecting up to 80% of patients treated with opioids[1-4]. OIC is frequently reported to be the most bothersome side effect associated with opioid therapy [2,5-7]. OIC has a negative impact on patients' quality of life, and has also been shown to be associated with lower work productivity, absenteeism and significant utilization of healthcare resources[2,6-9].

In the gastro-intestinal (GI) tract mu-opioid receptors are located throughout the entire enteral nervous system[10,11]. At a physiological level opioids cause inhibition of GI emptying by delaying GI transit, stimulating nonpropulsive motor activity, increasing intestinal tone, increasing fluid absorption by prolonging contact time, and decreasing the secretion of electrolytes and water into the intestinal lumen.[10-12]. Pancreatic, biliary, and intestinal secretions are depressed by opioid administration. The combined inhibition of intestinal fluid secretion and the enhancement of absorption contribute to the constipating effect of opioids[11,12]. At the tissue level, opioids exert effects on the smooth muscle located along the GI tract[4,11,12]. At the molecular level binding of opioids to GI-localized mu-opioid receptors inhibits gut motility. Opioids inhibit the firing of secretomotor and submucosal neurons as well as the release of vesicular-stored presynaptic neurotransmitters from these neurons[11,12]. Opioids inhibit the effects of the autonomic nervous system on GI smooth muscle and, thereby, decrease propulsive motility along the GI tracts[11,12]. Opioids further suppress GI motility by increasing autonomic nervous system sympathetic activity, which is mediated by enhanced release of vesicular-stored norepinephrine (noradrenaline) that subsequently acts on presynaptic α2-adrenoceptors located on enteric neurons[11,12]. The combined inhibition of enteric nerve activity, inhibition of propulsive motor activity and the inhibition of ion and fluid secretion all contribute to the development of constipation by opioid analgesics[11,12].

Current treatment standards and guidelines of OIC advice general non-pharmacological measures, like dietary advices and exercise, and the treatment with non-specific laxatives like bisacodyl, poly ethylene glycol with electrolytes and lactulose. However, about half of all opioid treated patients requiring laxatives do not achieve satisfactory relief from OIC, as most used laxative treatments for OIC are non-specific and do not

target the underlying cause of OIC[13-15]. Furthermore, laxatives themselves may lead to gastrointestinal adverse events and complications[4,13,15].

Over the last decade peripherally acting mu-opioid receptor antagonists (PAMORAs) and other locally, non-systemically acting agents have been developed for the treatment and prevention of OIC. In this review PAMORAs like methylnaltrexone (MNTX), naloxegol, alvimopan and naldemedine were considered as was as the locally, non-systemically acting prolonged release combination of oxycodone and naloxone (PR OXN)[12].

Peripherally-acting opioid receptor antagonists and the prolonged release combination of oxycodone and naloxone (PR OXN) block opioid actions at peripheral opioid receptors that mediate decreased intestinal secretion and propulsive colonic motility[10,12]. By blocking μ-opioid receptors in the gut, there is restoration of the function of the enteric nervous system, and propulsive motility and secretory functions can be generated by local enteric neural circuits in response to physiologic stimuli such as meal ingestion, or sensation of a bolus to evoke normal peristalsis[10,12].

As the number of PAMORAs increase it is important to explore their efficacy not only in randomized controlled trials but also in real-life settings and when possible explore their efficacy in comparison to each other. Therefore we performed a systematic literature review to describe the current evidence for the efficacy of opioid receptor antagonist in the treatment of opioid induced constipation caused by opioid treatment in patients with pain. The review questions of this publication is: What is the efficacy of opioid antagonists and PAMORA's with regard to improvement of OIC? Also the efficacy in special subgroups (e.g. laxative-refractory patients) was assessed when available.

METHODS

We conducted the systematic review and analysis in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines[16].

Data Sources and Searches

We searched Medline, the Cochrane Central Register of Controlled Trials, Embase, Web of Science and Google Scholar from inception to August 4th 2016, without language restrictions. The search strings for the different databases are depicted in table 1. We also manually checked reference lists of the identified reports and relevant reviews to identify potentially eligible articles. On February 8th, 2018 a PubMed search was performed searching published papers between August 4th 2016 to February 8th, 2018 to identify new RCT's using the PubMed search string depicted in table 1.

Table 1: Overview of used search strings per database.

Database	Search string
Embase.com	('narcotic analgesic agent'/exp OR (buprenorphine* OR fentanyl* OR hydromorphone* OR morphine* OR opioid* OR opiate* OR oxycodone* OR tapentadol* OR tramadol* OR (narcotic* NEXT/1 analgesic*)):ab,ti) **AND** ('constipation'/mj OR (constipat* OR obstipat* OR ((bowel* OR intestin*) NEAR/3 (function* OR dysfunction*))):ab,ti) **AND** ('opiate antagonist'/exp OR (((opioid* OR opiate*) NEAR/4 (antagonist*)) OR alvimopan* OR methylnaltrexone* OR naloxegol* OR naloxone* OR PAMORA*):ab,ti) **NOT** ([animals]/lim NOT [humans]/lim) **NOT** ('conference abstracts'/it)
Medline Epub (Ovid)	(exp "Analgesics, Opioid"/ OR exp "Morphinans"/ OR "Fentanyl"/ OR "Tramadol"/ OR (buprenorphine* OR fentanyl* OR hydromorphone* OR morphine* OR opioid* OR opiate* OR oxycodone* OR tapentadol* OR tramadol* OR (narcotic* ADJ1 analgesic*)).ab,ti.) AND ("Constipation"/ OR (constipat* OR obstipat* OR ((bowel* OR intestin*) ADJ3 (function* OR dysfunction*))).ab,ti.) AND (exp "Narcotic Antagonists"/ OR (((opioid* OR opiate*) ADJ4 (antagonist*)) OR alvimopan* OR methylnaltrexone* OR naloxegol* OR naloxone* OR PAMORA*).ab,ti.) **NOT** (animals NOT humans).sh. **NOT** (abstracts).pt.
Cochrane Central	(buprenorphine* OR fentanyl* OR hydromorphone* OR morphine* OR opioid* OR opiate* OR oxycodone* OR tapentadol* OR tramadol* (narcotic* NEXT/1 analgesic*)):ab,ti AND (constipat* OR obstipat* OR ((bowel* OR intestin*) NEAR/3 (function* OR dysfunction*))):ab,ti AND (((opioid* OR opiate*) NEAR/4 (antagonist*)) OR alvimopan* OR methylnaltrexone* OR naloxegol* OR naloxone* OR PAMORA*):ab,ti
Web of Science	**TS=(**(buprenorphine* OR fentanyl* OR hydromorphone* OR morphine* OR opioid* OR opiate* OR oxycodone* OR tapentadol* OR tramadol* (narcotic* NEAR/1 analgesic*)) **AND** (constipat* OR obstipat* OR ((bowel* OR intestin*) NEAR/2 (function* OR dysfunction*))) **AND** (((opioid* OR opiate*) NEAR/3 (antagonist*)) OR alvimopan* OR methylnaltrexone* OR naloxegol* OR naloxone* OR PAMORA*) **NOT (**animal* OR mice OR mouse OR rat OR rats **NOT** (human* OR patient*)**)) AND DT=**(Article)
Google Scholar	buprenorphine|fentanyl|hydromorphone|morphine|opioid|opiate|oxycodone|tapentadol|tramadol constipation|obstipation|"bowel|intestine function|dysfunction" antagonist|alvimopan|methylnaltrexone|naloxegol|naloxone|PAMORA
Additional PubMed search Feb 8th	(buprenorphine*[tiab] OR fentanyl*[tiab] OR hydromorphone*[tiab] OR morphine*[tiab] OR opioid*[tiab] OR opiate*[tiab] OR oxycodone*[tiab] OR tapentadol*[tiab] OR tramadol*[tiab]) AND ((constipat*[tiab] OR obstipat*[tiab]) OR ((bowel*[tiab] OR intestin*[tiab]) AND (function*[tiab] OR dysfunction*))) AND (alvimopan*[tiab] OR methylnaltrexone*[tiab] OR naloxegol*[tiab] OR naloxone*[tiab] OR naltrexone*[tiab] OR naldemedine*[tiab] OR PAMORA*[tiab]) NOT (animals[mesh] NOT humans[mesh])

Study Selection

Two reviewers (G. K. and Y. v. M.) independently assessed the eligibility of studies. Discrepancies, if any, were resolved by consensus by a third independent investigator (F.H.). Included studies were randomized controlled trials as well as prospective observational studies, we excluded animal studies, review studies and retrospective analyses. The prospective observational studies were divided in studies with prospective control arms and studies without control arms. All studies had to comply with predefined in- and exclusion criteria.

Study in- and exclusion criteria

Included studies had to comply with the following inclusion criteria. The studied population was adult patients on opioids for treatment of pain. The sample size (n) of each arm (or no. of included patients in case of uncontrolled studies) was set at n≥10. The interventions used should be peripherally acting (locally or non-systemically acting) opioid receptor antagonists (like opioid/naloxone combinations (PR OXN), methylnaltrexone (MNTX), naloxegol, alvimopan and other PAMORA's). Exclusion criteria were studies including subjects treated for addiction in methadone maintenance programs or with buprenorphine/naloxone combination, studies on healthy volunteers with opiate- or opioid-related constipation as a model to mimic the condition of patients on opioids, animal studies and basic laboratory-based research as well as studies with a group size of <10.

Outcome measures

The primary endpoint was opioid induced constipation (OIC). There is not one specific measure for OIC. A systematic review and consensus article by Gaertner et al.[17] has suggested that when measuring OIC a combination of outcomes should be measured, consisting of objective outcome measures, patient reported outcome measures and patient-reported global burden measures of OIC. Therefore the measures evaluated when looking at OIC consisted of a) objective measures of bowel movements (e.g. proportion of patients with normal bowel function based on ROME-3 criteria, complete spontaneous bowel movements [CSBM], spontaneous bowel movements [SBMs], rescue medication free bowel movements [RFBM], and bowel movements [BM], time to laxation, transit time, laxation within 4 hours and Brsitol Stool Form Scale [BSFS]) b) patient reported outcome measures (like Bowel Function Index [BFI], Patient Assessment of Constipation-symptom score [PAC-SYM], Global Clinical Impression of Change [GCIC]) c) patient-reported global burden measures of OIC (like Patient Assessment of Constipation-Quality of Life [PAC-QoL] and constipation distress) and d) additional laxative use. Secondary endpoint of the systematic search was pain relief measured with scales like Numeric Rating Scale (NRS), Numeric Analogue Scale (NAS), Verbal Rating Scale (VRS) or Verbal Analogue Scale (VAS).

Data Extraction and Quality Assessment

The predetermined outcome measures were extracted from each included study. The following items were recorded per study: registry number; registry number of extension study; treatment groups; study sample size; length of follow-up; and relevant patient characteristics including age, sex, predominant indication of pain. Two reviewers independently evaluated the potential risk of bias of each trial according to the GRADE-evaluation systematic.

Data Synthesis and Statistical Analysis

For the data synthesis and the statistical analysis Review Manager (RevMan) [Computer program]. (Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) and the GRADEpro Guideline Development Tool [Software] (McMaster University, 2015, developed by Evidence Prime, Inc.., Available from gradepro.org) were used. As all data were prospectively generated relative risks (RR), were used as summary statistics for binary variables, resulting in more easily interpretable data. Weighted (standardized) mean differences (WMDs) were effect estimates for continuous variables. The RR with a 95% CI as well as the W(S)MDs with 95% were derived from published study data. No enquiries for missing variables were performed. .

RCTs and prospective observational studies were analyzed separately. Not all outcomes were present in all studies. Only outcomes that were identified for multiple substance were compared. Pooled analyses were calculated with fixed-effect models (Mantel–Haenszel method) or random-effect models (DerSimonian and Laird) according to the extent of heterogeneity. Heterogeneity was assessed with the I^2 statistic and the Chi^2-test (Cochran Q-test). A p-value < 0.10 indicates significant heterogeneity and I-squared of 0% to 40%, 30% to 60%, 50% to 90% and 75% to 100% represent heterogeneity that might not be important, moderate heterogeneity, substantial heterogeneity and considerable heterogeneity, respectively. To test the robustness of the findings, we performed, when available, subgroup analyses on laxative refractory patients. Publication bias was assessed visually by performing Funnel plot analyses.

RESULTS

Study Selection and Characteristics

The systematic literature review identified 1279 unique citations and the additional literature check in PubMed on February 8th retrieved another 77 citations resulting in 1356 citations of which the title/abstracts (tiab) were independently scanned by 2 researchers as described by Bramer et al. 2017 using EndNote[18]. 1004 abstracts were dismissed by both reviewers and another 54 articles were discussed between both authors and thereafter dismissed. Resulting in 1058 excluded citations. The resulting 298 articles were reviewed again on article type. A further 226 articles were dismissed for being review articles, articles that were not in English or German, articles that were cost-effectiveness studies or articles that were abstracts presented on congresses. Together this resulted in the definite inclusion of 72 articles in the systematic review (Figure 1)[4,15,19-89]. Although sample size was part of the inclusion and exclusion parameters none of the studies were dismissed solely based on this criterion.

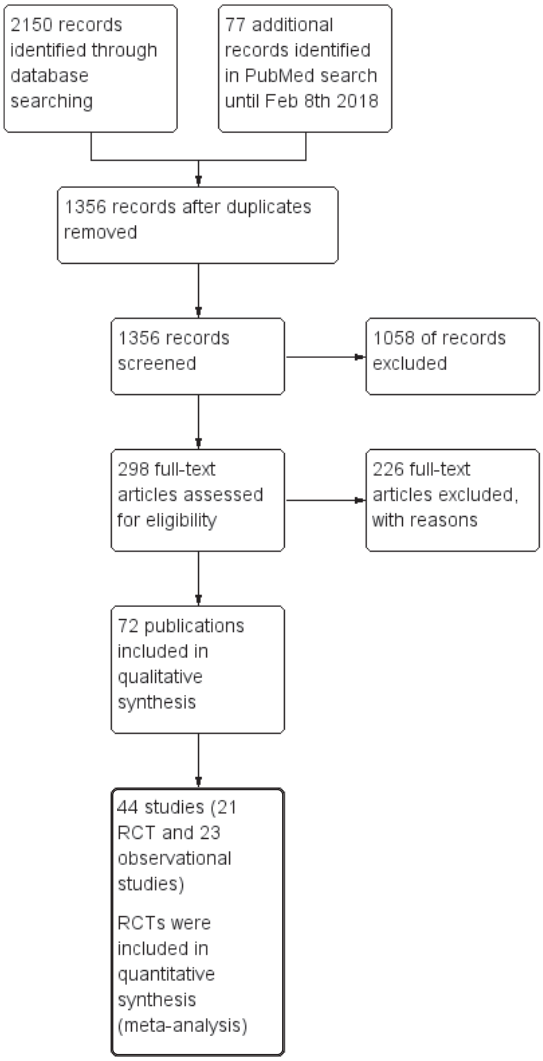

Figure 1: Flow diagram of studies identified, excluded, and finally included for the meta-analysis.

All 72 articles that were labelled as definite inclusion were uploaded in Review Manager (version 5.3) and clustered based on unique studies, as for some studies multiple papers appeared. This resulted in the identification of 44 unique studies (21 RCTs and 23 observational studies). For all unique studies outcomes were extracted. Detailed baseline characteristics as well as risk of bias assessment of included RCTs are presented in Table 2.

Table 2: Baseline characteristics and risk of bias assessment of included RCTs

Study	Clinicaltrials.gov identifier	Country, # centers, setting	Patient group (main indication, %)	Criteria for OIC at inclusion	Total no. Pts (% female)	Treatment-duration
Naloxegol						
KODIAC-04	NCT01309841	Australia, Germany, Slovakia, United States, 115 centers, outpatient	non-cancer-related pain, history of OIC (back pain 56.0%)	<3 spontaneous bowel movements (SBMs)/week and at least 1 OIC associated symptom at screening and had a confirmed diagnosis of OIC. Confirmed OIC was defined as: documented <3 SBMs/week on average over the 2-week OIC confirmation period. In addition to the SBM frequency criterion, patients must have reported ≥1 of the following symptoms in at least 25% of the bowel movements (BMs) recorded in the lectronic diary during the OIC confirmation period: Bristol Stool Scale stool type 1 or 2; moderate,severe, or very severe straining; incomplete BM.	641 (61.3%)	12 weeks (open label extension data available)
KODIAC-05	NCT01323790	Belgium, Croatia, Czech Republic, Hungary, Spain, Sweden, United Kingdom, and the United States (US), 142 centers, outpatient	non-cancer-related pain, history of OIC (back pain 56.8%)	<3 spontaneous bowel movements (SBMs)/week and at least 1 OIC associated symptom at screening and had a confirmed diagnosis of OIC. Confirmed OIC was defined as: documented <3 SBMs/week on average over the 2-week OIC confirmation period. In addition to the SBM frequency criterion, patients must have reported ≥1 of the following symptoms in at least 25% of the bowel movements (BMs) recorded in the lectronic diary during the OIC confirmation period: Bristol Stool Scale stool type 1 or 2; moderate,severe, or very severe straining; incomplete BM.	696 (63.4%)	12 weeks (open label extension data available)
Naloxone (OXN)						
OXN2001	NCT00513656	UK, 1 center, outpatient	diagnosis of cancer and a documented history of moderate/severe, chronic cancer pain. (breast (19%), lung (13%) and prostate (10%) cancer)	No criteria for OIC at inclusion	184 (49%)	4 weeks (open label extension available)
OXN10-KR-002	NCT01313780	Korea, 7 centers, outpatient	moderate to severe cancer-related pain (colorectal cancer, 40.9%)	No criteria for OIC at inclusion	117 (29.9%)	4 weeks

	Outcome measures used in review	Primary endpoint	Associated publications	Random Sequence Generation	Allocation Concealment	Blinding of participants or personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting/ reporting bias	Other Bias
	-response rate with respect to bowel function -rescue laxative use -change from baseline number of SBMs per week -PAC-SYM score -pain relief	Response rate defined as three or more spontaneous bowel movements (bowel movements without the use of rescue laxative treatment in the previous 24 hours) per week and an increase of one or more spontaneous bowel movements over baseline for at least 9 of 12 treatment weeks and at least 3 of the final 4 treatment weeks.	*Chey 2014, Coyne 2017, Holzer 2015, Lawson 2016, Tack 2015, Webster 2014, Webster 2017	LOW	LOW	LOW	LOW	LOW	LOW	LOW
	-response rate with respect to bowel function -rescue laxative use -change from baseline number of SBMs per week	Response rate defined as three or more spontaneous bowel movements (bowel movements without the use of rescue laxative treatment in the previous 24 hours) per week and an increase of one or more spontaneous bowel movements over baseline for at least 9 of 12 treatment weeks and at least 3 of the final 4 treatment weeks.	*Chey 2014, Coyne 2017, Lawson 2016, Tack 2015, Webster 2014, Webster 2017	LOW	LOW	LOW	LOW	LOW	LOW	LOW
	-Bowel Function Index (BFI-score) -PAC-SYM total score -pain relief	The null hypothesis for BFI was a zero difference (on average) between treatment groups at the final visit. The null hypothesis for BPI-SF was a difference of -1 (on average) between treatment groups at the final visit, in favour of Oxy PR (OXN PR inferior to OxyPR).	*Ahmedzai 2012, Ahmedzai 2014, Koopmans 2014	LOW	LOW	LOW	LOW	HIGH	LOW	LOW
	-pain relief	Change of pain intensity	Lee 2017	LOW	LOW	LOW	LOW	LOW	LOW	LOW

Table 2: Baseline characteristics and risk of bias assessment of included RCTs (*continued*)

Study	Clinicaltrials.gov identifier	Country, # centers, setting	Patient group (main indication, %)	Criteria for OIC at inclusion	Total no. Pts (% female)	Treatment-duration
OXN3001	NCT00412152	UK, Gemany, Spain, Czech Republic, 93 sites, outpatient	moderate-to-severe noncancer pain and constipation caused or aggrevated by an opioid (82.9% musculo-skeletal pain)	Citeria for constipation caused or aggrevated by an opioid not defined in publication	316 (unpublished)	12 weeks (open label extension data available)
OXN3006	NCTO0412100	Germany, Czech Republic, Finland, Hungary, Netherlands, UK, Spain, 172 centers, outpatient	moderate-to-severe, non-malignant pain and constipation (< 3 CSBMs/ week) caused or aggrevated by opioid therapy (back pain 61%)	constipation defined as <3 CSBMs/week	265 (68.3%)	12 weeks (open label extension data available)
OXN3506	NCT01438567	Australia, Czech Republick, Denmark, Finland, France, Germany, Israel, Poland, Romania, South Korea and UK, 66 centers, outpatient	cancer and non-cancer pain suffering from opioid-induced constipation caused or aggrevated by opioids.	Constipation caused or aggravated by opioids was confirmed by the patient and the investigator as an effect of the patient's pre-study opioid medication (at a comparable dose) and evidenced by a medical need of regular intake of laxatives to have at least three bowel evacuations per week or by having less than three bowel evacuations when not taking a laxative	243 (58.8%)	5 weeks (open label extension data available)
Kokki 2017	NCT02573922	Finland, 1 center, spinal surgery	patients scheduled to have an elective lumbar or cervical spinal surgery (spinal surgery, 100%)	No criteria for OIC at inclusion	180 (45%)	3 weeks

Outcome measures used in review	Primary endpoint	Associated publications	Random Sequence Generation	Allocation Concealment	Blinding of participants or personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting/ reporting bias	Other Bias
-Bowel Function Index (BFI-score) -proportion of patients with laxative use -PAC-SYM total score -proportion of patients with normal number of CSBMs (≥3/ week) -pain relief	improvement in constipation as measured using the Bowel Function Index (BFI)	Blagden 2014, Koopmans 2014, Löwenstein 2010, Sandner-Kiesling 2010, *Simpson 2008	HIGH	HIGH	LOW	LOW	HIGH	LOW	LOW
-Bowel Function Index (BFI-score) -proportion of patients with laxative use -PAC-SYM total score -proportion of patients with normal number of CSBMs (≥3/ week)	improvements in symptoms of constipation, as measured by the Bowel Function Index (BFI)	Blagden 2014, Koopmans 2014, Löwenstein 2010, *Löwenstein 2009	LOW	HIGH	LOW	LOW	HIGH	LOW	LOW
-Bowel Function Index (BFI-score) -pain relief	improvement in symptoms of constipation as measured by the Bowel Function Index (BFI)non-inferiority of OXN PR compared with OxyPR with respect to the analgesic efficacy	*Dupoiron 2017a, Dupoiron 2017b	LOW	LOW	LOW	LOW	UNCLEAR	UNCLEAR	LOW
-proportion of patients with laxative use	prevalence of constipation at 7 days after surgery	Kokki 2017	LOW	LOW	HIGH	HIGH	LOW	LOW	LOW

Table 2: Baseline characteristics and risk of bias assessment of included RCTs (*continued*)

Study	Clinicaltrials.gov identifier	Country, # centers, setting	Patient group (main indication, %)	Criteria for OIC at inclusion	Total no. Pts (% female)	Treatment-duration
methylnaltrexone (MNTX)						
Michna 2011	NCT00529087	US, 78 centers, outpatient	chronic non-malignant pain and a history of constipation due to opioid use and fewer than 3 RFBMs per week (back pain, 60.4%)	Constipation during the screening period was defined as fewer than 3 RFBMs per week (no laxative use within 24 hours prior to any bowel movement) that were associated with one or more of the following: a) a Bristol StoolFormScale score of 1 or 2 for at least 25% of the bowel movements; b) straining during at least 25% of the bowel movements; c) a sensation of incomplete evacuation after at least 25% of the bowel movements.	460 (60.2%)	4 weeks
Rauck 2017	NCT01186770	US, 117 centers, outpatient	chronic non-malignant pain and a history of OIC (back pain, 68.2%)	OIC defined as having < 3 rescue-free bowel movements (RFBMs) per week that were associated with ≥ 1 of the following: ≥ 25% of RFBMs categorized as type 1 or type 2 on theBristol Stool Form Scale; straining during ≥ 25% of RFBMs or ≥ 25% of RFBMs with a sensation of incomplete evacuation.	803 (62.9%)	4 weeks, extended with 8 weeks (4 weeks results presented)
study 4000/4001	NCT00672477 and NCT00672139	US, Australia, Belgium, Brazil, Canada, France, Germany, Italy, Mexico, Spain, Sweden, UK, 60, outpatient	advanced illness (defined as a terminal illness [e.g., incurable cancer or other end-stage disease]), a life expectancy of ≥ 1 month, and OIC and were receiving stable doses of laxatives and opioids (cancer 66.0%)	OIC defined as < 3 bowel movements in the last week and no bowel movement in 24 hours or no bowel movement in 48 hours	230 (48.7%)	2 weeks (10 weeks open label extension) (4 week results presented)

	Outcome measures used in review	Primary endpoint	Associated publications	Random Sequence Generation	Allocation Concealment	Blinding of participants or personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting/ reporting bias	Other Bias
	- RFBMs within 4 hrs of first dose -RFBMs within 24 hrs of first dose -No. of RFBMs/week -Rescue laxative use -Proportion of patients with normal bowel function -PAC-SYM score -pain relief	1) the proportion of subjects having a rescue-free bowel movement (RFBM) within 4 hours of the first dose, and 2) the percentage of active injections resulting in any RFBM within 4 hours	*Michna 2011, Iyer 2011	LOW	LOW	LOW	LOW	UNCLEAR	UNCLEAR	LOW
	- RFBMs within 4 hrs of first dose -No. of RFBMs/week	mean percentage of dosing days that resulted in an RFBM within 4 hours of dosing during weeks 1 to 4	Rauck 2017	LOW	LOW	LOW	LOW	LOW	LOW	LOW
	- RFBMs within 4 hrs of first dose -No. of RFBMs/week -Rescue laxative use	percentage of patients with a rescue-free bowel movement (RFBM) within four hours after ‡ 2 of the first 4 doses (i.e., the first week of treatment).RFBMwas defined as a bowel movement without use of any rescue medication or procedure within four hours before the bowel movement.	Bull 2015	LOW	UNCLEAR	LOW	LOW	HIGH	LOW	LOW

Table 2: Baseline characteristics and risk of bias assessment of included RCTs (*continued*)

Study	Clinicaltrials.gov identifier	Country, # centers, setting	Patient group (main indication, %)	Criteria for OIC at inclusion	Total no. Pts (% female)	Treatment-duration
Thomas 2008	NCT00402038	US, Canada, 27 , nursing homes, hospice sites, and palliative care centers.	advanced illness, which was defined as a terminal disease (incurable cancer or other end-stage disease) with a life expectancy and OIC (cancer, 58.2%)	opioid-induced constipation with either fewer than three laxations during the preceding week and no clinically meaningful laxation (as determined by the investigator) within 24 hours before the first study dose or no clinically meaningful laxation within 48 hours before the first study dose.	134 (56.7%)	2 weeks (3 month open label extension)
MNTX 301	NCT00401362	US, 17 centers, hospices and palliative care centers	advanced illness (life expectancy of 1-6 months) and OIC (cancer, 81.2%)	No clinically signifcant laxation within 48 hours prior to the frst study drug dose	154 (45.5%)	single-dose, 28 day open-label and 3 month extension
Alvimopan						
Paulson 2005		US, 22 centers, secondary and tertiary care	Patients on opioid therapy (88% chronic pain) with OIC (back pain, 38.7%)	<3 bowel movements per week without laxative use or enemas and at least one associated symptom: lumpy or hard stools, straining, sensation of anorectal obstruction, or sensation of incomplete evacuation	168 (58.3%)	3 weeks
SB767905/011		Australia, Germany, Greece, Italy, Portugal, US, Belgium, Canada, Denmark, 113 centers, outpatients	bowel dysfunction resulting from chronic opioid treatment for the management of pain of a non-cancer origin (back pain, 58.2%)	history of decreased bowel movement frequency since initiating opioid therapy and ≥1of the following symptoms: incomplete evacuation, hard stools, or straining, in ≥25% of bowel movements	522 (63.8%)	6 weeks
SB-767905/012		US, Canada, Europe, 148 centers, standalone research centers, pain centers, and non-pain practice external research centers.	persistent non-cancer pain and a recalled history of opioid-induced bowel dysfunction (back pain, 59%)	<3 spontaneous BMs (SBMs) per week and occurrence of at least 1 of the following symptoms for $25% of BMs— sense of incomplete evacuation after passing a stool, straining to pass a stool, or lumpy hard stools, or small pellets.	518 (63%)	12 weeks

Outcome measures used in review	Primary endpoint	Associated publications	Random Sequence Generation	Allocation Concealment	Blinding of participants or personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting/ reporting bias	Other Bias
- RFBMs within 4 hrs of first dose -RFBMs within 24 hrs of first dose -Proportion of patients with normal bowel function -pain relief	proportion of patients with rescue-free laxation within 4 hours after the first dose of the study drug and the proportion of patients with rescue-free laxation within 4 hours after two or more of the first four doses.	Thomas 2008	LOW	LOW	LOW	LOW	HIGH	LOW	LOW
- RFBMs within 4 hrs of first dose -RFBMs within 24 hrs of first dose -pain relief	proportion of patients with laxation within 4 hours after administration of the double-blind dose.	Nalamachu 2015, *Slatkin 2009	LOW	LOW	LOW	LOW	UNCLEAR	UNCLEAR	LOW
-number of bowel movements per week -pain relief	proportion of patients with at least 1 BM within 8 hours of study drug administration on each day during the 21-day treatment period, averaged across all patients.	Paulson 2005	LOW	LOW	LOW	LOW	UNCLEAR	UNCLEAR	LOW
-Proportion of patients with normal bowel function -number of bowel movements per week	change in weekly spontaneous bowel movement frequency during the first 3 weeks of the 6-week treatment period.	Webster 2008	LOW	UNCLEAR	LOW	LOW	UNCLEAR	LOW	LOW
-Proportion of patients with normal bowel function -number of bowel movements per week -proportion of patients using concomittant laxatives	proportion of 'responders', with responder defined as a patient experiencing 3 or more SBMs per week over the treatment period and an average increase from baseline of at least 1 SBM per week.	Jansen 2011	LOW	UNCLEAR	LOW	LOW	HIGH	UNCLEAR	LOW

Table 2: Baseline characteristics and risk of bias assessment of included RCTs (*continued*)

Study	Clinicaltrials.gov identifier	Country, # centers, setting	Patient group (main indication, %)	Criteria for OIC at inclusion	Total no. Pts (% female)	Treatment-duration
SB-767905/013		US, Canada, Europe, 153 centers, non–pain-practice research center extensions of clinical sites, research centers, and pain centers	persistent non-cancer pain and a recalled history of opioid-induced bowel dysfunction (back pain, 60%)	<3 spontaneous BMs (SBMs) per week and occurrence of at least 1 of the following symptoms for $25% of BMs— sense of incomplete evacuation after passing a stool, straining to pass a stool, or lumpy hard stools, or small pellets.	485 (64%)	12 weeks
Naldemedine						
COMPOSE-1	NCT01965158	USA, Austria, Czech Republic, Germany, Poland, Spain, UK, 68, outpatient	chronic non-cancer pain and OIC (unknown)	no more than four spontaneous bowel movements (SBMs) over the 14-day qualifying period with no more than three SBMs in a given week; at least one bowel symptom (presence of straining, lumpy or hard stools, sensation of incomplete evacuation, sensation of anorectal obstruction or blockage) in at least 25% of bowel movements	547 (60.1%)	12 weeks
COMPOSE-2	NCT01993940	USA, Austria, Czech Republic, Germany, Poland, Spain, 69, outpatient	chronic non-cancer pain and OIC (unknown)	no more than four spontaneous bowel movements (SBMs) over the 14-day qualifying period with no more than three SBMs in a given week; at least one bowel symptom (presence of straining, lumpy or hard stools, sensation of incomplete evacuation, sensation of anorectal obstruction or blockage) in at least 25% of bowel movements	553 (60.2%)	12 weeks
COMPOSE-4	JAPIC-CTI-132340	Japan, 70 sites	cancer pain and OIC (lung cancer, 45.1%)	five or fewer spontaneous bowel movements (SBMs; a bowel movement not induced by rescue laxatives) and experience with straining, incomplete evacuation, and/or hard stools in 25% or more of all BMs during the 2 weeks before random assignment.	193 (38.3%)	2 weeks (12 weeks open label extension study)

Outcome measures used in review	Primary endpoint	Associated publications	Random Sequence Generation	Allocation Concealment	Blinding of participants or personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting/ reporting bias	Other Bias
-Proportion of patients with normal bowel function -number of bowel movements per week -proportion of patients using concomittant laxatives	proportion of "responders," with responder defined as a patient experiencing 3 or more SBMs per week over the treatment period and an average increase from baseline of at least 1 SBM per week.	Irving 2011	LOW	UNCLEAR	LOW	LOW	HIGH	UNCLEAR	LOW
-proportion of patients with normal bowel function -change in number of SBMs per week -change in number of CSBMs per week -pain relief	proportion of responders, with a responder defined as a patient having at least three SBMs per week and an increase from baseline of at least one SBM per week for that week (a positive response week) for at least 9 weeks out of the 12-week treatment period and at least 3 of the last 4 weeks of the 12-week treatment period.	Hale 2017	LOW	LOW	LOW	LOW	UNCLEAR	LOW	LOW
-proportion of patients with normal bowel function -change in number of SBMs per week -change in number of CSBMs per week -pain relief	proportion of responders, with a responder defined as a patient having at least three SBMs per week and an increase from baseline of at least one SBM per week for that week (a positive response week) for at least 9 weeks out of the 12-week treatment period and at least 3 of the last 4 weeks of the 12-week treatment period.	Hale 2017	LOW	LOW	LOW	LOW	UNCLEAR	LOW	LOW
-proportion of patients with normal bowel function -change in number of SBMs per week -change in number of CSBMs per week -pain relief	proportion of SBM responders during the 2-week treatment period. An SBM responder was defined as a patients with three or more SBMs/week who had an increase of one or more SBM/week from baseline.	Katakami 2017	LOW	LOW	LOW	LOW	UNCLEAR	LOW	LOW

Pain relief

Pain relief was assessed in all randomized controlled trials. However, for a number of studies effects on pain relief were described in writing and no actual pain scores were reported. When assessing studies that did report on pain relief (either in numbers or graphs) the analysis showed that treatment with opioid antagonists did not interfere with pain relief. As expected there were no differences between treatments reflected by a standardized mean difference (95% CI) of 0.03 (-0.09, 0.03) and no heterogeneity was detected (I^2=0%) (see Figure 2).

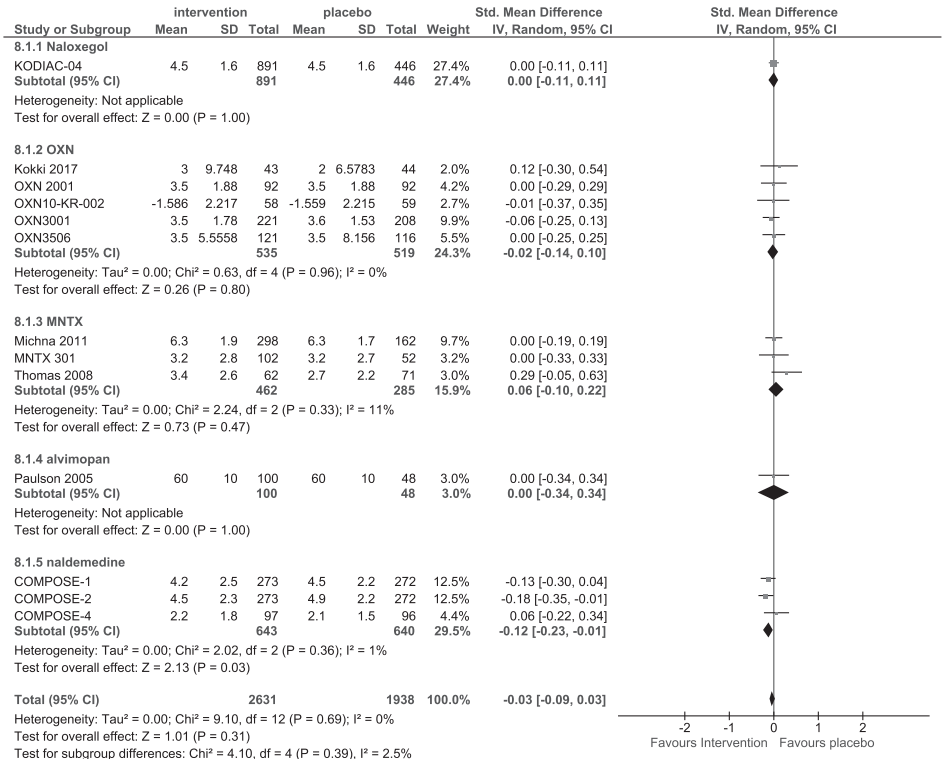

Figure 2: Forest plot of comparison: Effect of opioid antagonist treatment on pain relief (RCTs only).

The summary of findings table generated from the GradePro GDT platform for this parameter is presented in Table 3. The quality of the evidence varied from moderate to high.

