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Original Research Article

Laxatives Do Not Improve Symptoms of Opioid-Induced Constipation: Results of a Patient Survey

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Abstract

Introduction. Laxatives are commonly used to treat opioid-induced constipation, the commonest and most bothersome complication of opioids. However, laxatives have a nonspecific action and do not target underlying mechanisms of opioid-induced constipation; their use is associated with abdominal symptoms that negatively impact quality of life.

Objective. To assess the effects of laxatives in patients taking opioids for chronic pain.

Methods. One hundred ninety-eight UK patients who had taken opioid analgesics for at least one month completed a cross-sectional online or telephone survey. Questions addressed their pain condition, medication, and laxative use (including efficacy and side effects). The survey also assessed bowel function using the Bowel Function Index.

Results. Since starting their current opioid, 134 of 184 patients (73%) had used laxatives at some point and 122 (91%) of these were currently taking them. The most common laxatives were osmotics and stimulants. Laxative side effects were reported in 75%, most commonly gas, bloating/fullness, and a sudden urge to defecate. Side effects were more common in patients less than 40 years of age. Approximately half of patients said laxatives interfered with work and social activities, and one-fifth needed an overnight hospital stay because of their pain condition and/or constipation. Laxatives did not improve the symptoms of constipation, as assessed by the Bowel Function Index. Constipation was not related to opioid strength, dose of opioid, or number of laxatives taken.

Conclusions. Use of laxatives to treat opioid-induced constipation is often ineffective and associated with side effects. Instead of relieving the burden of opioid-induced constipation, laxative use is associated with a negative impact.

Key Words. Opioid; Opioid-Induced Constipation; Laxatives; Chronic Pain; Survey; Bowel Function Index

Introduction

Opioids have been important in pain management for a number of years. According to the World Health Organization's three-step analgesic ladder, weak opioids (e.g., codeine, dihydrocodeine, tramadol) should be used for moderate pain (at Step 2) and strong opioids (e.g., oxycodone, morphine) for severe pain (at Step 3) [1]. Despite being originally developed for cancer pain, this stepwise approach has been extended for use in chronic noncancer pain.

Opioids are known to cause a number of gastrointestinal (GI) side effects that are collectively termed opioid-induced bowel dysfunction (OIBD). OIBD is characterized by hard, dry stools, straining, incomplete evacuation, bloating, abdominal distension, and increased gastric reflux [2]. The most common symptom of OIBD is opioid-induced constipation (OIC) [3,4]. Opioids cause constipation by binding to μ-opioid receptors in the GI tract, which reduces GI secretions and peristaltic activity and increases fluid reabsorption [5]. The result is hard, dry stools that pass slowly through the gut. OIC is dose-dependent, and, unlike other GI symptoms, patients rarely develop tolerance to the constipating effects of opioids, so OIC does not resolve over time [6].

As well as being the most common symptom of OIBD, constipation is the most bothersome and debilitating [3,7,8]. Some patients will reduce or miss their dose of opioid medication to avoid OIC [7,8,9], preferring to tolerate the pain than experience constipation symptoms [10]. OIC negatively impacts patients' quality of life, no matter how advanced their disease or condition [11]. It also carries a significant economic burden in terms of both direct costs (patients may use additional health care resources) [12,13] and indirect costs (patients' ability to work may be affected, leading to both absenteeism and presenteeism) [13]. Studies carried out in Sweden and the United States showed that total health costs are significantly higher for patients with OIC than for those without [14–17].

Laxatives are commonly used to treat OIC. However, they do not target the underlying mechanism of OIC, as they do not impact binding to μ-opioid receptors in the GI tract, and many patients will not have their constipation resolved with this therapeutic approach. In one survey of patients with chronic noncancer pain, 54% of those treated for OIC with laxatives did not achieve the desired effect even half of the time [2]. In another survey, 96% of patients taking one laxative and 38% taking two laxatives had an inadequate response to treatment [9].

The multinational Prevalence, Severity, and Impact of Opioid-Induced Bowel Dysfunction (PROBE1) survey assessed OIBD in 322 patients who were receiving opioids for chronic pain and taking laxatives [7]. Eighty-one percent of patients reported that they experienced constipation despite taking laxatives, and more than half said that constipation had a "moderate-to-great" or "great" impact on their quality of life. Patients also reported a number of other symptoms, such as bloating and gas, which negatively impacted their quality of life. As all patients were taking laxatives, it may have been possible that this reflected the side effects of laxatives as well as the symptoms of OIBD. We therefore carried out a survey to specifically look at laxative use in patients receiving opioids, focusing on: 1) the types of laxatives used to treat OIC, 2) the effect of laxatives on symptoms of constipation, 3) the side effects associated with laxatives, and 4) the impact of laxatives on quality of life.

