



**HAL**  
open science

## Bowel function during pain therapy with oxycodone/naloxone prolonged-release tablets in patients with advanced cancer

Katri Elina Clemens, Ines Quednau, Eberhard Klaschik

► **To cite this version:**

Katri Elina Clemens, Ines Quednau, Eberhard Klaschik. Bowel function during pain therapy with oxycodone/naloxone prolonged-release tablets in patients with advanced cancer. *International Journal of Clinical Practice*, 2011, 65 (4), pp.472. 10.1111/j.1742-1241.2011.02634.x . hal-00623800

**HAL Id: hal-00623800**

**<https://hal.science/hal-00623800>**

Submitted on 15 Sep 2011

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

**Bowel function during pain therapy with  
 oxycodone/naloxone prolonged-release tablets in patients  
 with advanced cancer**

Journal:	<i>International Journal of Clinical Practice</i>
Manuscript ID:	IJCP-10-10-0536.R1
Wiley - Manuscript type:	Original Paper
Date Submitted by the Author:	11-Dec-2010
Complete List of Authors:	Clemens, Katri Elina; Malteser Hospital Bonn/Rhein-Sieg, Department of Science and Research, Centre for Palliative Medicine Quednau, Ines; Malteser Hospital Bonn/Rhein-Sieg, Department of Science and Research, Centre for Palliative Medicine Klaschik, Eberhard; Malteser Hospital Bonn/Rhein-Sieg, Department of Science and Research, Centre for Palliative Medicine
Specialty area:	

SCHOLARONE™  
 Manuscripts

**Bowel function during pain therapy with oxycodone/naloxone prolonged-release tablets  
in patients with advanced cancer**

**Katri Elina Clemens<sup>1,2</sup>, Ines Quednau<sup>1,2</sup>, Eberhard Klaschik<sup>1</sup>**

<sup>1</sup> Department of Science and Research, Centre for Palliative Medicine, University of Bonn

<sup>2</sup> Department of Palliative Medicine and Pain Therapy, Malteser Hospital Bonn/Rhein-Sieg

**Acknowledgements:**

The authors would like to thank Birgit Jaspers for careful review of this manuscript and English editing.

**Address for Correspondence:**

Katri Elina Clemens, MD

Department of Science and Research in Palliative Medicine

Centre for Palliative Medicine

University of Bonn

Malteser Hospital Bonn/Rhein-Sieg

Von-Hompesch-Str. 1

D-53123 Bonn

email: [katri-elina.clemens@malteser.org](mailto:katri-elina.clemens@malteser.org)

phone: + 49 (0)228-6481-13169

fax: + 49 (0)228-6481-9020

**Background:**

WHO-Step-III opioids are often required right from the start of pain therapy in order to achieve sufficient symptom control. Bowel dysfunction, particularly constipation, is one of the most frequent and persistent side effects of opioid therapy, and it is known to cause considerable distress in many patients. The aim of the study was to evaluate whether patients with advanced cancer and moderate to severe cancer pain will benefit from treatment with oxycodone/naloxone prolonged-release tablets (OXN), with particular regard to constipation.

**Material and Methods:**

In this exploratory, non-randomized, open-label, monocentre study we evaluated the bowel function in palliative care patients treated with OXN. During the treatment phase patients were titrated up to an adequate pain control. The Bristol Stool Form Scale (BSFS) (Type 1-7) and Bowel Function Index (BFI) (0-100) were used to assess consistency and frequency of bowel movements. Global patient satisfaction was assessed with Patient Global Impression of Change Scale (PGIC) (1-7). Statistics: mean±SD, significance  $p < 0.05$ .

**Results:**

26 patients (10 males (38.5%)) were included; mean age  $70.6 \pm 14.0$  y, length of stay  $22.6 \pm 21.2$  days. At admission all patients had opioid-induced constipation. During the observation period of 14 days the daily mean dose of OX was  $36.2 \pm 17.2$  mg and of N  $15.4 \pm 5.3$  mg. In 5 cancer patients pain control was not sufficient under the approved maximum total daily dose of 40/20 mg OXN; therefore switching to hydromorphone. BFI improved significantly in 21 patients ( $72.4 \pm 17.0$  vs.  $36.8 \pm 13.4$ ) ( $p < 0.0001$ ); stool consistency (BSFS) improved from type  $2.0 \pm 0.7$  to  $4.9 \pm 1.0$  ( $p < 0.0001$ ). PGIC at discharge was  $1.9 \pm 0.8$ .

**Discussion:**

Patients with OXN treatment throughout the whole study phase showed a clinically relevant improvement in pain intensity and bowel function as well as increased satisfaction. Well

1  
2  
3 known disadvantages of laxative treatment might be spared or even circumvented under OXN  
4  
5 treatment, if appropriate.  
6  
7  
8

9  
10 **What's already known about this topic?**

11  
12 There are no published data for clinical use of oxycodone/naloxone in patients with advanced  
13  
14 cancer  
15

16  
17 **What does this article add?**

18  
19 Data on clinical use of oxycodone/naloxone in patients with advanced cancer and cancer  
20  
21 related pain and opioid-induced constipation  
22  
23

24  
25  
26  
27  
28 *Key words: oxycodone, naloxone, opioid-induced constipation, cancer pain, palliative care*  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

## Introduction

Chronic pain occurs in up to 70% of patients with advanced cancer<sup>1</sup> and is known to have a significant impact on patients' ability to function and quality of life.<sup>2</sup>

Over the past twenty years opioid use for symptom relief has increased significantly in developed countries.<sup>3</sup> In many countries opioids are now being introduced at earlier stages in palliative care and used in higher doses.<sup>3,4</sup> This appropriate increase in the use of opioids resulted in the development and improvement of management strategies for dealing with unwanted effects such as opioid-induced constipation.