Bowel function efficacy outcomes

The outcomes proportion of patients with normal bowel movements were available for naloxegol, MNTX, alvimopan, PR OXN and naldemedine, the proportion of patients with additional laxative use were available for naloxegol, MNTX, alvimopan and PR OXN, PAC-SYM total scores were available for naloxegol, MNTX and PR OXN. All other identified

Table 3. The effect of opioid antagonist treatments compared to placebo on pain relief in patients with opioid treatment for pain and opioid induced constipation

Outcome	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with opioid antagonist treatments
Pain relief	4569 (13 RCTs)	-	-	-	SMD **0.03 lower** (0.09 lower to 0.03 higher)
Naloxegol	1337 (1 RCT)	⊕⊕⊕⊕ HIGH	-	-	SMD **0** (0.11 lower to 0.11 higher)
PR OXN	1054 (5 RCTs)	⊕⊕⊕◯ MODERATE [a]	-	-	SMD **0.02 lower** (0.14 lower to 0.1 higher)
MNTX	747 (3 RCTs)	⊕⊕⊕⊕ HIGH	-	-	SMD **0.06 higher** (0.1 lower to 0.22 higher)
Alvimopan	148 (1 RCT)	⊕⊕⊕⊕ HIGH	-	-	SMD **0** (0.34 lower to 0.34 higher)
Naldemedine	1283 (3 RCTs)	⊕⊕⊕⊕ HIGH	-	-	SMD **0.12 lower** (0.23 lower to 0.01 lower)

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** Confidence interval; **SMD:** Standardised mean difference

Explanations: a. Risk of bias was identified in 4 out of 5 studies with regard to: random sequence generation and treatment allocation (OXN3001 and OXN3006), blinding (Kokki 2017 and KF5503/60), incomplete outcome data (all but Kokki 2017 and OXN10-KR-002).

bowel function parameters were analyzed per active ingredient and are presented in supplementary figure S1-S7.

Proportion of patients with normal bowel movements

The proportion of patients with normal bowel function (>3 bowel movements per week) was reported in 12 RCTs, 2 studies with naloxegol (KODIAC-04 and KODIAC-05[32,36,42,64,82]), 2 studies with MNTX (Michna 2011[34,37,54,55] and Thomas 2008[41,53,60,83]), 2 studies with PR OXN (OXN3001[45,48,58,66,85] and OXN3006[58,59,66,85]), 3 studies with alvimopan (SB-767905/011, SB-767905/012, SB-767905/013[35,68,70]) and 3 studies with naldemedine (COMPOSE-1, COMPOSE-2 and COMPOSE-4[27,29]). None of the observational studies reported proportion of patients with normal bowel function based on ROME-3 criteria, subsequently all studies were RCTs. Treatment with opioid antagonists resulted in a statistically significant improvement of bowel function compared with rescue laxative use when looking at the proportion of patients with normal bowel movements according to ROME 3-criteria (RR:1.56; 95% CI 1.37-1.76; P<0.00001; Figure 3). Considerable heterogeneity was detected (I^2=73%, Chi2=7.12 df=11).

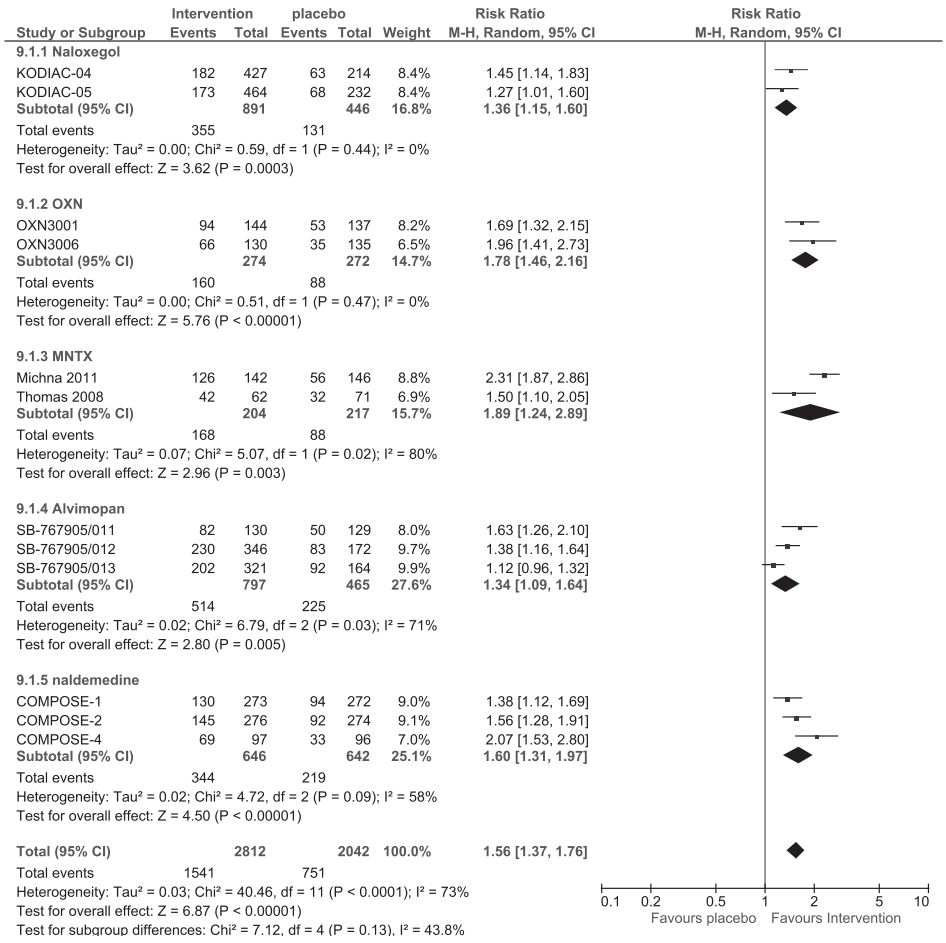

Figure 3: Forest plot of comparison: Effect of opioid antagonist treatment on bowel function (RCTs only), measured with the proportion of patients with normal bowel function (>3 bowel movements per week).

The summary of findings table generated from the GradePro GDT platform for this parameter is presented in table 4. The quality of the evidence varied from low to high, overall the risk difference of the proportion of patients with normal bowel function on opioid antagonist treatment was 206 (136 to 280) more per 1,000 treated patients.

Proportion of patients with additional laxative use

The proportion of patients with additional laxative use was reported in 9 RCTs, 2 studies with naloxegol (KODIAC-04 and KODIAC-05[32,36,42,64,82]), 2 studies with MNTX (Michna 2011[34,37,54,55] and study 4000/4001[84]), 3 studies with PR OXN (Kokki 2017[26], OXN3001[45,48,58,66,85] and OXN3006[58,59,66,85]) and 2 studies with alvimopan (SB-767905/012, SB-767905/013[68,70]. Treatment with opioid antagonists suggested a significant improve-

Table 4. The effect of opioid antagonist treatment compared to placebo on the proportion of patients with normal bowel function in patients with opioid treatment for pain and opioid induced constipation

Outcomes	No. of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with opioid antagonist treatments
Proportion of patients with normal bowel function	4854 (12 RCTs)	-	**RR 1.56** (1.37 to 1.76)	368 per 1,000	**206 more per 1,000** (136 more to 280 more)
Naloxegol	1337 (2 RCTs)	⊕⊕⊕⊕ HIGH	**RR 1.36** (1.15 to 1.60)	294 per 1,000	**106 more per 1,000** (44 more to 176 more)
PR OXN	546 (2 RCTs)	⊕⊕⊕◯ MODERATE [a]	**RR 1.78** (1.46 to 2.16)	324 per 1,000	**252 more per 1,000** (149 more to 375 more)
MNTX	421 (2 RCTs)	⊕⊕⊕◯ MODERATE [b]	**RR 1.89** (1.24 to 2.89)	406 per 1,000	**361 more per 1,000** (97 more to 766 more)
Alvimopan	1262 (3 RCTs)	⊕⊕◯◯ LOW [c,d]	**RR 1.34** (1.09 to 1.64)	484 per 1,000	**165 more per 1,000** (44 more to 310 more)
Naldemedine	1288 (3 RCTs)	⊕⊕⊕◯ MODERATE [e]	**RR 1.60** (1.31 to 1.97)	341 per 1,000	**205 more per 1,000** (106 more to 331 more)

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** Confidence interval; **RR:** Risk ratio.

Explanations: a. Downgraded because of uncertainty about Random Sequence Generation and treatment allocation (OXN3001 and OXN3006) as well as uncertainty about incomplete outcome data handling (OXN3001 and OXN3006) b. Downgraded because of significant heterogeneity between studies (I^2=80%). c. Downgraded because of uncertainty about treatment allocation (all three studies) and uncertainty about handling of incomplete outcome data (all three studies) d. Downgraded because of significant heterogeneity between studies (I^2=77%) e. Downgraded because of uncertainty about handling of incomplete outcome data

ment of bowel function compared with rescue laxative use when looking at the proportion of patients using additional laxatives (RR:0.76; 95% CI 0.69-0.84; P<0.001; Figure 4).

However, substantial heterogeneity was detected (I^2=65%, Chi2=22.60 df=8). The summary of findings table generated from the GradePro GDT platform for this parameter is presented in table 5. The quality of the evidence varied from moderate to high, overall the risk difference of the proportion of patients using additional rescue laxatives on opioid antagonist treatment was 157 (202 to 104) fewer per 1,000 treated patients.

PAC-SYM total score

The PAC-SYM total score was reported in 5 RCTs, 1 study with naloxegol (KODIAC-04[32,36,42,64,82]), 1 study with MNTX (Iyer 2011[69]) and 3 studies with PR OXN (OXN2001[66,88,89], OXN3001[45,48,58,66,85] and OXN3006[58,59,66,85]). None of the observational

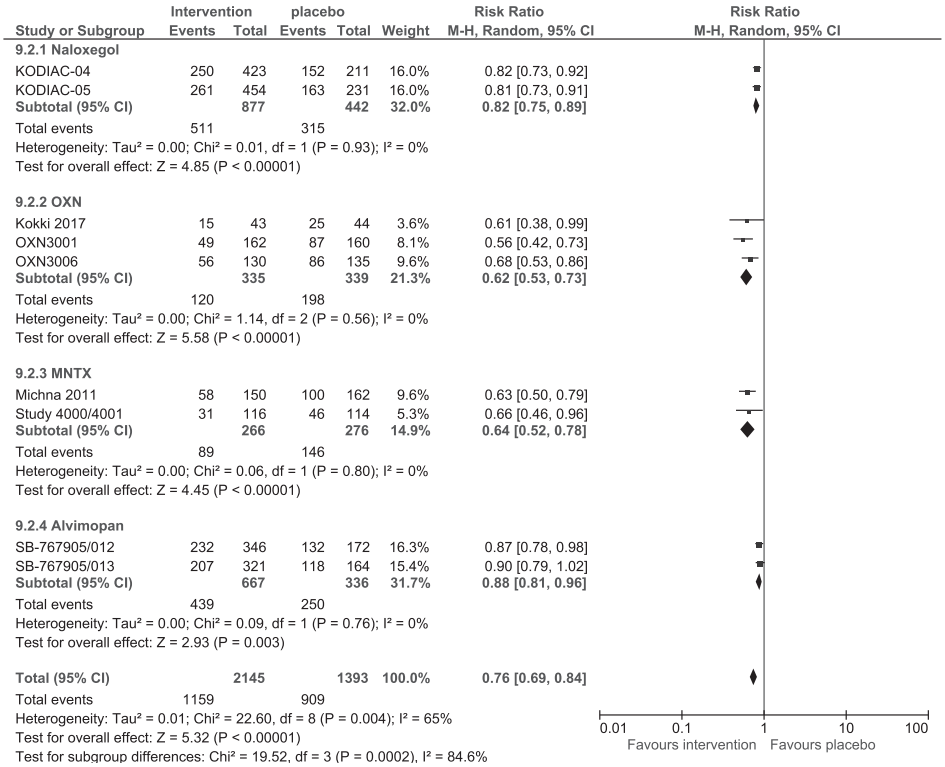

Figure 4: Forest plot of comparison: Effect of opioid antagonist treatment on bowel function (RCTs only), measured with the proportion of patients using rescue laxatives.

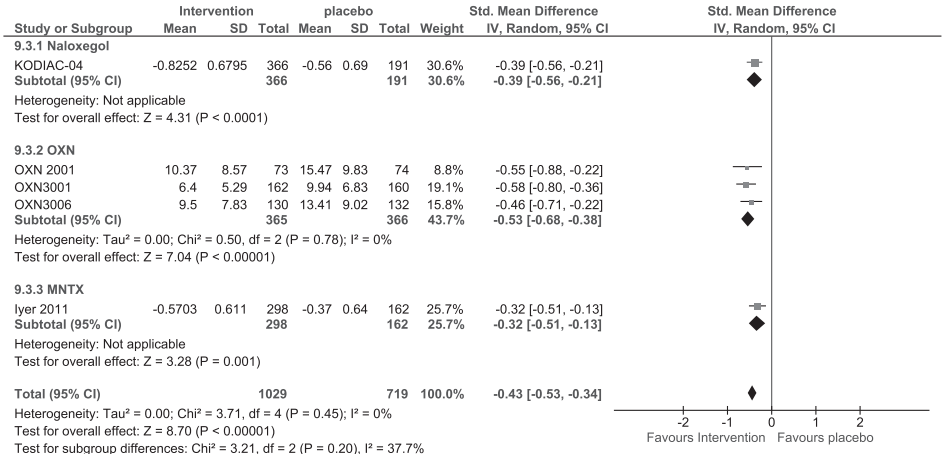

Figure 5: Forest plot of comparison: Effect of opioid antagonist treatment on bowel function (RCTs only), measured with the PAC-SYM total score.

Table 5. The effect of opioid antagonist treatments compared to placebo on the proportion of patients using rescue laxatives in patients with opioid treatment for pain and opioid induced constipation

Outcome	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with opioid antagonist treatments
Proportion of patients using rescue laxatives	3538 (9 RCTs)	-	**RR 0.76** (0.69 to 0.84)	653 per 1,000	**157 fewer per 1,000** (202 fewer to 104 fewer)
Naloxegol	1319 (2 RCTs)	⊕⊕⊕⊕ HIGH	**RR 0.82** (0.75 to 0.89)	713 per 1,000	**128 fewer per 1,000** (178 fewer to 78 fewer)
PR OXN	674 (3 RCTs)	⊕⊕⊕○ MODERATE [a]	**RR 0.62** (0.53 to 0.73)	584 per 1,000	**222 fewer per 1,000** (275 fewer to 158 fewer)
MNTX	542 (2 RCTs)	⊕⊕⊕⊕ HIGH	**RR 0.64** (0.52 to 0.78)	529 per 1,000	**190 fewer per 1,000** (254 fewer to 116 fewer)
Alvimopan	1003 (2 RCTs)	⊕⊕⊕○ MODERATE [b]	**RR 0.88** (0.81 to 0.96)	744 per 1,000	**89 fewer per 1,000** (141 fewer to 30 fewer)

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** Confidence interval; **RR:** Risk ratio.

Explanations: a. Downgraded because of uncertainty about Random Sequence Generation and treatment allocation (OXN3001 and OXN3006) as well as uncertainty about incomplete outcome data handling (OXN3001 and OXN3006) and uncertainty about blinding (Kokki 2017)

b. Downgraded because of uncertainty about treatment allocation (all studies) and uncertainty about handling of incomplete outcome data (all studies)

studies reported a PAC-SYM total score, subsequently all studies were RCTs. Treatment with opioid antagonists resulted in a statistically significant improvement of PAC-SYM total score compared with rescue (St. Mean Difference: -0.43; 95% CI -0.53, -0.34; P<0.00001; Figure 5).

No heterogeneity was detected (I^2=0%, Chi2=3.71 df=4). The summary of findings table generated from the GradePro GDT platform for this parameter is presented in table 6. The quality of the evidence varied from moderate to high.

Bowel function efficacy within the laxative refractory population

For naloxegol (KODIAC-04 and KODIAC-05[32,36,42,64,82]) and PR OXN (OXN2001, OXN3001 and OXN3006[66]) efficacy data with respect to bowel function were available. However, the reported data were not suitable for inclusion in the meta-analysis. For laxative refractory patients using naloxegol the proportion of patients responding to therapy

Table 6. The effect of opioid antagonist treatments compared to placebo on the PAC-SYM total score in patients with opioid treatment for pain and opioid induced constipation

Outcome	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with opioid antagonist treatments
PAC-SYM total score	1748 (5 RCTs)	-	-	-	SMD **0.43 lower** (0.53 lower to 0.34 lower)
Naloxegol	557 (1 RCT)	⊕⊕⊕⊕ HIGH	-	-	SMD **0.39 lower** (0.56 lower to 0.21 lower)
PR OXN	731 (3 RCTs)	⊕⊕⊕○ MODERATE [a]	-	-	SMD **0.53 lower** (0.68 lower to 0.38 lower)
MNTX	460 (1 RCT)	⊕⊕⊕○ MODERATE [b]	-	-	SMD **0.32 lower** (0.51 lower to 0.13 lower)

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** Confidence interval; **RR:** Risk ratio; **SMD:** Standardised mean difference

Explanations: a. Downgraded because of uncertainty about Random Sequence Generation and treatment allocation (OXN3001 and OXN3006) as well as uncertainty about incomplete outcome data handling (OXN2001, OXN3001 and OXN3006) b. Downgraded because of uncertainty about treatment allocation and incomplete data handling

significantly improved in line with results in the total study population (RR: 1.50; 95% CI [1.21, 1.86]; p=0.0003; Supplementary figure S8).

For patients using PR OXN a significant improvement in BFI-score was seen similar to the improvement seen in the total population (WMD: -8.93; 95%CI [-16.26, -1.59]; P=0.02; supplementary figure S7). However, the lower patient numbers result in uncertainty about the results.

Bowel function efficacy in observational studies

Most identified published observational studies were performed with PR OXN (22 unique studies). One prospective uncontrolled study with MNTX was identified[34]. In this phase 3, multicenter, open-label trial, adults with chronic noncancer pain (n=1034) received subcutaneous methylnaltrexone 12 mg once daily for 48 weeks. 64.7% of included patients were female and the most common indication for pain treatment was back pain 53.8%. The median number of weekly methylnaltrexone injections was 5.98 (range 0.05–7.14), with the greatest number of patients (49.6%) requiring more than six or seven doses per week. A statistically significant increase in mean weekly BM rate from baseline (mean=1.5 BM/wk) was observed throughout the entire 48-week period (mean=5.3 BMs; mean change=1.5 BM/wk;P<0.001). After 48 weeks 34.1% of the 1034

injections resulted in a BM within 4 hrs, which is comparable to the values found in the RCTs, suggesting that effects seen in daily practice resemble the effects seen in RCTs.

For PR OXN 15 studies (17 publications) included patients with OIC at study start (n =17085)[4,28,33,38,46,49,56,61,62,67,71-73,77-79,81]. The studies mainly differed in the included pain population (e.g. non-malignant pain, malignant pain, elderly, neuropathic pain and laxative refractory pain patients), resulting in considerable heterogeneity, Despite the heterogeneity the mean weighted improvement in BFI was -29.22 95 % CI [-35.22, -23.22] (p<0.00001) similar to the improvement seen in the RCTs -27.4 95%CI[-19.1 to -35.7] (see supplementary figure S9), suggesting that effects seen in daily practice resemble the effects seen in RCTs. Patients with laxative refractory OIC (3 studies, n=110) had the largest improvement in BFI-scores, mean weighted improvement in BFI was -49.03 95% CI [-53.63, -44.42] (P<0.00001). This improvement. is greater than mean weighted improvement seen in the laxative refractory subpopulation of the RCTs (-20.1; 95% CI [-13.6 to -26.6]). Together this suggests that effects seen in daily practice are at least comparable to the effects seen in RCTs.

In 10 studies (14 publications) patients without OIC at study start were included (n =4693)[21,24,38-40,46,50,57,63,71-75]. The mean weighted improvement was -3.38 95% CI [-10.37, 3.61]. The studies differed substantially, mainly in the included pain population (e.g. non-malignant pain, malignant pain, elderly, neuropathic pain and laxative refractory pain patients), resulting in considerable heterogeneity (I^2=96%, Chi^2=215.39, df=9) (see supplementary figure S10). Within these heterogeneous studies three groups of studies could be identified, studies reporting no change in BFI, studies reporting an improvement in BFI and studies reporting a worsening of BFI, where all individual publications reported no significant and clinically relevant changes in BFI (a clinically relevant change in BFI is defined as a change of 12 points or more). Five studies showed a substantial improvement of BFI-score and mean weighted improvement of BFI in this group was -11.83 95% CI [-13.25, -10.41](p<0.00001) with no important heterogeneity in this subgroup (I^2=0%). Two studies showed a worsening of the BFI score with mean weighted worsening of 11.25 95% CI [8.13, 14.37] (p<0.00001), with no important heterogeneity (I^2= 6%). Another 3 studies did not show a difference in BFI-score and mean weighted improvement in this subgroup was -0.17 95% CI [-2.85, 3.19] (p=0.91), with no important heterogeneity (I^2=4%). Results of these analyses suggest that there appeared to be no significant clinically relevant changes in the bowel function index (a change in BFI of 12 points or more) even when the data are analyzed in the defined subgroups, suggesting that patients do not develop OIC during treatment with an opioid (supplementary figures S10-S13).

DISCUSSION

This study aimed to demonstrate that treatment with opioid antagonists is a valuable treatment option in patients that experience OIC when using opioid treatment for pain. Moreover, available observational data were analyzed to provide insight in to usage of opioid antagonist treatment in daily practice.

Despite significant heterogeneity between studies all identified randomized controlled trials showed that the efficacy of opioid antagonist treatment was superior to control treatment with respect to the proportion of patients achieving normal bowel function, the proportion of patients needing additional laxatives as well as the PAC-SYM total score. The Number Needed to Treat (NNT) to obtain normal bowel function is ~5 (~3.5-7; the reciproke of the anticipated absolute risk difference with opioid antagonist treatments), which is comparable to the meta-analysis by Nee et al. Also variables that were not studied for all agents, like (change in) BFI and (change in) number of bowel movements, showed that opioid antagonist treatments were superior to control treatment.

With respect to pain relief the RCTs showed that treatment with opioid antagonists did not significantly interfere with pain relief (13 RCTs, 4569 participants, SMD 0.03 lower (0.09 lower to 0.03 higher). The quality of the evidence using the GRADE-systematic was rated low for alvimopan, moderate for PR OXN, MNTX and naldemedine and high for naloxegol.

A further indication on the efficacy of opioid antagonist treatment in daily practice could be derived from prospectively designed observational studies predominantly performed with PR OXN. When analyzing the Bowel Function Index at start of opioid antagonist treatment and at final study visit it was shown that the BFI decreased significantly with 29.2 points (ΔBFI=-29.9 95% CI -35.2to -23.2; n=8524) in patients with OIC at study entry, a decrease that is considered to be clinically relevant (a change in BFI of 12 points or more is considered clinically relevant) indicating that bowel function improves significantly and that the improvement is also clinically relevant. For patients without OIC at study start the BFI did not significantly change (ΔBFI -3.4 95%CI -10.4 to 3.6; n=2341), indicating that treatment with PR OXN might prevent worsening of bowel function usually seen on opioid treatment.

An interesting population with respect to opioid induced constipation is the laxative refractory population. Therefore we also included analyses for the subgroup of laxative refractory patients. Five RCTs (KODIAC-4, KODIAC-5, OXN2001, OXN3001 and OXN3006) were identified that reported on bowel function efficacy in laxative refractory patients or laxative inadequate responders.

For naloxegol the RR was 1.5 (95% CI 1.21 to 1.86; n=481), resulting in an NNT of ~6.7. For PR OXN the change in BFI was less pronounced compared with the total popula-

tion (MD -8.93 95%CI -16.26 to -1.59; n=75). Within the naloxegol and PR OXN studies no heterogeneity was detected. However, a difference between both studies was the definition with respect to laxative refractory patients and laxative inadequate responder patients. For the PR OXN study a patient was considered laxative refractory if the patients still experienced OIC (defined as a BFI>28.8) despite the use of at least 2 laxatives from a different therapeutic class (e.g. macrogol and bisacodyl). For naloxegol a patient was considered a laxative inadequate responder when the patient took medication from one or more laxative classes for a minimum of 4 days within 2 weeks before screening and still experienced moderate, severe, or very severe symptoms in at least one of four stool-symptom domains of a laxative-response questionnaire.

For PR OXN also prospective observational studies were available in this population. In the observational studies the definition for laxative refractory patients was comparable to the laxative regimens used in daily practice, a patient that was considered laxative refractory had failed on the standard of care laxative regimens used in daily practice. The analysis showed a significant and clinically relevant improvement of the BFI in this population (ΔBFI -49.0 95%CI -53.6 to -44.4; n=110), suggesting that despite failing normal laxative regimens patients can still benefit from using opioid antagonist treatment.

Although no direct comparisons between PAMORA's and/or PR OXN are available, we did not observe differences in efficacy between PAMORA's and PR OXN in the meta-analyses. As no differences are observed in efficacy and side effects, treatment choice should be made on pharmaceutical properties of the products, patient preferences, costs and product availability. For instance, MNTX is only available as subcutaneous injection which might be perceived a burden to patients, whereas first results of treatment can occur already within 4 hours of the first injection. PR OXN is an oral combination product limiting the choice of opioid to oxycodone. The oral combination however might be a benefit to therapy adherence in comparison to single oral products, but this remains to be elucidated. Furthermore, between countries differences exist between products with regard to availability to patients due to differences in registered indication (e.g. between EU versus US) and local reimbursement decisions which can differ per country.

Limitations

There are some limitations to our analyses. Firstly, there is heterogeneity in the analyses of the bowel function outcomes, this heterogeneity might be caused by differences in the trial populations. Detected differences identified were differences with respect to OIC at baseline due to differences in definitions for OIC as well as differences is the underlying pain conditions (e.g. malignant pain and non-malignant pain). Other differences that could affect bowel function might have been: use of chemotherapeutics and other drugs[90], level of physical activity and co-morbidities[11]. To reduce heterogeneity due to trial populations when studying OIC and the efficacy/effect with respect to OIC,

Poulsen et al. have developed a model for OIC in healthy volunteers, in which these population differences can be ruled out and it will be interesting to see results of comparing opioid antagonists in healthy volunteers with laxative-refractory OIC with at least 4 weeks treatment duration[91].

Another limitation was the fact that we could not rule out publication bias for all studies as not all protocols were published online. For this we acknowledge a positive trend that the more recent studies protocols were freely available. Finally, although the observational study data support the data from clinical trials (at least for PR OXN and in patients with OIC at study entry), it is not possible to use these data for definite conclusions as there is a strong heterogeneity in the data and publication bias could not be ruled out.

Another limitation of the study is related to increasing concerns in the US and Europe with respect to opioid therapy, especially in non-malignant pain patients. In this systematic review also studies were included in which patients with non-malignant pain were treated. For the patients in these studies physicians decided that opioid therapy was required and could not be stopped. In daily practice an alternative option in especially non-malignant pain patients might be strictly evaluating the need for opioid therapy, as cessation of opioid therapy will also improve OIC.

CONCLUSION

Opioid antagonists, have been approved for the treatment of opioid induced constipation for a decade (first approval in EU dating from 2008 for PR OXN and MNTX). Despite approval and growing consensus with regard to using these agents in clinical practice the uptake in formal guidelines is still minimal. Together with the study by Nee et al. 2018 (describing the safety and efficacy with regard to non-responders on opioid antagonists) this study provides further evidence on the efficacy with respect to bowel function and pain of opioid antagonists, like naloxegol, alvimopan, naldemedine, PR OXN and MNTX, in the treatment of OIC in patients with opioid treatment for chronic pain.

TRANSPARENCY

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Disclosures

F.J.P.M. Huygen has nothing to disclose. As employers of Mundipharma Pharmaceuticals B.V. Y.J.B. van Megen and G. Koopmans-Klein report personal fees from Mundipharma Pharmaceuticals BV, during the conduct of the study and personal fees from Mundipharma Pharmaceuticals BV, outside the submitted work.

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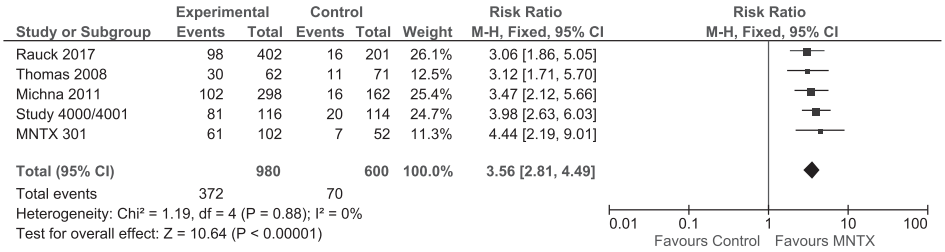
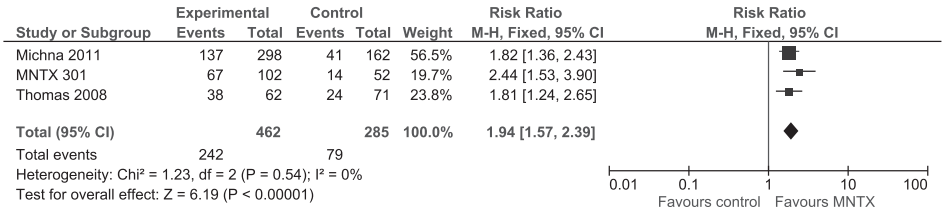
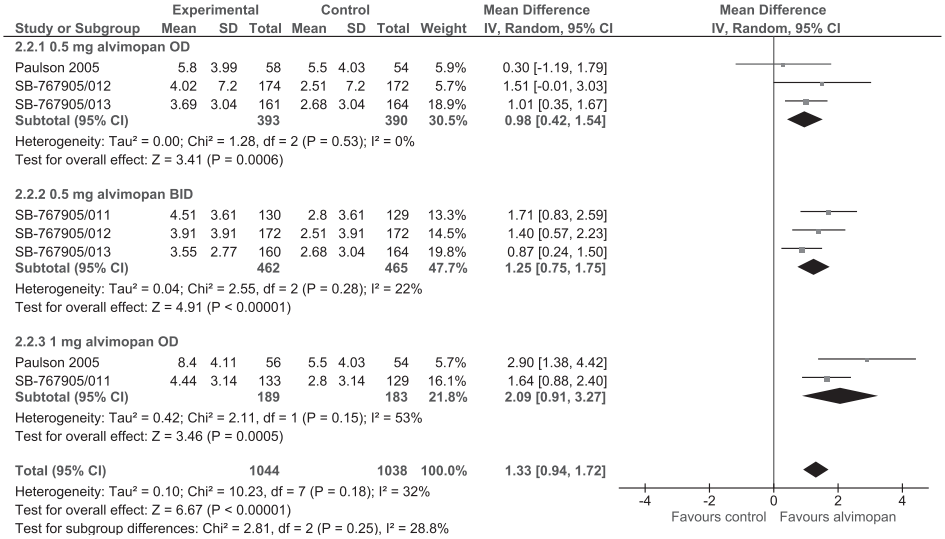
SUPPLEMENTARY FIGURES



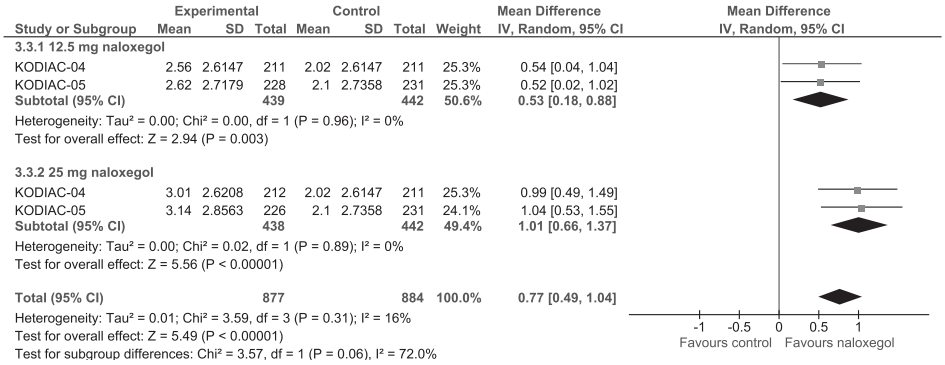
Supplementary Figure 1: Forest plot of comparison: Effect of methylnaltrexone on bowel function efficacy (RCTs) with respect to Rescue Free Bowel movements (within 4 hours after first dose).



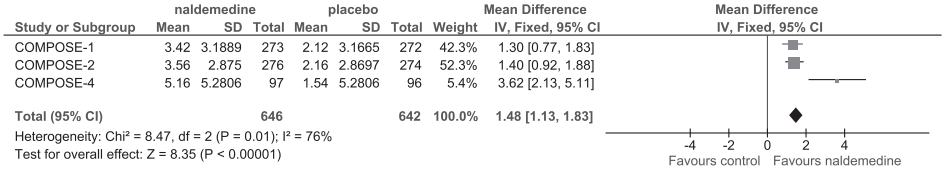
Supplementary figure 2: Forest plot of comparison: Effect of methylnaltrexone on bowel function efficacy (RCTs), with respect to Rescue Free Bowel movements (within 24 hours).



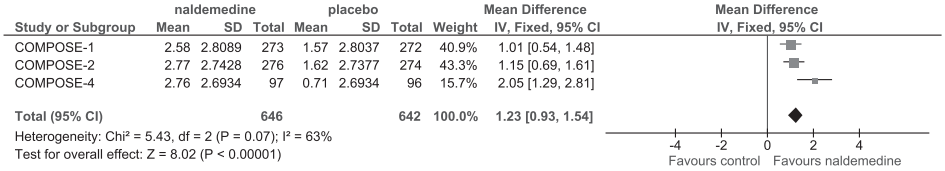
Supplementary figure 3: Forest plot of comparison: Effect of alvimopan on bowel function efficacy (RCTs), with respect to Number of bowel movements per week.



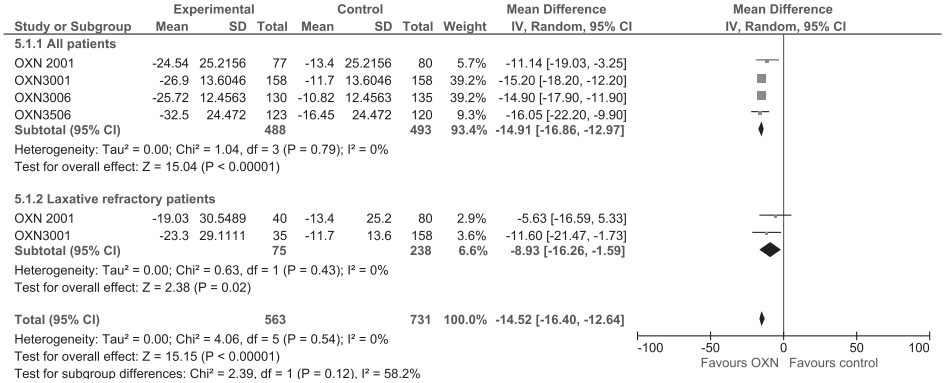
Supplementary figure 4: Forest plot of comparison: Effect of naloxegol treatment on bowel function efficacy (RCTs), with respect to Change from baseline number of SBMs per week.



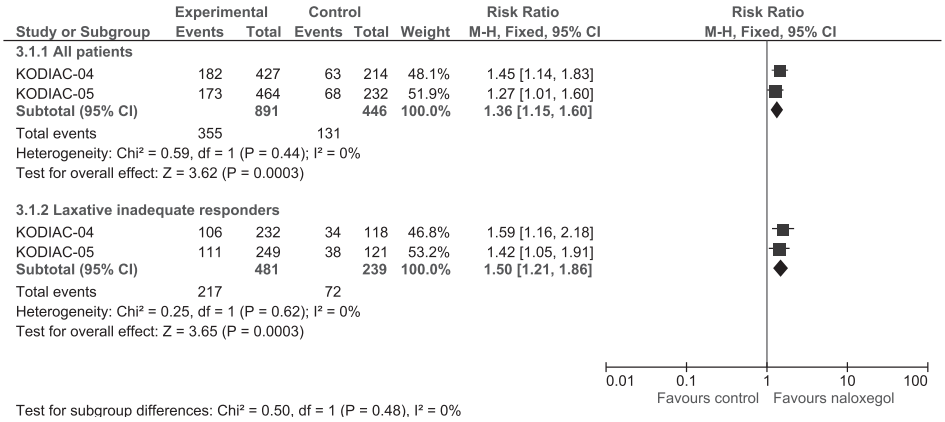
Supplementary figure 5: Forest plot of comparison: Effect of naldemedine treatment on bowel function efficacy (RCTs), with respect to Change in number of SBMs per week.