Methods

This was a cross-sectional survey carried out in the United Kingdom between May 2013 and October 2014. Patients were recruited via social media, pharmacies, and advertisements in newspapers and on patient websites. Patients with any pain condition (including back pain, arthritis, cancer, headache and nerve pain) who had been taking Step 2 or 3 oral opioid medication (e.g., codeine, dihydrocodeine, oxycodone, morphine, or tramadol) for at least one month were eligible to take part. Back pain could include failed back surgery, osteoporosis, and nonspecific pain. At screening, any patients who had not been taking opioids for at least one month were excluded from completing the full survey and no further details were collected.

Patients completed the survey online or over the telephone. The survey included questions on patients' pain condition, opioid medication, laxative use, bowel movements, and contact with health care professionals.

Patients who said they were using laxatives were asked to select side effects they had experienced from a list of common symptoms. Those who reported at least one side effect were then asked how much laxatives interfered with their work and social activities on a five-point scale, where 1 = all of the time and 5 = none of the time. Patients were also asked about any other measures they had taken to try and ease their constipation. Bowel movements were assessed using the Bowel Function Index (BFI) [18]. Patients rated ease of defecation, feeling of incomplete bowel evacuation, and personal judgement of constipation on a scale of 0–100, where a lower score indicated better bowel function [18]. Their total BFI score was calculated as the mean of these three scores. Normal bowel function was defined as a BFI score of 28.8 or lower [19]. The BFI is a validated tool [20,21] that has been endorsed by the

American Academy of Pain Medicine Foundation and the American Gastroenterological Association for assessment of OIC [22,23].

The study was submitted to the National Research Ethics Centre, who confirmed that it would not require formal approval.

Data were analyzed descriptively. For categorical variables, the number and percentage falling into each category were reported. For continuous variables, the mean, standard deviation, median, interquartile range (IQR), and range were reported. Statistical analyses were performed using SAS v9.2.

Results

Patient Characteristics

In total, 362 patients were screened and 198 were eligible to participate. Their median age was 50.2 years; 81% were over age 40 years. Most (85%) were female, and just over half (52%) reported they were unable to work owing to illness or disability (Table 1). Most (65%) were recruited via advertisements on the internet (Table 1).

Back pain, nerve pain, and arthritis were the most common indications for opioid use (Table 2). The most common types of back pain were sciatica, arthritis of the spine, and slipped disc. Codeine and codeine combinations were the most common currently prescribed opioids (Table 3). The mean (±SD) number of opioids prescribed was 1.5 (±0.6), and 84 patients (42%) reported that they were currently prescribed two or more opioids; of these, 40 patients were taking a combination of weak and strong opioids. One hundred fifty-four patients (154/183, 84%) had been on their current opioid for at least six months; 82 of 188 patients (44%) reported that codeine and codeine combinations were their longest-prescribed opioid.

Table 1 Patient demographics

	Analysis population (N = 198) N (%)	
Age, y		
N (missing)	194	(4)
Mean (±SD)	49.36	(11.60)
Median (IQR)	50.22	(43.46–56.53)
Min, max	18.48, 79.74	
Age category		
N (missing)	194	(4)
<40 y, N (%)	37	(19.1)
>40 y, N (%)	157	(80.9)
Sex		
N (missing)	198	(0)
Male, N (%)	29	(14.6)
Female, N (%)	169	(85.4)
Current employment status, N (%)		
N (missing)	181	(17)
Employed/in education, N (%)	62	(34.3)
Retired, N (%)	19	(10.5)
Unable to work owing to illness/ disability, N (%)	94	(51.9)
Other, N (%)	6	(3.3)
Method of recruitment to study, N (%)		
N (missing)	196	(2)
Internet advert	128	(65.3)
Newspaper article	5	(2.6)
Pain clinic	6	(3.1)
Patient organization website	10	(5.1)
Pharmacist leaflet	4	(2.0)
Other	43	(21.9)

IQR = interquartile range.