The prevalence of constipation in patients with cancer generally ranges from 70% to 100%.<sup>5-7</sup> Evidence suggests that up to ninety percent of patients treated with opioids will experience chronic constipation and of those receiving standard laxative treatments over half will remain dissatisfied with the outcome.<sup>5,8</sup> Constipation is a distressing complication for oncology patients that is often underassessed and undertreated and may occur as a side effect of tumour growth or an adverse effect of drug therapy. For cancer patients, additional causative factors include gastrointestinal obstruction, electrolyte abnormalities such as hypercalcaemia or hypokalaemia, opioid-analgesic use, other drugs, and other concurrent processes (e.g. organ failure), decreased mobility, and depression.<sup>6,9,10</sup> Physiologic factors that exacerbate constipation are inadequate oral intake of fluids, dehydration, inadequate intake of dietary fibre, or organ failure. Constipation may potentially lead to further symptoms such as nausea and vomiting due to delayed gastric emptying as well as gas distention and abdominal cramps associated with generalised bowel dysfunction.<sup>11</sup>

However, constipation is the most frequent and most persistent side effect of opioid treatment. Unlike other side effects of opioid medication, such as nausea and emesis, there is no, or extremely slow, tolerance build-up to the constipatory effects of opioids and most patients continue to require laxative therapy for the duration of opioid use.<sup>12,13</sup> The (wherever possible

1  
2  
3 causal) treatment of constipation requires taking a thorough medical history and examination  
4  
5 of the patient. Further, sound knowledge of the complex processes in the pathophysiology of  
6  
7 constipation and effective mechanisms of laxatives is crucial. Untreated constipation may  
8  
9 progress to life threatening complications associated with bowel obstruction.<sup>14</sup>  
10  
11

12 For improvement of the quality of life of patients with advanced tumour disease optimum  
13  
14 control of all distressing symptoms is required, without negative impact on the efficacy of  
15  
16 pain control.  
17  
18

### 21 **Pathophysiology of opioid-induced constipation**

22  
23  
24 Peripheral as well as intrathecal and intraventricular administration of opioids will lead to a  
25  
26 prolonged colon passage of the bowel content, since opioid-induced constipation is caused by  
27  
28 linkage of the opioid receptors in the gut and the central nervous system.<sup>15,17</sup> The inhibition of  
29  
30 the release of acetylcholine from the myenteric plexus leads to a relaxation of the longitudinal  
31  
32 musculature of the colon and small intestine. Subsequently, the propulsive motor activity  
33  
34 decreases. Furthermore, opioids cause an increase in segmental intestinal contraction. This  
35  
36 will cause a prolonged transit of intestinal contents; leading to a withdrawal of water and  
37  
38 faecal impaction. Further, the intestinal, gastric, biliary, and pancreatic secretions decrease.  
39  
40 An increase in the tonus of the intestinal sphincters and a decrease in the defaecatory reflex  
41  
42 add to the constipatory effect. Meissner et al, in a non-randomized controlled study, showed  
43  
44 that enteral application of naloxone can reduce opioid-induced constipation without impairing  
45  
46 or suspending the pain-relieving effects of the opioid.<sup>18</sup> A combination drug consisting of the  
47  
48 opioid oxycodone and the opioid antagonist naloxone has been available for some time.  
49  
50

51  
52 The aim of the study was to evaluate whether patients with advanced cancer and moderate to  
53  
54 severe cancer pain will benefit from the treatment with oxycodone/naloxone prolonged-  
55  
56 release tablets (OXN), with particular regard to constipation and assessment of global patient  
57  
58 satisfaction.  
59  
60

## Methods

In this exploratory, non-randomized, open-label, monocentre study we evaluated the bowel function in palliative care patients admitted to our palliative care unit and switched to OXN during the first 14 days of the treatment period. During the treatment phase patients were titrated up to an adequate pain control (approved maximum total daily dose 40/20 mg OXN). If required, rescue doses of oxycodone (1/6 of the calculated daily dose) for management of breakthrough pain were administered as immediate-release formula. If rescue doses were required more than thrice, basic doses of sustained-release formula of oxycodone (without naloxone) were increased. The total doses of oxycodone – as reported in this paper - included rescue doses.