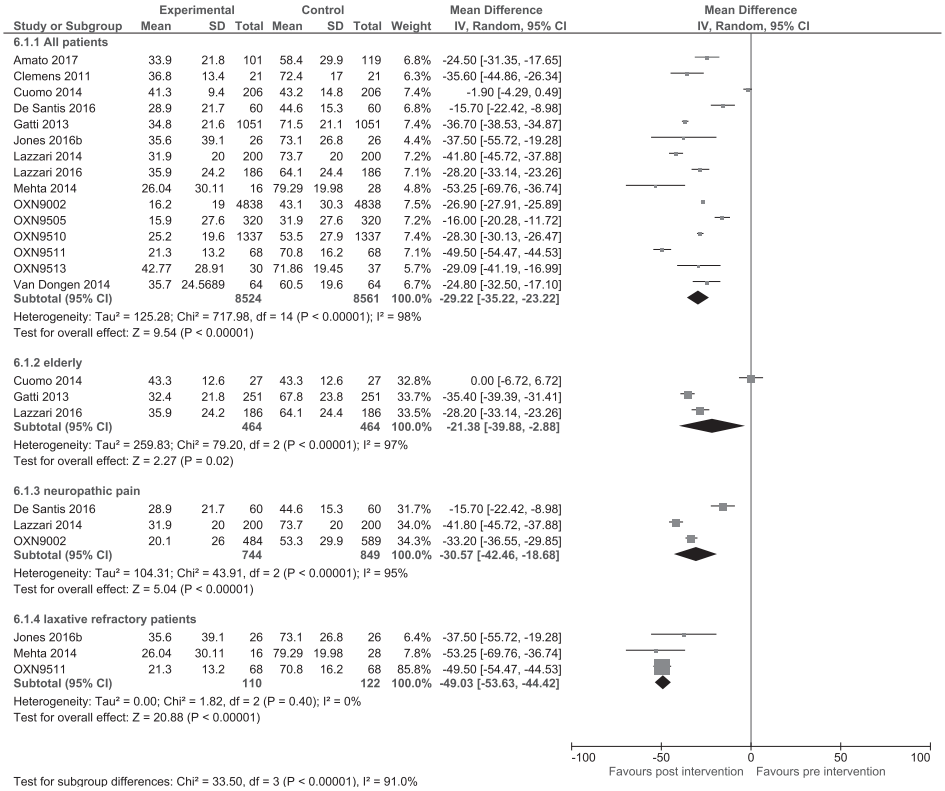
Supplementary figure 6: Forest plot of comparison: Effect of naldemedine treatment on bowel function efficacy (RCTs), with respect to Change in number of CSBMs per week.



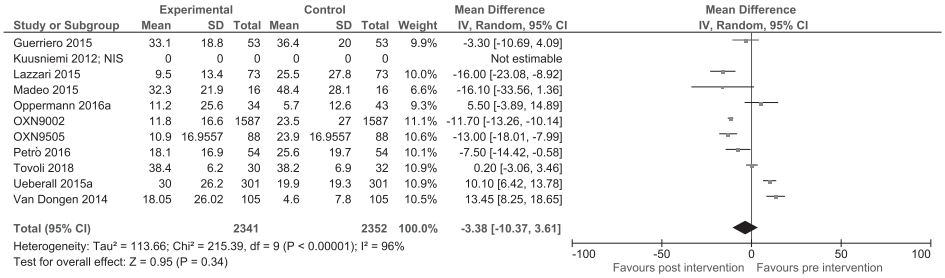
Supplementary figure 7: Forest plot of comparison: Effect of oxycodone/naloxone treatment on bowel function efficacy (RCTs), with respect to Bowel Function Index.



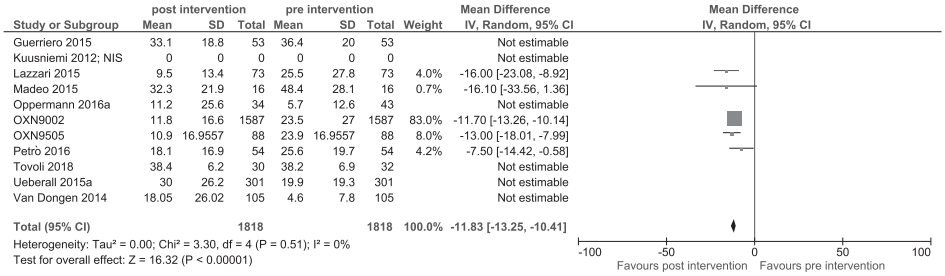
Supplementary figure 8: Forest plot of comparison: Effect of naloxegol treatment on bowel function efficacy (RCTs), with respect to Response rate (≥3 SBMs per week and increase of ≥1 SBMs for ≥9 of 12 weeks and for ≥3 of the 4 final weeks).



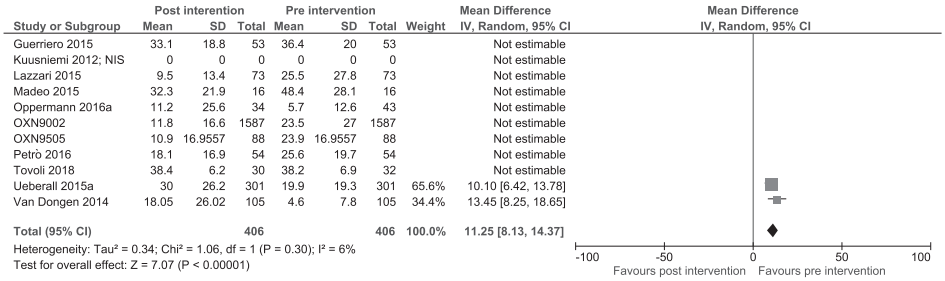
Supplementary figure 9: Forest plot of comparison: Effect of oxycodone/naloxone treatment on bowel function efficacy in patients with OIC at study start (observational studies), with respect to Bowel Function Index.



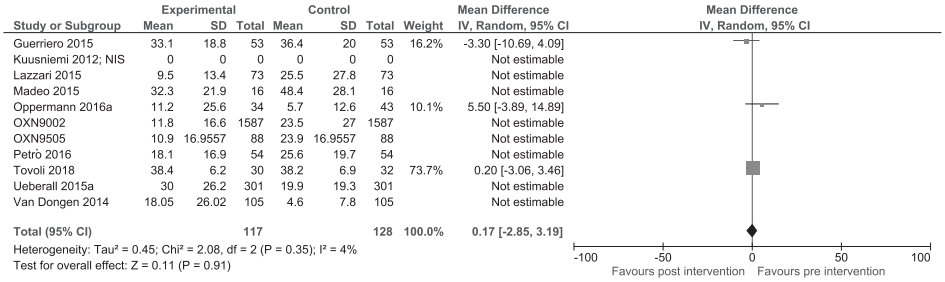
Supplementary figure 10: Forest plot of comparison: Effect of oxycodone/naloxone treatment on bowel function efficacy in patients without OIC at study start (observational studies), with respect to Bowel Function Index.



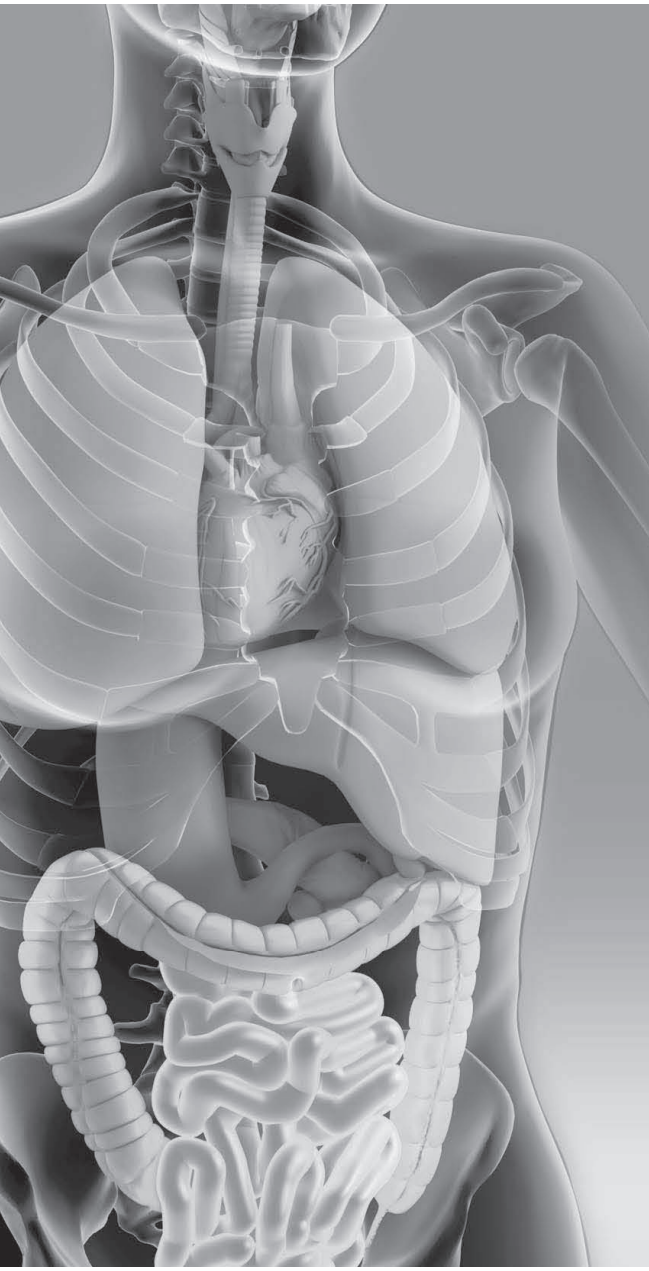
Supplementary figure 11: Forest plot of comparison: Effect of oxycodone/naloxone treatment on bowel function efficacy in patients without OIC at study start (observational studies, improvement of BFI), with respect to Bowel Function Index.



Supplementary figure 12: Forest plot of comparison: Effect of oxycodone/naloxone treatment on bowel function efficacy in patients without OIC at study start (observational studies, worsening BFI), with respect to Bowel Function Index.



Supplementary figure 13: Forest plot of comparison: 12 Effect of oxycodone/naloxone treatment on bowel function efficacy in patients without OIC at study start (observational studies, unchanging BFI), with respect to Bowel Function Index.



Chapter 4

Fixed ratio (2:1) prolonged-release oxycodone/ naloxone combination improves bowel function in patients with moderate-to-severe pain and opioid induced constipation refractory to at least two classes of laxatives

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ABSTRACT

Objective

The effects of combined oxycodone/naloxone prolonged release tablets (OXN PR) were investigated in patients with moderate-to-severe chronic cancer-related or non-cancer pain. All patients had opioid induced constipation (OIC) which persisted despite substantial laxative therapy.

Research design and methods

This pooled analysis included 75 patients with OIC at study entry that was refractory to at least two laxatives with different modes of action. Patients completed randomized, double-blind treatment with OXN PR 20–120 mg/day for either 12 weeks (OXN 9001: non-cancer pain study) or 4 weeks (OXN 2001: cancer-related pain study). Analgesia and bowel function were assessed using the Brief Pain Inventory Short Form and Bowel Function Index (BFI), respectively. Use of laxative medication and safety were assessed throughout the studies.

Clinical trial registration

NCT00513656, EudraCT 2005-002398-57, EudraCT 2005-003510-15.

Results

Statistically and clinically significant improvements in bowel function were observed following double-blind treatment with OXN PR. Mean (SD) reduction in BFI score was 21.2 (28.8) and comparable in patients with cancer-related (19.0 [28.9]) and non-cancer pain (23.3.[29.0]; P_0.0002). Furthermore, the proportion of patients with a BFI score within normal range (_28.8) increased from 9.5% at screening to 43.1% at Day 15 of OXN PR. While all patients used _2 laxatives of different classes at screening, during study treatment 36% stopped using laxatives (P50.001). OXN PR provided effective analgesia, evidenced by stable pain scores during study treatment, and there were no unanticipated adverse events.

Conclusions

OXN PR significantly improved bowel function and reduced the use of laxatives in patients with OIC, previously unresponsive to at least two different classes of laxatives. OXN also provided effective analgesia for patients with moderate-to-severe cancer-related pain and non-cancer-related pain.

INTRODUCTION

Chronic pain places a significant burden on patients, affecting many activities of daily living as well as resulting in loss of independence, anxiety and depression[1,2]. Moderate-to-severe chronic pain has a prevalence of approximately 20% in Europe, and is even more common in patients with cancer, affecting most individuals with advanced disease [1,3,4].

Opioid analgesics are effective treatments for moderate to severe cancer-related and non-cancer pain and are recommended in this setting[5–8]. However, as a therapeutic class, opioids are associated with side effects, including opioid-induced bowel dysfunction (OIBD). OIBD arises from the interaction of exogenous opioids with enteric μ-opioid receptors located throughout the gastrointestinal tract. This can result in inhibited gastric emptying, decreased peristalsis, decreased secretion of intestinal fluids, increased absorption of water as well as dysfunction of esophageal and anal sphincters. These effects can result in gastro-esophageal reflux, nausea and vomiting, and symptoms of opioid-induced constipation (OIC) including abdominal pain and distension, hard stools which are difficult to pass, hemorrhoids and incomplete evacuation[9–12]. OIC affects up to 80% of patients treated with opioid analgesia and is frequently reported to be the most bothersome side effect associated with this therapy[13–15]. OIC has a negative impact on patients' quality of life, and has also been shown to be associated with lower work productivity, absenteeism and significant utilization of healthcare resources[13,15–17].

Treatment guidelines recommend that laxatives should be used in conjunction with opioid analgesics in patients with cancer-related and non-cancer pain[7,8,18]. However, evidence is lacking regarding the type, dosage and timing of laxative therapy[19,20]. Many patients report that laxatives fail to relieve symptoms of OIC. For example, a large-scale study of patients taking opioid analgesia revealed that over half reported fewer than three bowel movements per week despite taking laxatives[13]. In this study, 44% of patients reported using two or more different types of laxatives in the preceding 3 months, and a similar proportion reported using laxatives on at least 5 days of the week[13]. Furthermore, despite taking laxatives, one-third of patients reduce the dosage or stop taking opioids in order to make it easier to have a bowel movement, thereby sacrificing effective pain relief[13].

Given the nature of chronic pain, effective management often requires prolonged opioid therapy. However, as well as the financial cost, bloating, flatulence and abdominal cramps associated with laxative treatments, it is noteworthy that continuous, long-term use of laxatives may lead to electrolyte imbalances as well as having a negative impact on daily activities due to loss of bowel control and unpredictable timing of laxation[17,21–24].

The opioid analgesic oxycodone (Oxy) has proven efficacy for the management of moderate-to-severe cancer related and non-cancer-related pain[25,26]. In order to address the opioid class-effect symptoms of OIC, Oxy was combined with the opioid-receptor

antagonist, naloxone in a prolonged-release formulation (OXN PR). Following oral administration, naloxone has ≤2% systemic availability due to extensive first-pass hepatic metabolism, and consequently acts on opioid receptors in the gastrointestinal tract where it has greater affinity than Oxy[27]. Importantly, the addition of naloxone to oxycodone was shown to be capable of counterbalancing oxycodone-induced delay of colonic transit, as measured with 99mTc-labelled tablets[28].

Clinical trials have demonstrated that OXN PR is associated with analgesia comparable with Oxy PR while providing significantly superior bowel function in patients with non-cancer-related pain and in those with cancer related pain[29–32]. These beneficial effects of OXN PR were associated with improvements in quality of life compared with previous analgesic therapy[33], and were prolonged, being observed during long-term treatment for up to 52 weeks[34,35]. Furthermore, the efficacy and safety of OXN PR in real-world treatment settings has been demonstrated in non-interventional studies involving over 10,500 patients with cancer-related pain and non-cancer related pain[36,37].

However, little is known about the effect of OXN in patients who have OIC which is particularly difficult to treat. This includes patients experiencing no relief from OIC despite taking several different types of laxatives. Therefore a pooled analysis of randomized, controlled trials was conducted, focused on patients with moderate to severe pain who were randomized to OXN PR and had OIC at screening, despite the use of two or more laxatives with different modes of action.

PATIENTS AND METHODS

Patients and study design

This pooled analysis comprised patients aged ≥18 years with moderate-to-severe, chronic pain that required round-the-clock opioid therapy, and had received OXN PR in prior double-blind, multicenter, randomized studies, designed to assess the efficacy and safety of OXN PR. At study entry, all patients included in this pooled analysis had OIC. Their OIC was associated with prior, non-study opioid therapy and persisted despite the use of at least two laxatives with different mechanisms of action (Anatomical Therapeutic Chemical [ATC] 4). The design of these studies has been described previously. In brief, Study OXN9001 was a pooled analysis of two Phase III studies of similar design (OXN3001; EudraCT: 2005-002398-57; and OXN3006; EudraCT: 2005-003510-15). Patients with non-cancer pain were randomized to 12 weeks of OXN PR or Oxy PR at doses equivalent to 20–50 mg/day (OXN3001)[32], or 60–120 mg/day of Oxy (OXN3006)[30], following a run-in period (7–28 days), in which patients were titrated to an effective analgesic dose of Oxy PR[30–32]. Study OXN2001 was a Phase II study of patients with moderate-to-severe cancer-related pain (ClinicalTrials. gov: NCT00513656). Following

a screening period (3–10 days), patients were switched from their pre-study opioid to treatment with OXN PR or Oxy PR for 4 weeks at doses of 20–120 mg/day (a run-in, dose-titration period was not included)[29].

In all studies, oral bisacodyl (10 mg/day) was permitted as rescue laxative medication (OXN9001: 72 hours after a bowel movement but could be taken sooner if patients exhibited discomfort; OXN2001: maximum of five doses in seven consecutive days). The studies were conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization Guidelines for Good Clinical Practice, were approved by local ethics committees, and all patients gave informed, written consent prior to enrolment.

Outcomes and assessments

The primary objective of this pooled analysis was to evaluate bowel function in patients randomized to OXN PR who had OIC at study entry, despite the use of two different classes of laxatives. This was performed using the validated Bowel Function Index (BFI; Copyright for the Bowel Function Index is owned by Mundipharma GmbH, Switzerland, 2002; the BFI is subject of European Patent Application Publication No. EP 1,860,988 and corresponding patents and applications in other countries)[38,39]. BFI score comprised the arithmetic mean score of three items rated on a numerical analogue scale (NAS) of 0–100: ease of defecation (0=easy/no difficulty to 100=severe difficulty), feeling of incomplete bowel evacuation (0=not at all to 100=very strong), and personal judgment of constipation (0=not at all to 100=very strong). BFI score was assessed at screening, start of double-blind treatment and end of double-blind treatment. Laxative use (bisacodyl and non-study laxatives) throughout the studies was

documented. Analgesic efficacy was monitored using the Brief Pain Inventory Short Form (BPI-SF) to assess average pain over the last 24 hours (single question on NAS; 0=no pain to 10=worse pain ever). Use of oxycodone immediate release tablets (Oxy IR) as analgesic rescue medication throughout the studies was recorded. Safety was monitored via the documentation of adverse events (AEs, classified by system organ class and Medical Dictionary for Regulatory Activities [MedDRA] preferred terms) and serious adverse events (SAEs); monitoring of vital signs, hematology, blood chemistry, and electrocardiograms.

Statistical methods

Analyses were performed in the intention-to-treat population. The change in BFI score from the start to end of study treatment was analyzed using paired t-tests, with a change of ≥12 points being considered clinically meaningful[38]. Change in BPI-SF score and frequency of analgesic rescue medication use (Oxy IR) during study treatment were assessed using signed-rank tests, while change in laxative use was assessed using a

McNemar test. All statistical analyses were performed using SAS version 9.1.3 software (SAS Institute Inc., Cary, NC, USA).

RESULTS

Patient characteristics and study treatment

In total 75 patients with chronic, moderate-to-severe pain and OIC at study entry despite the use of at least two laxatives with differing mechanisms of action had been randomized to double-blind treatment with OXN PR. Just over half the patients (n=40, 53.3%) had cancer related pain (OXN2001) and 46.7% (n=35) had non-cancer pain (OXN9001). There were no significant differences in the demographic characteristics of the two groups. Median (range) age was 62.0 (40, 80) years (OXN2001:61.5 [40, 80]; OXN9001: 62.0 [40, 77]) and approximately two-thirds of patients (69.3%) were ≤65 years (OXN2001: 65.0%; OXN9001: 74.3%). There was a trend for more women with non-cancer pain (71.4%) versus cancer pain (47.5%). OXN PR dosage remained relatively stable throughout the trials. Across the studies, the mean daily dose of OXN PR at the start of treatment (28.5 mg/day) increased by 6.0 mg/day at the end of the double-blind treatment. Mean changes in OXN PR dosage during treatment were similar in patients with cancer-related pain and non-cancer pain (OXN2001: 7.0 mg/day, OXN9001: 4.9 mg/day).

Bowel function index

Overall, the mean (SD) BFI score at screening was 62.5 (18.7) and was comparable in patients with cancer-related pain and non-cancer pain (OXN2001: 62.8 [17.4], OXN9001: 62.1 [20.4]). At the start of the double-blind treatment phase, high BFI scores were recorded (OXN2001: 66.4 [15.9], OXN9001: 61.3 [23.2]). Improvements in bowel function, indicated by a decrease in BFI score, were observed at the end of the double-blind treatment with OXN PR. Overall, BFI score decreased by a mean (SD) of 21.2 (28.8) to 43.0 (31.1). Patients with cancer-related pain had a decrease of 19.0 (28.9) after a mean of 24.7 days of treatment, while patients with non-cancer related pain experienced a decrease in BFI score of 23.3 (29.0) following 69.5 days of treatment. The reductions in BFI score were clinically and statistically significant in both groups of patients (P≤0.0002; Figure 1).

The shorter mean duration of treatment with OXN PR in patients with cancer-related pain compared with non-cancer related pain reflected differences in the treatment durations defined in the study protocols (4 weeks versus 12 weeks). In addition to the significant improvements in BFI scores associated with OXN PR, an increase in the proportion of patients who had a BFI score within the normal range (validated as≤28.8 in non-constipated patients with chronic pain[39]) was observed within the first 2 weeks of treatment.

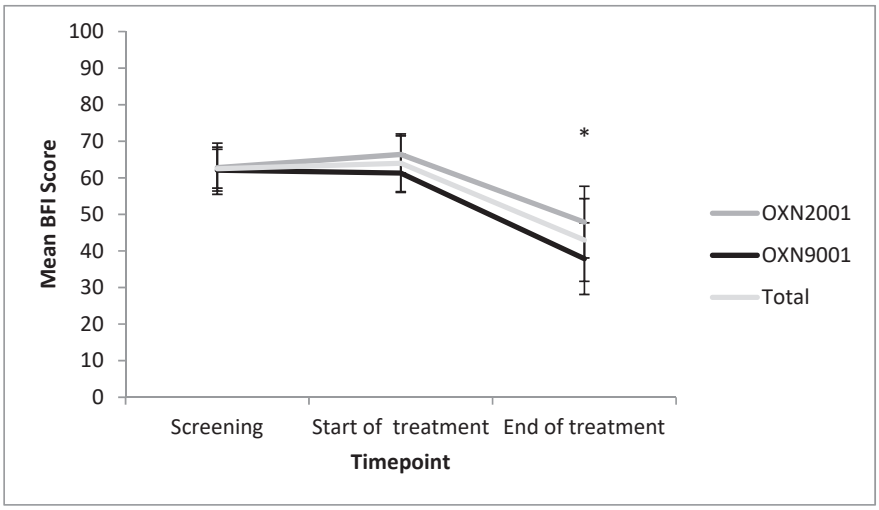

Figure 1. Bowel Function Index during treatment.
Mean ± confidence interval. BFI score 0–28.8 is the reference range for non-constipated patients with chronic pain[39].
*BFI score at end of double-blind treatment minus score at start of double-blind treatment, assessed using paired t-test: OXN2001 P=0.0002; OXN9001<.0001; and Total P<0.0001. OXN2001: patients with cancer-related pain randomized to OXN PR for 4 weeks. OXN9001: patients with non-cancer-related pain randomized to OXN PR for 12 weeks.

Prior to randomization, 9.5% of patients had a BFI score ≤28.8 (5.1% in OXN2001 and 14.3% in OXN9001). At Day 8 of OXN PR, this increased to 31.9% (27.8% in OXN2001 and 36.4% in OXN9001), and at Day 15 of OXN PR, 43.1% (36.4% OXN2001 and 50.0% OXN9001) had a normal BFI score (Table 1).

Table 1: Patients with normal Bowel Function Index score.

		Duration of treatment with OXN PR					
BFI score ≤28.8	Screening % (n/N)	Day 1 % (n/N)	Day 8 % (n/N)	Day 15 % (n/N)	Day 29 % (n/N)	Day 57 % (n/N)	Day 85 % (n/N)
OXN2001	5.1 (2/39)	0 (0/40)	27.8 (10/36)	36.4 (12/33)	22.2 (8/36)	–	–
OXN9001	14.3 (5/35)	8.6 (3/35)	36.4 (12/33)	50.0 (16/32)	44.8 (13/29)	48.1 (13/27)	40.0 (14/35)
Total	9.5 (7/74)	4.0 (3/75)	31.9 (22/69)	43.1 (28/65)	32.3 (21/65)	–	–

BFI score 0–28.8 is the reference range for non-constipated patients with chronic pain.
OXN2001: 40 patients with cancer-related pain randomized to OXN PR for 4 weeks
OXN9001: 35 patients with non-cancer-related pain randomized to OXN PR for 12 weeks

Laxative use

All patients in this analysis had been using at least two laxatives of different mechanistic classes at study entry without success. Contact laxatives (n=72, 96.0%) and osmotically

acting laxatives (n=67, 89.3%) were most commonly used, while enemas, stool softeners/emollients and other laxatives were used by 8 (10.7%), 4 (5.3%) and 12 (16.0%) patients, respectively. In total, 64.0% (n=48) required the study laxative (bisacodyl) during study treatment. Four patients (5.3%) used non-study laxatives in addition to bisacodyl: one patient in OXN9001 (polyethylene glycol and lactulose) and three patients in OXN2001 (lactulose [n=2], polyethylene glycol [n=1]). During study treatment, no patients started using laxatives while 36.0% stopped using laxatives (McNemar test, P<0.001). As expected, use of the study laxative was more frequent in patients with cancer-related pain (82.5%; median [range] 6.0 [1–20] tablets) than in those with non-cancer-related pain (42.9%; 10 [1–36] tablets). Mean daily doses of study laxative were 2.1 mg for patients in OXN2001 and 4.3 mg for those in OXN9001. Data indicate that study laxative was used as needed; for patients with non-cancer pain, the mean number of days with study laxative use (4.2 days) was less than the mean number of days receiving study medication (69 days) (Table 2).

Table 2: Use of study laxative (bisacodyl) during double-blind treatment with OXN PR.

BFI Score		**OXN2001 (n=40)**	**OXN9001 (n=35)**
Any study laxative used	% (n/N)	82.5 (33/40)	42.9 (15/35)
Any non-study laxative used	% (n/N)	NR	2.9 (1/35)
Number of days study laxative used	n	NR	15
	Mean (SD)	NR	4.2 (2.8)
	Median	NR	5.0
	Min, max	NR	1, 8
Duration of study treatment (days)	n	33	15
	Mean (SD)	24 (7.5)	69 (33)
	Median	28	77
	Min, max	1, 34	7, 146
Daily dose of bisacodyl (mg/day)	n	33	15
	Mean (SD)	2.1 (1.7)	4.3 (4.0)
	Median	1.82	3.1
	Min, max	0.2, 8.3	0.3, 11.3

OXN2001: 40 patients with cancer-related pain randomized to OXN PR for 4 weeks
OXN9001: 35 patients with non-cancer-related pain randomized to OXN PR for 12 weeks

This is in contrast to the period prior to receiving double-blind treatment with OXN PR in which all patients used at least two laxatives of different ATC class. At this time, 67% of patients used at least one laxative on a daily basis (70% of patients with cancer-related pain and 63% of patients with non-cancer pain).

Analgesic efficacy and safety

Overall, there was no significant difference in 'average pain over the last 24 hours' scores from the start to end of double-blind treatment with OXN PR. While pain response remained stable in patients with non-cancer related pain (OXN9001: mean change in score 0.1, P=0.481), there was a non-significant trend for improvement in pain scores reported by patients with cancer related pain (OXN2001: mean change in score -0.4, P=0.311). Use of Oxy IR analgesic rescue medication decreased following double-blind treatment with OXN PR. In patients with cancer-related pain (OXN2001) there was a significant decrease in the median dose of rescue medication (Oxy IR) from the start of study treatment (Days 1–7: 3.93 mg) to the end of study treatment (Days 29–35: 1.25 mg; P¼0.0018). Similarly, in patients with non-cancer related pain median dose of rescue medication (Oxy IR) in the run-in period (5.0 mg) was significantly greater than that at the end of study treatment (Days 57–84; 0.3 mg; P=0.006). The percentage of patients who used Oxy IR remained stable throughout double blind treatment with OXN PR in both studies.

AEs related (definitely, probably or possibly) to study medication were reported in one-third of patients

(OXN2001: 27.5%, OXN9001: 40.0%). SAEs were more common in patients with cancer-related pain (OXN2001: 25.0%, OXN9001: 2.9%). All four deaths during the study occurred in patients with cancer-related pain but none were considered related to study medication. During double-blind treatment with OXN PR, the most common AEs were nausea (9.3%), constipation (9.3%) and vomiting (8.0%; Table 3).

Table 3: All causality adverse events occurring during double-blind treatment with OXN PR (≥2 patients).

System organ class and MedDRA preferred term	Total (N=75) n (%)
Blood and lymphatic system disorders	**2 (2.7)**
Anaemia	2 (2.7)
Lymphopenia	2 (2.7)
Gastrointestinal disorders	**27 (36.0)**
Abdominal pain	2 (2.7)
Abdominal pain upper	4 (5.3)
Constipation	7 (9.3)
Diarrhoea	2 (2.7)
Dry mouth	2 (2.7)
Nausea	7 (9.3)
Vomiting	6 (8.0)
General disorders and administrative site conditions	**21 (28.0)**
Asthenia	5 (5.3)
Drug withdrawal syndrome	2 (2.7)
Fatigue	3 (4.0)

Table 3: All causality adverse events occurring during double-blind treatment with OXN PR (≥2 patients). (*continued*)

System organ class and MedDRA preferred term	Total (N=75) n (%)
Odema peripheral	4 (5.3)
Pain	4 (5.3)
Pyrexia	2 (2.7)
Investigations	**16 (21.3)**
Blood glucose increased	2 (2.7)
Haemoglobin decreased	3 (4.0)
Neutrophil count increased	2 (2.7)
Metabolism and nutritional disorders	**9 (12.0)**
Anorexia	3 (4.0)
Hyperkalaemia	3 (4.0)
Hyperuricaemia	2 (2.7)
Hypoalbuminaemia	3 (4.0)
Hypocalcaemia	2 (2.7)
Neoplasms (benign, malignant, unspecified)	**9 (12.0)**
Cancer pain	4 (5.3)
Malignant neoplasm progression	4 (5.3)
Nervous system disorders	**12 (16.0)**
Dizziness	2 (2.7)
Headache	4 (5.3)
Respiratory, thoracic and mediastinal disorders	**6 (8.0)**
Dyspnoea	3 (4.0)
Skin and subcutaneous disorders	**6 (8.0)**
Hyperhidrosis	3 (4.0)
Pruritis	2 (2.7)

Adverse events reported documented in only one patient are not shown
OXN2001: 40 patients with cancer-related pain randomized to OXN PR for 4 weeks
OXN9001: 35 patients with non-cancer-related pain randomized to OXN PR for 12 weeks

DISCUSSION

This pooled analysis of randomized clinical trials demonstrates that OXN PR is associated with significantly improved bowel function in patients with moderate-to-severe pain and OIC that is refractory to at least two different ATC class 4 laxatives. Switching from opioid analgesic plus multiple laxatives to OXN PR was associated with statistically significant and clinically relevant improvements in BFI scores as well as significant reductions in the use of laxatives.

Apart from the underlying cause of pain, there were no notable differences between patients with cancer-related pain and non-cancer-related pain in terms of demographic factors and dose of OXN PR received during the studies. At screening, when patients were receiving opioid analgesia of any type and at least two different types of laxatives, high BFI scores were observed in both groups (mean score 62.5), indicating these patients were suffering with constipation. While BFI scores at the start of treatment were greater in patients with cancer-related pain (66.4), statistically significant and clinically relevant improvements in OIC were observed in both groups of patients at the end of double-blind treatment with OXN PR (mean reductions in BFI scores of 19.0 and 23.3 points, respectively, P≤0.002). It is noteworthy that individuals with cancer-related pain received OXN PR for a shorter duration than those with non-cancer-related pain (4 weeks versus 12 weeks), since the design of the OXN2001 trial reflected the limited life expectancy of these patients. The positive effect of OXN PR on bowel function is further emphasized by the finding that the proportion of patients who had a BFI score within the normal range (≤28.8) increased by over four-fold from screening (9.5%) to Day 15 of OXN PR (43.1%).

In addition to the significant improvements in bowel function, OXN PR was also associated with reduced use of laxatives. While all patients were using at least two different classes of laxatives at screening, not all patients required laxatives during study treatment; 36.0% of patients stopped using laxatives and no patients started using laxatives during double-blind treatment with OXN PR (P<0.001). Furthermore, for patients with nonmalignant pain (OXN9001), the mean number of days with study laxative use (4.2 days) was approximately two-thirds less than the mean number of days receiving study medication (15.4 days). More patients with cancer-related pain (82.5%) used study laxative during study treatment compared with those with pain of a non-cancer origin (42.9%). This difference may be due to the other etiologies of constipation in patients with cancer in addition to opioid medication, including the malignancy itself, general debility, less mobility, other medications such as chemotherapeutic agents and concomitant diseases[40,41].

While treatment guidelines recommend laxatives are prescribed to be used in conjunction with opioid analgesics in patients with cancer-related and non-cancer pain, many patients report that laxatives fail to relieve symptoms of OIC and/or are associated with unpleasant complications[7,8,13,15,18,22,23]. Given the unique etiology of OIC and the effects of opioids on neural activity, motility and secretion throughout the entire gastrointestinal tract[11], it is unsurprising that laxatives frequently fail to counteract the symptoms of OIC[13,15]. Instead, treatment of OIC should target the etiology of this condition via a μ-opioid receptor mediated approach such as that of naloxone (a non-selective opioid antagonist), rather than just focus on symptomatic management[10,11].

As demonstrated in previous studies, OXN PR can significantly improve bowel function without affecting the pain relief observed with Oxy PR in patients with moderate-to-severe chronic pain[29–32]. This pooled analysis demonstrates that these effects are also valid for patients with persisting OIC despite the use of at least two different types of laxatives, and provides further confirmation that naloxone addresses OIC from a pathophysiological point of view rather than merely a symptomatic standpoint. In this pooled analysis, OXN PR provided effective analgesia for patients with moderate-to-severe pain with OIC that is refractory to at least two different classes of laxatives. The stable average pain scores during study treatment were comparable to observations in the patients randomized to Oxy PR in the primary studies for OXN2001 and OXN9001[29,31]. These findings add to the substantial body of evidence that addition of naloxone to Oxy PR (in the combination of OXN PR) can prevent symptoms of OIC while not interfering with the pain relief obtained with Oxy PR[42,43].

CONCLUSION

In summary, the results of this pooled analysis add to the body of evidence for the unique mechanism of action and therapeutic value of OXN PR. In patients with persisting OIC despite the use of two different classes of laxatives, OXN PR resulted in a significant and clinically relevant improved bowel function, significantly reduced the use of laxatives, and provided effective analgesia for patients with moderate-to-severe cancer-related pain and non-cancer related pain.

TRANSPARENCY

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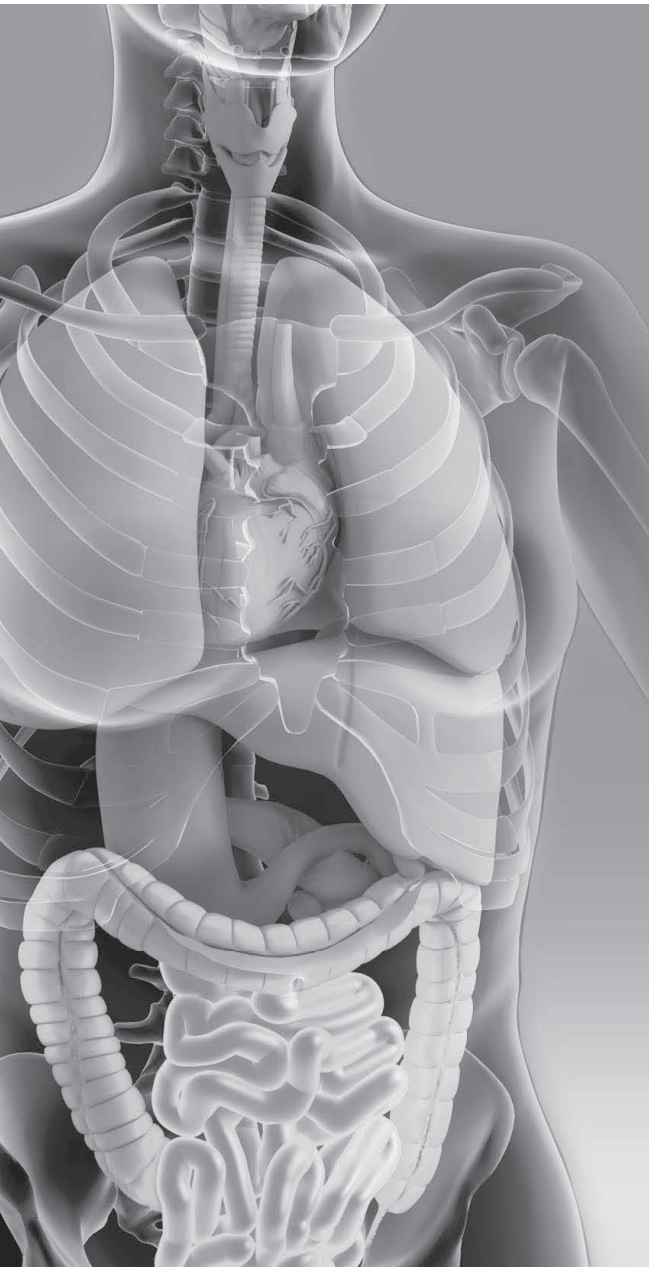

Chapter 5

Treatment with Prolonged Release Oxycodone/Naloxone improves pain relief and Opioid Induced Constipation compared with Prolonged Release Oxycodone in patients with chronic severe pain and laxative-refractory constipation

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ABSTRACT

Purpose

Laxative-refractory OIC (defined as opioid-induced constipation despite using 2 laxatives with a different mechanism of action (based on the Anatomical Therapeutic Chemical (ATC) Classification System level 4 term, e.g. contact laxatives, osmotically acting laxatives, softeners/emollients, enema's and others)) has a great impact on the treatment and quality of life (QoL) of patients with severe chronic pain. This non-interventional observational, real-life study in Belgium investigates the efficacy of prolonged release oxycodone/naloxone combination (PR OXN) treatment regarding pain relief and OIC, compared to previous prolonged release oxycodone (PR OXY) treatment for laxative-refractory OIC patients in daily clinical practice.