Constipation and Laxative Use

More than three-quarters of patients reported that they had no history of constipation before taking opioids (142/185, 77%). Eighty-eight patients (88/198, 44%) said that their general practitioner had discussed constipation with them, and most patients said they had made lifestyle changes to try and help with their symptoms: 142 (72%) reported altering their diet (e.g., eating more fiber and increasing water intake), and 40 (20%) reported starting exercise (e.g., walking or swimming) or physical therapy. However, it was not clear whether patients made these lifestyle changes as a result of GP advice. More than half of patients (110/198, 56%) said that their GP had offered no advice on dealing with their constipation.

Since starting their current opioid, 134 of 184 patients (73%) had taken a laxative at some point; of these, 122 (91%) were currently taking them. The mean (±SD) number of laxatives currently used was 1.36 (±0.81). Twenty-eight (23%) of the 122 patients currently taking laxatives were taking two or more, and 74 (61%) had been taking them for more than six months. The most common laxatives used were osmotics and stimulants (Table 4). In general, laxatives had been prescribed by a health care professional; over-the-counter (OTC) use was low, with the exception of stimulants: 50 (37%) of the 134 patients who had used laxatives since being prescribed their current opioid said that they had used OTC stimulants (most often senna).

Side Effects and Impact on Quality of Life

Three-quarters of patients currently taking opioids reported side effects with their use (91/122, 75%). The most common side effects were gas, bloating or fullness, and sudden urge to defecate (Table 5). Side effects were more common in younger patients: 83% of

Table 2 Pain conditions

Pain type	Number of patients (%) (N=198)	
Back pain	130	(65.7)
Osteoporosis	12	(6.1)
Slipped disc	34	(17.2)
Arthritis of the spine	44	(22.2)
Failed back surgery	20	(10.1)
Sciatica	62	(31.3)
Nonspecific back pain	27	(13.6)
Other	45	(22.7)
Not sure	7	(3.5)
Arthritis	81	(40.9)
Osteoarthritis	48	(24.2)
Rheumatoid arthritis	17	(8.6)
Other	6	(3.0)
Not sure	16	(8.1)
Cancer	3	(1.5)
Headache	45	(22.7)
Nerve pain	95	(48.0)
Ongoing pain after accident	33	(16.7)
Ongoing pain after surgery	43	(21.7)
Other	44	(22.2)
Not sure	2	(1.0)

Patients could record more than one type of back pain or arthritis.

Table 3 Currently prescribed opioid medications

	Number of patients (%) (N=198)	
Prescribed opioid medication		
Codeine and codeine combinations	102	(51.5)
Dihydrocodeine	28	(14.1)
Hydromorphone	2	(1.0)
Methadone	3	(1.5)
Morphine	65	(32.8)
Oxycodone	18	(9.1)
Tapentadol	1	(0.5)
Tramadol and tramadol combinations	78	(39.4)
Strength of prescribed opioid		
Strong only	42	(21.2)
Weak only	116	(58.6)
Combination of weak and strong	40	(20.2)

Patients could record more than one opioid.

patients (19/23) younger than age 40 years reported at least one side effect, compared with 73% (69/95) older than age 40 years. The most common side effects in younger patients were gas, sudden urge to defecate,

Table 4 Types of laxatives used

Laxative type	Number of patients (%) (N=134)	
Osmotic		
Ever prescribed	62	(46.3)
Ever OTC	7	(5.2)
Currently taking	53	(39.6)
Stimulant		
Ever prescribed	46	(34.3)
Ever OTC	50	(37.3)
Currently taking	56	(41.8)
Bulk forming		
Ever prescribed	12	(9.0)
Ever OTC	8	(6.0)
Currently taking	16	(11.9)
Softener		
Ever prescribed	8	(6.0)
Ever OTC	1	(0.7)
Currently taking	9	(6.7)
Enema		
Ever prescribed	7	(5.2)
Ever OTC	3	(2.2)
Currently taking	5	(3.7)
Suppository		
Ever prescribed	3	(2.2)
Ever OTC	5	(3.7)
Currently taking	5	(3.7)
Other		
Ever prescribed	5	(3.7)
Ever OTC	13	(9.7)
Currently taking	9	(6.7)

Patients could record more than one type of laxative.
OTC = over the counter.

and false alarm (Table 5). There appeared to be no association between side effects and opioid strength or occupational status (data not shown).