The Bristol Stool Form Scale (BSFS)<sup>19</sup> (Type 1-7) was used to assess stool consistency. To assess the bowel function a new, validated scale was used: The Bowel Function Index (BFI) (0-100).<sup>20</sup> This score is the mean of three distinct bowel dysfunction components: ease of defaecation (numerical analogue scale [NAS] 0-100; 0= easy/no difficulty, 100=severe difficulty); feeling of incomplete bowel evacuation (0-100); 0=not at all, 100=very strong); and judgement of constipation (0-100, 0=not at all, 100=very strong). A score lower than or equal to 30 is considered to reflect normal bowel function; higher scores indicated poor bowel function. Global patient satisfaction was assessed with the Patient Global Impression of Change Scale (PGIC) (1-7) on day 7 and 14. The intensity of pain was measured using a numeric rating scale (NRS 0-10). The intensity of pain was defined as follows: NRS 0 = no pain, NRS 1-3 = mild pain, NRS 4-7 = moderate pain, NRS > 7 severe pain. Ratings were recorded at rest. Presence of constipation prior to OXN treatment was defined according to the Rome III criteria,<sup>21</sup> which is defined by the presence of two or more of the following symptoms for a period of at least three months: 1. Straining at least 25 percent of the time, 2. Hard stools at least 25 percent of the time, 3. Incomplete evacuation at least 25 percent of the



1  
2  
3 time, 4. Two or fewer bowel movements per week. All adverse events were also documented  
4  
5 and analysed.  
6

7  
8 Demographic patient- and disease-related data, such as cancer diagnosis or previous illnesses,  
9  
10 were documented, including the laboratory values of serum electrolytes (sodium, potassium,  
11  
12 and calcium), serum creatinine and CRP and all further clinically relevant laboratory  
13  
14 parameters. If patients exhibited discomfort during the study period regarding constipation,  
15  
16 oral sodium picosulfate (20 gtt) could be taken as a rescue laxative. If no bowel movement  
17  
18 had occurred within 24 h, sodium picosulfate intake could be repeated and, if still  
19  
20 unsuccessful after another 24h, an enema could be used.  
21  
22  
23

24  
25 The study protocol was reviewed and approved by the Research and Ethics Committees of the  
26  
27 Medical Association of North Rhine, Germany, and was in accordance with the  
28  
29 recommendations found in the Helsinki Declaration of 1975. The written consent of all  
30  
31 patients was obtained.  
32  
33

### 34 35 36 **Inclusion Criteria**

37  
38 Included were: patients with opioid-induced constipation, i.e. patients with a history of  
39  
40 constipation, defined according to the Rome III criteria, since onset of opioid treatment  
41  
42 without accompanying laxative treatment; patients who could provide informed consent and  
43  
44 who were 18 years of age or older, with documented diagnosis of advanced, terminal cancer  
45  
46 or other terminal incurable disease, and who were likely to improve from pain therapy with  
47  
48 oxycodone/naloxone.  
49  
50  
51  
52

### 53 54 55 **Exclusion Criteria**

56  
57 Exclusion criteria included contraindications regarding switching to oxycodone hydrochloride  
58  
59 and/or naloxone hydrochloride, age <18 years, communication problems, diagnosed  
60  
significant structural abnormalities of the gastrointestinal tract or gastrointestinal

1  
2  
3 diseases/diseases with impact on the gastrointestinal tract, missing consent, or patients in the  
4 pre-final phase; defined as patients with a life expectancy of a few days or hours.  
5  
6  
7  
8  
9

### 10 **Data Analysis and Statistics**

11  
12 Data were anonymized and inputted into an Excel 5.0 database. The programme SPSS was  
13 used for statistical evaluation. Descriptive methods (mean±SD (range) and medians (1/3  
14 quartiles), respectively, were used. Comparative tests (Wilcoxon) were employed. The P  
15 values cited were two-sided, and P values <0.05 were judged as statistically significant.  
16  
17  
18  
19  
20  
21  
22  
23  
24

### 25 **Results**

26  
27 All patients tolerated the study session well. Of the 26 patients included in this trial (age  
28 70.6±14.0 years) 10 (38.5%) were male. Diagnoses at admission were breast cancer (n=6),  
29 colon cancer (n=6), prostate cancer (n=4), carcinoma of the lung (n=3), urothelial cancer (n=  
30 3), ovarian cancer (n=2) and carcinoma of unknown primary (CUP) (n=2). Observation period  
31 was 14 days. Patients' demographic and disease-related data is shown in *table 1*. The type of  
32 pain was somatic in 14 (53.8%) patients and visceral in 10 (38.5%). Two patients were  
33 suffering from somatic pain with neuropathic components All patients were pre-treated with  
34 opioids (WHO step III) and had opioid-induced constipation. Laxatives were not used or  
35 prescribed prior to their admission and since intake of opioids. Of the 26 patients in this study  
36 11 were pre-treated with fentanyl TTS, 8 with oxycodone, 6 with morphine and 1 with  
37 hydromorphone for symptomatic pain control. Mean oral morphine equivalent dose at  
38 admission was 53.1±23.8 mg. At admission, opioid pre-treatment was discontinued and  
39 switched to oxycodone/naloxone (daily mean dose 36.2±17.2 mg OX/15.4±5.3 mg N). PGIC  
40 in mean at on day 7 was 3.5±1.0 and on day 14 was 1.9±0.8 ( $p<0.0001$ ) (*figure 3*).  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 BFI improved significantly in 21 patients ( $72.4 \pm 17.0$  vs.  $36.8 \pm 13.4$ ) ( $p < 0.0001$ ), changes are  
4 shown in *figure 1*; stool consistency (BSFS) improved in mean from type  $2.0 \pm 0.7$  to  $4.9 \pm 1.0$   
5 ( $p < 0.0001$ ) (*figure 2*).  
6  
7