Methods

Laxative-refractory OIC patients with severe chronic pain were treated with PR OXN for 12 weeks (3 visits). Pain relief (numerical rating scale [NRS]) and OIC (Bowel Function Index [BFI]) were evaluated at each visit. A responder was defined as a patient who had a) no worsening of pain at last visit compared to visit 1, or an NRS ≤ 4 at visit 3/last visit, as well as b) a reduction in BFI ≥ 12 units at visit3/last visit compared to visit 1, or c) a BFI ≤28.8 at visit 3/last visit.

Findings

68 laxative-refractory OIC patients with severe chronic pain were treated during 91 days with PR OXN (median daily dose 20 mg). Treatment with PR OXN resulted in a significant and clinically relevant decrease of pain with 2.1 units ($p<0.001$, 95% CI: 1.66, 2.54) and of BFI with 48.5 units ($p<00.001$; 95% CI: 44.4, 52.7) compared to PR OXY treatment, while use of laxatives was significantly reduced ($p<0.001$). 95.1% of patients was a responder and QoL (EQ-5D) improved significantly. Adverse events were opioid related and PR OXN treatment was well tolerated.

Implications

Treatment with PR OXN results in a significant and clinically relevant reduction of OIC compared to previous PR OXY treatment for patients with severe chronic pain and laxative-refractory OIC. Treatment with PR OXN also resulted in a significant improvement in pain relief and quality of life.

Clinical Trial Registry number

ClinicalTrials.gov identifier: NCT01710917

INTRODUCTION

Opioids are widely used for treatment of patients with severe chronic pain. However, adverse drug reactions associated with the use of opioids, particularly opioid-induced bowel dysfunction (OIBD), can be very problematic and severely affect quality of life[1]. Opioid-induced constipation (OIC) is the most distressing lead symptom of OIBD and occurs in approximately 40% of opioid-treated patients[2, 3]. In contrast to opioid-related adverse effects mediated through the central opioid receptors, occurring at the start of the treatment and usually decreasing rapidly, OIC is mediated through intestinal opioid receptors, often persisting throughout opioid treatment without diminishing in intensity[4]. OIC is the most troublesome opioid-related side effect reported by patients, resulting in reduction or discontinuation of opioid treatment in a third of opioid-treated patients[1]. Laxatives are the most common drugs used for relieving OIC. However, since laxatives do not address the underlying mechanisms of OIC they are insufficiently effective in the majority of patients suffering from OIC[5, 6] . Moreover, there are no direct comparative data on different laxatives in the prevention or treatment of OIC, resulting in a lack of generally accepted guidelines on laxative use in OIC[6].

A strategy to minimize or prevent OIC while maintaining analgesic efficacy is blocking intestinal opioid receptors while allowing the activation of central opioid receptors[6]. To this end, a prolonged release tablet consisting of oxycodone and naloxone (PR OXN) in a 2:1 ratio has been developed. Oxycodone has been shown to be an effective analgesic in different types of pain[7]. Naloxone is an opioid receptor antagonist with low systemic bioavailability (<3%) primarily used as an injectable solution for treatment of opioid overdose by its antagonizing effect on central opioid receptors. When administered orally, naloxone antagonizes the opioid receptors in the gut wall, thereby counteracting OIC, while its extensive first pass hepatic metabolism ensures the lack of antagonist effect on the central analgesic effect of oxycodone[8].

Several randomized controlled studies demonstrated comparable analgesic efficacy of PR OXN and prolonged release oxycodone (PR OXY) with a significant and clinically relevant improvement in OIC of PR OXN compared to PR OXY in different types of pain even after long-term treatment[9-15]. The frequency of adverse events was similar between PR OXN and PR OXY treatment. This has been confirmed in a daily clinical practice in Germany for patients with a wide variety of pain etiologies[16].

PR OXN is indicated for the treatment of severe pain which can only be adequately managed with opioid analgesics. In Belgium reimbursement for PR OXN is strictly limited to patients who have been treated with PR OXY for at least the last 30 days prior to PR OXN treatment and who suffer from laxative-refractory OIC (defined as OIC despite the use of at least 2 laxatives with different mechanisms of action (based on the Anatomical Therapeutic Chemical (ATC) Classification System level 4 term, e.g. contact laxatives,

osmotically acting laxatives, softeners/emollients, enema's and others; level 4 ATC term) during previous PR OXY treatment.

This study was requested by the Belgian reimbursement authorities to investigate PR OXN efficacy regarding both pain relief and OIC in chronic pain patients eligible for PR OXN reimbursement in Belgium in real-life. Besides evaluation of efficacy regarding pain relief and OIC use of laxatives and analgesic rescue medication, quality of life and safety during PR OXN treatment compared to the previous PR OXY treatment were also evaluated.

METHODS

Study design

This non-interventional, observational, real-life study was designed to evaluate the pain relief and OIC of the PR OXN treatment in daily practice in patients with chronic severe pain compared to previous PR OXY treatment. PR OXN treatment started at visit 1. The study was performed with electronic Case Record Forms (eCRF). All parameters collected at visit 1 reflected the PR OXY treatment. Evaluations were performed during 2 follow up visits. Visit 2 was scheduled after PR OXN dose titration and visit 3 was scheduled at least 12 weeks after visit 1.

This study was conducted in accordance with Belgian and European health law and controlled drug regulations.

Patients

Patients enrolled in this study met the reimbursement conditions for PR OXN in Belgium as well as the summary of product characteristics (SPC) for PR OXN. In Belgium patients are eligible for reimbursement if they meet the following conditions:

a) all patients had to be ≥ 18 years, with a documented history of severe pain requiring around-the-clock opioid therapy, treated with PR OXY during at least 30 days with insufficient pain relief and/or unacceptable side effects AND b) all patients had to be suffering from OIC (Bowel Function Index [BFI] ≥ 28.8, see section methods) despite the use of at least 2 laxatives with different mechanisms of action (level 4 ATC term) during the previous PR OXY treatment.

Patients were excluded from the study if any of the following criteria based on the SPC were met: any history of hypersensitivity to oxycodone, naloxone, related products or other ingredients; active alcohol or drug abuse and/or history of opioid abuse; patients who participated in a clinical research study involving a new chemical entity or an experimental drug within 30 days of study entry; surgery completed prior to the start of the study, or planned surgery during the study that would influence pain or bowel func-

tion; patients who had taken naloxone □30 days prior to the start of the study; patients suffering from diarrhoea and/or opioid withdrawal; patients with any situation in which opioids were contra-indicated; patients suffering from severe respiratory depression with hypoxia and/or hypercapnia, severe obstructive pulmonary disease, cor pulmonale, severe bronchial asthma, non-opioid induced paralytic ileus, moderate to severe liver function impairments, and pregnant or breastfeeding women. Written informed consent was obtained from patients for the anonymous use of the data.

Medication

PR OXN is available in 5mg/2,5mg; 10mg/5mg; 20mg/10mg and 40mg/20mg (oxycodone/naloxone) tablets and was prescribed to the patients according to the SPC.Patients were switched immediately from PR OXY to PR OXN with equal oxycodone doses. After switch to PR OXN the PR OXN dose could be titrated as needed, Use of laxatives and analgesic rescue medication as well as other co-medication was allowed during PR OXN treatment as in daily clinical practice and documented (yes/no was mandatory, type and dosage was optional).

Study assessments

Primary parameter

The primary parameter was the percentage of responders after 12 weeks of PR OXN treatment. The response was based on the parameters pain and OIC as described below.

Pain

Pain was assessed at each visit by the physician on a numerical rating scale (NRS) from 0 (no pain) to 10 (worst pain).

OIC

OIC was evaluated by the physician using the validated BFI*[17,18]. This index uses a numerical scale from 0 (easy/no difficulty) to 100 (severe difficulty/very strong) to record a patients' subjective assessment of three items related to OIC: ease of defecation, feeling of incomplete bowel evacuation and personal judgement of OIC. The BFI is calculated as the arithmetic mean of the scores for these three items. A lower score indicates a better bowel function. A score of ≤28.8 is considered a normal bowel function with respect to OIC and a BFI change of ≥12 points is considered a clinically relevant change[17,18,19].

* Copyright for the BFI is owned by Mundipharma Laboratories GmbH, Switzerland 2002; the BFI is subject of European Patent Application Publication No. EP 1 860 988 and corresponding patents and applications in other countries.

Responders

A patient was defined as a responder if the patient had:

- no worsening of pain (NRS increase ≤ 1 unit at visit 3/last visit compared to visit 1 or a NRS ≤ 4 at visit3 /last visit AND
- had a reduction in BFI of ≥ 12 units at the last visit compared to visit 1 or a BFI ≤ 28.8 at visit 3/last visit.

Secondary parameters

Secondary parameters included the use of laxatives and analgesic rescue medication, evaluation of the quality of life and safety assessment during PR OXN treatment compared to the previous PR OXY treatment.

Use of laxatives

Laxative use was assessed by asking if the patient had used laxatives in the last 7 days prior to the each study visit (yes or no) and whether laxative use had increased/decreased or remained constant compared to previous visit was also registered (decrease/constant/increase). If laxatives were used in the last seven days prior to the study visit, notation of type, dose and frequency of the used laxatives were optional due to the non-interventional character of the study. The percentage of patients using laxatives in the last 7 days before each visit and the percentages of patients reporting increased/decreased/stable laxative use at visits 2 and 3 compared to visit 1 were calculated.

Use of analgesic rescue medication

The assessment of the use of analgesic rescue medication was similar to the assessment of laxative use as described above.

Quality of Life

The patient's quality of life was evaluated via the standardized EQ-5D questionnaire. The EQ-5D score and EQ-5D VAS health score was recorded at visit 1 and at the last visit. A derived EQ-5D score was calculated from the 5 items (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) as well as the absolute change in EQ-5D score and EQ-5D VAS health score between the last visit and visit 1.

Safety

Safety assessments consisted of monitoring and recording all (Serious) Adverse Events ((S)AEs) and adverse reactions (ARs) at all visits.

Statistical analysis

For the efficacy parameters the analyses were performed for all patients meeting the inclusion criteria who received at least one dose of PR OXN treatment and who had at least one post-dose efficacy evaluation (full analysis population). Patients using laxatives during the 30 days PR OXY treatment were included in this full analysis. Since patients were not asked pro-actively about the laxative treatment before start, and since the laxative use during last 7 days was evaluated at the consecutive visits, it was decided to analyze the primary parameter also for patients who used laxatives in the last 7 instead of 30 days before study inclusion (per protocol population). The safety analysis was performed for all patients who had received at least one dose of study medication and had at least one safety assessment after the last dose (safety population). Descriptive statistics of all demographic, baseline variables and study parameters were provided overall. Continuous data were summarized by their mean, standard deviation, 95% confidence interval of the mean, median, minimum and maximum. Categorical and ordinal data were summarized by frequency and percentages. No imputation of missing data was performed. A paired t-test was used to test if there was a change in mean pain NRS, BFI and EQ- 5D score between the first and last visit. The McNemar test for paired data was used to test if there was a change in use of laxatives or use of analgesic rescue medication between the first and the last visit. The effect of the treatment time on changes in mean BFI scores was studied in more detail using linear mixed effect models. All statistical tests were performed using a two-sided significance level of 5%.

RESULTS

A total of 68 patients were included in the full analysis population (Figure 1). 91.2% of the patients (62 out of 68) completed the study. Three patients (4.4%) discontinued the study on their own choice, one patient stopped due to an adverse event and 2 patients (2.9%) for other reasons (Figure 1). For 3 subjects no laxative intake for the last 7 days was documented and therefore 65 patients were included in the per protocol analysis (Figure 1).

Table 1 shows age, gender and diagnosis of pain for enrolled patients. The median study duration was 91 days (7 - 127 days), with 37.5 days (3-85) for visit 2 (dose titration) and 91 day for visit 3 (39-127). These variations in study durations were due to the non-interventional set-up of the study. The median (range) dose of PR OXY treatment used before start of the study (visit 1) was 20 (5-360) mg. The median (range) prescribed dose of PR OXN at visit 1 was similar to that of PR OXY, 20 (10-360) mg. At visit 2 and visit 3 the median (range) dose of PR OXN remained stable at 20 (10-360) mg.

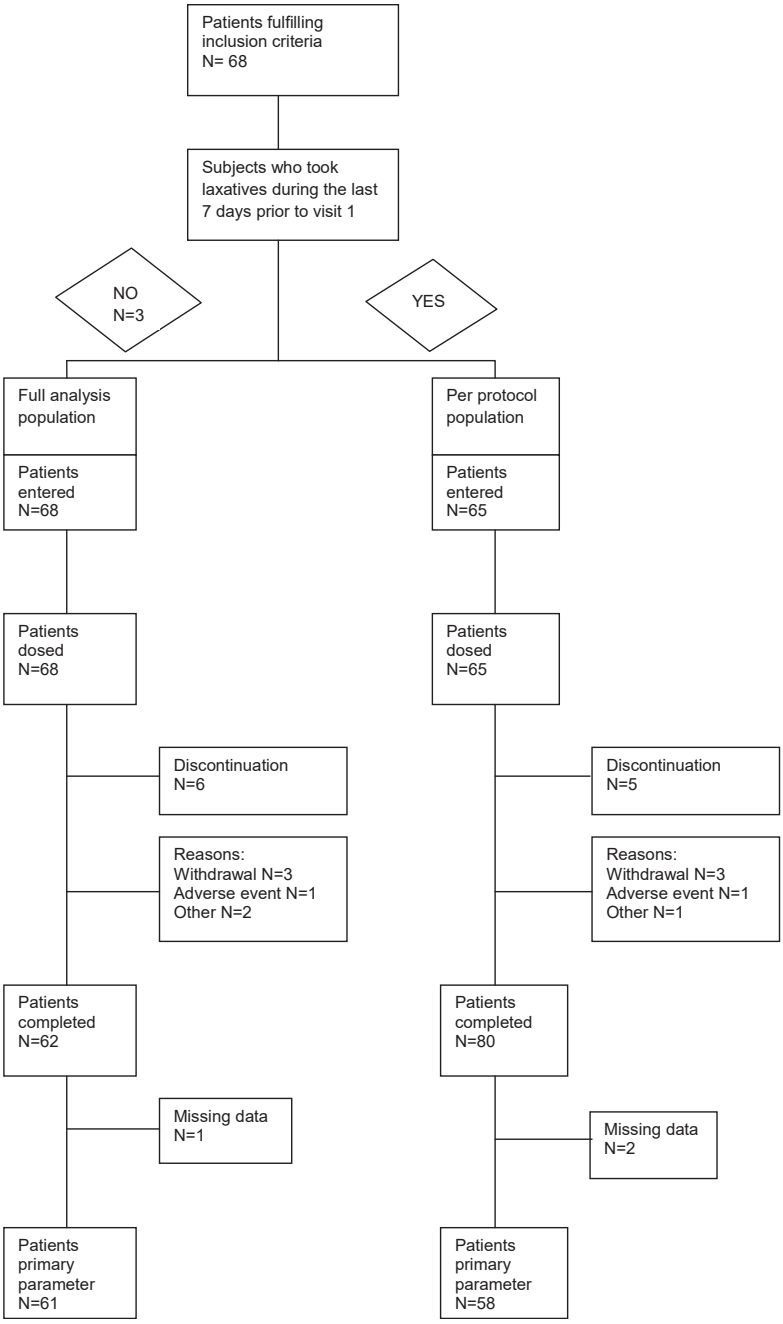

Figure 1: Patient diagram

The full analysis population included all patients meeting the inclusion criteria who received at least one dose of PR OXN treatment during the study and who had at least one post-dose efficacy evaluation. The per protocol population included all patients meeting the inclusion criteria who took laxatives in the last 7 days before study inclusion.

Table 1: Baseline characteristics of the patients (n=68, full analysis population)

Characteristic	Value
Age (years), Mean (SD)	59.8 (13.3)
Sex, no. (%)	
Male	22 (32.4)
Female	46 (67.6)
Pain diagnosis, no. (%)	
Malignant	4 (5.9)
Non-malignant*	62 (91.2)
Osteoarthritis	19 (30.6)
Arthritis	1 (1.6)
Low back pain	26 (41.9)
Neuropathic pain	22 (35.5)
Osteoporosis	2 (3.2)
Post-operative pain	6 (9.7)
Other	9 (14.5)
Unknown	2 (2.9)

*For patients with non-malignant pain, multiple diagnoses were possible

Efficacy of PR OXN treatment with regard to pain relief

The pain NRS reduced significantly ($p<0.001$) with on average 2.1 units (95% CI: 1.66, 2.54) between visit 1 (mean(SD) 6.8±1.5) and visit 3 (mean(SD) 4.6±1.5) (Figure 2). The average pain NRS was also significantly decreased over time during PR OXN treatment to 3.8 after 18 weeks.

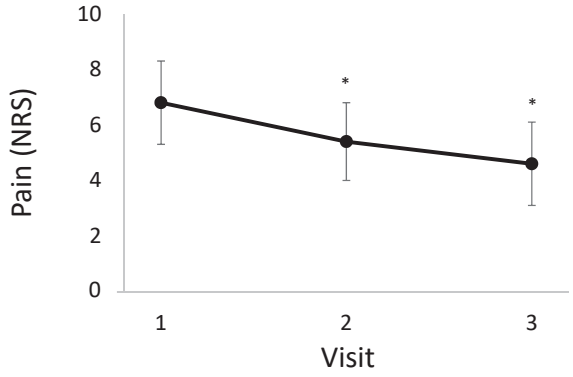

Figure 2: Average pain score (NRS) with standard deviation per visit (FA population).
Number of patients at visit 1 n=60, visit 2 n=59 and visit 3 n=54. * Indicate a significant reduction in pain NRS in comparison with visit 1 ($p<0.001$, linear mixed effect model).

Efficacy of PR OXN treatment with regard to OIC

The BFI reduced significantly (p<0.001) with on average 48.5 units (95% CI: 44.4, 52.7) between visit 1 (mean(SD) 70.8±16.2) and visit 3 (mean(SD) 21.3±13.2) (Figure 3).

The BFI improved significantly (p<0.001) with on average 3.4 units (95% CI: -3.8, -3.0) per week during PR OXN treatment. This improvement of BFI was clinically relevant with an average of 13.6 units (95% CI: 12, 15.2) after already 4 weeks of PR OXN treatment. After 6 weeks of PR OXN treatment, the average BFI was <28.8 and thus patients were considered not constipated anymore.

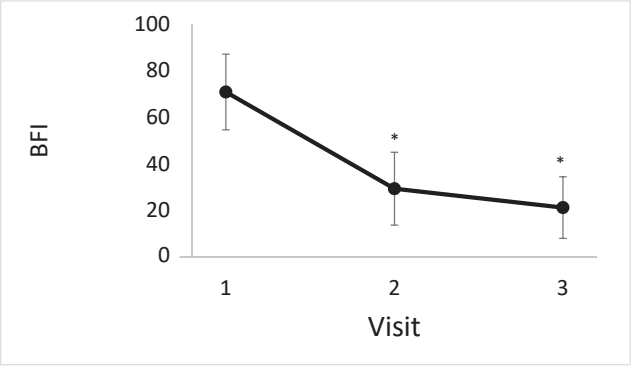

Figure 3: Average bowel function index (BFI) with standard deviations per visit (FA population). Number of patients at visit 1 n=67, visit 2 n=66 and visit 3 n=61. * Indicate a significant reduction in BFI in comparison with visit 1 p,.001, linear mixed effect model).

Efficacy of PR OXN treatment in terms of responders

The efficacy of PR OXN regarding pain relief and OIC was expressed as the percentage of responders following 12 weeks PR OXN treatment compared to the previous PR OXY treatment. Data for 1 and 2 patients were missing for the full analysis and per protocol populations respectively (Figure 1, primary parameter). Among the full analysis population, 58 out of 61 patients were qualified as responders (95.1%, 95% CI: 86.0%; 98.9%) and for the per protocol population 55 out of 58 patients (94.8%, 95% CI: 85.3%; 98.8%) were qualified as responders.

Use of laxatives

The number of patients using laxatives in the last 7 days before each visit decreased significantly from 65 patients (95.6%) at start to 24 patients (38.7%) at visit 3 (McNemar test $\chi^2(1) = 37.0$, p<0.001)(Table 2).

The optional field for type of laxative was registered for 32 out of 65 patients at visit 1; the majority of these patients (73%) used polyethylene glycol (PEG), 30% bisacodyl,

Table 2: Laxative use in the 7 days before the study visit. Data are given as no. (%).

Laxative use	Visit 1 [A] *n* (%)	Visit 2 [B] *n* (%)	Visit 3 [B] *n* (%)	Last visit [B] *n* (%)
Yes / No	65 / 3 (95.6 / 4.4)	41 / 26 (60.3 / 38.2)	24 / 38 (38.7 / 61.3)	26 / 42 (38.2 / 61.8)
Decrease / Constant / Increased [C]	NA	37 / 3 / 1 (90.2 / 7.3 / 2.4)	20 / 4 / 0 (83.3 / 16.7 / 0)	21 / 5 / 0 (80.8 / 19.2 / 0)
Missing data	0	1 (1.5)	0	0

NA = not available

[A] Laxative used in last 7 days before study inclusion. These data are considered data for laxative use during the previous PR OXY treatment.

[B] Laxative used in last 7 days before study visit: yes/no and increased, decreased or constant laxative use during PR OXN treatment compared to the preceding PR OXY treatment.

[C] Decrease / Constant / Increased laxative use for patients who used laxatives during the preceding PR OXY treatment

17% sodium picosulphate, 17% senna, 8% lactulose and 8% rectal laxatives. Since more than one laxative could be registered the sum of these percentages is >100%.

Within the group of 41 patients using laxatives at visit 2, 37 patients (90.2%) reported a decreased use of laxatives in the last 7 days compared to the preceding PR OXY treatment. Of the 24 patients using laxatives at visit 3, 20 patients (83.3%) reported a decreased use of laxatives in the last 7 days compared to the preceding PR OXY treatment.

Use of analgesic rescue medication

The number of patients using analgesic rescue medication in the last 7 days before each study visit decreased significantly from 44 patients (64.7%) at start to 26 patients (41.9%) at visit 3 (McNemar test $\chi^2(1) = 13.1$, $p<0.001$). The optional field for type of rescue medication was registered for 28 out of 44, 19 out of 37 and 15 out of 26 patients at visit 1,2 and 3 respectively. The majority of these patients (V1 68%, V2 63% and V3 66%) used oxycodone as rescue medication.

Quality of life

The EQ-5D score increased significantly with on average 0.275 units (95% CI: 0.202; 0.347) between visit 1 (mean(SD) 0.247±0.233) and the last visit (mean 0.522±0.275) ($p<0.001$) . The EQ-5D VAS health score increased significantly with on average 25.2 units (95% CI: 20.1; 30.3) between visit 1 (mean(SD) 33.0±13.0) and the last visit (mean 58.2±16.8) ($p<0.001$).

Safety analysis

Only two patients (2.9%) reported an adverse event. One patient reported euphoria and drowsiness at visit 2. The other patient had an epileptic seizure after visit 2, however, this

was considered to be unrelated to PR OXN treatment. AEs were of average intensity and were pharmacologically treated, leading to disappearance of the AE. No serious adverse event (SAE) was reported throughout the study.

DISCUSSION

This study, requested by the Belgian reimbursement authorities evaluated the efficacy of PR OXN regarding pain relief and OIC in 68 patients with chronic pain who were treated with PR OXY during at least the last 30 days before PR OXN treatment and who suffered from OIC despite the use of at least 2 laxatives with different mechanisms of action (level 4 ATC term). To the best of our knowledge, this is the only non-interventional study of opioid treatment where laxative use is documented before and during opioid treatment.

This study shows that PR OXN was superior to PR OXY regarding pain relief, OIC and quality of life in chronic pain patients previously treated with PR OXY and suffering from OIC despite the use of at least 2 different laxatives. The mean pain NRS reduced significantly with on average 2.1 units during treatment with PR OXN, comparable to other studies previously demonstrating similar analgesic efficacy of PR OXN and PR OXY even after long-term treatment with PR OXN[4, 9, 12-15]. The median PR OXN daily dose of 20 mg remained constant throughout the study and was equal to the PR OXY dose during the preceding PR OXY treatment. Moreover, the use of analgesic rescue medication decreased significantly during PR OXN treatment compared to the preceding PR OXY treatment. The observed improved pain relief during PR OXN treatment can therefore not be explained by an increased dose or increased use of analgesic rescue medication and is probably related to the improved OIC during PR OXN treatment.

This is the first non-interventional study in which the effect of PR OXN on OIC was evaluated using two parameters, i.e. the BFI and laxative use. The BFI showed a statistically significant and clinically relevant improvement of 49 points from visit 1 to the last visit. A change in BFI of ≥ 12 points is proven to be related to clinically meaningful changes of bowel habits in patients with OIC[18].This study confirms that after 4 weeks of treatment with PR OXN a clinically relevant improvement of OIC is attained in patients suffering from laxative-refractory OIC. The average BFI was below 28.8 after 6 weeks of PR OXN treatment, indicating that patients were on average not constipated anymore despite the opioid treatment[19].

In addition to the BFI, PR OXN efficacy regarding OIC was investigated by comparing the use of laxatives between the previous PR OXY treatment and PR OXN treatment. The number of patients using laxatives declined significantly during PR OXN treatment compared to PR OXY. If laxatives were needed, the vast majority of patients using laxatives during PR OXN treatment indicated decreased laxative use during PR OXY treat-

ment. Therefore, the improvement in OIC observed during PR OXN treatment cannot be explained by an increased use of laxatives. This supports the rationale that PR OXN treatment counteracts OIC through other mechanisms than laxatives do and that PR OXN addresses the underlying mechanism of OIC. The results of this non-interventional study are in line with results of a pooled analysis of laxative-refractory OIC patients from studies with PR OXN with respect to BFI and laxative use[20]. This pooled analysis showed that PR OXN significantly improved bowel function and reduced the use of laxatives in patients with OIC, previously unresponsive to at least two different classes of laxatives.

PR OXN also provided effective analgesia for patients with moderated-to-severe cancer-related pain and non-cancer-related pain. The efficacy of PR OXN regarding pain relief and OIC was expressed as the percentage responders following PR OXN treatment compared to the previous analgesic treatment with PR OXY. The percentage of responders was 95.1% after 12 weeks of PR OXN treatment, indicating that almost all patients experienced a pain NRS score ≤ 4 or improved pain relief in the absence of OIC (BFI ≤ 28.8) or with a clinical improvement in OIC (BFI improvement ≥ 12 units) compared to the preceding PR OXY treatment.

Quality of life improved significantly during PR OXN treatment. The overall EQ-5D score and EQ-5D VAS health score increased significantly with on average 0.275 units and 25.2 units resp. after 12 weeks of PR OXN treatment compared to PR OXY. This improved quality of life probably reflects the improved pain relief and OIC during PR OXN treatment and is in line with previous studies[4, 16, 21].

PR OXN treatment was well tolerated in this study. No SAEs were reported during this study. The frequency of AEs was lower compared to other studies, which can be explained by the observational design of this study.

Remarkably, in this study one patient was directly switched from a daily dose of 360 mg oxycodone to an equivalent dose of 360 mg/180 mg oxycodone/naloxone. In current literature daily doses of up to 240 mg/120 mg oxycodone/naloxone have been described using a stepwise switch from oxycodone to oxycodone/naloxone with different outcomes[14,22]. Close review of the patient's records revealed that the patient responded well to the direct switch. Pain relief on oxycodone was comparable to pain relief on oxycodone/naloxone (pain NRS score was 3 throughout the 87 days treatment period). Moreover, no adverse events were reported, the patient did not require any analgesic rescue medication or other concomitant medication and a decrease in laxative medication was reported alongside an improvement in bowel function after switch from oxycodone to oxycodone/naloxone (BFI decreased from 46.7 to 0).

Of course a non-interventional study has limitations, one of them being that we could not ensure that all data were documented in the database. This limitation was tackled by marking important parameters (e.g. BFI, pain relief, laxative use yes/no and rescue

medication yes/no) as mandatory fields in the electronic CRF, as a result there were hardly any missing data for these mandatory fields.

Whilst keeping the inherent limitations of a non-interventional study in mind the effects of PR OXN in real-life clinical practice in Belgium for those patients who were eligible for reimbursement, demonstrated significant reduction of OIC during treatment of PR OXN in laxative-refractory OIC patients. The results of this real-life study confirmed the improvement seen in a pooled analysis from pivotal studies with PR OXN in a comparable patient group[20].

CONCLUSION

In this real-life study in Belgium, patients with chronic severe pain and OIC despite the use of at least 2 laxatives with different mechanisms of action (level 4 ATC term) experienced a significant improved pain relief, a significant and clinically relevant reduction of OIC as well as a significant improvement of quality of life after PR OXN treatment compared to previous PR OXY treatment. The percentage of responders was 95.1% after 12 weeks of PR OXN treatment, indicating that almost all patients experienced no pain or improved pain relief in the absence of OIC or with a clinical improvement in OIC compared to the preceding PR OXY treatment.

TRANSPARENCY

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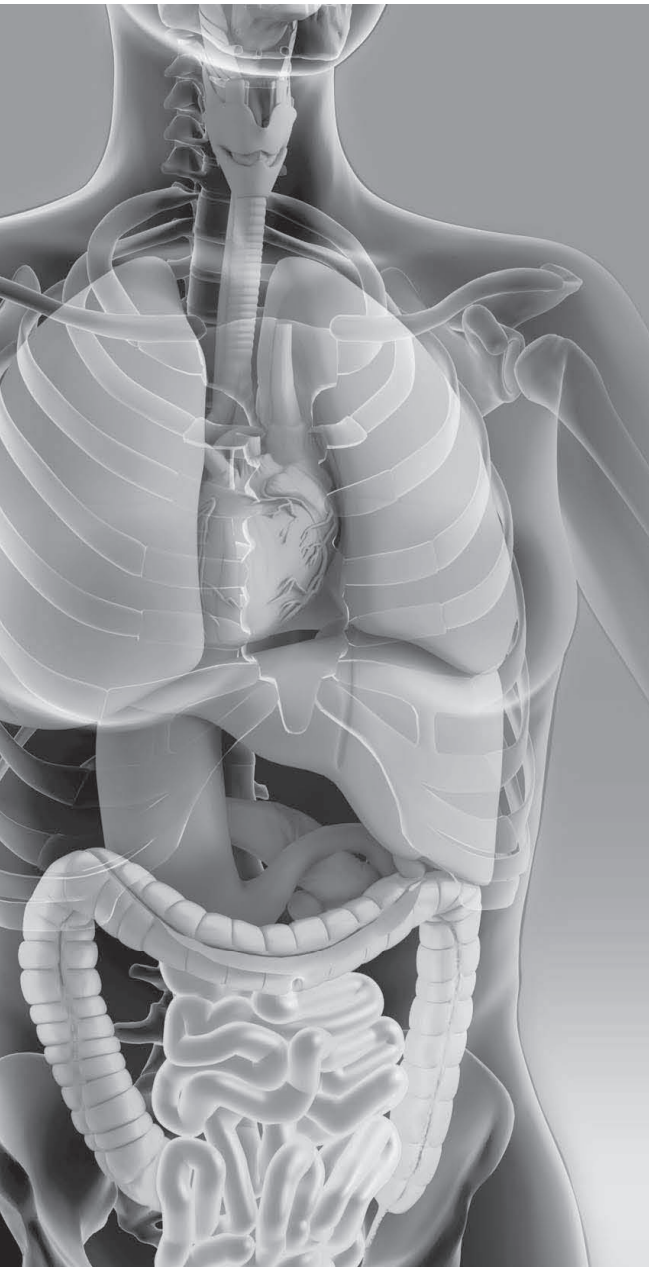

Chapter 6

Prolonged release oxycodone and naloxone treatment counteracts opioid induced constipation for patients with severe pain compared to previous analgesic treatment.

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ABSTRACT

Objective

Treatment with prolonged-release oxycodone/naloxone (PR OXN) has been shown to improve opioid induced constipation (OIC) in constipated patients. This publication reports on a real-life observational study investigating the efficacy of PR OXN with regard to bowel function in patients switching to PR OXN from WHO-step 1, step 2 and step 3 opioids.

Methods

Patients with chronic pain experiencing insufficient pain relief and/or unacceptable side effects were switched to PR OXN and monitored in this observational study with respect to efficacy regarding bowel function and efficacy regarding pain relief in comparison with previous analgesic therapy. A patient was considered responder with respect to efficacy if this assessment was 'slightly better', 'better' or 'much better' compared with previous therapy. Bowel function index, pain intensity, quality of life, laxative medication use, and safety analgesic were also evaluated.

Results

1,338 patients (mean (sd) age 64.3 (14.9), 63% female) were observed for 43 [3-166] days (median [range]) during treatment with PR OXN. Overall response rate regarding bowel function efficacy was 82.5%. Patients with symptoms of constipation at study entry obtained a clinically relevant improvement of the bowel function index (BFI) within the first 2 weeks of PR OXN treatment. Non-constipated patients at study entry maintained normal bowel function despite switching to treatment with the opioid PR OXN.

Conclusion

In conclusion, treatment with PR OXN results in a significant and clinically relevant improvement of bowel function. During the observation of the treatment with PR OXN patients reported an improvement of QoL. More interestingly, non-constipated patients maintained a normal bowel function, showing prevention of constipation despite the use of an opioid.

INTRODUCTION

The prevalence of chronic pain in adults is about 19% in Europe [1]. Chronic severe pain, has important implications for the individual's quality of life and is a major public health challenge because of the impact on work performance and the increased use of health-care services[2].

Strong opioids are a treatment option for pharmacological management of chronic moderate to severe pain of malignant and non-malignant origin[3-6]. However, 30% of the patients with malignant pain and 12% with non-malignant pains treated with an opioid do not achieve an adequate level of analgesia and/or suffer from intolerable or dose-limiting adverse effects[7]. Opioid-induced constipation (OIC) is the most common and most dominant adverse effect of opioid treatment[8] affecting up to 80% of patients treated with opioids[9-11]. Opioids contribute to OIC by activation of opioid receptors in the gastrointestinal wall leading to reduced motility of the gut and opioids can increase circular muscle activity (hence causing cramping pain) at the expense of longitudinal muscle. In addition, opioids contribute to OIC by increasing water withdrawal from the bowel[8-11]. OIC negatively impacts the patient's quality of life[12], resulting in a lack of compliance in up to one third of the patients[10] potentially leading to insufficient pain relief. Moreover, OIC can in itself also be a cause for pain; the majority of patients with OIC report pain caused by OIC. Pain caused by OIC may result in more discomfort than pain caused by the underlying condition [10, 13, 14]. In contrast to other opioid-related side effects OIC is unlikely to improve over time and most patients do not develop tolerance to OIC[10, 15-17].

Treatment of OIC comprises general non-pharmacological measures, like dietary advices and excercise, and the treatment with non-specific laxatives like bisacodyl, poly ethylene glycol with electrolytes and lactulose. However, about half of all opioid treated patients requiring laxatives do not achieve satisfactory relief from OIC, as most used laxative treatments for OIC are non-specific and do not target the underlying cause of OIC[17, 18]. Furthermore, laxatives themselves may lead to gastrointestinal adverse events and complications[17].

Prolonged release oxycodone/naloxone (PR OXN) is a fixed combination of oxycodone/naloxone. When co-administered orally with oxycodone, naloxone counteracts OIC by antagonizing opioid receptors in the gastrointestinal wall, while its limited availability following first pass metabolism ensures its lack of interference on the analgesic effect of oxycodone mediated by activation of opioid receptors in the central nervous system[19]. In several randomized controlled trials PR OXN has shown to provide effective pain relief, while effectively counteracting OIC[20-27]. Several prospective, observational studies confirmed the efficacy of PR OXN in real-life studies[28-30].

In this real-life observational study, the efficacy of PR OXN regarding bowel function was evaluated in patients with severe pain switching from WHO-step 1, step 2 and/or step 3 medication to PR OXN due to insufficient pain relief and/or unacceptable side effects in daily clinical practice in Belgium, taking into account previous used medication and constipation status at study entry.

METHODS

Study design and patient population

This publication describes the results of a phase IV, open label, multicenter, prospective, observational, real-life study conducted in Belgium between April and December 2011 approved by the ethical committees of the participating centers.

The decision to switch to open-label PR OXN preceded the decision to participate in the study and written informed consent was obtained before study entry.Adult patients with severe pain previously treated with WHO-step1, step 2 and/or step 3 (excluding PR OXN) analgesics that had been switched to PR OXN because of insufficient pain relief and/or unacceptable side effects on their previous medication were consecutively included and treatment with open-label PR OXN as in daily clinical practice was monitored. Unacceptable side effects were defined as side effects that could not be tolerated by the patient. Patients were excluded in case of alcohol abuse, a history of active drug abuse, use of hypnotics or CNS depressants that might pose a risk of additional CNS depression, opioid therapy for opioid addiction, confirmed diagnosis of irritable bowel syndrome, evidence of clinically significant GI disease, and abnormalities of the GI tract or suffering from diarrhea and/or opioid withdrawal.