Laxatives were considered to interfere "at least a little of the time" with work for 58 of the 122 patients currently taking them (48%) and with social activities for 62 (51%). Sixteen patients (13%) reported that laxatives substantially interfered with social activities; this was most commonly attributed to gas, bloating, urge/fecal incontinence, and false alarm.

Almost half of the patients (95/198, 48%) reported that they had used other interventions to help with their constipation since starting their current laxative. These included herbal remedies, massage, and use of enemas. Forty-two patients (21%) said that they removed hard or dry stools by hand. Almost half of patients who had experienced frequent constipation before starting opioids, 20 of 43 (47%), used manual evacuation methods (colon irrigation therapy, enemas, massage, and

Table 5 Side effects experienced by laxative users

	N (%)					
	All patients (N = 122)		Age < 40 y (N = 23)		Age 40+ y (N = 95)	
None	31	(25.4)	4	(17.4)	26	(27.4)
Unpleasant taste/texture	21	(17.2)	7	(30.4)	13	(13.7)
Nausea	22	(18.0)	6	(26.1)	15	(15.8)
Bloating or fullness	37	(30.3)	5	(21.7)	31	(32.6)
Gas	52	(42.6)	13	(56.5)	39	(41.1)
Dehydration	20	(16.4)	5	(21.7)	15	(15.8)
Urge/fecal incontinence	18	(14.8)	5	(21.7)	11	(11.6)
Sudden urge to defecate	31	(25.4)	9	(39.1)	21	(22.1)
False alarm	25	(20.5)	8	(34.8)	15	(15.8)
Other	6	(4.9)	1	(4.3)	5	(5.3)

Patients could record more than one side effect. Age was not recorded for four patients.

removal by hand), compared with 42 of 142 (30%) who were not previously constipated.

Health Care Contacts

Most patients (169/198, 85%) reported that they had seen either a GP or a practice nurse about their pain condition and/or constipation since starting current treatment. One hundred and eight patients (55%) reported that they had visited their GP more than five times about their pain condition. For constipation alone, the corresponding figure was 15 patients (8%). Some patients had also had health care contacts in a secondary care setting, including 39 (20%) who had required an overnight stay in the hospital (Table 6).

Bowel Function Index

In total, 185 patients completed the BFI questionnaire. Their mean (±SD) total score was 52.1 (±31.5), and 75% had a total score higher than 28.8 (i.e., were constipated). Patients' BFI scores according to laxative use, opioid strength, and number of laxatives taken are shown in Table 7. Laxative use did not appear to improve the symptoms of constipation: patients who had used laxatives (N = 134) since starting their current opioid had a mean (±SD) BFI score of 58.2 (±30.2), compared with 36.5 (±29.0) for patients who had not used laxatives (N = 50). BFI scores were not related to opioid strength, with a mean difference of less than two points in the total score between patients taking weak and strong opioids. Taking more laxatives did not improve BFI scores; in fact, the mean total score and the proportion of patients with a total score higher than 28.8 increased with increasing number of laxatives used.

Table 6 Health care contacts owing to pain and/or constipation

	Number of patients (%) (N=198)	
Primary care		
Pain and/or constipation	169	(85.4)
Neither	29	(14.6)
Emergency care		
Pain and/or constipation	47	(23.7)
Neither	151	(76.3)
Outpatients department		
Pain and/or constipation	97	(49.0)
Neither	101	(51.0)
Overnight hospital stay		
Pain and/or constipation	39	(19.7)
Neither	159	(80.3)
Other		
Pain and/or constipation	28	(14.1)
Neither	170	(85.9)

Patients could record more than one health care contact.

Forty-three patients (43/185, 23%) reported that they had experienced frequent constipation before starting their current opioid, suggesting that they may have been particularly prone to the condition. A post hoc analysis revealed that the BFI scores in these individuals did not differ from those of the total study cohort: their mean (±SD) total score was 51.8 (±31.4), and 32 (74%) had a BFI score higher than 28.8.

Opioid Exposure

A post hoc analysis showed that patients were taking a median daily morphine equivalent dose of 40 mg (range = 4.8–580 mg) (Table 8). The descriptive data suggested there was no relationship between increasing daily morphine equivalent dose and higher BFI scores (although this was not formally tested). Patients' median daily morphine equivalent doses were similar, regardless of whether they had experienced frequent constipation before starting on opioids or not (Table 8). The descriptive data also suggested there was also no clear relationship between daily morphine equivalent dose and laxative use (again, this was not formally tested). Patients who had never taken a laxative tended to be taking lower morphine equivalent doses than those who had used a laxative at some point since starting their current opioid (Table 8).