8  
9  
10 Furthermore, there was a significant decrease in the intensity of pain at rest (NRS  $5.7 \pm 2.2$  vs.  
11  $2.6 \pm 1.3$ ) ( $p < 0.0001$ ) (*figure 4*).  
12  
13

14  
15 In 5 cancer patients (2 of them with neuropathic pain components) with severe pain, pain  
16 control was not sufficient under OXN therapy with the – at the time of the study - maximal  
17 licensed daily dose of 40/20 mg; therefore these patients were switched to hydromorphone.  
18  
19

20  
21 Spontaneous bowel movements increased during therapy with OXN in all patients: reported  
22 movements of  $1.0 \pm 0.7$  / week prior to admission vs.  $3.6 \pm 0.8$  / week on day 14 ( $p < 0.0001$ ).  
23  
24

25  
26 As anticipated with opioid analgesics, the most common class of adverse events was  
27 gastrointestinal. Nausea (n=9) and abdominal pain (n=5) were the most frequently reported  
28 adverse events during the first five days of therapy with OXN. Two of the patients reported  
29 suffering from treatment-related diarrhoea for four, respectively five, days. Gastrointestinal  
30 infections could be excluded in both patients. None of the patients reported worsening of  
31 constipation during the therapy with OXN. Opioid withdrawal symptoms could be excluded.  
32  
33

34  
35 Use of rescue laxative was documented in four patients during the first four days: three  
36 patients had one intake of 20 gtt sodium picosulfate and in the fourth patient another sodium  
37 picosulfate intake as well as the use of an enema was required.  
38  
39  
40

## 41 42 43 44 45 46 47 48 49 50 51 **Discussion**

52  
53 Opioids are currently the mainstay of pain management for patients with cancer pain.<sup>1,22</sup>  
54  
55 Successful pain management requires that analgesia is achieved without excessive tolerability  
56 issues that would jeopardize the overall improvement in the patients' quality of life.  
57  
58

59  
60 While many opioid side effects occur at the beginning of pain treatment and are attenuated or  
disappear over time, constipation and related symptoms, including nausea, abdominal pain or

1  
2  
3 even dizziness, persist or can even become worse.<sup>15,23</sup> Consequently, a high proportion of  
4 patients receiving opioids require one or more laxative treatments.<sup>22</sup> However, even the most  
5 aggressive laxative regimens are often ineffective, as they do not target the underlying  
6 mechanisms of opioid action in the gastro-intestinal tract<sup>22</sup> and can cause additional side  
7 effects.  
8  
9

10  
11  
12  
13  
14  
15  
16  
17 Opioid-induced constipation is a frequent symptom in patients with advanced illness receiving  
18 analgesic treatment with opioids and is mediated predominantly by opioid receptors in the  
19 gut. Sykes<sup>24</sup> demonstrated in a prospective study of 498 hospice inpatients with advanced  
20 cancer that laxatives were required by 87% of patients taking oral strong opioids. Pappagallo  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
Opioid-induced constipation has to be treated rigorously or, as far possible, avoided altogether  
by means of prophylactic treatment. Unfortunately, even though prophylaxis is recommended  
as standard regimen in patients receiving opioids for pain control on a regular basis, this has  
not yet become part of the medical routine in Germany, as was experienced by the patients  
included in this study. None of these patients was given prophylactic laxative treatment  
together with their opioid medication in the primary care setting. However, although many  
treatment strategies are available, opioid-induced constipation still poses therapeutic  
challenges particularly in the treatment of patients with poor health status and advanced  
illness. Thorough knowledge of the pathophysiology of the symptom opioid-induced  
constipation is essential for targeted treatment. An alternative therapeutic strategy to  
conventional oral laxatives has evolved by selectively blocking peripheral opioid-receptors

1  
2  
3 while maintaining desired action of opioids on central receptors that mediate analgesia. At the  
4  
5 time of the study, the combination drug OXN was being introduced to the German market. As  
6  
7 it is well-known that it adds to quality of life when the number of drugs that need to be taken  
8  
9 can be kept as small as possible, the effectiveness of this alternative treatment was studied in  
10  
11 patients who had not received laxative treatment previous to admission to our palliative care  
12  
13 unit.  
14  
15  
16  
17  
18  
19