At the first baseline visit, patients were switched from their previous analgesic medication to the most appropriate twice-daily PR OXN dose (5 mg/2.5 mg, 10 mg/5 mg, 20 mg/10 mg or 40 mg/20 mg) according to the physician's judgment, taking into account that PR OXN is as effective for pain relief as oxycodone. Pain intensity and bowel function were recorded at the first baseline visit (visit 1) and at two follow-up visits (visit 2 and 3) during PR OXN treatment as in daily clinical practice.

Due to the observational real-life study design follow-up of patients was performed as in daily practice. In daily practice follow-up of patients during treatment differs per physician, therefore no fixed time points were set for the follow-up visits (visit 2 and 3). For efficacy analyses over time (efficacy regarding pain relief and efficacy regarding bowel function) the following intervals were defined; a) 2 ±2 weeks (visits on day 1 -28 after first visit) b) 6±2 weeks(visits on day 29- 56 after first visit); c) 11±3 weeks(visits day 57-98) and d) 17±3 weeks(visits day 98-140). For patients with more than one visit in one

time period, only the last visit in that period was considered for analysis of the efficacy endpoints.

BFI was analyzed at baseline (visit 1) and follow-up visits (visit 2 and 3) as well as over time (baseline, 2±2 weeks, 6±2 weeks, 11±3 weeks and 17±3 weeks). Data on laxative use, and adverse drug reactions were recorded over the period between visit 1 and 2 at visit 2, and over the period between visit 2 and 3, at visit 3. Quality of life was evaluated at the first and last study visit per patient (see supplementary table 1 for an overview of the study and study schedule).

Outcome measurements

Outcome measurements included efficacy of PR OXN regarding bowel function compared to the previous analgesic treatment as evaluated by the physician using a 7-point ordinal scale (much worse, worse, slightly worse, same, slightly better, better and much better) and bowel function was also evaluated with the (Bowel Function Index ([BFI][31, 32]; Copyright for the BFI is owned by Mundipharma Laboratories GmbH, Switzerland 2002; the BFI is subject of European Patent Application Publication No. EP 1 860 988 and corresponding patents and applications in other countries).

For analysis, the 7-point physician evaluation scale was converted to a binary scale, where patients were considered responder if their bowel function during PR OXN treatment was evaluated as 'slightly better', 'better', or 'much better'.

The BFI is the arithmetic mean value of the patients' evaluation on the difficulty of bowel movement, feeling of incomplete bowel evacuation and personal judgment of constipation during the last 7 days, each scored from 0 (no problem/no difficulty) to 100 (severe difficulty/problem). A BFI <28,8 is validated as a normal bowel function[33] and a change in BFI≥ 12 is considered as a clinically relevant change in bowel function[31].

Outcome measurements for pain relief included the efficacy of PR OXN regarding pain relief compared to the previous analgesic treatment as evaluated by the physician using a 7-point ordinal scale (much worse, worse, slightly worse, same, slightly better, better and much better). Pain relief was also evaluated with the Numeric Rating Scale ([NRS] from 0 to 10.

For analysis, the 7-point physician evaluation scale was converted to a binary scale, where patients were considered responder if their pain relief during PR OXN treatment was evaluated as 'slightly better', 'better', or 'much better'. The percentages of patients using laxatives or analgesic rescue medication at the follow-up visits were calculated. The quality of life of patients was evaluated via the standardized EuroQol (EQ-5D) questionnaire with 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The total EQ-5D score was calculated using Belgian population based tariffs that could range between -0.158 (all criteria scored a value of 3) and 1

(perfectly healthy). Additionally, patients assessed their QoL using the EQ-5D VAS (from 0 to 100, worst to best possible health status), indicating the patient's self-rated health.

Ethical considerations

The study was registered with the Federal Agency for Medicinal Products and Health Products in Belgium (study code OXN9510) and was registered on clinicaltrials.gov with the identifier NCT01983137. The study was conducted in accordance with all applicable ethical guidelines and legislations. All patients provided written informed consent before inclusion.

Statistics

All data were analyzed by descriptive statistics and statistical comparisons for all study parameters over time and between previous analgesic WHO-step treatments groups were performed. Patients were categorized by the previous WHO step group based on the highest WHO step group. All efficacy endpoints were analyzed for the full analysis (FA) population, defined as all eligible patients who received at least one dose of PR OXN and had at least one post-dose evaluation; safety endpoints were analyzed for the safety population, defined as all patients who received at least one dose of PR OXN and for whom at least one post dose safety assessment was recorded. Additionally, post hoc analyses on all efficacy parameters were performed on patients with symptoms of constipation (BFI≥28.8, constipated patients) and without symptoms of constipation (BFI<28.8, non-constipated patients) at study entry.

ANOVA and two-sample t-tests were used to compare subgroups at baseline and to compare changes from study entry and at last visit in bowel function (BFI), pain intensity (NRS) and QoL (EQ-5D) between the different subgroups. Categorical variables were compared using the Fisher's exact test.

RESULTS

Patient population and demographic characteristics

229 general practitioners and 55 specialists screened 1,429 patients experiencing severe pain (272 patients were screened by specialists and 1,157 by GPs), of whom 1,369 patients were treated with PR OXN. The safety population consisted of 1,367 patients of whom safety evaluations were available. 31 patients were excluded from the full analysis population (FA-population) because there were no data available on previous analgesic treatment (n=27) or pain NRS score was "0" at study entry (n=2) or follow up data were unavailable (n=2), rendering 1,338 patients in the full analysis (FA)-population (Figure 1). The vast majority of patients (84.0%) terminated the study conforming to the protocol.

Reasons for early study discontinuation were adverse drug reactions (2.1%), insufficient effectiveness (1.3%), patients choice (3.4%), other reasons, such as planned surgical procedures and interventions (2.8%) and due to the observational nature of the study lost to follow-up (6.5%).

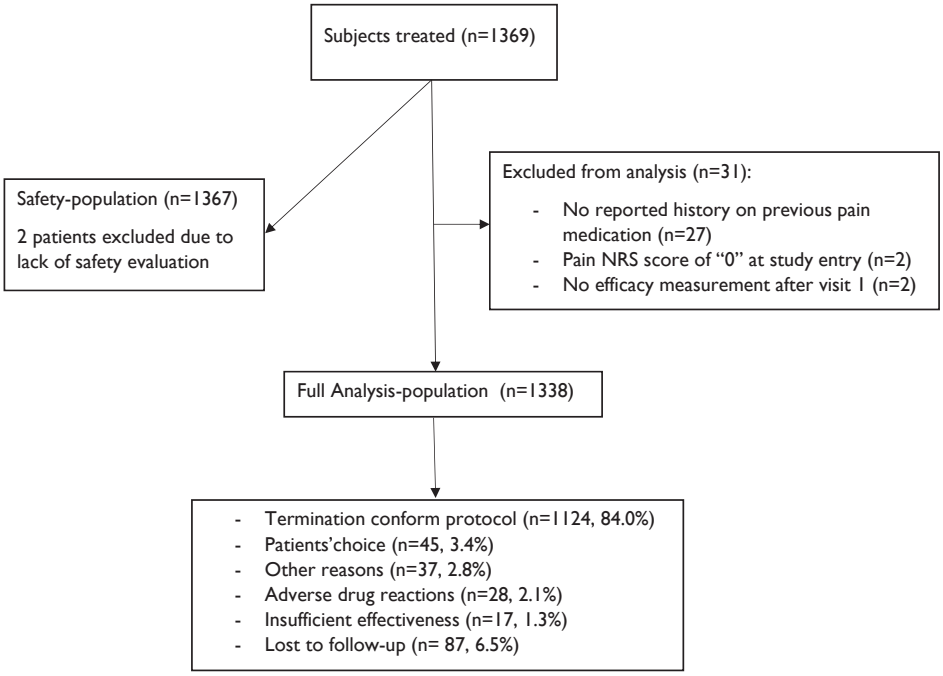

Figure 1. Flow diagram of the patients' disposition

Patient demographics and characteristics for the overall population and the analyzed subgroups are summarized in Table 1. The mean age of the overall population was 64.3±14.9 years, and 63% were female. Significantly more constipated patients (defined by a BFI>28.8 at study entry) were older ($p<0.001$) and of female gender ($p=0.039$). The majority of patients suffered from non-malignant pain (77%), mainly caused by osteoarthritis (53%), low back pain (49%) and neuropathic pain (34%) (multiple pain indications could be chosen for one patient resulting in a sum >100%). Nearly a quarter of the patients (23%) suffered from malignant pain, mainly caused by cancer of lung (16%), breast (16%), colon (16%) and prostate (10%). For patients with pain of malignant origin the majority suffered pain due to metastatic disease (n=127), 41 suffered from advancing disease and 20 suffered from post-treatment/post-operative pain. For 121 patients no specifications were given. Most malignant as well as non-malignant pain patients were treated by their GP (242 and 861 patients, respectively).

Table 1. Demographics and baseline characteristics of patients (Full Analysis-population)

	Previous WHO Step Analgesic			Bowel function		Total
	Step 1 n = 142	**Step 2 n = 625**	**Step 3 n = 571**	**Non-constipated n=289**	**Constipated n=1,048**	**N = 1,338**
Age in years						
Mean ± SD	63.0±15.6	63.8±14.9	65.0±14.7	60.8±15.2	65.2±14.7	64.3±14.9
Gender: %Female (n/N)	57.7% (82/142)	62.2% (389/625)	65.3% (373/571)	57.8% (167/289)	64.5% (676/1048)	63.1% (844/1338)
Type of pain						
Malignant % (n/N)	16.4% (23/140)	19.6% (122/621)	28.8% (164/570)	17.8% (51/287)	24.7% (258/1043)	23.2% (309/1331)
Non-malignant % (n/N)	83.6% (117/140)	80.4% (499/621)	71.2 (406/570)	82.2% (236/287)	75.3% (785/1043)	76.8% (1021/1331)
Bowel Function Index (BFI)						
Mean ± SD	31.8±26.4	47.7±27.6	65.3±23.0	10.4±9.3	65.4±17.8	53.5±27.9
Pain intensity (NRS)						
Mean ± sd	7.3±1.3	7.7±1.1	6.7±2.0	7.6±1.3	7.2±1.7	7.2±1.7
Bowel function						
BFI ≥28.8, % (n/N)	50.4% (71/141)	72.8% (455/625)	91.4% (522/571)	n.a	n.a.	78.4% (1048/1337)
EQ-5D Total Score						
Mean ± SD	0.32±0.26	0.25±0.23	0.26±0.26	0.27±0.24	0.26±0.25	0.26±0.25
Reasons for switch						
Insufficient effectiveness	94.5%	94.9%	50.1%	93.8%	73.9%	78.9%
Unacceptable side effects	17.9%	56.9%	86.2%	33.4%	67.7%	65.4%

At the start of PR OXN treatment, 10.6% of patients were previously treated with WHO step 1, 46.7% with WHO step 2 and 42.7% with WHO step 3 analgesics. Patients with malignant pain were more often treated with WHO-step 3 analgesics than with WHO-step 1 and WHO-step 2 analgesics ($p<0.001$). At study entry, the pain score was significantly lower in the WHO-step 3 group compared to the other WHO-step groups ($p<0.001$) and pain score of constipated patients was significantly (but not clinically relevant) lower compared to non-constipated patients ($p=0.002$).

Mean BFI at study entry was high (53.5± 27.9), with significant differences between the WHO-step groups ($p<0.001$). Interestingly, the percentage of constipated patients at study entry (BFI>28.8) in the WHO-step 1 group was already 50.4% and this was even higher in the WHO-step 2 group and in the WHO-step 3 group (72.8% and 91.4% respectively). The overall mean EQ-5D total score at study entry was low 0.26±0.25, with statistically significant differences between the WHO-step groups, with the lowest scores for the WHO step 2 and WHO step 3 group (0.25 and 0.26 respectively ($p=0.005$).

PR OXN treatment

Overall, patients were followed in the study for mean ± sd 47.8±25.2 days (N=1338) and 45.5%were followed between 4 to 8 weeks with no significant differences between the subgroups. The mean daily dose of PR OXN increased from 11.6 mg at visit 1 to 15.2 mg at last visit in the total group (Table 2).

The highest dose was prescribed in WHO-step 3 pretreated patients and the mean dose of PR OXN was numerically higher for constipated patients at study entry. However, there were no statistically significant differences in mean PR OXN dose between the three WHO-step subgroups and the two bowel function subgroups.

Table 2. Daily dose of the oxycodone component of PR OXN

	Previous WHO step analgesic			Bowel function		Total
	Step 1	Step 2	Step 3	Non-constipated	Constipated	
Daily Oxycodone Dose (mg) Visit 1						
Mean ± SD	7.5±5.2	8.8±7.2	15.8±13.3	8.7±6.9	12.5±11.4	11.6±10.7
(N)	(141)	(622)	(565)	(287)	(1041)	(1328)
Daily Oxycodone Dose (mg) Visit 2						
Mean ± SD	8.4±5.3	10.8±8.1	18.4±14.6	9.9±7.5	14.8±12.6	13.7±11.9
(N)	(140)	(622)	(557)	(284)	(1034)	(1319)
Daily Oxycodone Dose (mg) Visit 3						
Mean ± SD	8.6±5.7	12.3±10.4	20.0±16.8	11.0±8.6	16.3±14.8	15.2±13.9
(N)	(125)	(573)	(527)	(249)	(975)	(1225)

Efficacy regarding bowel function

The mean BFI at study entry was 53.5± 27.9 for the overall population (Table 3). As expected BFI at study entry was significantly higher in patients pre-treated with WHO-step 3 medication (65.3± 23.0, n=571) compared with WHO-step 1 (31.8± 26.4, n=141) and WHO-step 2 (47.7± 27.7, n=625) medication ($p<0.001$).

The response rate with respect to bowel function during PR OXN treatment was 82.5% at last visit, indicating that bowel function during PR OXN treatment was evaluated as 'slightly better' to 'much better' for the majority of patients. Highest response was seen in the WHO-step 3 group (89.0%) and lower responses were seen in the WHO-step 2 and WHO-step 1 group (81.0% and 63.1% respectively).

In line with the response rate a significant and clinically relevant decrease (Δ BFI (mean± sd) -28.39 ± 26.45; $p<0.0001$) in BFI was observed during PR OXN treatment compared to previous analgesic treatment between visit 1 and last visit for the overall group, with the largest (and clinically relevant) decrease in the WHO-step 3 subgroup and the lowest non clinically relevant decrease of 10.5 points in the WHO-step 1 subgroup (Δ BFI (mean ± sd) -10.5 ± 20.86 for WHO-step 1 group; -24.6 ± 26.20 for WHO-step 2 group and -36.87 ± 24.78 for WHO-step 3 group). After 6 weeks of PR OXN treatment, the mean± sd BFI values for the overall population, WHO-step 1 and WHO-step 2 groups

were below the constipation threshold of 28.8 and around that threshold for the WHO-step 3 group (30.33±19.48) (Figure 2).

Table 3. Bowel function (BFI scores) over time per subgroup and overall

	Previous WHO step analgesic			Bowel Function		Total
Bowel function (BFI score)	**Step 1 N = 142**	**Step 2 N = 625**	**Step 3 N = 571**	**Non-constipated N=289**	**Constipated N=1048**	**N = 1338**
Study start (visit 1)						
Mean ± SD	31.8±26.5	47.7±27.6	65.3±23.0	10.4±9.3	65.4±17.8	53.5±27.9
(N)	(141)	(625)	(571)	(289)	(1048)	(1337)
Week 2±2						
Mean ± SD	26.1±20.4	27.8±20.5	34.5±21.0	11.9±15.4	35.9±18.9	30.3±20.9
(N)	(106)	(426)	(372)	(213)	(690)	(903)
Week 6±2						
Mean ± SD	23.3±20.1	24.7±19.6	30.3±19.5	11.6±15.6	30.5±18.9	26.9±19.8
(N)	(86)	(427)	(367)	(168)	(711)	(879)
Week 11±3						
Mean ± SD	22.4±16.5	21.2±17.0	28.8±20.9	9.3±9.6	28.2±18.9	24.6±19.1
(N)	(31)	(198)	(173)	(78)	(324)	(402)
Week 17±3						
Mean ± SD	11.3±14.9	26.9±26.2	31.7±23.1	13.6±29.5	31.5±21.5	27.8±24.2
(N)	(5)	(22)	(26)	(11)	(42)	(53)
Study End (Last visit)						
Mean ± SD	21.6±18.9	23.0±19.0	28.4±19.9	10.7±16.7	28.2±19.7	25.2±19.6
(N)	(141)	(625)	(571)	(288)	(1048)	(1337)

For patients with constipation at study entry (N=1048; BFI (mean ± sd) 65.40 ± 17.81) a significant and clinically relevant decrease (mean -36.40 ± 22.90; p<0.0001) in BFI was observed during PR OXN treatment between visit 1 and last visit. Analysis over time showed that already in the first 2 weeks of PR OXN treatment a fast and clinically relevant BFI reduction was observed (BFI (mean ± sd) 35.99 ± 18.96 (N=690)). After 11 weeks PR OXN treatment, the BFI (mean ± sd) had further decreased to 28.24±18.97 (N=324) (Figure 3A).

For patients without constipation at study entry (n=289), the mean BFI remained well below 28.8 up to 17 weeks of PR OXN treatment (Figure 3A). Table 3 gives the actual BFI-values over time.

Laxative use during the study

Despite the high level of constipation at study entry between visit 1 and visit 2 in the total population only 31.3% (419/1337) of patients used additional laxatives during the study and this additional laxative use was significantly higher in patients pretreated

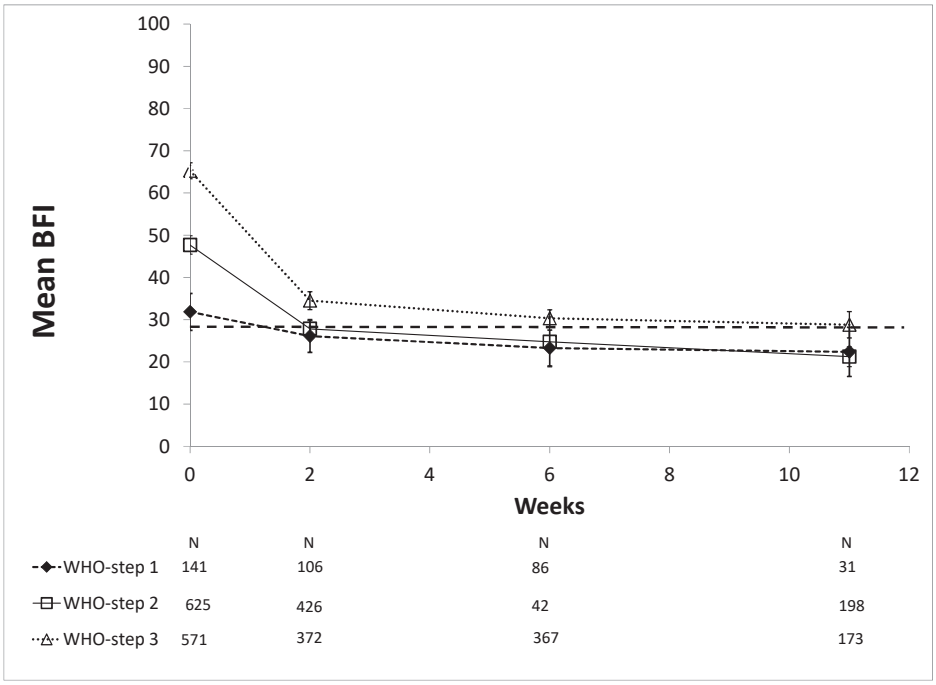

Figure 2. Bowel function measured by BFI over time for patients in WHO-step 1, WHO-step 2 and the WHO-step 3 groups (Full analysis-population)

Dashed line and closed diamonds represent the WHO-step 1 group, solid line and open squares represent the WHO-step 2 group and the dotted line and open triangles represent the WHO-step 3 group. The dotted line at BFI 28,8 represents the cut-off for constipation. Error bars represent the 95% confidence interval of the mean BFI. Patient numbers at weeks 0, 2, 6 and 11 are listed below the graph.

with WHO-step 3 medication (41.7%, 238/571) compared with patients pretreated with WHO-step 1 medication (20.4%, 29/241) and WHO-step 2 medication (24.3% 152/625; $p<0.001$). The percentage of patients using laxatives did not change significantly during the study for the WHO-step groups.

Looking at constipated patients versus non-constipated patients at study entry laxative use during the study was significantly higher in constipated than non-constipated patients (36.9% (387/1048) vs. 11.1% (32/289) respectively, $p<0.001$). Despite treatment with PR OXN, laxative use between visit 1 and visit 2 versus laxative use between visit 2 and visit 3 did not change significantly for non-constipated patients at study entry (10.1% to 9.1%), which is in line with the stable BFI. For patients with constipation at study entry a numerical but not statistically significant decrease in laxative use was seen (35.5% to 28.6%), which is in line with the improvement seen in the BFI (Figure 3B).

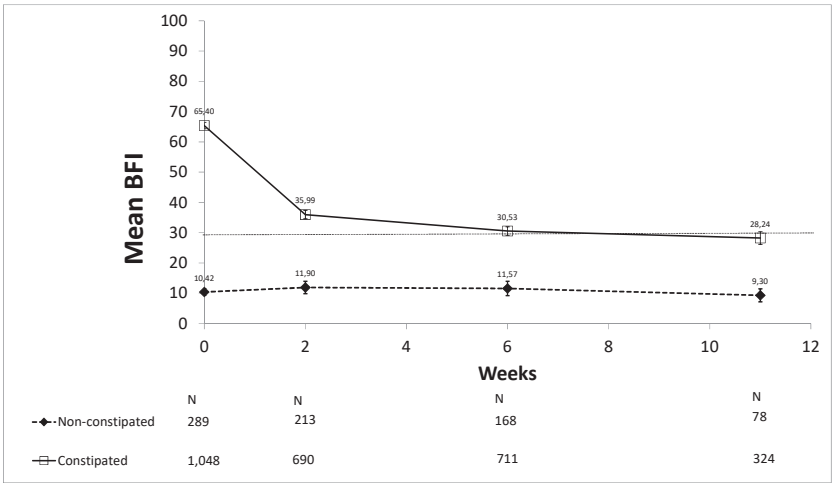

Figure 3A. Bowel function measured by BFI over time for constipated and non-constipated patients (FA population)

Dotted line and closed diamonds represent non-constipated patients (BFI<28.8) and the solid line and open squares represent constipated patients (BFI≥28.8). The line at BFI 28,8 represents the cut-off value between constipated and non-constipated patients. Error bars represent the 95% confidence interval of the mean BFI. Patient numbers at weeks 0, 2, 6 and 11 are listed below the graph.

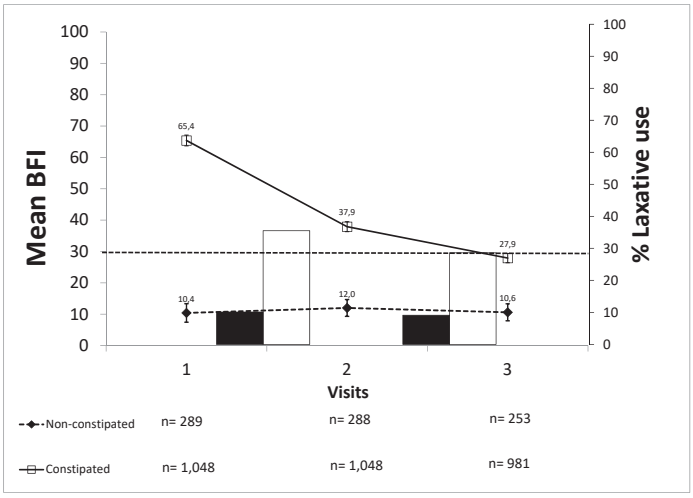

Figure 3B. Bowel function measured by BFI per visit and laxative use for constipated patients and non-constipated patients (Full analysis population)

Dotted line and closed diamonds represents non-constipated patients (BFI<28.8) and the solid line and open squares represents constipated patients (BFI≥28.8). The line at BFI 28 represents the cut-off value between constipated and non-constipated patients. Error bars represent the 95% confidence interval of the mean BFI. Solid filled black bars represent the percentage of non-constipated patients using laxatives between visit 1 and 2 (29/288 (10.1%)) and between visit 2 and 3 (23/253 (9.1%)). Open bars represent the percentage of constipated patients using laxatives between visit 1 and 2 (372/1,048 (35.5%)) and between visit 2 and 3 (281/981 (28.6%)). Patient numbers at visit 1, 2 and 3 are listed below the graph.

Efficacy regarding pain relief

The response rate regarding pain relief at last visit after PR OXN treatment was 84.5%, indicating that analgesic efficacy of PR OXN treatment was evaluated as 'slightly better', 'better' or 'much better' compared to the previous analgesic medication for the majority of patients. As expected responses were high in all groups, with a significantly lower response rate in the WHO-step 3 group (77.1%, p<0.001) compared with response rates of 91.5% and 89.8% in the WHO-step 1 and WHO-step 2 groups respectively. Looking more closely at subjects with and without constipation, at visit 2 and visit 3, response was significantly higher in the non-constipated subgroup (85.8% at visit 2 and 92.1% at visit 3) than in the constipated subgroup at visit 2 and visit 3 (80.2 (p=0.033) and 85.7% (p=0.006) respectively).

Table 4 gives the actual pain intensity scores over time.

Table 4. Pain intensity scores over time per subgroup and overall.

	Previous WHO step analgesic			Bowel Function		Total
Pain intensity score (NRS)	**Step 1 N = 142**	**Step 2 N = 625**	**Step 3 N = 571**	**Non-constipated N=289**	**Constipated N=1048**	**N = 1338**
Study start (visit 1)						
Mean ± SD	7.3±1.3	7.7±1.1	6.7±2.0	7.6±1.3	7.2±1.7	7.2±1.7
(N)	(141)	(625)	(571)	(289)	(1048)	(1337)
Week 2±2						
Mean ± SD	4.3±2.1	4.7±1.9	4.7±2.0	4.2±2.1	4.8±1.8	4.7±1.9
(N)	(106)	(426)	(372)	(213)	(690)	(904)
Week 6±2						
Mean ± SD	3.9±2.1	4.0±1.9	4.2±1.7	3.7±2.0	4.2±1.8	4.1±1.8
(N)	(86)	(427)	(368)	(168)	(712)	(881)
Week 11±3						
Mean ± SD	4.2±2.4	3.5±1.6	4.3±1.9	3.4±1.8	4.0±1.8	3.9±1.8
(N)	(31)	(198)	(173)	(78)	(324)	(402)
Week 17±3						
Mean ± SD	5.4±0.9	3.4±1.5	4.3±1.6	4.5±1.6	4.0±1.6	4.1±1.6
(N)	(5)	(22)	(26)	(11)	(42)	(53)
Study End (Last visit)						
Mean ± SD	3.8±2.2	3.7±1.9	4.1±1.9	3.5±2.1	4.0±1.9	3.9±1.9
(N)	(141)	(625)	(571)	(288)	(1048)	(1337)

Quality of life

Patients reported that during treatment with PR OXN all aspects of quality of life (QoL) improved, resulting in a significant increase of 0.31± 0.26 (95% CI [0.30,0.32]) in the EQ-D5 score from first to last visit. QoL improved significantly in all three WHO-step groups

with a significantly larger increase in both WHO-step 1 and WHO-step 2 groups (both 0.34±0.26) compared to the WHO-step 3 group (0.27±0.26; p< 0.0001).

Similarly, the self-reported EQ-5D VAS health scores showed an increase of 16.5 ± 26.8 (95% CI 15.0,18.0) between the first (41.2±22.0) and last visit (58.2±21.7). The improvement was significantly larger for the WHO-step 2 group (19.6 ± 27.5) compared to the WHO-step 1 group (17.4 ± 27.0) and the WHO-step 3 group (13.0 ± 25.5; p = 0.0002).

QoL also improved significantly in both bowel function groups, with a statistically significant larger increase in non-constipated patients (0.38±0.27) versus constipated patients (0.29±0.25; p<0.0001). No statistically significant differences are seen in changes from baseline to last visit in EQ-5D Vas health scores between non-constipated (18.2 ± 32.0) and constipated groups (16.1 ± 25.3).

Safety

Overall, 4.8% of the patients in the safety population reported at least one adverse drug reaction (ADR) during OXN treatment (77 ADRs reported by 66 out of 1369 patients). The most frequently reported ADRs were nausea (1.2%), constipation (0.9%), drowsiness (0.5%), vertigo/dizziness (0.5%) and somnolence (0.3%). Most ADRs documented as mild (36.9%) or moderate (44.6%) mainly affecting the gastrointestinal system and the central nervous system (Table 5).

Table 5. Number of patients with at least one adverse drug reaction, severity and relation to study medication of reported adverse drug reactions (safety population)

	Total N = 1369
Any Adverse Drug Reaction	4.8% (66/1369)
Maximal ADR Severity Reported, % (n/N)	
Mild	36.9% (24/65)
Moderate	44.6% (29/65)
Severe	18.5% (12/65)
Missing	1
Maximal ADR Relation Reported, % (n/N)	
Not related	3.3% (2/60)
Possibly related	28.3% (17/60)
Probably related	51.7% (31/60)
Definitely related	16.7% (10/60)
Missing	6

ADR, adverse drug reaction

Twelve ADR (18.5%) were severe and mainly affected the gastrointestinal system (nausea and constipation). No additional ADR compared to the ADR mentioned in the

SmPC were reported. No serious ADRs were documented. Twenty-eight patients (2.2 %) reported stopping the study because of an adverse drug reaction. The incidence of drug related adverse events was comparable between analgesic pretreatment-groups (WHO-step 1, WHO-step 2 and WHO-step 3) as well as between constipated and non-constipated patients.

DISCUSSION

The present study showed that the majority of patients in the total population (78.4%) and in all WHO-step groups experienced symptoms of constipation as defined by a BFI≥28.8 (50.4%, 72.8% and 91.4% for WHO-step 1, WHO-step 2 and WHO-step 3 respectively)[33]. It was shown that significantly more patients with symptoms of constipation at study entry were older and of female gender, both factors that are known to be associated with constipation and patients with pain are less mobile which could also have contributed to constipation[9-11]. Moreover, it is possible that there is a bias in the percentage of constipated patients in this observation as in Belgium PR OXN was marketed especially for patients with a BFI above 30. Also in literature it has been demonstrated that treatment with WHO-step 1 and WHO-step 2 analgesics, like NSAIDs, codeine and tramadol are strongly associated with occurrence of constipation. This might have contributed to the high percentage of constipated patients in the WHO-step 1 and WHO-step 2 groups, together with the other factors that are associated with constipation that are present in the study population[34-37].

Already after 2 weeks of PR OXN treatment a clinically relevant improvement of bowel function (defined by a reduction in BFI of 12 points or more) was observed in the overall population and in the WHO-step 2 and WHO-step 3 groups. Mean BFI dropped below 28.8 after 6 weeks of PR OXN treatment for the overall population and the WHO-step 1 and WHO-step 2 groups. In the WHO-step 3 group mean BFI reached 28.8 after 11 weeks of PR OXN treatment. The observed reduction in BFI for all groups was maintained over time. These results indicate that during the observation bowel function can restore over time irrespective of the previous analgesic treatment, despite initiation of the opioid PR OXN. The reduction in BFI is in line with reduction of BFI reported in previous observational studies with PR OXN for patients with neuropathic pain[28], constipated patients with non-malignant pain[29] and patients with severe pain[30]. In this observation also patients switching from WHO-step 1 and WHO-step 2 medication, as well as patients without constipation at start of the observation were included, which is in contrast to previous studies, in which patients already experienced OIC or were switched from WHO-step 3 medication to PR OXN.

When looking more closely at constipated patients at study entry (irrespective of previous analgesic treatment), it was shown that treatment with PR OXN led to a clinically relevant improved bowel function already in the first two weeks of PR OXN treatment and the improvement was maintained over time. After 17 weeks, BFI was close to the threshold of 28.8 showing that bowel function was almost restored to normal values despite the treatment with the opioid PR OXN. Interestingly, for patients not constipated at study entry the BFI remained below 28.8 even during PR OXN treatment up to 17 weeks. This indicates that treating pain adequately with strong opioids in non-constipated patients normal bowel function is maintained despite the initiation of the opioid PR OXN, even in patients stepping-up from non-opioid treatment. This study adds to the evidence found in previous studies with PR OXN which have also shown that switching non-constipated patients to PR OXN maintained their bowel function in a more controlled study setting (one clinical trial and one prospective open-label study with a blinded endpoint)[38, 39].

Importantly, the reduction in BFI cannot be explained by increased use of laxatives. The percentage of patients using laxatives at subsequent visits in the overall population and all subgroups remains stable indicating that the clinically relevant improvement in bowel function during PR OXN treatment cannot be attributed to an increased use of laxatives. This adds to the evidence that PR OXN is a pathophysiological treatment for OIC targeting the underlying cause of OIC and not a symptomatic treatment for OIC as is the case with laxatives[40, 41]. These results suggest that for patients with pre-existing risk-factors for constipation (like older age, female gender and immobility) as well as for patients with pre-existing symptoms of constipation, PR OXN might be a valuable option to treat severe pain, whilst maintaining or even restoring normal bowel function.

In Belgium patients have a co-payment for laxatives which could have led to a lower level of patients using laxatives at start of the observation. The percentage of patients using laxatives during the observation is also low, 31.3% of patients used laxatives during the observation. PR OXN has been shown to improve and prevent symptoms of constipation with reduced laxative use compared with prolonged release oxycodone. Treatment with PR OXN and co-payment for laxatives in Belgium might have led to the low level of laxative use in this observation.

This study also showed that pain relief during PR OXN treatment was "slightly better", "better" or "much better" for the vast majority of patients with severe pain as compared to the previous analgesic treatment. Response rate with respect to pain relief (proportion of patients with pain relief that was "slightly better", "better" or "much better") was significantly lower in WHO-step 3 pretreated patients (77.1%) compared with WHO-step 1 and WHO-step 2 pretreated patients (91.5% and 89.9%, respectively). This was as expected since treatment was stepped-up for patients pretreated with WHO-step 1 and or WHO-step 2 analgesics to a WHO-step 3 analgesic. Counter-intuitively, there were no

significant differences in mean PR OXN dose between the subgroups, which might contribute to a lower efficacy for pain relief in the WHO-step 3 subgroup. Patients pretreated with WHO-step 3 analgesics treatment were switched to another WHO-step 3 analgesic with the addition of naloxone and all randomized clinical trials and observational trials so far have shown that the addition of naloxone to oxycodone did not influence pain relief compared with oxycodone [20-27]. As the majority of patients in the WHO-step 3 pretreated group were switched to PR OXN due to side effects of the WHO-step 3 pretreatment (86.2%), physicians might have been more conservative in titrating the PR OXN dose.

We observed that there was a small but significant difference in pain relief during PR OXN treatment when looking at constipated versus non-constipated patients at study entry favoring non-constipated patients. This might be explained by the fact that 49.8% of constipated patients were pretreated with WHO-step 3 medication and these WHO-step 3 pretreated patients had a significantly lower response rate with respect to pain relief (77.1%) compared with WHO-step 1 and WHO-step 2 pretreated patients (91.5% and 89.8% respectively). Logistic regression analyses with adjustment for age, gender, type of pain and constipation level, showed that the previously used WHO step analgesic is a statistically significant predictor for response to pain relief at last visit.

In the present observational study, patients reported a significant increase in their self-perception of quality of life compared to previous analgesic treatment. The improvement in QoL was significantly higher in patients previously treated with WHO-step 1 and 2 analgesics. This might be expected taking into account that patients previously treated with WHO-step 3 analgesics had significantly less pain relief during the study compared to the other WHO-step subgroups. Improvement in QoL also significantly improved in constipated patients and non-constipated patients, with the improvement being significantly higher in non-constipated patients compared with constipated patients.

However, both the significant increase in pain relief and the significant decrease in OIC could have contributed to the increase in QoL in this study. It has been consistently reported that pain has an inverse correlation between the extent of its relief and the associated QoL[42] and that OIC has a negative impacts on QoL too[1, 10, 12].

Unfortunately, with the current study design it is not possible to distinguish between the contribution of improved bowel function and pain relief to the improvement of QoL. Further studies are warranted to investigate the impact of OIC on QoL of pain patients taking into account their level of pain control as well as pain medication used.

The nature of the adverse drug reactions reported during the study are among those documented for oxycodone/naloxone as outlined in the SmPC. The incidence of drug related adverse events was comparable between subgroups of patients. The frequency of ADR reported in this study are lower than reported in the SmPC. Despite the fact that at each study visit the physicians had to actively answer a question about the oc-

currence of adverse drug reactions in the period before the study visit as a reminder to report all ADRs, we suspect that there is under reporting of ADRs. Unfortunately, this is a well-known and common problem, especially in observational studies[43]. Moreover, the adverse drug reaction profile seen with oxycodone/naloxone is very similar to the profile of oxycodone and oxycodone is a well-known compound to physicians. Therefore the expectations of the physician regarding ADRs with oxycodone/naloxone might have also led to underreporting of ADRs in this observation.

Limitations of the present study include its prospective observational open-label design and the lack of a control arm not using PR OXN. However, the strict in- and exclusion criteria seen in randomized controlled clinical trials were not used in this real-life non-interventional prospective observational study, resulting in findings that are applicable to real-life patient populations.