20 Since the adverse effects of opioids on gastro-intestinal function are believed to be  
21  
22 predominately mediated by interactions between opioids and opioid receptors in the gastro-  
23  
24 intestinal tract,<sup>15,26</sup> a potential therapeutic target is to selectively antagonize the gastro-  
25  
26 intestinal adverse effects caused by opioids by co-administering an opioid antagonist that has  
27  
28 limited systemic bioavailability.<sup>22</sup> Oxycodone is a pure opioid agonist exerting its analgesic  
29  
30 effect primarily through  $\mu$ -opioid receptors in the central nervous system.<sup>16,17</sup> It is available  
31  
32 in immediate-release and prolonged-release preparations; prolonged-release oxycodone  
33  
34 provides a fast onset of analgesia within 1 hour and pain relief for a 12-hour period.<sup>27</sup> The  
35  
36 first attempt to selectively target opioid receptors in the periphery was made with naloxone.<sup>15</sup>  
37  
38 Naloxone is a pure competitive antagonist of opioid receptors in both the central and  
39  
40 peripheral nervous system and devoid of any intrinsic agonist activity. After oral  
41  
42 administration, naloxone has negligible systemic bioavailability (approximately 2%) due to  
43  
44 extensive first-pass hepatic metabolism.<sup>28</sup> It inhibits the action of opioids locally in the gastro-  
45  
46 intestinal system, without interrupting the centrally mediated analgesic effect of the opioid  
47  
48 administered concomitantly.<sup>8-31</sup>  
49  
50  
51  
52  
53  
54  
55  
56

57 Prolonged-release oxycodone/naloxone is the first analgesic therapy to combine oxycodone, a  
58  
59 strong opioid, with naloxone, an opioid antagonist, in an oral prolonged-release tablet [23]. Its  
60

1  
2  
3 use is indicated in moderate to severe pain, which can be adequately managed only with  
4  
5 opioid analgesics.<sup>23</sup>  
6  
7

8 It needs to be realised; however, that the opioid-antagonist naloxone can easily cross the  
9  
10 blood-brain barrier and hence, despite its low oral bioavailability, can reverse analgesia.<sup>15</sup>  
11

12 Thus the therapeutic range of naloxone is rather narrow because of the need to titrate  
13  
14 peripherally versus centrally active doses.<sup>30</sup> Despite of this limitation, a combination of oral  
15  
16 oxycodone and naloxone at the weight ratio 2:1 has been licensed in Germany, given that a  
17  
18 phase II trial had shown that the combination has low potential to induce opioid-induced  
19  
20 bowel dysfunction whereas the analgesic effect is preserved.<sup>18</sup>  
21  
22  
23  
24  
25  
26

27 The primary objective was to investigate whether patients with advanced cancer with  
28  
29 moderate to severe malignant pain and opioid-induced constipation receiving oxycodone  
30  
31 /naloxone (prolonged-release) had clinically significant improvement in symptoms of  
32  
33 constipation as measured by BFI, BSFS and PGIC. A secondary efficacy variable was to  
34  
35 assess the average pain intensity using the numeric rating scale. Our study results demonstrate  
36  
37 that 21 patients receiving OXN achieved a significant change and improvement in bowel  
38  
39 function, especially with respect to constipation over 14 days treatment period. Stool  
40  
41 consistency was generally improved in all patients after 14 days. The improvement in bowel  
42  
43 function was achieved without affecting the analgesic efficacy of the oxycodone component.  
44  
45 The results of this study add also further support to the data from Colluzi et al.,<sup>32</sup>  
46  
47 demonstrating the efficacy of the oxycodone/naloxone (prolonged-release) combination with  
48  
49 respect to both bowel function and analgesic efficacy in patients with advanced cancer.  
50  
51 Although this study investigated the efficacy of oxycodone/naloxone (prolonged-release) in  
52  
53 patients with chronic cancer-pain, oxycodone is verifiably also an effective treatment option  
54  
55 for non-malignant pain as proven in phase II and III trials.<sup>32-35</sup> Identical results to these phase  
56  
57 II and III trials<sup>32-35</sup> were achieved in our study population.  
58  
59  
60

1  
2  
3  
4  
5  
6 The adverse events seen in this study are consistent with the expected adverse event profile of  
7  
8 opioids. As with other opioid analgesics, the most common adverse event, observed in our  
9  
10 study, was of gastrointestinal nature, except constipation. However, further analysis revealed  
11  
12 no safety concerns arising from the use of oxycodone/naloxone (prolonged-release) in higher  
13  
14 doses than used in this study.

15  
16  
17 The reported abdominal pain might indicate an increase in gut motility. Importantly, the  
18  
19 incidence of diarrhoea was generally low.  
20  
21

### 22 23 24 **Limitations of the study**

25  
26 We are well aware of the fact that the non-randomised, non-control group design is a  
27  
28 limitation of the study. Nevertheless is this the first prospective study of OXN in patients with  
29  
30 chronic cancer pain in the palliative setting. The study was designed to assess bowel function  
31  
32 over a 14 days time period. Two weeks may be too short a period for observing differences in  
33  
34 constipation regarding to long term use of oxycodone/naloxone prolonged-release tablets.  
35  
36 Also, the assessed patient group was not very large. However, at the time of the study, the  
37  
38 licensed maximum daily dose of OXN was 40/20 mg in Germany. Few cases of insufficient  
39  
40 analgesia under doses up to 60-80 mg OXN treatment of patients with severe pain were  
41  
42 experienced in clinical practice and reported in the literature.<sup>34</sup> Therefore an extremely  
43  
44 cautious inclusion process of palliative care patients was clinically and ethically required. The  
45  
46 recently licensed new maximum daily dose that is twice as high as before will allow including  
47  
48 more patients in the palliative setting.  
49  
50  
51  
52  
53  
54  
55