CONCLUSIONS

The results of this real-life non-interventional prospective observational study performed in daily clinical practice in Belgium show thatpatients with severe pain report a significant and clinically relevant improvement of bowel function as well as an improvement of QoL compared to the previous WHO analgesic treatment during PR OXN treatment. The majority of patients (84.5%) with severe pain switching from their preceding analgesic treatment to PR OXN indicate the efficacy of PR OXN regarding pain relief as 'slightly better', 'better' or 'much better' compared to the previous analgesic medication at last visit.

More interesting, constipated subjects showed a significant and clinically relevant improvement in bowel function(BFI) over time, while laxative use numerically decreased.

In non-constipated subjects, the BFI remains well below the threshold value for normal bowel function (28.8) whilst laxative use remains low (~10%), showing a prevention of constipation despite the use of an opioid. This confirms that treatment with PR OXN improves bowel function in constipated subjects and might maintain bowel function in non-constipated patients even during treatment with opioid analgesics, reflecting the local action of opioids in the gut and the pathophysiological action of naloxone (in PR OXN) on bowel function.

All adverse drug reactions observed were well-known opioid-related AEs raising no additional safety concerns.

TRANSPARENCY

Declaration of funding

This study was designed by Mundipharma Pharmaceuticals BV and Mundipharma Comm. VA, and conducted by qualified investigators under the sponsorship of Mundipharma Pharmaceuticals BV and Mundipharma Comm. VA. Data were gathered by the sponsor and evaluated jointly by the authors and the sponsor. There is no financial interest linked to the preparation, scientific advice and authorship of the article for the authors. No grants, equipment or drugs were supplied by the sponsor. F.J.P.M. Huygen and I. Mancini provided scientific advice to Mundipharma Pharmaceuticals BV. H. Prenen participated as investigator in the study. All authors were involved in the development, writing, critical reviewing and approval of this manuscript.

Declaration of financial/other relationships

I. Mancini, H. Prenen and F.J.P.M. Huygen have nothing to disclose.

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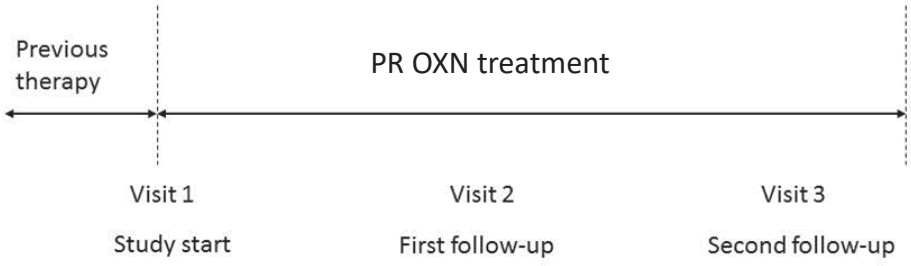
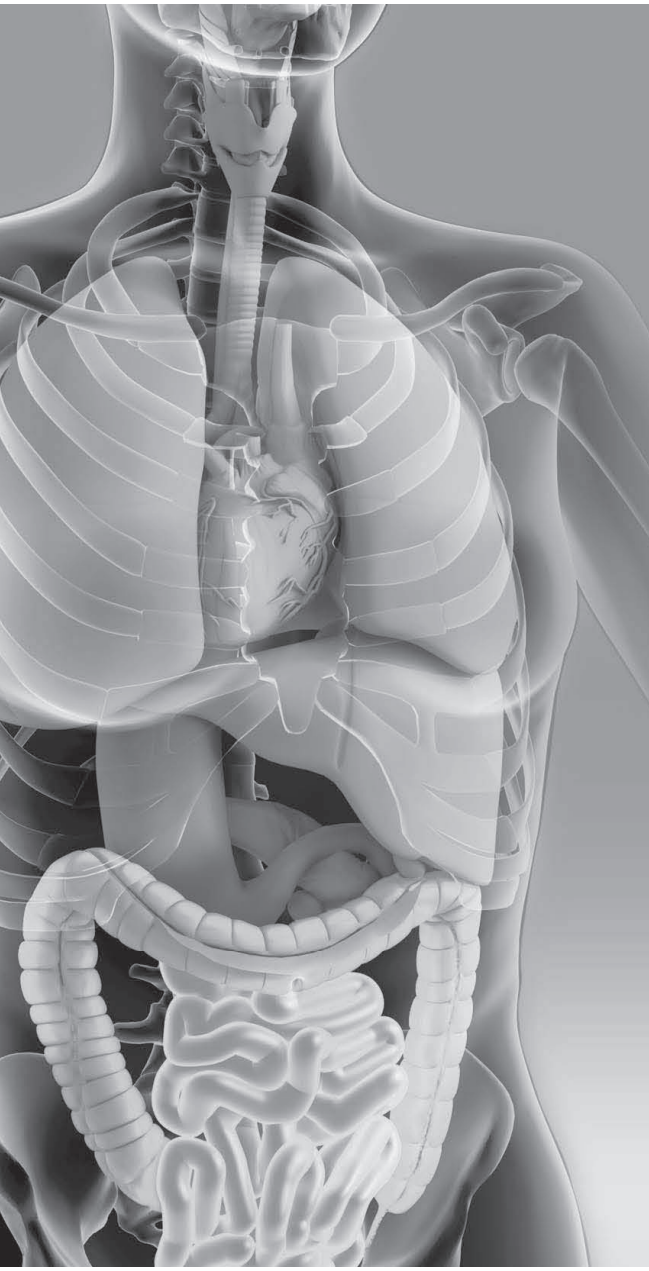
SUPPLEMENTARY FIGURES



Study Visit	Visit 1 Start	Visit 2 First follow-up	Visit 3 Second follow-up
Inclusion/exclusion criteria	X		
Demography	X		
Medical history	X		
Current medication use	X		
Efficacy evaluation (pain relief)[a]		X	X
Pain (NRS) score (0-10)	X[e]	X	X
Bowel Function Index[b]	X[e]	X	X
Efficacy evaluation (bowel function)[a]		X	X
Laxative use[c]		X	X
Concomitant therapies		X	X
Analgesic rescue medication[d]		X	X
Adverse Drug Reactions		X	X
EQ-5D	X[e]	X[f]	X
PR OXN dispensation	X	X	X[g]

a. efficacy of treatment, 7 categories (i.e. much worse, worse, slightly worse, same, slightly better, better, much better)
b. patients assessment of difficulty of bowel movements, feeling of incomplete bowel evacuation, and personal judgement of constipation over the past 7 days.
c. laxative use to be recorded by physician (yes/no, if yes: continuously, intermittently or rarely)
d. record the use of analgesic rescue medication (yes/no)
e. assessments related to use of previous analgesic medication (step 1, step 2 or step 3)
f. only in case of discontinuation at Visit 2
g. at the discretion of the physician

Supplementary Figure 1. Study diagram and outline of study procedures



Chapter 7

Cost-utility analysis of prolonged release oxycodone/naloxone for the treatment of patients with non-malignant moderate-to-severe pain and laxative refractory opioid induced constipation in The Netherlands

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ABSTRACT

Objective

To compare the cost effectiveness of prolonged release (PR) oxycodone/naloxone (OXN) and prolonged release oxycodone (PR OXY) in patients with moderate-to-severe pain of non-malignant origin suffering from laxative-refractory opioid induced constipation (OIC) from the perspective of the Dutch healthcare system.

Methods

The pharmaco-economic model was a cohort cost-utility model with constipated and non-constipated health states. It was adapted from a model which was previously used in non-malignant chronic pain in the UK context and published in 2012 by Dunlop et al.[1]. Data from a pooled analysis of two phase III randomized, controlled trials (RCTs) focusing on patients with non-malignant chronic moderate to severe pain and laxative refractory OIC under PR OXY treatment were used. Dutch costs data were used to calculate the cost difference between treatments in the model by combining the costs of pain therapy, costs of laxative use, costs of additional constipation treatments as well as costs of other resources used to manage constipation. The base case analysis was from a societal perspective, including societal costs. EuroQol-5 dimensions (EQ-5D) utility values for constipation were derived from a study performed in the Netherlands by Penning-van Beest et al.[2]. EQ-5D utility and disutility due to constipation were used to calculate the quality adjusted life year (QALY) gains. Deterministic and probabilistic sensitivity analyses were performed.

Results

The incremental cost of PR OXN versus PR OXY was €763 for the average treatment duration of 52 weeks per patient. PR OXN gave an incremental QALY gain of 0.110 per patient. The estimated incremental cost-effectiveness ratio (ICER) was €6,924 per QALY gained. Sensitivity and scenario analyses gave a maximum ICER of € 21,284 per QALY gained when increasing the probability of constipation in the PR OXN arm by 25%. Key drivers of the model are the utility value for non-constipated patients, the probability of constipation in the PR OXN arm and the mean daily dose of opioid per day. Probabilistic sensitivity analysis showed that PR OXN had approximately 96% probability of being cost effective at the €20,000 threshold.

Limitations

The main limitations of the analysis were the limited data of costs of constipation. These were obtained from a 2-round Delphi panel of 12 Dutch GPs and were therefore based on the perceptions of primary care physicians[3]. As indicated by Dunlop et al.[1], other

groups of healthcare professionals, like nurses and secondary care specialists treating constipation, may report different resource use and costs. A second limitation might be a possible lack of power of the Penning-van Beest study providing the utility scores and disutility[2]. Moreover, the health states were based on constipation, the most common side-effect of opioid treatment. However, PR OXN may counteract other aspects of opioid-induced bowel disorders (such as abdominal pain, cramping and bloating) that may require additional healthcare resources. It is therefore possible that a model examining these aspects on top of OIC may show a greater incremental QALY gain from PR OXN compared with PR OXY.

Conclusions

The present pharmaco-economic study demonstrated PR OXN was estimated to be a cost-effective option for treating patients with non-malignant moderate to severe pain and laxative-refractory OIC. Several sensitivity and scenario analyses show the robustness of the model.

INTRODUCTION

Opioids are an effective analgesic therapy recommended by the World Health Organization for a specific group of patients[4]. The WHO three-step analgesic ladder is used as a reference in several international guidelines, including the European Society for Medical Oncology (ESMO[5]), and the European Association for Palliative Care (EAPC[6]). Besides treatment of malignant pain opioids are also used in the treatment of severe nociceptive non-malignant pain[7].

Side effects of opioids are well known and often require a dose limitation, and sometimes a treatment discontinuation[8]. Constipation, nausea, somnolence/dizziness, dry mouth and respiratory depression remain commonly reported adverse events of opioid usage[9].

Opioid induced constipation (OIC) is defined as "a change when initiating opioid therapy from baseline bowel habits that is characterized by any of the following: reduced bowel movement frequency, development or worsening of straining to pass bowel movements, a sense of incomplete rectal evacuation, or harder stool consistency"[10]. On top of impacting the correct intake of the opioid treatment, OIC has a major impact on patient's quality of life (QoL)[2,9,11-13] and can eventually lead to debilitating complications like external peri-anal thrombosis, anal fissures or rectum prolapse[14]. Therefore OIC is an additional burden especially for patients with chronic moderate-to-severe pain, a vulnerable group of patients [15-18].

In current practice the advice is to treat patients on opioid analgesics prophylactically with a laxative regime. In Dutch clinical practice this laxative regime consists of treatment with at least one laxative in an adequate dosage (e.g. macrogol plus electrolytes or lactulose) and if needed addition of a second laxative of a different therapeutic class (e.g. bisacodyl)[19]. However, some patients still experience OIC despite the use of this laxative regime and/or do not tolerate the adverse events of the laxative regime; i.e. patients with laxative-refractory OIC[20,21]. Current management of OIC episodes includes the symptomatic treatment with oral laxatives (osmotic laxatives, stimulant laxatives and stool softeners), rectal laxatives and lavements. Laxatives have been found to be ineffective to treat OIC[19,22]. Moreover, treatment with laxatives causes side effects and complications[10,23]. Opioid receptor antagonists like methylnaltrexone, naloxegol and naloxone are used for the pathophysiological treatment of OIC [24-26]. They inhibit binding of opioids to the opioid receptors in the gut, thereby preventing OIC[10,22].

PR OXN combines the strong opioid receptor agonist oxycodone and the opioid receptor antagonist naloxone. When administered orally, a reduction of constipation can be achieved due to a local action of naloxone in the gut without affecting pain relief by oxycodone[27-29]. PR OXN has proven equivalent analgesic efficacy to PR OXY with significant improvements in bowel function in chronic non-malignant pain[30-35] as well

as in moderate/severe malignant pain[36,37]. It is important to assess cost utility of PR OXN treatment for laxative-refractory patients, as treatment with PR OXN is more expensive than treatment with PR OXY.

The present publication describes the methodology and findings of a Dutch cost-utility analysis for PR OXN for patients with non-malignant moderate-to-severe pain who need treatment with an opioid to obtain adequate analgesia and laxative-refractory OIC.

METHODS

Patients and treatments

The model used data from a pooled analysis of two randomized, controlled, double-blind, parallel-group studies in non-malignant pain patients published in 2014 by Koopmans et al.[21]. This pooled analysis included 35 patients with non-malignant pain with OIC at study entry that was refractory to at least two laxatives with different modes of action (at least two laxatives of a different ATC-level 4 class). Patients completed randomized, double-blind treatment with PR OXN 20–120 mg/day for 12 weeks with an extension phase of up to 52 weeks. The primary objective of this pooled analysis was to evaluate bowel function in patients randomized to PR OXN who had OIC at study entry, despite the use of at least two different classes of laxatives. Assessment of bowel function was performed using the validated Bowel Function Index (BFI* (*Copyright for the BFI is owned by Mundipharma Laboratories GmbH, Switzerland 2002; the BFI is the subject of European Patent Application Publication No.EP1860988 and corresponding patents and applications in other countries)[38-40]. BFI score comprised the arithmetic mean score of three items rated on a numerical analogue scale (NAS) of 0–100: ease of defecation (0=easy/no difficulty to 100=severe difficulty), feeling of incomplete bowel evacuation (0=not at all to 100=very strong), and personal judgment of constipation (0=not at all to 100=very strong). Normal bowel function is defined as a score of ≤28.8; this was determined in a study that reported that 95% of non-constipated patients had a BFI score ≤28.8. BFI score was assessed at screening, start of double-blind treatment and end of double-blind treatment. Laxative use (bisacodyl and non-study laxatives) throughout the studies was documented. Full details of the study populations have been previously described[21,30-35]. The study showed statistically significant and clinically relevant improvements in bowel function following double-blind treatment with PR OXN. Mean (SD) reduction in BFI score was 23.3 [29.0] ($P \leq 0.0002$). Furthermore, the proportion of patients with a BFI score within normal range (≤28.8) increased from 8.6% at screening to 50.0% at Day 15 of PR OXN. While all patients used ≥2 laxatives of different classes at screening, during study treatment 36% stopped using laxatives ($P<0.001$). PR OXN provided effective analgesia, evidence by stable pain scores during study treatment,

and there were no unanticipated adverse events. The mean (sd) dose of oxycodone used was 54.5 (29.5) mg and was relatively stable, changing with 4.9 (12.5) mg from start of treatment to end of treatment.

Model structure and overview

A cohort cost-utility model was developed in Microsoft Excel 2007 (Microsoft Corporation, Redmond, WA, USA) with constipated and non-constipated health states. The model calculated the incremental cost-effectiveness ratio (ICER) defined as Δcost/Δeffectiveness, where effectiveness was defined in terms of quality adjusted life-years (QALY) gained[1]. Utility values were derived from an article by Penning-van Beest describing the impact of OIC on QoL, using the EQ-5D score[2]. Pain control was not included as a health state as based on the study data, it was assumed to be equal between treatments. The model included laxative use as patients treated with opioids require laxative treatment to prevent OIC. For this subpopulation of laxative-refractory OIC patients all patients in the oxycodone arm (PR OXY) are per definition treated with two laxatives of a different Anatomical Therapeutic Chemical (ATC) level 4 class (e.g. the ATC level 4 code of macrogol is A 06 AD 15) and for the PR OXN arm laxative use was based on the use of rescue laxative in the study by Koopmans et al. 2014[21]. Figure 1 shows the structure of the model.

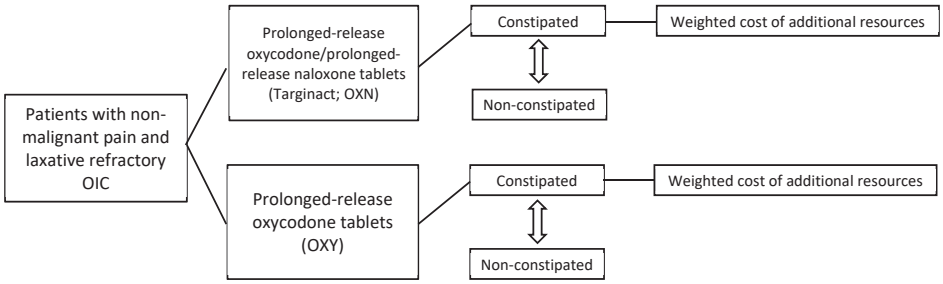

Figure 1: Model structure.

Most patients started in a constipated health state to mimic laxative-refractory OIC as well as the data from the pooled analysis. Over time patient movement occurred between the constipated and non-constipated health states, with the constipated health state incurring an additional cost. The model had weekly time intervals. The time horizon used in the base case analysis was 365 days, according to the average duration of treatment with PR OXY tablets in patients with non-malignant chronic pain. Cost and effects were not discounted owing to the time horizon being less than 1 year.

The following equations were used in the model:

Total cost of drug (laxative and pain treatment)

C_{OXN}=total cost of drug in treatment group over the treatment period for patients treated with PR OXN and C_{OXY}= total cost of drug in treatment group over the treatment period for patients treated with OXY. K=the expected duration of each treatment, which is estimated at 52 weeks, hence K=52.

D_{OXN} is the average weekly cost of PR OXN and D_{OXY} is the average weekly cost of PR OXY. Therefore, D_{OXN}=cost per mg of PR OXN x average (mean) dose (mg) PR OXN per day x 7 (days) and D_{OXY}=cost per mg of PR OXY x average (mean) dose (mg) PR OXY per day x 7 (days).

L_{OXN} is the average weekly cost of as needed bisacodyl use in the OXN treatment group. L_{OXN}=cost per mg bisacodyl x average (mean) dose (mg) bisacodyl per day x 7 (days). L_{OXY} is the average weekly cost of optimal laxative use in the OXY treatment group L_{OXY}=average cost of optimal laxative use per day x 7 days.

Hence, $C_{OXN} = K(D_{OXN}+ L_{OXN})$ and $C_{OXY}=K(D_{OXY}+L_{OXY})$

Resource use costs

Pi_{OXN} is the proportion of patients with constipation in the PR OXN treatment group at each week (i, i=week 1,2….,52) and Pi_{OXY} is the proportion of patients with constipation in the PR OXY treatment group at each week.

The total average weekly cost per patient of additional resource use is V, where V=average cost of additional resource use per constipated patient per week. Costs of additional resource use do not differ between patients in the PR OXN and PR OXY group. Therefore, using a half-cycle correction, the additional healthcare costs in the PR OXN treatment group (Z_{OXN}*) is given by:

$(P0_{OXN}+P1_{OXN})/2*V+(P1_{OXN}+P2_{OXN})/2*V+(P2_{OXN}+P3_{OXN})/2*V+….+(P51_{OXN}+P52_{OXN})/2*V$

And the additional healthcare costs in the PR OXY treatment group (Z_{OXY}*), using a half-cycle correction is given by:

$(P0_{OXY}+P1_{OXY})/2*V+(P1_{OXY}+P2_{OXY})/2*V+(P2_{OXY}+P3_{OXY})/2*V+….+(P51_{OXY}+P52_{OXY})/2*V$

The incremental cost is therefore $(C_{OXN}-C_{OXY})+(Z_{OXN}*-Z_{OXY}*)$

Utilities

If the utilities for the constipated patients in the PR OXN treatment group at each week are denoted

$U_{OIC, OXN}$i then, the total QALY gain across all 52 weeks for the constipated patients in the PR OXN treatment group can be defined as $U_{OIC, OXN}$ is:

$U_{OIC,\ OXN}$ =((P0$_{OXN}$+P1 $_{OXN}$)/2*($U_{OIC,\ OXN}$0+ $U_{OIC,\ OXN}$1)/2)+(P1 $_{OXN}$+P2 $_{OXN}$)/2*($U_{OIC,\ OXN}$1+ $U_{OIC,\ OXN}$2)/2+(P2 $_{OXN}$+P3 $_{OXN}$)/2*($U_{OIC,\ OXN}$2+ $U_{OIC,\ OXN}$3)/2+….+(P51$_{OXN}$+P52$_{OXN}$)/2*($U_{OIC,\ OXN}$51+ $U_{OIC,\ OXN}$52)/2).

If the utilities for the non-constipated patients in the PR OXN treatment group at each week are denoted

$U_{non\text{-}OIC,\ OXN}$i then, the total QALY gain across all 52 weeks for the non-constipated patients in the PR OXN treatment group defined as $U_{non\text{-}OIC,\ OXN}$ is:

$U_{non\text{-}OIC,\ OXN}$ =(1-(P0$_{OXN}$+P1 $_{OXN}$)/2)*($U_{non\text{-}OIC,\ OXN}$0+ $U_{non\text{-}OIC,\ OXN}$1)/2)+(1-(P1 $_{OXN}$+P2 $_{OXN}$)/2)*($U_{non\text{-}OIC,\ OXN}$1+ $U_{non\text{-}OIC,\ OXN}$2)/2+(1-(P2 $_{OXN}$+P3 $_{OXN}$)/2)*($U_{non\text{-}OIC,\ OXN}$2+ $U_{non\text{-}OIC,\ OXN}$3)/2+….+(1-(P51$_{OXN}$+P52$_{OXN}$)/2)*($U_{non\text{-}OIC,\ OXN}$51+ $U_{non\text{-}OIC,\ OXN}$52)/2).

U_{OXN}*= $U_{OIC,\ OXN}$ + $U_{non\text{-}OIC,\ OXN}$

If the utilities for the constipated patients in the PR OXY treatment group at each week are denoted

$U_{OIC,\ OXY}$i then, the total QALY gain across all 52 weeks for the constipated patients in the PR OXN treatment group defined as $U_{OIC,\ OXY}$ is:

$U_{OIC,\ OXY}$ =((P0$_{OXY}$+P1 $_{OXY}$)/2*($U_{OIC,\ OXY}$0+ $U_{OIC,\ OXY}$1)/2)+(P1 $_{OXY}$+P2 $_{OXY}$)/2*($U_{OIC,\ OXY}$1+ $U_{OIC,\ OXY}$2)/2+(P2 $_{OXY}$+P3 $_{OXY}$)/2*($U_{OIC,\ OXY}$2+ $U_{OIC,\ OXY}$3)/2+….+(P51$_{OXY}$+P52$_{OXY}$)/2*($U_{OIC,\ OXY}$51+ $U_{OIC,\ OXY}$52)/2).

If the utilities for the non-constipated patients in the PR OXN treatment group at each week are denoted

$U_{non\text{-}OIC,\ OXY}$i then, the total QALY gain across all 52 weeks for the non-constipated patients in the PR OXN treatment group defined as $U_{non\text{-}OIC,\ OXY}$ is:

$U_{non\text{-}OIC,\ OXY}$ =(1-(P0$_{OXY}$+P1 $_{OXY}$)/2)*($U_{non\text{-}OIC,\ OXY}$0+ $U_{non\text{-}OIC,\ OXY}$1)/2)+(1-(P1 $_{OXY}$+P2 $_{OXY}$)/2)*($U_{non\text{-}OIC,\ OXY}$1+ $U_{non\text{-}OIC,\ OXY}$2)/2+(1-(P2 $_{OXY}$+P3 $_{OXY}$)/2)*($U_{non\text{-}OIC,\ OXY}$2+ $U_{non\text{-}OIC,\ OXY}$3)/2+….+(1-(P51$_{OXY}$+P52$_{OXY}$)/2)*($U_{non\text{-}OIC,\ OXY}$51+ $U_{non\text{-}OIC,\ OXY}$52)/2).

U_{OXY}*= $U_{OIC,\ OXY}$ + $U_{non\text{-}OIC,\ OXY}$

The ICER is therefore given by

((C_{OXN}-C_{OXY})+(Z_{OXN}*-Z_{OXY}*))/U_{OXN}*-U_{OXY}*

Model inputs

Cost inputs

Unit costs were based on the pharmacy purchase price (AIP) of each strength of PR OXN and PR OXY and were retrieved from the Dutch national list prices database (source:www.z-index.nl, January 2015)). The pack costs for PR OXN were €78.63 (90 tablets 5 mg), €106.50 (90 tablets 10 mg), €197.52 (90 tablets 20 mg) and €388.54 (90 tablets 40 mg).

The cost of PR OXY was a weighted average of the different available presentations (OxyContin® and its generic versions). The weight was based on the actual dispensed units of the different oxycodone strengths from the different manufacturers (source: www.farminform.nl). The weighted average pack costs for PR OXY were €3.73 (30 tablets 5 mg), €5.31 (30 tablets 10 mg), €9.09 (30 tablets 20 mg) and €40.87 (30 tablets 40 mg). The model used dispensed unit data for PR OXN and PR OXY to calculate a weighting that was then used to estimate cost per mg. The weightings applied were 29.7% (5 mg), 49.8% (10 mg), 17% (20 mg) and 3.5% (40 mg). It yielded average costs per mg of € 0.12 for OXN and € 0.02 for OXY (Table 1).

Table 1: Information for PR OXN and PR OXY weighted average price calculation used in the model

Strength	**Sales**	**OXN**			**OXY**		
mg opioid	**%**	**Pack size**	**AIP/pack**	**€/mg**	**Pack size**	**AIP/pack**	**€/mg**
5	29.7%	98	€78.63	€ 0.16	30	€ 3.73	€ 0.02
10	49.8%	98	€106.50	€ 0.11	30	€ 5.31	€ 0.02
20	17.0%	98	€197.52	€ 0.10	30	€ 9.09	€ 0.02
40	3.5%	98	€388.54	€ 0.10	30	€ 40.87	€ 0.03
Total	**100%**			**€ 0.12**			**€ 0.02**

The average daily dose of opioid during treatment of laxative-refractory patients was 54.5 mg (Koopmans et al.)[21,]. As opioid antagonist treatment does not interfere with pain relief this dose was used in both arms. The dose was multiplied with the average cost per mg of each drug to estimate the cost of opioid treatment in each arm of the model. The weighted cost per week of OXY was €7.62; the weighted cost per week of PR OXN was €46.69.

The average costs of laxative use for patients on PR OXN treatment was based on laxative costs derived from the Dutch national list prices database (Table 2; source:www.z-index.nl, January 2015) as well as laxative use from patient data (Koopmans et al.)[21]. 42.9% of laxative-refractory patients received 'as needed' bisacodyl, with an average daily dose of 4.32mg[21].

For patients on PR OXY treatment the average costs of laxative use were based on current Dutch practice and guidelines which recommend laxative treatment during opioid treatment for all patients. It was therefore assumed that 100% of patients were receiving the laxative treatment, being a combination of lactulose/movicolon+ bisacodyl on a daily basis[19,41]. The national public claims database user information showed that 11% of patients are using lactulose and 89% macrogol plus electrolytes (source: www.gipdatabank.nl). The average cost of optimal laxative use per day in the PR OXY arm was estimated using the weighted average cost of lactulose/macrogol combinations based on number of users derived from the national public claims database (GIP-databank) and medication costs from the national list prices database (Z-index) (Table 2). The corresponding weekly cost of laxatives in addition to opioid treatment were calculated was estimated at €0.09 with PR OXN and €2.11 with PR OXY.

A two-round Delphi panel including 24 Dutch GPs in first round and 12 Dutch GPs in second round showed that patients with laxative-refractory OIC regularly require treatments in addition to a laxative regime to temporarily obtain relief from OIC over time[3]. Moreover, patients with laxative-refractory OIC can suffer from complications caused by OIC. The medical resources, including additional laxatives, visits, diagnostic tests and procedures required to temporarily relieve OIC and to treat OIC complications as well as the frequency of additional required OIC treatment and the percentage of patients suffering from complications during an additional treatment for OIC were also collected in the Delphi panel. Costs for productivity losses and costs for transportation during periods with additional OIC treatments were also collected in the Delphi panel. Each item was multiplied with its unit cost to obtain the average total cost per additional OIC treatment. The costs of complications are linked with the number of additional OIC treatments needed and the average total cost for OIC complications.

Table 2: Average costs of laxative use per week for patients using OXN and OXY.

OXN	**% of patients using laxative**	**Average daily dose**	**Cost/unit (€)**	**Cost/day (€)**
Costs of Bisacodyl per day	42.9%	4.32mg	0.0073/mg	€ 0.0135
Total laxative cost with OXN per week				**€ 0.09**
OXY	**% of patients using laxative**	**MDD***	**Cost/unit (€)**	**Cost/day (€)**
Costs of Lactulose per day	11%	1 bag, 15 ml (12 g granules)	0.0146/ml	€ 0.024
Macrogol plus electrolytes per day	89%	1 bag, 25 ml	0.0092/ml	€ 0.205
Bisacodyl per day	100%	10mg	0.0073/mg	€ 0.073
Total laxative cost with OXY per day				€ 0.302
Total laxative cost with OXY per week				**€ 2.11**

*MDD=minimal daily dosage as per SmPC.

As the Dutch national guidelines on opioid treatment and OIC prevention have not changed significantly since 2008, the type and frequency of medical resources used obtained from the Delphi panel performed in 2008 were not updated[19,41]. The corresponding unit costs for visits and treatments in different settings were retrieved from the 2010 costing manual (2009 costs) and were inflated to 2014 using the evolution of the consumer price index (CPI), Health compound, between 2009 (102.55) and the most recent year available (2014: 105.88, factor 1.03) as per national guidelines. A further assumption was required in order to estimate the additional total cost of OIC on average per year.

Delphi-panel outcomes

On average, in the Delphi panel the experts reported that additional OIC treatment to temporarily relief OIC in laxative-refractory OIC patients was needed on average 6 (range 3.0-10.0) times over a 12 month period[3]. Most frequently reported resources for additional OIC treatment in laxative-refractory patients within the Delphi-panel were medications (up to 64%), GP (home) visits (up to 53%) and in hospital treatments (up to 30%). The corresponding cost of one additional OIC treatment course in constipated patients was estimated at €171.67 per additional OIC treatment; or €19.81 per week (Table 3)[3].

Table 3: Costs for additional OIC treatments, costs for OIC complications, costs of productivity loss and transport costs.

Cost item	€ / OIC per additional OIC treatment course	95% CI	€ / week*	95% CI
Total additional OIC treatment	**171.67**	**[129-215]**	**19.81**	**[15-25]**
Total OIC complications	**318.90**	**[204-434]**	**36.80**	**[24-50]**
Average cost of productivity loss caused by OIC, per additional OIC treatment	**107.32**	**[19-195]**	**12.38**	**[2-23]**
Average transport costs home-hospital, per additional OIC treatment (due to additional OIC treatments and treatment of OIC complications)	**2.04**	**[1-3]**	**0.24**	

*assuming 6 courses of additional OIC treatment per year in the base case analysis.
95% confidence intervals (CI) were estimated based on the certainty scores provided by the experts from the panel during the second round. 1-certain, low risk of the figure being wrong (± 10% relative divergence possible); 2-reliable, some risk of being wrong (± 20%); 3-risky, substantial risk of being wrong (± 40%); or 4-unreliable, great risk of being wrong (more than 40%). Based on these results, average, lower and upper limit of resources used were calculated, and then multiplied with the unit cost of that item of resource use in order to obtain, respectively, the average, lower and upper limit of costs.

The most frequently reported complications of OIC reported in the Delphi-panel were fecal impaction, overflow diarrhea, anal fissures and hemorrhoids, resulting in drug costs, GP (home visits), tests and in-hospital procedures. The corresponding cost of

treating OIC complications in constipated patients was estimated at €318.90 or €36.80 per week (Table 3)[3].

The average cost of productivity loss was also estimated based on the Delphi panel outcomes. The Dutch GPs estimated that on average 23% range 17-29%] of the chronic pain patients who are receiving opioids are professionally active. Of these patients, on average 30% [range 22-38%] was unable to work due to constipation or due to complications of constipation. In these patients with prescribed sick leaves, there were on average 6.2 [range 4.6-7.8] working days absent per additional OIC treatment course. The hourly rate was estimated from the most recent manual of cost research (2010). In 2009, the average salary was €30.02 per hour, which was inflated to € 31.50 in 2014 based on the evolution of the prices of the collective labour agreement as per national guidelines ("Collectieve Arbeidsovereenkomst" (CAO), index varied from 125.4 in 2009 to 131.6 in 2013 –latest yearly value available at the time of the analysis). Assuming an average working day of 8 hours, the average cost of a working day loss was estimated at € 252.03. Combined with the Delphi panel data, the resulting indirect cost of OIC per patient was €107.32 per additional OIC treatment course (=252.0 x 0.23 x 0.30 x6.2). The corresponding cost of productivity losses caused by OIC in constipated patients was estimated at on average €107.32 [range 19-195] per additional OIC treatment course and on average €12.38 [range 2-23] per week (Table 3).

The direct costs not related to health care were estimated as the cost of transport from the patient's home to the hospital and back, including a parking cost. The 2009 unit costs per km with a personal car (€0.22/km) and the average parking cost (€3.36) were obtained from the 2010 costing manual values, inflated to 2014 using the Dutch CPI index. The transport cost for each treatment performed in the hospital (day clinic or in-hospital) was calculated as follows: (7km (as per national guidance) x €0.22) x 2 + €3.36 = €6.30. It was then multiplied with the proportion of patients requiring the treatment. The total transport costs remained marginal given the relative small proportion of patients going to the hospital for additional OIC treatment and treatment of OIC complications. The corresponding cost of transport related to additional OIC treatment and treatment of OIC complications in the hospital (day-care or in-hospital stay) or out-patient hospital visits was estimated at €2.04 per intervention and €0.24 per week (Table 3).

Inputs for health states

The treatment effect was modeled according to the analysis performed by Koopmans et al. [21,] for the laxative-refractory OIC population, which is a sub-group of patients in the OXN9001 trial. Patients were considered laxative-refractory when their BFI was above 28.8 despite the use of at least 2 laxatives of a different ATC level 4 class. A switch from opioids plus laxative treatment to PR OXN was associated with a reduction in the proportion of constipated patients over time[21]. The weekly rates of OIC are presented in Table

4. In the PR OXY arm, the baseline rate of constipated patients (91.4%; not all patients were constipated some patients did not tolerate the laxative treatment) was assumed unchanged until the end of the model horizon. The rational for the latter assumption was the absence of other treatments in this specific patient population treated with opioids and suffering from laxative-refractory OIC. The patients need a treatment with opioids and are unresponsive to laxatives. So in clinical practice these patients will be kept on an optimal laxative schedule and they will receive additional OIC treatment to temporarily relieve OIC when needed[19] (Table 4).

To allow modelling beyond 12 weeks, it was assumed that the BFI values achieved at the end of 12-week treatment period would remain constant for both treatment groups until the end of the model (52 weeks). This was a conservative assumption given long-term extension phase study results, showing sustained benefit of PR OXN relative to PR OXY over a 12-month period[42].

Table 4. Weekly proportions of OXN patients in "constipated" and "non-constipated" health states

Week	Non constipated (« normal BFI score »)	Constipated (BFI score >28.8)	95% CI
	n/N (%)	n/N (%)	
Week 0 (Day 1)	3/35 (8.6%)	32/35 (91.4%)	[82-100]
Week 1 (Day 8)	12/33 (36.4%)	21/33 (63.6%)	[47-80]
Week 2 (Day 15)	16/32 (50.0%)	16/32 (50.0%)	[33-67]
Week 4 (Day 29)	13/29 (44.8%)	16/29 (55.2%)	[37-73]
Week 8 (Day 57)	13/27 (48.1%)	14/27 (51.9%)	[33-71]
Week 12 (Day 85)	14/35 (40.0%)	21/35 (60.0%)	[44-76]

95% confidence intervals (CI) around each proportion p were estimated as follows: p +/- sqrt(p*(1-p)/N)

Quality of life inputs (utility values)

For laxative-refractory patients no utility values were available in the pooled analysis, since there were a limited number of non-constipated patients in the trial[21]. To obtain utilities specifically related to constipation status a literature search was performed which revealed three publications in which impact QoL was measured in relation to constipation in the Netherlands[2]. The article by Penning-van Beest was the only article describing the impact of OIC on QoL, using the EQ-5D score. In this publication the OIC-specific impact on QoL of patients treated with opioids for pain was measured in terms of disutility, applied to constipated vs. non-constipated patients with non-advanced disease[2]. The utility level was determined by the presence or absence of OIC. In a population with non-advanced disease (assumed to represent a non-malignant-pain population), the average EQ-5D utility was 0.65 [0.22-0.78] without OIC ($=U_{non\text{-}OIC}$) and 0.31 [0.17-0.73] with OIC (U_{OIC}), i.e. a disutility of 0.34 [0.32-0.36] due to OIC.

Deterministic sensitivity analyses

It was important to determine which inputs had the most significant impact on model results and whether particular inputs increased or decreased the ICER. The variations of a number of variables were tested separately and their impact on the ICER was presented in a Tornado diagram. Table 5 represents the variables that were tested separately including the range tested as well as the method used.