### 56 57 **Conclusions**

58  
59 The treatment with oxycodone/naloxone prolonged-release tablets produced a clinically  
60  
significant improvement in BFI and BFSF in our study population without a negative impact

1  
2  
3 on the analgesic efficacy of the oxycodone component, as evidenced by pain intensity scales  
4 and assessment of global patient satisfaction. The most frequent adverse events associated  
5 with oxycodone/naloxone (prolonged-release) are consistent with those reported for strong  
6 opioid analgesics. Taken together, these results demonstrate that the fixed combination tablet  
7 of oxycodone/naloxone (prolonged-release) provides an improved treatment option for  
8 patients with moderate to severe cancer pain. The recently licensed increased maximum daily  
9 dose of 80/40mg will allow including more patients from palliative care settings in OXN  
10 treatment. Randomised investigations are desirable.  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60



## References

1. Colvin L, Forbes K, Fallon M. Difficult pain. *BMJ* 2006;332:1081–1083
2. Portenoy RK, Lesage P. Management of cancer pain. *Lancet* 1999;353:1695-700
3. World Health organization (1996) Cancer pain relief, 2<sup>nd</sup> ed. Report of WHO Expert Committee. Geneva: WHO,
4. Bruera E, Macmillan K, Hanson J, MacDonald RN. Palliative care in a cancer center: results in 1984 versus 1987. *J Pain Symptom Manage* 1990; 5:1-5
5. Mancini I, Bruera E. Constipation in advanced cancer patients. *Support Care Cancer* 1998;6:356-364
6. Vainio A, Auvinen A (1996) Prevalence of symptoms among patients with advanced cancer: an international collaborative study. *J Pain Symptom Manage* 12: 3–10
7. Fallon MT Constipation in cancer patients: prevalence, pathogenesis, and cost-related issues. *Eur J Pain* 1999; 3(suppl):3–7
8. Twycross RG, Lack SA (eds.) (1986) Control of Alimentary Symptoms in Far Advanced Cancer. London: Churchill Livingstone: pp166-207
9. McMillan SC. Assessing and managing opiate-induced constipation in adults with cancer. *Cancer Control* 2004; 11(3 suppl):3-9
10. Avila JG. Pharmacologic treatment of constipation in cancer patients. *Cancer Control* 2004;.11(3 suppl):10-18
11. Thomas J. Opioid-induced bowel dysfunction. *J Pain Symptom Manage* 2008; 35: 103-113
12. Clemens KE, Klaschik E (2008) Management of constipation in palliative care patients. *Curr Opin Support Palliat Care* 2: 22-27
13. Clemens KE, Klaschik E. Managing nausea, emesis and constipation in palliative care. *Dtsch Arztebl* 2007; 104(5): 269–78
14. Drossmann et al .Identification of sub-groups of functional gastrointestinal disorders. *Gastroenterol Int* 1990; 3:159-72
15. Kurz A, Sessler DI. Opioid-induced bowel dysfunction: pathophysiology and potential new therapies. *Drugs* 2003; 63:649–71
16. Kalso E. Oxycodone. *J Pain Symptom Manage* 2005; 29:47–56
17. Nozaki C, Saitoh A, Tamura N, Kamei J. Antinociceptive effect of oxycodone in diabetic mice. *Eur J Pharmacol* 2005; 524:75-9

18. Meissner W, Leyendecker P, Mueller-Lissner S, et al. A randomised controlled trial with prolonged-release oral oxycodone and naloxone to prevent and reverse opioid-induced constipation. *Eur J Pain* 2009; 13:56–64
19. Lewis SJ, Heaton KW. Stool Form Scale as a useful guide to intestinal transit time. *Scand J Gastroenterol* 1997; 32(9):920-4
20. Rentz AM, Yu R, Müller-Lissner S, Leyendecker P. Validation of the Bowel Function Index to detect clinically meaningful changes in opioid-induced constipation. *Journal of Medical Economics* 2009, 12(4), 371-383
21. Chang L. From Rome to Los Angeles – The Rome III Criteria for the Functional GI Disorders. *Gastroenterology* 2006; 130: 1480–91
22. Pappagallo M. Incidence, prevalence, and management of opioid bowel dysfunction. *Am J Surg* 2001; 182:11S–18S
23. Berde C, Nurko S. Opioid Side Effects – Mechanism-based Therapy. *N Engl Med* 2008; 358 (22):2400-2402
24. Sykes NP. The relationship between opioid use and laxative use in terminally ill cancer patients. *Palliat Med* 1998; 12(5):375-82
25. Wirz S, Klaschik E. Management of constipation in palliative care patients undergoing opioid therapy: is polyethylene glycol an option? *Am J Hosp Palliat Care* 2005; 22(5):375-81
26. Holzer P. Opioids and opioid receptors in the enteric nervous system: from a problem in opioid analgesia to a possible new prokinetic therapy in humans. *Neurosci Lett* 2004; 361:192–5
27. Mandema JW, Kaiko RF, Oshlack B, et al. Characterization and validation of a pharmacokinetic model for controlled-release oxycodone. *Br J Clin Pharmacol* 1996; 42:747–56
28. Liu M, Wittbrodt E. Low-dose oral naloxone reverses opioid-induced constipation and analgesia. *J Pain Symptom Manage* 2002; 23:48–53
29. Meissner W, Schmidt U, Hartmann M, et al . Oral naloxone reverses opioid-associated constipation. *Pain* 2000; 84:105–9
30. Sykes NP. An investigation of the ability of oral naloxone to correct opioid-related constipation in patients with advanced cancer. *Palliat Med* 1996;10:135-144
31. Clemens KE, Mikus G. Combined oral prolonged-release oxycodone and naloxone in opioid-induced bowel dysfunction: review of efficacy and safety data in the treatment

- 1  
2  
3 of patients experiencing chronic pain. *Expert Opin Pharmacother*. 2009 Dec 23. [Epub  
4 ahead of print]  
5  
6  
7 32. Colluzi F, Mattia C. Oxycodone. Pharmacological profile and clinical data in chronic  
8 pain management. *Minerva Anesthesiol* 2005; 71(7-8):451-60  
9  
10 33. Vondrackova D, Leyendecker P, Meissner W, et al. Analgesic efficacy and safety of  
11 oxycodone in combination with naloxone as prolonged release tablets in patients with  
12 moderate to severe chronic pain. *J Pain* 2008; 9(12):1144-54  
13  
14 34. Simpson K, Leyendecker P, Hopp M, et al. A randomized double-blind trial of  
15 combined prolonged release oxycodone and naloxone in patients with moderate-to  
16 severe non-cancer pain. *Curr Med Res Opin* 2008; 24(12):3503-12  
17  
18 35. Löwenstein O, Leyendecker P, Hopp M, et al. Combined prolonged-release  
19 oxycodone and naloxone improves bowel function in patients receiving opioids for  
20 moderate-to-severe non-malignant chronic pain: a randomised controlled trial. *Expert  
21 Opin Pharmacother* 2009; 10:531–43  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

**Table 1: Demographics (n=26)**

		n (%)	
Sex	male		10 (38.5)
	female		16 (61.5)
Age (mean) years			70.6±14.0
Duration of stay (mean) days			22.6±21.2
Karnofsky Index (median) %			50 % (20-80) %
Type of pain	somatic		14 (53.8)
	visceral		10 (38.5)
	somatic with neuropathic pain components		2 (7.7)
Daily dose (mean) mg	oxycodone		36.2±17.2
	naloxone		15.4±5.3
Bowel Function Index (BFI) (mean)	admission		72.4±17.0
	day 14		36.8±13.4
Bristol Stool Form Scale (BSFS) (mean)	admission		2.0±0.7
	day 14		4.9±1.0
Laboratory values at admission	sodium	mval/l	139.0±5.0
	potassium	mval/l	4.0±0.7
	calcium	mval/l	3.9±0.7
	creatinine	mg/dl	1.0±0.5
	CRP	mg/dl	10.1±8.3
Patient Global Impression of Change Scale (PGIC) (mean)	day 7		3.5±1.0
	day 14		1.9±0.8

**Figure 1.** Bowel Function Index (BFI) in palliative care patients (n=26) at admission and on day 14 during therapy with oxycodone/naloxone.

Wilcoxon-Test  $p < 0.0001$

Bowel Function Index:

1. Ease of defecation (NAS) during the last 7 days:

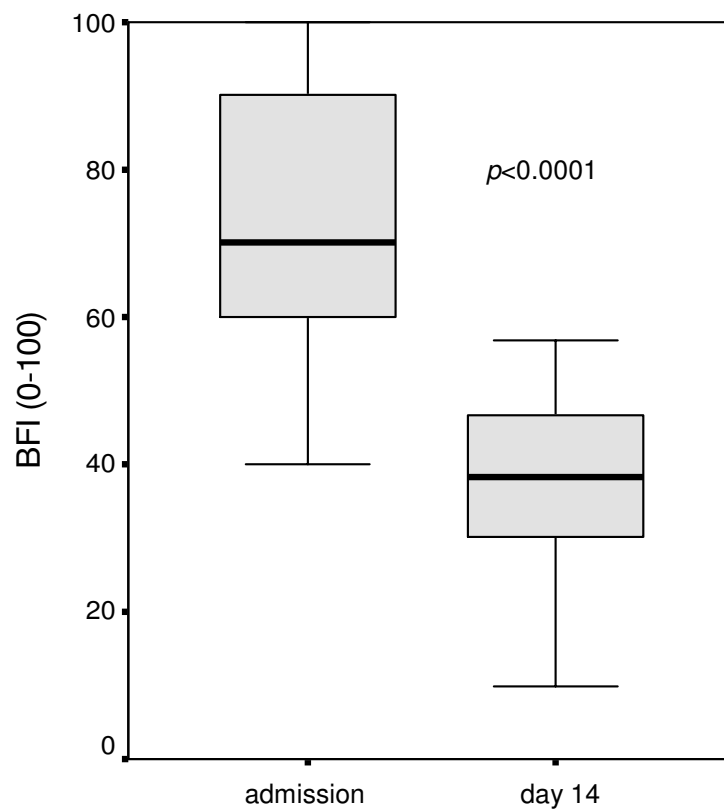
0 = easy / no difficulty - 100 = severe difficulty