Table 5. Parameter limits used in the univariate sensitivity analysis

Model parameter	Mean Base case	Range (lower limit-upper limit	Source
Scenario 1, base case			
% of patients with OIC, OXN arm	cf Table 1	+/- 25%	Koopmans 2014, as per 95% confidence intervals
% of patients with OIC, OXY arm	Cf Table 1	+/- 25%	Koopmans 2014, as per 95% confidence intervals
N opioid mg/day, OXN	54.5mg	+/- 25%	Koopmans 2014
Model duration	52 wks	12 wks	Koopmans 2014 Blagden 2014
Treatment duration	100% of time	25-80%	Assumption
Utility constipated state	0.65	0.22-0.78	Penning van Beest 2010, as per published 95% CI
Disutility due to OIC	0.34	+/-25%	Penning van Beest 2010, as per 95% CI around the disutility
Cost of resources use (incl. complications), per week	€56.60	+/-33%	Delphi NL (updated 2014), as per certainty scores* (Table 7 and Table 10)
Cost of productivity loss caused by OIC, per week	€12.38	+/-80%	Delphi NL (updated 2014) as per certainty scores*

StdErr: standard error;

Probabilistic sensitivity analysis

The model conducted probabilistic sensitivity analysis (PSA) on the following major model inputs: utility values; probability of constipation over time; average oxycodone dose; unit costs of additional OIC treatment in constipated patients; cost of laxatives. A second order Monte-Carlo simulation i.e. probabilistic sensitivity analysis (PSA) was undertaken based on 3000 simulations.

Beta distributions were used for probabilities and disutility score, gamma distributions for costs, and normal distributions for other continuous variables (dosages, durations). The details on the distributions used in the PSA are presented in Table 6.

A cost-effectiveness plane representing the outcome of each simulation as a dot with QALYs gained with OXN vs. OXY on the x-axis and incremental costs on the y-axis and an acceptability curve showing the probability for OXN to be cost-effective compared to OXY depending on the willingness-to-pay (WTP) of the health care payer were derived

Table 6. Distribution and parameter limits used in the probabilistic sensitivity analysis

Model parameter	Mean	Distri. PSA	Distri. Param.
% of pts with OIC, OXY (week 0)	91.4%	Beta	718-68
% of pts with OIC, OXN, week 1	64%	Beta	20-12
% of pts with OIC, OXN, week 2	50%	Beta	16-16
% of pts with OIC, OXN, week 4	55%	Beta	15-13
% of pts with OIC, OXN, week 8	52%	Beta	13-13
% of pts with OIC, OXN, week >=12	60%	Beta	20-14
N opioid mg/day	54.5mg	Normal	54.5, 0.60
Laxative cost with OXY per day	€2.11	Gamma	1, 2.11
Laxative cost with OXN, per day	€0.09	Gamma	1, 0.24
Utility non constipated	0.65	Beta	7-4
Disutility due to OIC	0.34	Beta	531-1031
Costs additional OIC treatment,	€ 19.75	Gamma	1, 19.75
Costs of OIC complications cost,	€ 36.70	Gamma	1, 36.70
costs of OIC-related transport costs,	€ 0.24	Gamma	1, 0.24
Costs of OIC-related productivity loss	€ 12.38	Gamma	1, 12.38

from the PSA. To ease the interpretation of the PSA results a range of WTP thresholds was used: from 20,000 €/QALY, which is the threshold mentioned in The Netherlands for diseases with a low burden of disease to 50,000 €/QALY, as can be encountered when the burden of disease is higher.

Scenario analyses

Besides deterministic and probabilistic sensitivity analyses also a set of different scenarios were analyzed, based on feedback from real-life studies[43,44]. First scenario a scenario in which 3 OIC interventions per year were assumed based on low value obtained in the Delphi panel (base case 6 interventions). Other scenario's involved excluding costs of constipation-related complications and excluding indirect costs. A last scenario involved a scenario in which costs were derived from Dik et al. 2014[44] who investigated constipation-related direct medical costs in 16 887 patients newly diagnosed with chronic constipation in the Netherlands.

RESULTS

Base case

Table 7 shows the base case results. Patients treated with PR OXN had higher analgesia costs (€2,032) compared to PR OXY. Compared to OXY, patients treated with PR OXN

had lower laxative treatment costs, lower additional OIC treatment costs and lower OIC complication costs as well as lower costs for OIC-related productivity loss and lower OIC-related transport costs (total savings amounted to €1269 over 52 weeks). The incremental cost of PR OXN versus PR OXY was € 762.90 over 52 weeks. Relative to PR OXY, PR OXN gave an incremental QALY gain of 0.1102. Resulting in an ICER of € 6,924 per QALY gained. This value is deemed cost-effective, assuming a willingness-to-pay threshold of €20,000 per QALY gained.

Table 7: Incremental and total costs in the base case analysis

Cost item	OXN	OXY	Incremental OXN vs. OXY
Opioid costs (pain therapy)	€ 2,427.88	€ 396.24	€ 2,031.64
Laxative treatment costs (concomitant to opioid)	€ 4.92	€ 109.77	-€ 104.84
Additional OIC treatment costs	€ 606.00	€ 938.88	-€ 332.88
OIC complications costs	€ 1,125.71	€ 1,744.07	-€ 618.36
OIC-related transport costs for in-hospital additional OIC treatment and treatment of OIC complications	€ 7.36	€ 11.41	-€ 4.04
OIC-related costs for productivity losses	€ 379.78	€ 588.40	-€ 208.62
Total cost (Societal)	**€ 4,551.66**	**€ 3,788.75**	**€ 762.90**
QALY	**0.4494**	**0.3392**	**0.1102**

Results are undiscounted (time horizon < 1 year).
ICER base case analysis (societal perspective):€6,924, ICER base case analysis (without societal costs):€8,853

Univariate (deterministic) sensitivity analyses

The results of the univariate sensitivity analysis testing relative variations around the base case values as described in table 5 are presented in the Tornado diagram in Figure 2.

The utility level of the "non-constipated" patients resulted in an ICER variation changing the value to PR OXN dominated (lower costs and more QALYs gained relative to PR OXY) and € 5,009 per QALY gained when the utility in the "non-constipated" health state was changed to from 0.22 and 0.78, respectively (base case = 0.65). Increasing the utility level of non-constipated patients results in a lower ICER.

The variations of -25% to +25% around the base case OIC rate of the weekly proportions of patients with OIC in the PR OXN arm resulted in a higher ICER to €1,470 and 21,284 per QALY gained. As expected the proportion of patients with OIC in the PR OXN arm has an impact on the ICER.

Varying the mean daily dose of opioid received in the PR OXN and PR OXY arms, with variations from 41 to 68mg/day resulted in an ICER change to € 2,318 and 11,535 QALY gained. However, the average dispensed daily dose of PR OXY per patient has been stable during the years 2009-2013 at approximately 35 mg per day (www.gipdatabank.

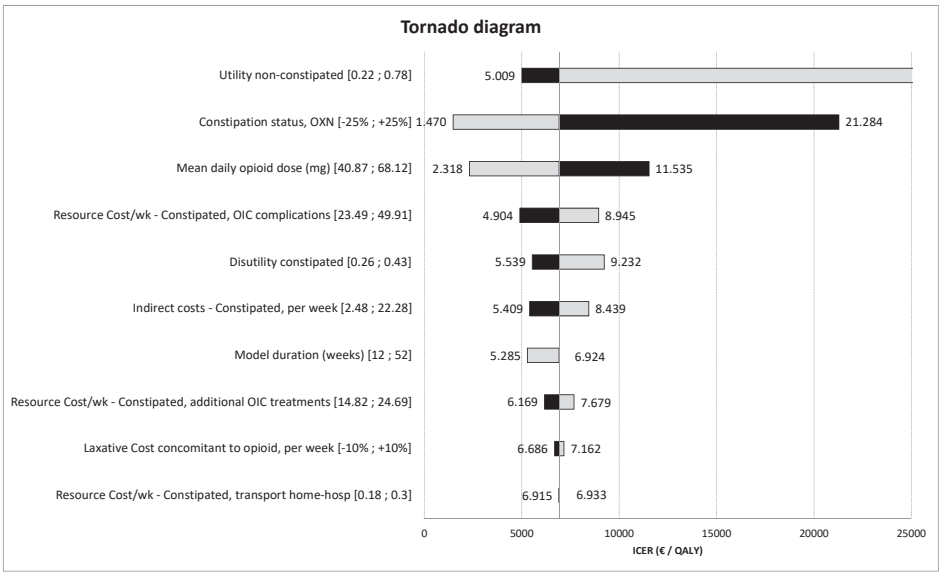

Figure 2: Tornado diagram, ICER of OXN vs. OXY, societal perspective (univariate sensitivity analysis). In blue: ICER obtained with the low value of the parameter; in red: ICER with the high value parameter. ICER base case analysis: €6,924 per QALY gained.

nl). An increase to an average daily dose of 68 mg is not expected as PR OXN results in comparable pain relief compared to PR OXY. When costs of OIC complications or costs of additional OIC treatment course are varied from -36% to +36% around the base case value, ICER changed to €8,945 and €4,904 per QALY gained. Varying the disutility associated with the "constipated" state to 0.26 and 0.43 results in a change in ICER to € 9,232 and € 5,539 per QALY gained. The ICER increases when the impact of OIC on patients' QoL increases. When the mean indirect costs (costs of OIC-related productivity losses) are varied from -80% to +80% around the base case value during additional OIC treatment courses the ICER changes to €8,439 and €5,409 per QALY gained.

Probabilistic sensitivity analysis

The PSA outcomes are described in Table 8.

On average over 3000 simulations, the mean (SD) QALYs gained with PR OXN vs. PR OXY were 0.11 (0.022) and the mean (SD) incremental costs were € 765 (822) per patient, resulting in an ICER of €6,953 per QALY gained. This result is in line with the base case deterministic conclusion. The cost-effectiveness plane (scatter plot) is shown in Figure 3.

Each dot represents the outcome of a simulation. There were 15% in the South-East quadrant (lower costs, higher QALYs i.e. dominant situation of PR OXN vs. PR OXY).At a threshold of €20,000 per QALY gained a total of 96% simulations are cost-effective and

100% at a €50,000 per QALY gained threshold. The acceptability curve is shown in Figure 4 and confirms the findings above.

Table 8: PSA outcomes OXN vs. OXY, 3000 simulations

Strategy	Mean (SD) Cost	Mean (SD) ΔCosts	Mean (SD) QALYs	Mean (SD) ΔQALYs
OXY (ref)	3,754.4 (2,112.6)		0.343 (0.116)	
OXN	4,519.2 (1,371.9)	764.8 (821.6)	0.453 (0.118)	0.11 (0.022)

ΔCosts: difference in cost per patient treated with OXN vs. OXY
ΔQALYs: difference in QALYs gained per patient treated with OXN vs. OXY
SD: standard deviation.

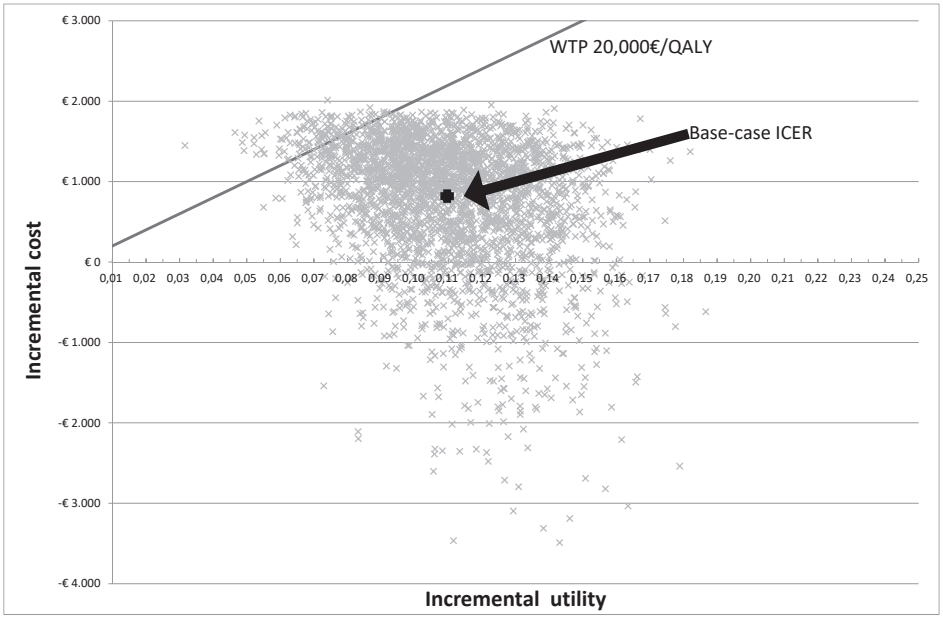

Figure 3: Cost-effectiveness plane.

Other scenario analyses

Scenario assuming 3 additional OIC treatment courses per year (base case 6 courses per year)
This scenario demonstrates that decreasing the number of additional OIC treatment courses results in an increase of the ICER to €11,241 per QALY gained.

Scenario excluding indirect costs (OIC-related productivity costs)
This scenario shows that there is an impact of OIC-related productivity loss on the ICER. As expected exclusion of these costs led to a higher ICER of €8,818 per QALY gained.

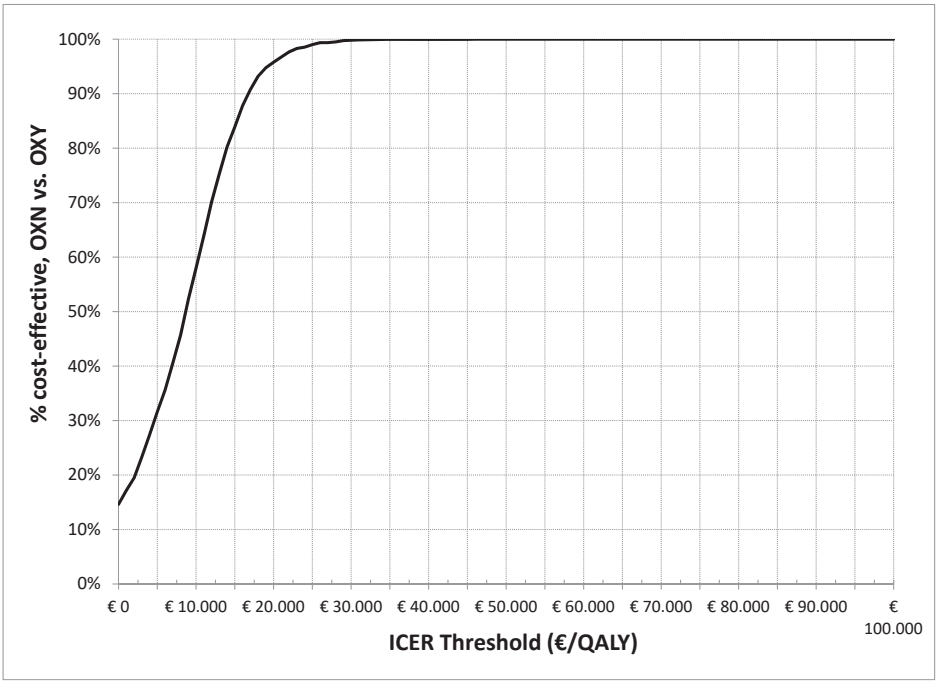

Figure 4: Acceptability curve PR OXN vs. PR OXY, PSA

Scenario excluding costs OIC complications

As expected costs of OIC complications have an impact on the ICER increasing it to €12,536.

Scenario using Chronic constipation related costs from Dutch Health Insurance Claims database (Dik et al.).

When using chronic constipation related costs in patients with persistent constipation from the Dutch health care insurance claims database the ICER increases to €14,761. In this publication all costs in the claims database related to chronic constipation were included from secondary care.

The results of the base case analysis, deterministic and probabilistic sensitivity analyses as well as the scenario analyses are depicted in table 9.

Table 9: Results of univariate sensitivity & scenario analyses

Subject	**Δcosts**		**ΔQALYs**			**ICER (€/QALY)**
Base case	**762.9**		**0.1102**			**6,924**
univariate sensitivity analyses	LOW			HIGH		
	Δcosts	**ΔQALYs**	**ICER (€/QALY)**	**Δcosts**	**ΔQALYs**	**ICER (€/QALY)**
Model duration (weeks) [12 ; 52]	148.3	0.028	5,285	762.9	0.110	6,924
Mean daily opioid dose (mg) [40.875 ; 68.125]	255.4	0.110	2,318	1270.9	0.110	11,535
Resource Cost/wk - Constipated, additional OIC treatments [14.82 ; 24.69]	846.1	0.110	7,679	679.7	0.110	6,169
Resource Cost/wk - Constipated, OIC complications [23.49 ; 49.91]	985.5	0.110	8,945	540.3	0.110	4,904
Resource Cost/wk - Constipated, transport home-hosp [0.18 ; 0.3]	763.9	0.110	6,933	761.9	0.110	6,915
Laxative Cost concomitant to opioid, per week [-10% ; +10%]	789.1	0.110	7,162	736.7	0.110	6,686
Indirect costs - Constipated, per week [2.476 ; 22.284]	929.8	0.110	8,439	596.0	0.110	5,409
Disutility constipated [0.255 ; 0.425]	762.9	0.083	9,232	762.9	0.138	5,539
Utility non-constipated [0.221 ; 0.78]	762.9	-0.029	OXN Dominated	762.9	0.152	5,009
Constipation status, OXN [-25% ; +25%]	235.4	0.160	1,470	1287.7	0.061	21,284
	Δcosts		**ΔQALYs**			**ICER (€/QALY)**
Scenario analyses						
3 additional OIC treatment courses/year	1,238.5		0.1102			11,241
Excluding OIC indirect costs (OIC-related productivity loss)	971.5		0.1102			8,818
Excluding costs of OIC complications	1,381.2		0.1102			12,536
Costs from Health insurance claims database (secondary care, Dik 2014)	1,626.34		0.1102			14,761

DISCUSSION

PR OXN combines the strong opioid receptor agonist oxycodone and the opioid receptor antagonist naloxone. PR OXN has proven equivalent analgesic efficacy to PR OXY with significant improvements in bowel function in chronic non-malignant pain[30-35] as well as in moderate/severe malignant pain[36,37]. It is important to assess cost utility of PR OXN treatment for laxative-refractory patients, as treatment with PR OXN is more expensive than treatment with PR OXY.

This cost-utility analysis demonstrates that treatment with PR OXN generates an ICER well below the commonly applied thresholds in the Netherlands. The ICER is similar

to that generated in a previous cost-utility model of PR OXN compared with PR OXY[1]. Under a conservative approach taking into account the optimal laxative schedule and assuming a continuous opioid treatment, it demonstrated cost-effectiveness of PR OXN plus rescue bisacodyl for opioid-treated patients with non-malignant pain suffering from laxative-refractory OIC compared to OXY plus a laxative regime with an ICER of €6,924 per QALY gained.

Several sensitivity and scenario analyses show the robustness of the model (ICERs between €1,470 and €21,284 per QALY gained; the latter in patient who are unresponsive to treatment with PR OXN). The probability of being cost-effective for PR OXN vs. PR OXY was 96% and 100% at a WTP threshold of €20,000 to €50,000 per QALY gained, respectively.

The univariate sensitivity analysis in which the proportion of constipated patients in the OXN-arm was increased with 25% resulted in the highest ICER €21,284 per QALY gained. In general, it can be discussed that patients with OIC unresponsive to treatment with PR OXN most probably suffer from constipation caused by other factors than constipation . For these patients other more invasive pain management methods could be explored in real-life.

A scenario analyzing the impact of decreasing the number of additional OIC courses per year from 6 to 3 resulted in increase of the ICER to €11,241 per QALY gained. However, in this specific patient population patients on opioids who are suffering from laxative-refractory OIC it is not expected that the number of additional OIC treatment courses will decrease. Actually in the Delphi panel it was shown that in this specific patient population the number might increase to 1 additional OIC treatment course every month i.e. 12 per year, implying a conservative base case.

Also a scenario was analyzed in which the costs of complications were excluded. This is in line with the pharmaco-economic report of subcutaneous (sc) methylnaltrexone that was submitted to obtain reimbursement in the Netherlands, in which also no costs for complications were added[45]. As expected costs of OIC complications have an impact on the ICER increasing it to €12,536 per QALY gained. However, this ICER is still lower than the national threshold of €20,000 per QALY gained. In comparison the ICER obtained with sc methylnaltrexone was €33,464 per QALY gained. Both patient populations consisted of laxative refractory OIC patients. Difference between the population is the palliative care setting for sc methylnaltrexone compared with the non-malignant patients in our analysis.

Finally, a scenario was analyzed using chronic constipation related costs in patients with persistent constipation from the Dutch health care insurance claims database. In this scenario the ICER increased to €14,761[42]. However, according to the authors of the publication there might be an underestimation of costs as laxatives and treatments for constipation might also have been prescribed as part of the treatment for the underly-

ing disease. In those cases, diagnostic related groups (DRGs) for chronic constipation might not be claimed, leading to an underestimation of the actual chronic constipation related direct medical costs. Also GP-related care (primary care) was not included in the costs. According to the Delphi panel a substantial proportion of costs of additional OIC management OIC complications originated from GP-care (primary care).

In current guidelines a laxative regime is advised for the prevention and treatment of OIC[19,41]. Despite the use of this laxative regime, a group of patients will suffer from laxative-refractory OIC[19,41]. Recently, for these patients besides PR OXN, subcutaneous (sc) methylnaltrexone and naloxegol have also become available in the Netherlands for non-malignant pain patients. These options have not been taken into account in this model. However, medication costs of PR OXN are the lowest with current list-prices of these medications; sc methylnaltrexone approximately €178,- per week (assuming 4 flacons with 0.6 ml 20 mg/ml methylnaltrexone per week), naloxegol approximately €36,75 per week (assuming 1 tablet of 25 mg per day) and PR OXN approximately €16,13 per week (assuming 14 tablets of 10 mg per week) and assuming a comparable clinical benefit of PR OXN, sc methylnaltrexone and naloxegol on OIC, (source: www.medicijnkosten.nl; last accessed: april 29th 2018). However, until now there are no data available that compare the clinical benefit between the different peripherally acting mu-opioid receptor antagonists (PAMORA's) and the comparability found in systematic reviews still needs to be confirmed. Moreover, also side effects and ease of administration should be taken into account in establishing the clinical benefit from a societal perspective.

No utility values were available in the pooled analysis for this specific sub-population of patients, since there were a limited number of non-constipated patients in the trial[21] There is no doubt that constipation contributes to the QoL in chronic pain patients[1,2]. In this economic evaluation the utility level corresponding to the health states "constipated" and "non-constipated" in a Dutch population treated with opioids for pain caused by a non-advanced disease was taken from the article by Penning-van Beest et al. (2010)[2]. These utilities were also used in the economic evaluation of sc methylnaltrexone[45]. Moreover, several observational studies in the real-world treatment setting support improvements in quality of life for patients with chronic pain receiving PR OXN[43,46-49].

Limitations

The main limitations of the analysis are pertaining to: (1) the economic data inputs, which were obtained from a Delphi panel of 12 Dutch GPs so that the outcomes are based on the perceptions of primary care physicians. As indicated in Dunlop et al. 2012, other groups of healthcare professionals, like nurses and secondary care specialists treating constipation, may report different resource use and costs[1]. To address this problem also a scenario analysis was performed and discussed using the costs in secondary care from the Dutch Health Insurance Claims Database as described by Dik et al. 2014[44].;

(2) Model and cost inputs were from 2015. Since 2015 drug prices might have changed as also generic macrogol plus electrolytes has entered the market. Moreover, also costs of PR OXN have dropped whereas costs for PR OXY have not dropped further. However, costs for additional OIC treatments and costs of treating OIC complications had a far greater impact on the cost-difference than laxative costs. Besides generic entry also other PAMORA's like sc methylnaltrexone, oral naloxegol and naldemedine will and/or have become available to patients with laxative-refractory OIC which could impact the model. As described above PR OXN seems to be a cheaper treatment option than sc methylnaltrexone and naloxegol for patients using oxycodone, but the impact of all PAMORA's on cost-utility of OIC treatments from a societal perspective remains to be elucidated; (3) a possible lack of power of the Penning-van Beest study[2] providing the utility scores and disutility. Although the difference in utility level between OIC and non-OIC patients was significant in the non-advanced disease population ($p<0.01$) the confidence intervals around the utility scores were wide. This is reflected by the univariate sensitivity analysis which showed the sensitivity of the model to the utility level of non-OIC patients; (4) the rate of OIC was based on trial data until week 12 and extrapolated based on extension trial data until week 52. A potential area for future research is to develop parametric survival curves to more accurately estimate the treatment benefits beyond 12 weeks; (5) constipation status was based on relatively low patient numbers in the analysis. However, real-life observational studies in larger patient populations suggest similar response rates[43,49]. (6) finally, the health states were based on constipation, the most common side-effect of opioid treatment. However, PR OXN may counteract other aspects of opioid-induced bowel disorders (such as abdominal pain, cramping and bloating) that may require additional healthcare resources. It is therefore possible that a model examining these aspects on top of OIC may show a greater incremental QALY gain from PR OXN compared with OXY[1].

Appropriateness comparator

In order to have an appropriate comparison the model should reflect treatment in real-life practice. In this model PR OXN was compared to its opioid component PR OXY, as the addition of naloxone does not affect pain relief of oxycodone nor the safety-profile (with the exception of constipation). Furthermore oxycodone is the most prescribed oral strong opioid in the Netherlands[50]. In current guidelines a laxative regime is advised for the prevention and treatment of OIC[19,41]. Therefore patients in the PR OXY-arm received laxative therapy on top of their opioid treatment and for patients with PR OXN as needed bisacodyl was used in the model, as was the case in the clinical trials. Other peripherally acting mu-opioid receptor antagonists like sc methylnaltrexone and naloxegol, were not used as a comparator since at time of model preparation they were not licensed in the Netherlands for the treatment of OIC in non-malignant pain patients.

CONCLUSIONS

The present pharmaco-economic study is based on available evidence in non-malignant pain patients treated with opioids and suffering from laxative-refractory OIC, using pivotal trial data. It demonstrated cost-effectiveness of PR OXN for opioid-treated patients with non-malignant pain suffering from laxative-refractory OIC with an ICER of € 6,924 per QALY gained. Several sensitivity and scenario analyses show the robustness of the model. The overall conclusion is that PR OXN has a probability of being cost-effective compared to PR OXY of 96% and 100% at WTP thresholds of respectively € 20,000 to €50,000 per QALY.

TRANSPARENCY

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Declaration of financial/other relationships

M. Dirckx and F.J.P.M. Huygen have nothing to disclose.

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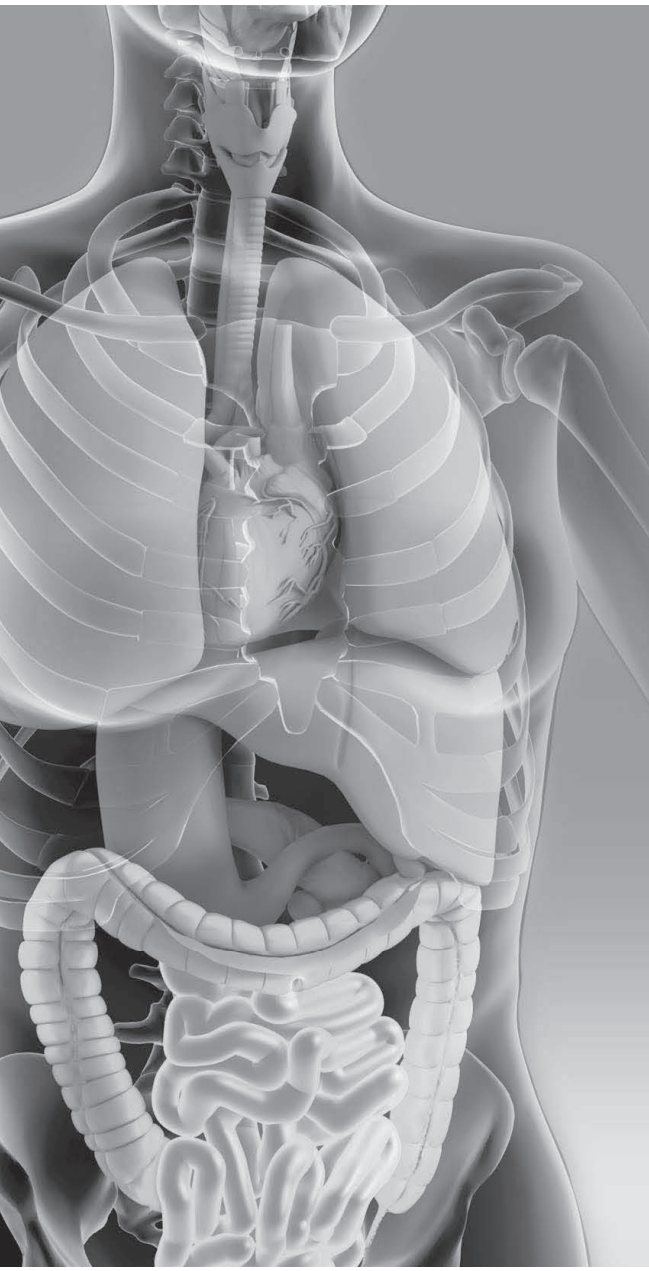

Chapter 8

General Discussion

GENERAL DISCUSSION

Binding of opioids to μ-receptors within the gastrointestinal (GI) tract can lead to impairment of motility and secretion and induce a variety of symptoms, including nausea, gastro-paresis, secondary pseudo-obstruction and constipation[1]. This complex of impairment and symptoms is called Opioid Induced Bowel Dysfunction (OIBD)[1-3]. Opioid Induced Constipation (OIC) is the most common symptom of OIBD[2-7] and in contrast to other side effects of opioid treatment patients do not develop a tolerance to constipation[2-7]. OIC develops predominantly as a result of activation of enteric μ-opioid receptors which are distributed throughout the GI tract[1,2]. They mediate a number of effects that influence the function of the GI-tract when activated by opioids[1,2].

In current practice the advice for treatment and prevention of OIC is to treat patients on opioid analgesics prophylactically with a laxative regime in addition to lifestyle modifications, such as increased exercise, greater fluid intake, and dietary changes[1,2]. In Dutch clinical practice a prophylactic laxative regime is advised consisting of treatment with at least one laxative in an adequate dosage (e.g. macrogol plus electrolytes or lactulose) and if needed addition of a second laxative of a different therapeutic class (e.g. bisacodyl)[8,9]. A regime that is comparable with the Belgian laxative regime (source: www.bcfi.be). Despite this laxative regimen, literature describes that some patients still experience OIC and/or do not tolerate the adverse events of the laxative regime; i.e. patients with laxative-refractory OIC[10,11]. Furthermore, literature describes that laxatives are ineffective to treat OIC[1,2]. Moreover, treatment with laxatives causes side effects and complications[3,12].

Over the years opioid receptor antagonists like methylnaltrexone, naloxegol and naloxone are increasingly being used for the pathophysiological treatment of OIC[13-15]. Peripherally-acting opioid receptor antagonists (PAMORA's) and prolonged release oxycodone/naloxone (PR OXN) block opioid actions at peripheral opioid receptors that mediate decreased intestinal secretion and propulsive colonic motility[1,2]. By blocking μ-opioid receptors in the gut, there is restoration of the function of the enteric nervous system, and propulsive motility and secretory functions can be generated by local enteric neural circuits in response to physiologic stimuli such as meal ingestion, or sensation of a bolus to evoke normal peristalsis[1,2].

In the work presented in this thesis the efficacy of treatments for OIC were studies. In a pilot study the efficacy of a Dutch laxative regime was studied. The efficacy of PAMORA's and PR OXN were analyzed in a systematic review and meta-analysis. And the treatment of OIC with PR OXN has been examined in real-life with a focus on the laxative refractory population, to gain more insight in the efficacy of PR OXN in patients with laxative-refractory OIC in daily practice.

Although literature on treatment of OIC at time of Dutch guideline development was sparse and non-conclusive, based on expert opinion was assumed that the Dutch laxative regime would be a suitable regime to prevent and treat OIC. To gain more insight in the efficacy of a Dutch laxative regimen in daily clinical practice as well as to obtain insights for future randomized controlled trials, the laxative regime has been examined in a pilot study. Our pilot study indicated that this laxative regime, might not be effective and feasible for the prevention and treatment of OIC. Moreover, the results show that a larger clinical study is warranted investigating the efficacy and tolerability of the laxative regime for the prevention and treatment of OIC.

A particular challenge for the study is patient recruitment. In our pilot study it already became apparent that the majority of physicians expected that an "as needed" laxative regime would be more appropriate for the treatment and prevention of OIC. This is also reflected by a project started by de Graeff et al.. In this project the aim was to assess the efficacy of two laxatives (polyethylene glycol (PEG) with electrolytes versus magnesium(hydr)oxide) on the prevention of OIC. This project was terminated early due to insufficient patient recruitment (5 patients in 1.5 years) (source: http://www.zonmw.nl/nl/projecten/project-detail/preventie-van-obstipatie-bij-gebruik-van-opioiden-magnesiumhydroxide-versus-macrogolelektrolyte/voortgang/).

Given the unique etiology of OIC and the effects of opioids on neural activity, motility and secretion throughout the entire gastrointestinal tract[1,2], it is unsurprising that laxatives frequently fail to counteract the symptoms of OIC[11,13,16]. Instead, treatment of OIC should target the etiology of this condition via a μ-opioid receptor mediated approach such as that of the PAMORA's and naloxone (a non-selective opioid antagonist), rather than just focus on symptomatic management[2,14].

To gain insight on the efficacy on OIC between the PAMORA's and PR OXN a systematic review and meta-analysis was performed. A systematic review and consensus article by Gaertner et al.[17] has suggested that when measuring OIC a combination of outcomes should be measured. Therefore the measures evaluated consisted of objective outcome measures, patient reported outcome measures and patient-reported global burden measures of OIC. Despite significant heterogeneity between studies all identified randomized controlled trials showed that the efficacy of opioid antagonist treatment was superior to control treatment with respect to the proportion of patients achieving normal bowel function, the proportion of patients needing additional laxatives as well as the PAC-SYM total score. The Number Needed to Treat (NNT) to obtain normal bowel function was ~5 (~3.5-7; the reciproke of the anticipated absolute risk difference with opioid antagonist treatments), which is comparable to the meta-analysis by Nee et al.[18]. Also variables that were not studied for all agents, like (change in) Bowel Function Index (BFI) and (change in) number of bowel movements, showed that opioid antagonist treatments were superior to control treatment.

With respect to pain relief the RCTs showed that treatment with opioid antagonists did not significantly interfere with pain relief. The quality of the evidence using the GRADE-systematic was rated low for alvimopan, moderate for PR OXN, MNTX and naldemedine and high for naloxegol.

An interesting population with respect to OIC is the laxative refractory population. Therefore we also included analyses for the subgroup of laxative refractory patients. Five RCTs (KODIAC-4, KODIAC-5, OXN2001, OXN3001 and OXN3006) were identified that reported on bowel function efficacy in laxative refractory patients or laxative inadequate responders. For naloxegol the NNT was ~6.7. For PR OXN the change in BFI was less pronounced compared with the total population (MD -8.93 95%CI -16.26 to -1.59; n=75). Within the naloxegol and OXN studies no heterogeneity was detected. However, a difference between both studies was the definition with respect to laxative refractory patients and laxative inadequate responder patients. For PR OXN a patient was considered laxative refractory if the patients still experienced OIC (defined as a BFI>28.8) despite the use of at least 2 laxatives from a different therapeutic class (e.g. macrogol and bisacodyl). For naloxegol a patient was considered a laxative inadequate responder when the patient took medication from one or more laxative classes for a minimum of 4 days within 2 weeks before screening and still experienced moderate, severe, or very severe symptoms in at least one of four stool-symptom domains of a laxative-response questionnaire. There are some limitations to our analyses. Firstly, there is heterogeneity in the analyses of the bowel function outcomes, this heterogeneity might be caused by differences in the trial populations. Detected differences identified were differences with respect to OIC at baseline due to differences in definitions for OIC as well as differences is the underlying pain conditions (e.g. malignant pain and non-malignant pain).

To reduce heterogeneity due to trial populations when studying OIC and the efficacy/effect with respect to OIC, Poulsen et al.[19] have developed a model for OIC in healthy volunteers, in which these population differences can be ruled out. It will be interesting to see whether healthy volunteers can be identified that develop laxative-refractory OIC. For this it might be interesting whether predictive factors can be identified that can be used to select high-risk populations for laxative-refractory OIC. There has been one publication that discussed the elucidation of predictive markers for OIC[20]. Unfortunately, Rosti et al. did not elucidate predictive markers for identification of laxative-refractory OIC. Another interesting approach would be head-to-head comparisons of opioid antagonists in patients with laxative-refractory OIC.

Based on clinical trials of PR OXN and the mechanism of action of PR OXN expectations were that PR OXN is a suitable option for the treatment of OIC in patients refractory to at least 2 different laxatives (ATC level 4 class) with a different mode of action. A post-hoc analysis was performed exploring the efficacy of PR OXN in this patient population. At screening, when patients were receiving opioid analgesia of any type and at least two

different types of laxatives, patients had a reduced bowel function (BFI>28.8). During treatment with PR OXN, statistically significant and clinically relevant improvements in bowel function were observed in both groups of patients at the end of double-blind treatment with OXN. The positive effect of OXN PR on bowel function is further emphasized by the finding that the proportion of patients who had a normal bowel function increased by over four-fold from screening with a decrease in laxative use. This post-hoc analysis suggested that the effects seen in the randomized controlled clinical trial program are also valid for patients with persisting OIC despite the use of at least two different types of laxatives, and provides further confirmation that naloxone addresses OIC from a pathophysiological point of view rather than merely a symptomatic standpoint.