2. Feeling of incomplete bowel evacuation (NAS) during the last 7 days:

0 = not at all - 100 = very strong

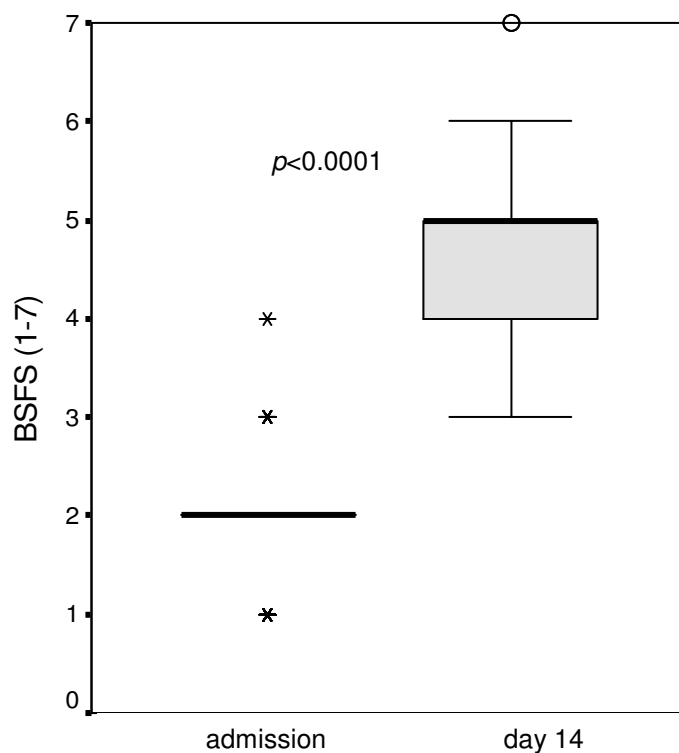
3. Personal judgment of patient (NAS) regarding constipation during the last 7 days:

0 = not at all - 100 = very strong



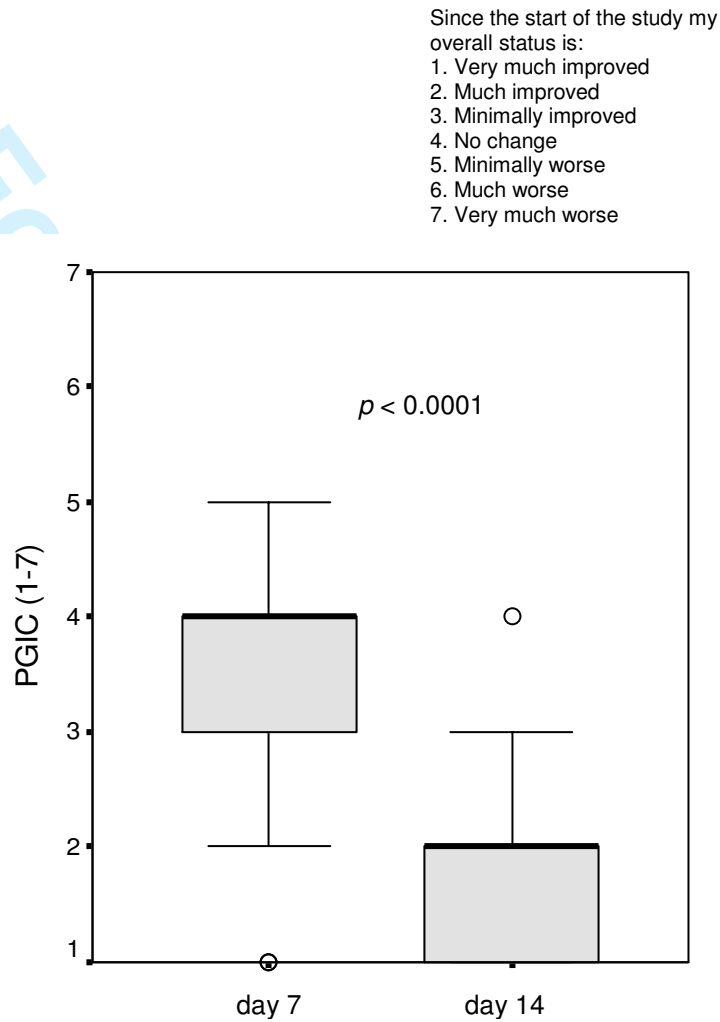
**Figure 2:** Bristol Stool Form Scale (BSFS) in palliative care patients (n=26) at admission and on day 14 during therapy with oxycodone/naloxone  
 Wilcoxon-Test  $p < 0.0001$

Bristol Stool Form Scale (BSFS)



**Figure 3:** Patient Global Impression of Change Scale (PGIC) in palliative care patients and on day 7 and 14 after start of treatment, respectively

Wilcoxon Test:  $p < 0.0001$



**Figure 4:** Changes in intensity of pain at rest and at admission and on day 14 during therapy with oxycodone/naloxone ( $p < 0.0001$ ) (Wilcoxon Test) ( $n = 21$ )