However, with current guidelines it is likely that patient switched to PR OXN already have been extensively treated with laxatives for a prolonged period. Moreover, patients included in the clinical trials might not represent the patient population in real-life. Therefore, an observational study was performed that followed laxative-refractory patients that were switched to PR OXN in Belgium. The laxative regime in the Benelux is very similar and laxatives prescribed in Belgium are similar to the laxatives prescribed in the Netherlands (source: www.bcfi.be and www.farmacotherapeutischkompas.nl). In Belgium, patients were eligible for reimbursement of PR OXN if they met the following conditions: (1) all patients had to be aged≥18 years, with a documented history of severe pain requiring around-the-clock opioid therapy, treated with prolonged release oxycodone (PR OXY for at least 30 days with insufficient pain relief and/or unacceptable adverse effects; and (2) all patients had to be experiencing OIC (Bowel Function Index [BFI]>28.8) despite the use of at least 2 laxatives with different mechanisms of action (level 4 ATC term) during the previous PR OXY treatment. The study found that PR OXN was superior to PR OXY in terms of pain relief, OIC, and quality of life in patients with chronic pain previously treated with PR OXY and experiencing OIC despite the use of at least 2 different laxatives. This study confirmed that after 4 weeks of treatment with PR OXN, a clinically relevant improvement in OIC was attained in patients experiencing laxative-refractory OIC. The average BFI was ≤28.8 after 6 weeks of PR OXN treatment, indicating that most patients were no longer constipated despite the opioid treatment. Also the number of patients needing additional laxatives declined significantly during the study and the majority of patients using laxatives indicated that the laxative use had decreased. These results support the rationale that PR OXN treatment counteracts OIC through mechanisms other than those of laxatives and that PR OXN addresses the underlying mechanism of OIC. However, an observational study has limitations, one of them being that we could not ensure that all data were documented. This limitation was addressed by marking important parameters (e.g., BFI, pain relief, laxative use yes/no, rescue medication yes/no) as mandatory fields in the electronic case record form; as a result, few data were missing for these fields.

As the reimbursement guidelines for laxative-refractory OIC were very strict, also an observational study was performed in which patients were followed after switching from WHO-step 1, WHO-step 2 or WHO-step 3 medication to PR OXN treatment. Patients had been switched to PR OXN because of insufficient pain relief and/or unacceptable side effects on their previous medication and the presence of OIC was not an inclusion parameter. The present study showed that the majority of patients in the total population and in all WHO-step groups experienced symptoms of constipation as defined by a BFI≥28.8. It was shown that significantly more patients with symptoms of constipation at study entry were older and of female gender, both factors that are known to be associated with constipation and patients with pain are less mobile which could also have contributed to constipation. Moreover, it is possible that there is a bias in the percentage of constipated patients in this observation as in Belgium PR OXN was marketed especially for patients with a BFI above 30. Already after 2 weeks of PR OXN treatment a clinically relevant improvement of bowel function (defined by a reduction in BFI of 12 points or more) was observed in the overall population and in the WHO-step 2 and WHO-step 3 groups. Mean BFI dropped below 28.8 after 6 weeks of PR OXN treatment for the overall population and the WHO-step 1 and WHO-step 2 groups. In the WHO-step 3 group mean BFI reached 28.8 after 11 weeks of PR OXN treatment. The reduction in BFI is in line with reduction of BFI reported in previous observational studies with PR OXN for patients with neuropathic pain28, constipated patients with non-malignant pain29 and patients with severe pain30. When looking more closely at constipated patients at study entry (irrespective of previous analgesic treatment), it was shown that treatment with PR OXN led to a clinically relevant improved bowel function already in the first two weeks of PR OXN treatment and the improvement was maintained over time. After 17 weeks, BFI was close to the threshold of 28.8 showing that bowel function was almost restored to normal values despite the treatment with the opioid PR OXN. Interestingly, for patients not constipated at study entry the BFI remained below 28.8 even during PR OXN treatment up to 17 weeks. This indicates that treating pain adequately with strong opioids in non-constipated patients normal bowel function is maintained despite the initiation of the opioid PR OXN, even in patients stepping-up from non-opioid treatment. This study adds to the evidence found in previous studies with PR OXN which have also shown that switching non-constipated patients to PR OXN maintained their bowel function in a more controlled study setting (one clinical trial and one prospective open-label study with a blinded endpoint)[21-23].

To evaluate whether PR OXN is a cost-effective option for the treatment of patients with laxative-refractory OIC a cost-utility analysis was performed. This analysis demonstrated cost-effectiveness of PR OXN for opioid-treated patients with non-malignant pain suffering from laxative-refractory OIC with an incremental cost-effectiveness ratio (ICER) of € 6,924 per quality adjusted life year (QALY)gained. The model did not

include other peripheral opioid antagonists as comparator. However, medication costs of PR OXN are the lowest with current list-prices of these medications; subcutaneous (sc) methylnaltrexone approximately €178,- per week (assuming 4 flacons with 0.6 ml 20mg/ml per week), naloxegol approximately €36,75 per week (assuming 1 tablet of 25 mg per day) and PR OXN approximately €16,13 per week (assuming 14 tablets of 10 mg per week) and assuming a comparable clinical benefit of PR OXN, sc methylnaltrexone and naloxegol on OIC, (source: www.medicijnkosten.nl; last accessed: April 29th 2018). However, until now there are no data available that compare the clinical benefit between the different peripherally acting μ-opioid receptor antagonists (PAMORA's) and the comparability found in the systematic reviews still needs to be confirmed. Moreover, also side effects and ease of administration should be taken into account in establishing the clinical benefit from a societal perspective.

Over the years a lot of evidence has been generated that unravels that effect and efficacy of PR OXN treatment. In this thesis also the efficacy of PR OXN treatment in laxative-refractory patients has been evaluated. Unfortunately, as of today PR OXN is still not reimbursed in the Netherlands, caused by uncertainty of the effect due to low patient numbers suffering from laxative-refractory OIC within the clinical studies and in the observational studies, as well as the bias introduced by the study designs in this specific population and uncertainty on the appropriateness of the comparator.

In order to know when sufficient patient numbers have been studied the prevalence of laxative-refractory OIC needs to be elucidated in daily practice. However, in literature already two definitions are being used for the term laxative-refractory. One definition is derived from laxative inadequate responder (defined as a patient that took medication from one or more laxative classes for a minimum of 4 days within 2 weeks before screening and still experienced moderate, severe, or very severe symptoms in at least one of four stool-symptom domains of a laxative-response questionnaire).The other was derived from treatment guidance for OIC (a patient is laxative-refractory if the patient still experienced OIC (defined as a BFI>28.8) despite the use of at least 2 laxatives from a different therapeutic class (e.g. macrogol and bisacodyl)). This would most likely result in differences in prevalence. Prevalence could also be estimated from insurance data, but as laxatives are commonly used for other conditions and a number of laxatives are available as over the counter medications this is not very promising. Looking at the number of users of a peripheral opioid antagonist in the Drug Information System of the National Health Care Institute probably underestimates the total number of laxative-refractory patients, as only 436 users were registered using in 2016 (source: www.gipdatbank.nl). Elucidating the prevalence of laxative-refractory OIC in daily practice would be an important first step.

To address study design issues a randomized controlled double-blind trial would be the gold standard. However, this would most probably result in ethical issues as

comparing PR OXN to PR OXY with a standardized laxative regimen (e.g. macrogol plus electrolytes and bisacodyl as needed) as is usual in Dutch practice would be the appropriate comparison. This would result in patients that are refractory to laxatives having to continue the ineffective treatment with the addition of frequent use of enema's and an increased risk of developing haemorrhoids and anal fissures[6]. Another option would be to perform a prospective open-label blinded-endpoint (PROBE) study in patients with laxative-refractory OIC[21,23]. A similar study was already performed to compare the efficacy of PR OXN with PR OXY and PR morphine. Patients could use unblinded laxative-treatment as in daily practice and results showed that under the conditions of the PROBE design, PR OXN was associated with a significantly better tolerability, a lower risk of OIC and a significantly better analgesic efficacy than PR OXY and PR Morphine[21,23].

In the past years the debate on opioid use is increasing, especially when used chronically and for patients with non-malignant pain. Of course stopping opioid use would result in improvement of OIC and this can be seen as an easy option for the treatment of OIC. However, we should be careful that we don't withhold opioid treatment for those patients who do benefit from opioid treatment on specific indication, like severe pain during short-lived painful events and at the end of life. Opioid treatment should also be available for carefully selected patients with chronic pain who can be managed in a monitored setting. Within this monitored setting precautions can be taken to avoid misuse and diversion and closely monitor adverse events (https://www.iasp-pain.org/Advocacy/OpioidPositionStatement?navItemNumber=7225).

This monitored opioid prescribing should in our opinion be accompanied by adequate pain education for all health-care professionals in the (chronic) pain patient pathway as well as pain education for patients and their caregivers. Moreover, monitored opioid prescribing is an opportunity to closely monitor OIC, an adverse event that still results in unnecessary hospital admissions (https://www.nivel.nl/sites/default/files/bestanden/Vervolgonderzoek_Medicatieveiligheid_Eindrapport.pdf).

In contrast to guidelines in the Netherlands several European guidance and guidelines have already included opioid antagonists (including PR OXN) in the treatment algorithms of OIC[1,2,14,15,24]. Unfortunately, despite the wealth of available data from RCTs and observational studies, the national healthcare institute did not grant reimbursement for PR OXN in the Netherlands and it is unlikely that PR OXN will be reimbursed in the near future with the current assessment framework for reimbursement.

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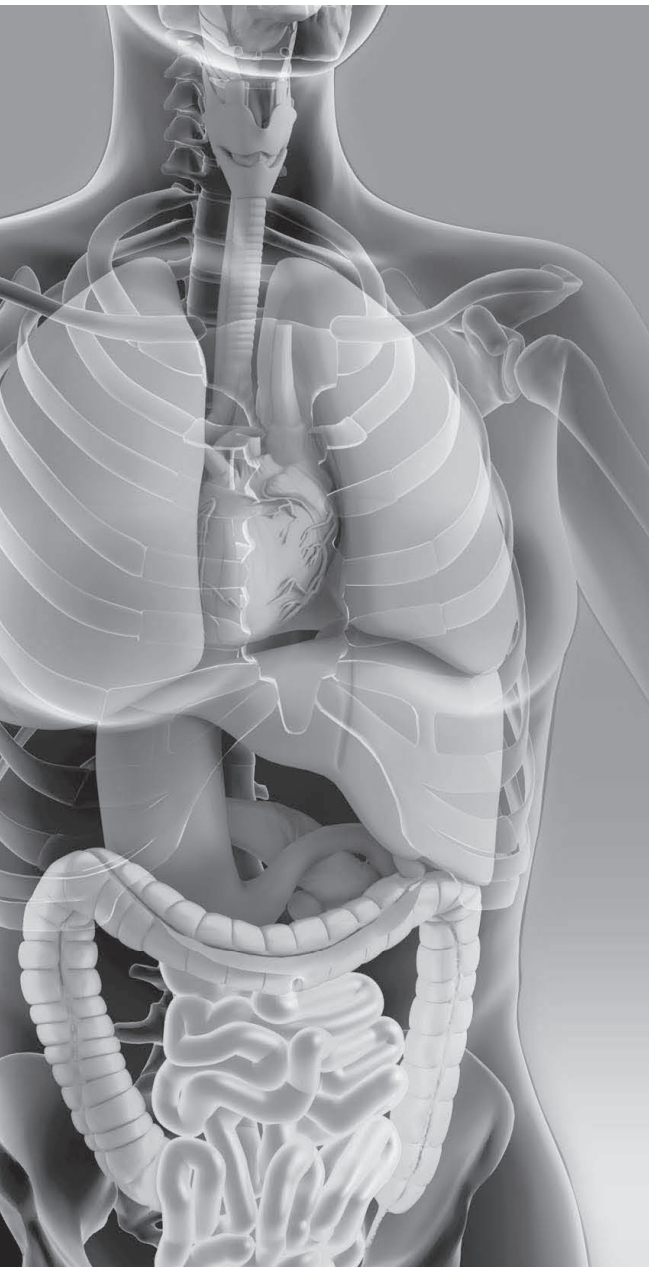


Chapter 9

Summary

Nederlandse samenvatting

SUMMARY

Chapter 1

The introduction describes the rationale for this thesis. Binding of opioids to μ-receptors within the gastrointestinal (GI) tract can lead to impairment of motility and secretion and induce a variety of symptoms, including nausea, gastro-paresis, secondary pseudo-obstruction and constipation. This complex of impairment and symptoms is called Opioid Induced Bowel Dysfunction (OIBD). Opioid Induced Constipation (OIC) is the most common symptom of OIBD. In current practice the advice for treatment and prevention of OIC is to treat patients on opioid analgesics prophylactically with a laxative regime in addition to lifestyle modifications, such as increased exercise, greater fluid intake, and dietary changes. Despite this laxative regimen, literature describes that some patients still experience OIC and/or do not tolerate the adverse events of the laxative regime; i.e. patients with laxative-refractory OIC. Over the years opioid receptor antagonists like methylnaltrexone, naloxegol and naloxone are increasingly being used for the pathophysiological treatment of OIC. The efficacy of laxative treatment and pathophysiological treatment with a prolonged release combination of oxycodone/naloxone (PR OXN) in daily practice is not clear. Therefore, the efficacy of the current Dutch laxative regime in daily practice was explored. Also the efficacy of PR OXN in daily practice was further explored, with a focus on patients with laxative-refractory OIC.

Chapter 2

In the Netherlands patients on opioids are treated prophylactically with laxatives for the prevention of OIC. However, literature on treatment of OIC at time of Dutch guideline development was sparse and non-conclusive, based on expert opinion was assumed that the Dutch laxative regime would be a suitable regime to prevent and treat OIC. This chapter presents the results of an observational pilot study to test the efficacy of the laxative regime for the prevention and treatment of OIC in daily practice. The findings of the study indicate that the laxative regime might not be effective and feasible for the prevention and treatment of OIC and a larger clinical study is warranted investigating the efficacy and tolerability of the laxative regime for the prevention and treatment of OIC.

Chapter 3

Given the unique etiology of OIC and the effects of opioids on neural activity, motility and secretion throughout the entire gastrointestinal tract11, treatment of OIC should target the etiology of this condition via a μ-opioid receptor mediated approach. PAMORA's and naloxone (a non-selective opioid antagonist), are considered to be pathophysiological treatment for OIC. Chapter 3 describes the result on a systematic review and meta-

analysis performed to gain insight on the efficacy on OIC between the PAMORA's and PR OXN. Despite significant heterogeneity between studies all identified randomized controlled trials showed that the efficacy of opioid antagonist treatment was superior to control treatment with respect to the proportion of patients achieving normal bowel function, the proportion of patients needing additional laxatives as well as the PAC-SYM total score. The Number Needed to Treat (NNT) to obtain normal bowel function was ~5 (~3.5-7). An interesting population with respect to opioid induced constipation is the laxative refractory population. Therefore we also included analyses for the subgroup of laxative refractory patients. For naloxegol the NNT was ~6.7. For PR OXN the change in BFI was less pronounced compared with the total population (MD -8.93 95%CI -16.26 to -1.59; n=75). Within the naloxegol and PR OXN studies no heterogeneity was detected. The results indicate that PAMORA's and PR OXN are effective treatments for OIC, even in patients with laxative-refractory OIC. However, further studies are warranted using similar definitions for OIC as well as for laxative-refractory.

Chapter 4

Based on clinical trials of PR OXN and the mechanism of action of PR OXN expectations were that PR OXN is a suitable option for the treatment of OIC in patients refractory to at least 2 different laxatives (ATC level 4 class) with a different mode of action. This chapter described a post-hoc analysis that was performed exploring the efficacy of PR OXN in this patient population. During treatment with PR OXN, statistically significant and clinically relevant improvements in bowel function were observed in patients at the end of double-blind treatment with OXN. The positive effect of PR OXN on bowel function is further emphasized by the finding that the proportion of patients who had a normal bowel function increased by over four-fold from screening with a decrease in laxative use. This post-hoc analysis suggested that the effects seen in the randomized controlled clinical trial program are also valid for patients with persisting OIC despite the use of at least two different types of laxatives, and provides further confirmation that naloxone addresses OIC from a pathophysiological point of view rather than merely a symptomatic standpoint.

Chapter 5

In this chapter the results of an observational study that followed laxative-refractory patients that were switched to PR OXN in Belgium are presented. The aim of the trail was to evaluate the efficacy of PR OXN on bowel function and pain after switching from opioids to PR OXN in patients that met the reimbursement-criteria for PR OXN. The study found that PR OXN was superior to PR OXY in terms of pain relief, OIC, and quality of life in patients with chronic pain previously treated with PR OXY and experiencing OIC despite the use of at least 2 different laxatives. This study confirmed that after 4 weeks of

treatment with PR OXN, a clinically relevant improvement in OIC was attained in patients experiencing laxative-refractory OIC.

Chapter 6

As the reimbursement guidelines for laxative-refractory OIC were very strict, also an observational study was performed in which patients were followed after switching from WHO-step 1, WHO-step 2 or WHO-step 3 medication to PR OXN treatment. Patients had been switched to PR OXN because of insufficient pain relief and/or unacceptable side effects on their previous medication and the presence of OIC was not an inclusion parameter. This chapter describes the results of that study.

Chapter 7

Chapter 7 describes the results of a cost-utility analysis of PR OXN in patients suffering from laxative refractory OIC. This analysis demonstrated cost-effectiveness of PR OXN for opioid-treated patients with non-malignant pain suffering from laxative-refractory OIC with an ICER of € 6,924 per QALY gained.

Chapter 8

In the general discussion, the focus of this dissertation is explicated. The findings of the studies performed are enumerated and commented. In addition, the current state of knowledge and theory concerning opioid induced constipation summarized. It discusses the importance of clear definitions for OIC as well as for laxative-refractory OIC. And it discusses future research possibilities to investigate the efficacy of PR OXN for the treatment of OIC in comparison to the current laxative regime and other opioid antagonists.

NEDERLANDSE SAMENVATTING

Hoofdstuk 1

De introductie beschrijft de achtergrond en aanleiding van deze thesis. De binding van opioïden aan μ-receptoren in het gastro-intestinale (GI, maag-darm) stelsel kan leiden tot gebreken in de motiliteit en secretie en kan een variëteit aan symptomen veroorzaken, waaronder misselijkheid, vertraagde maaglediging, secundaire pseudo-obstructie en obstipatie. Dit complex aan gebreken en symptomen wordt opioïd geïnduceerde darm dysfunctie genoemd (OIBD). Opioïd geïnduceerde obstipatie (OIC) is het meest voorkomende symptoom van OIBD. In de huidige dagelijkse praktijk is het advies voor de behandeling en preventie van OIC, een profylactische behandeling met laxantia voor alle patiënten die opioïden gebruiken in combinatie met leefstijl aanpassingen, zoals beweging, voldoende drinken en aanpassing van het voedingspatroon. Ondanks dit laxans regime, wordt er in de literatuur beschreven dat sommige patiënten nog steeds OIC ontwikkelen en ervaren en/of dat ze de bijwerkingen van het laxansregime niet tolereren; deze patiënten hebben laxans-refractaire OIC. In de afgelopen jaren worden opioïd receptor antagonisten, zoals methylnaltrexon, naloxegol en naloxon, steeds vaker gebruikt vanwege de pathofysiologische werking op OIC. De effectiviteit van laxansbehandeling, alsook de pathofysiologische behandeling met oxycodon/naloxon met verlengde afgifte (PR OXN) in de dagelijkse praktijk is echter nog niet duidelijk. Daarom werd de effectiviteit van het huidige Nederlandse laxansregime onderzocht in de dagelijkse praktijk. Daarnaast werd de effectiviteit van PR OXN in de dagelijkse praktijk verder onderzocht, met speciale aandacht voor patiënten met laxans-refractaire OIC.

Hoofdstuk 2

In Nederland worden patiënten die met opioïden behandeld worden profylactisch behandeld met laxantia om OIC te voorkomen. Echter de literatuur voor de behandeling van OIC was op het moment van de ontwikkeling van de Nederlandse richtlijn spaarzaam en niet eenduidig, gebaseerd op de opinie van de experts werd aangenomen dat het laxans-regime een gepast regime zou zijn voor de preventie en behandeling van OIC. Dit hoofdstuk beschrijft de resultaten van een observationele pilot studie naar de effectiviteit van dit laxansregime voor de preventie en behandeling van OIC in de dagelijkse praktijk. De bevindingen van deze studie tonen dat het huidige laxans-regime mogelijk niet effectief is voor de preventieve en behandeling van OIC. Een grotere klinische studie is noodzakelijk waarin de effectiviteit en verdraagbaarheid van het laxans-regime voor de preventie en behandeling van OIC wordt onderzocht.

Hoofdstuk 3

Gegeven de unieke etiologie van OIC en de effecten van opioïden op neurale activiteit, motiliteit en secretie in het maag-darm stelsel, zou de behandeling van OIC gericht moeten zijn op deze etiologie via een mu-opioïd receptor gemedieerde aanpak. Perifeer werkende mu-opioïd receptor antagonisten (PAMORA's) en naloxon (een niet selectieve opioïd antagonist), worden beschouwd als een pathofysiologische behandeling voor OIC. Hoofdstuk 3 beschrijft de resultaten van een systematisch review en meta-analyse welke werd uitgevoerd om inzicht te krijgen in de effectiviteit voor de behandeling van OIC tussen de PAMORA's en PR OXN. Hoewel er significante heterogeniteit was tussen de studies, toonden alle geïdentificeerde gerandomiseerde gecontroleerd trials (RCTs) dat de effectiviteit van de behandeling met opioïd antagonisten superieur was aan de controle behandeling, met betrekking tot het proportie patiënten dat een normale darmfunctie bereikte, de proportie patiënten die additionele laxantia gebruikten alsook de PAC-SYM totaal score. De Number Needed to Treat (NNT) om een normale darmfunctie te verkrijgen was ~5 (~3.5-7). Een interessante populatie met betrekking tot OIC was de laxans-refractaire populatie, wat leidde tot een subgroep analyse van deze laxans-refractaire patiënten. De NNT van naloxegol was ~6.7 en voor PR OXN was de verandering in BFI minder sterk in vergelijking met de totale populatie (MD -8.93 95%BI -16.26 tot -1.59; n=75). Binnen de studies met naloxegol en PR OXN werd geen heterogeniteit gedetecteerd. De resultaten suggereren dat PAMORA's en PR OXN effectieve behandelingen zijn voor OIC, ook bij patiënten met laxans-refractaire OIC. Echter, verdere studies zijn noodzakelijk waarbij vergelijkbare definities gehanteerd worden voor OIC, alsook voor laxans-refractaire OIC.

Hoofdstuk 4

Gebaseerd op klinische studies van PR OXN en het werkingsmechanisme van PR OXN was de verwachting dat PR OXN een passende optie is voor de behandeling van OIC bij patiënten met laxans-refractaire OIC (waarbij de patiënten refractair zijn aan ten minste 2 verschillende laxantia (ATC-klasse niveau 4) met een verschillend werkingsmechanisme. Dit hoofdstuk beschrijft een post-hoc analyse die werd uitgevoerd om de effectiviteit van PR OXN in deze patiëntenpopulatie te onderzoeken. Gedurende de behandeling met PR OXN, werden statistisch significante en klinisch relevante verbeteringen van de darmfunctie aangetoond aan het eind van de dubbelblinde behandeling met PR OXN. Het positieve effect van PR OXN op de darmfunctie werd verder ondersteund door de waarneming dat de proportie patiënten met een normale darmfunctie in viervoud toenam ten opzichte van de screening, terwijl het laxans-gebruik verminderde. Deze post-hoc analyse suggereert dat de effecten welke gezien werden in het klinische studieprogramma ook gelden voor patiënten met OIC die persisteert ondanks het gebruik

van ten minste 2 verschillende typen laxantia. Het bevestigt het standpunt dat naloxon een pathofysiologische behandeling is van OIC.

Hoofdstuk 5

In dit hoofdstuk worden de resultaten beschreven van een observationele studie in België welke patiënten met laxans-refractaire OIC volgde die gestart waren met PR OXN. De doelstelling van de studie was om de effectiviteit van de behandeling met PR OXN op de darmfunctie en de pijnstilling te analyseren na het overstappen van oxycodon naar PR OXN. Alle patiënten voldeden aan de vergoedingscriteria voor PR OXN. De studie toonde dat PR OXN superior was aan oxycodon m.b.t. pijnstilling, OIC en kwaliteit van leven bij patiënten met chronische pijn welke behandeld werd met oxycodon en laxans-refractaire OIC ervaarden. De studie bevestigde dat na 4 weken behandeling met PR OXN een klinisch relevante verbetering van de darmfunctie werd behaald bij patiënten met laxans-refractaire OIC.

Hoofdstuk 6

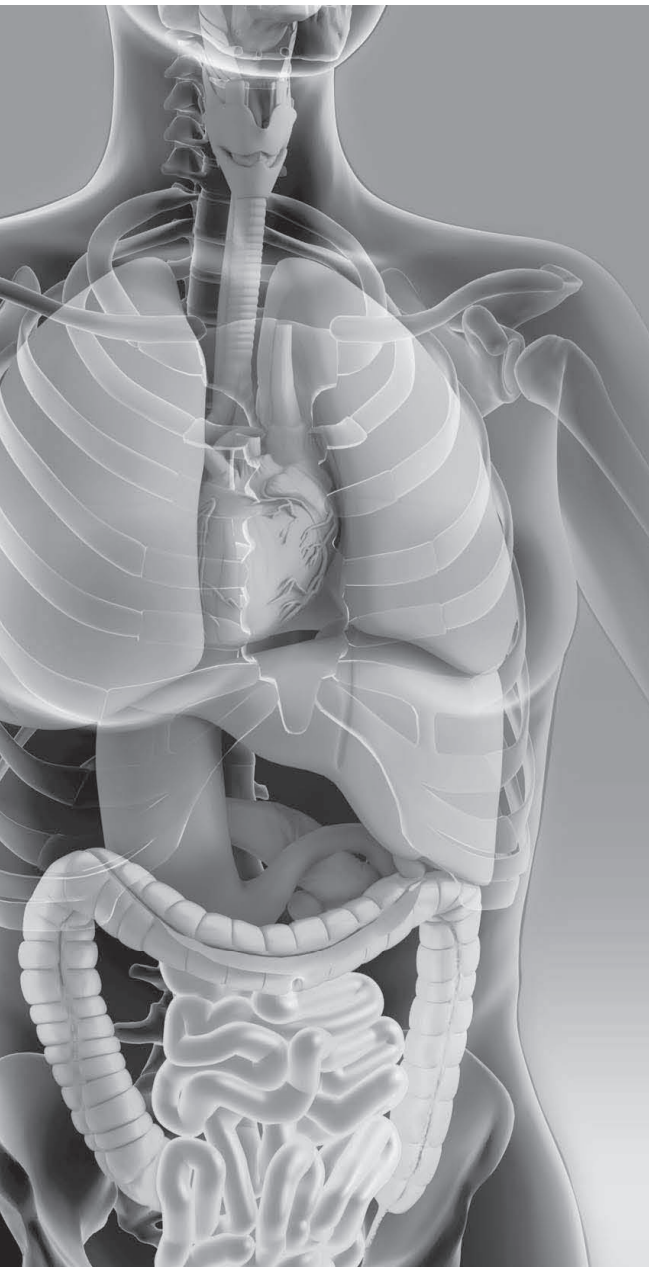
Omdat de vergoedingsrichtlijnen voor laxans-refractaire OIC zeer strikt waren, werd ook een observationele studie uitgevoerd, waarin patiënten gevolgd werden die gestart waren met PR OXN na behandeling met WHO-stap 1, WHO-stap 2 of WHO-stap 3 medicatie. De patiënten startten met PR OXN vanwege onvoldoende pijnstilling en/of onacceptabele bijwerkingen op de voorgaande medicatie, OIC was geen onderdeel van de inclusie-parameters. Dit hoofdstuk beschrijft de resultaten van die studie.

Hoofdstuk 7

Omdat kosten in het huidige gezondheidszorgstelsel van belang zijn werd ook een kosten-utiliteit analyse uitgevoerd. Hoofdstuk 7 beschrijft de resultaten van de kosten-utiliteit analyse van PR OXN bij patiënten met laxans-refractaire OIC. De analyse toonde dat PR OXN kosteneffectief is bij patiënten met niet-maligne pijn en laxans-refractaire OIC met een incrementele kosteneffectiviteit ratio (ICER) € 6,924 per gewonnen levensjaar in goede kwaliteit (quality adjusted life years (QALY)).

Hoofdstuk 8

In de discussie wordt de focus van dit proefschrift besproken. De bevindingen van de uitgevoerde studies worden besproken en bediscussieerd. Verder wordt de huidige kennis en theorie over OIC samengevat. Het bediscussieert het belang van duidelijke definities voor OIC en laxans-refractaire OIC. Daarnaast worden toekomstige mogelijkheden besproken voor vergelijkend onderzoek naar PR OXN in de behandeling van OIC vergeleken met het huidige laxans regime en andere opioïd antagonisten.



Appendices

DANKWOORD

Eindelijk is mijn proefschrift klaar en is de finish in zicht. Ik wil een aantal mensen bedanken, die het mogelijk hebben gemaakt om naast mijn dagelijkse werkzaamheden voor Mundipharma Pharmaceuticals B.V. een promotie-traject te kunnen volgen bij het Centrum voor Pijngeneeskunde aan het Erasmus MC te Rotterdam.

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Mijn copromotor, Dr. M. Dirckx. Beste Maaike, op de één of andere manier wist je altijd precies op het juiste moment te vragen hoe het ervoor stond. Ook jouw praktische tips hebben mij geholpen om de laatste periode zo soepel mogelijk door te komen. Dank voor de begeleiding die je me de afgelopen jaren hebt geboden.

Mijn dagelijks leidinggevende, Dr. Y.J.B. van Megen, MBA. Beste Yvonne. Als dagelijks leidinggevende was je meteen enthousiast over mijn voorstel. Tegelijkertijd gaf je ook aan dat ik er dan wel voor moest gaan en dat ik er niet te makkelijk over moest denken zo naast mijn werk (even een "reality-check" voor mij). Jouw kennis, oplossingsgerichtheid, optimisme en enthousiasme hebben zeker bijgedragen aan het resultaat. Ik wil je bedanken voor je vertrouwen in mij en hoop dat we nog vele jaren mogen samenwerken.

Mw. A. van Toor. Beste Anita, dank je wel voor jouw secretariële ondersteuning.

Mijn paranimfen Simone van der Meer en Mariëlle Koopmans. Wat ben ik blij dat jullie mijn paranimfen willen zijn. Simone: Hoewel we al een paar jaar geen kamer meer delen vond ik het fijn dat ik af en toe mijn frustraties bij je kwijt kon onder het genot van een kopje koffie of thee. Mariëlle: Niet iedereen kan zeggen dat je schoonzus ceremoniemeester was op je bruiloft en nu ook paranimf bij de promotie, ik ben blij dat je me opnieuw bij wilt staan.

Mijn collega's en oud-collega's van de Medische Afdeling, in het bijzonder Joanne en Corinne bedankt voor alle plezier en gezelligheid.

Natuurlijk wil ik ook alle patiënten en artsen die hebben geholpen om de data te verzamelen heel erg bedanken. Zonder jullie geen onderzoek en zonder onderzoek geen proefschrift.

Tot slot wil ik mijn man en kinderen bedanken, Lieve André, het proefschrift is eindelijk klaar. Bedankt voor al je geduld, steun en hulp thuis zodat ik weer een paar uurtjes kon schrijven. Marit, Niels en Lieke, het boekje is eindelijk klaar. Na deze drukke jaren, waarin jullie mij veel thuis achter de laptop hebben zien zitten, gaan we vast meer tijd krijgen voor nog meer leuke dingen.

LIST OF PUBLICATIONS

- **Koopmans-Klein G.,** Van Op den Bosch J., van Megen Y., Prenen H., Huygen F., Mancini I. Prolonged release oxycodone and naloxone treatment counteracts opioid-induced constipation in patients with severe pain compared to previous analgesic treatment.
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- **Koopmans-Klein G**, Wagemans MF, Wartenberg HC, Van Megen YJ, Huygen FJ.
  The efficacy of standard laxative use for the prevention and treatment of opioid induced constipation during oxycodone use: a small Dutch observational pilot study.
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CURRICULUM VITAE

Gineke Koopmans-Klein werd op 13 november 1976 geboren in Hoogeveen. In 1995 behaalde zij haar VWO diploma aan het Menso Alting College te Hoogeveen. Van 1995 tot 1999 studeerde zij Biomedische Chemie aan de Hogere Laboratorium Opleiding van de Hogeschool Drenthe te Emmen. Haar stage en afstudeeronderzoek voerde zij uit bij de divisie Vaat- en bindweefselonderzoek van TNO Preventie en Gezondheid te Leiden. Na het behalen van haar diploma studeerde zij Biochemie aan de Rijksuniversiteit Groningen te Groningen. Na het behalen van haar doctoraalbul in 2001 ging zij onderzoek doen bij de afdeling Kinderoncologie van het Universitair Medisch Centrum Groningen te Groningen. In 2006 verruilde ze het onderzoek voor een baan in de farmaceutische industrie bij Mundipharma Pharmaceuticals B.V., waar ze op dit moment werkzaam is als Medical Manager. In 2015 is zij gestart met haar promotie-traject bij het Erasmus MC, waarvan de resultaten beschreven zijn in dit proefschrift, onder begeleiding van Prof. Dr. F.J.P.M. Huygen en Dr. M. Dirckx. Dr. Y.J.B. van Megen, MBA was verantwoordelijk voor de dagelijkse begeleiding bij Mundipharma Pharmaceuticals B.V.

PHD PORTFOLIO

Summary of PhD training and teaching activities

Name PhD student: G. Koopmans-Klein	PhD period:2015-2018
Erasmus MC Department: Anesthesiology - Center for Pain Medicine	Promotor(s):Prof. Dr. F.J. P. M. Huygen
Research School:	Supervisor: Dr. Y.J.B. van Megen, MBA

1. PhD training

	Year	Workload (ECTS)
General academic skills		
- Research Integrity (GCP and monitoring and refreshments, Profess Academy, similar to BROK, inclusive of updates)	2010, 2013, 2014 and 2016	1.5
Research skills		
- Statistics (in-house training by dr P. Koopmans, Signidat BV)	2018	8 hours/0.3
- Systematic Literature Retrieval (in PubMed, Medische Bibliotheek Erasmus MC)	2015	4 hours/0.15
- Systematic Literature Retrieval (in other databases, Medische Bibliotheek Erasmus MC)	2015	4 hours/0.15
In-depth courses (e.g. Research school, Medical Training)		
- Curriculum Medical Affairs (Smelt BV):	2010	8 hours/0.3
- Het vergoedingsdossier en de financiering van geneesmiddelen	2011	8 hours/0.3
- Clinical Development	2012	8 hours/0.3
- Clinical Trial Regulations: Klinische studies na Registratie als gevolg van voorwaardelijke toelating	2015	10 hours/0.4
- Masterclass Transferability HTA Resultaten (iMTA)	2015	16 hours/0.6
- Medical Technology Assessment (DutchCC)	2018	12 hours/0.45
- Value Based Health Care, the basics (The Decision Group)		
- Materclass Patient Support Programs (Smelt BV)	2018	8 hours/0.3
- VBHC green belt traject:		
- Lean and other VBHC tools	2018	8.5 hours
- Your role in implementation	2018	8.5 hours
- VBHC Core Concepts	2019	8.5 hours
- VBHC implementation challenges	2019	8.5 hours
Presentations (0.5/presentation)		
- Refereeravond Pijngeneeskunde	2015	
- Internal conference Mundipharma International	2016	
- Wetenschapsdag Anesthesiologie	2017	
International conferences and symposia (0.3/dag)		
- 8th Congress of The European Pain Federation EFIC® , "Pain in Europe VIII" in Florence, Italy, October 9-12, 2013 (poster presentation	2013	1
- 7th World congress of the World Institute of Pain, Maastricht (poster presentation)	2014	1
- 9th Congress of the European Pain Federation, EFIC®, "Pain in Europe IX" in Vienna, Austria, September 2-5, 2015	2015	1
- ERS International Congress, London, September 3-7, 2016	2016	1
- ERS International Congress, Milan, September 9-13, 2017	2017	1
- IRW conference, March 15-16, Groningen	2018	1

Seminars and workshops		
- GRADE-cursus Vereniging Innovatieve Geneesmiddelen	2015	4 hours/0.15
- GRADE workshop Academisch Medisch Centrum (moderators: Miranda Langendam and Annefloor van Ernst)	2015	8 hours/0.3
- Three 4-hour workshops about therapy adherence inhalation medication (LAN)	2017/2018	12 hours/ 0.25
- Pain Franchise Training Meeting on low-dose methoxyflurane	2016	16 hours/0.6
2. Teaching activities		
	Year	**Workload (Hours/ECTS)**
Lecturing		
- Several medical lectures and training according to farmeduca guidance of national Mundipharma Pharmaceutical B.V. employees (e.g. national sales manager, product managers, receptionists and accountmanagers) on: pain, pain management and opioids	2015-2016	32 hours/1
- the respiratory system, asthma, asthma management, inhalation corticosteroids and long acting β2- agonists.	2016-ongoing	56 hours/2

ECTS (European Credit Transfer and Accumulation System) are training credits ('studiepunten'). One ECTS stands for around 28 working hours (including preparation, self study, examinations etc.).