Discussion

The results of our survey confirm that constipation is very common among patients receiving oral opioids to

Table 7 Results from the Bowel Function Index questionnaire

	Total population		Ever used laxatives?*				Opioid strength†				Number of laxatives‡					
			Yes		No		Weak only		Strong only		1		2		≥3	
	(N = 198)		(N = 134)		(N = 50)		(N = 116)		(N = 42)		(N = 92)		(N = 19)		(N = 9)	
N (missing)	185	(13)	134	(0)	50	(0)	106	(10)	39	(3)	92	(0)	19	(0)	9	(0)
BFI total score, mean (SD)	52.06	(31.51)	58.24	(30.24)	36.52	(29.00)	49.83	(31.01)	51.35	(33.05)	55.80	(29.50)	65.30	(32.57)	85.59	(13.42)
BFI total score >28.8, N (%)	139	(75.1)	109	(81.3)	30	(60.0)	80	(75.5)	27	(69.2)	74	(80.4)	16	(84.2)	9	(100.0)

BFI = Bowel Function Index.
*Excludes 14 patients whose laxative use was unknown.
†Excludes 40 patients taking combined strong and weak opioid therapy.
‡Excludes 50 patients taking no laxatives.

treat pain and does not appear to be related to opioid strength or dose. Laxatives do not appear to resolve the problem; instead they frequently added to the patients' burden by causing unpleasant side effects and negatively impacting quality of life.

An important message for practice is that, despite constipation being a common side effect of opioid treatment, less than half of the patients in our survey received any advice on how to manage it. More than one in five patients said they had to resort to removing stools by hand, giving an indication of the severity of the constipation still endured by them, despite treatment with laxatives. The use of manual evacuation techniques was not restricted just to patients who had frequently experienced constipation before starting opioids and may have been predisposed to rectal evacuation disorders: approximately a third of those who had not experienced constipation previously found they also had to use one or more such interventions. A number of patients decided to try nonpharmacological methods (e.g., 72% altered their diet and 20% took up exercise), but these appear not to have worked, as almost three-quarters of patients reported that they had used laxatives since being prescribed their current opioid. This indicates an important role for the health care professional, not just the patient, in managing OIC. The range of patients who took part in the survey shows that OIC cannot be predicted by demographics or employment status, so each patient needs to be assessed individually.

In the absence of any formal guidance, a wide range of laxatives was prescribed, the most common being osmotics and stimulants. This is consistent with prescribing patterns seen among UK respondents in a pan-European survey of female patients with chronic idiopathic constipation [24]. OTC use was lower than we had anticipated based on our own clinical experience and results from previous surveys [9,24]. The exception was use of OTC stimulants, which was assumed to be driven by the use of senna.

Three-quarters of patients reported side effects with their laxatives. The most common (e.g., gas and bloating) were typical of laxatives. These unwanted effects reflect the lack of specificity in the mode of action of laxatives, which leads to overstimulation of the GI tract. Interestingly, younger patients reported more side effects than older patients. This is rather surprising given that older patients are generally considered to be more susceptible to side effects than younger patients [25]. One explanation could be that the relative minority of younger respondents represented a group who were more distressed by their symptoms.

Approximately half of patients reported that laxatives interfered with their work or social life; this could tie in with the higher incidence of side effects in younger patients and points to a socioeconomic impact of laxative use in patients with OIC. Gas and bloating were two of the most common factors cited by patients reporting a substantial interference with work or social life. This supports the findings of a pan-European survey in which female patients with chronic constipation reported that

Table 8 Morphine equivalent doses

	Total population	BFI category*		Previously constipated?†		Ever used laxatives?‡		Currently using laxatives?§	
		≤28.8	>28.8	Yes	No	Yes	No	Yes	No
	(N = 198)	(N = 46)	(N = 139)	(N = 43)	(N = 142)	(N = 134)	(N = 50)	(N = 122)	(N = 12)
Total daily morphine equivalent, mg									
N (missing)	126 (72)	30 (16)	92 (47)	30 (13)	92 (50)	90 (44)	31 (19)	82 (40)	8 (4)
Mean (SD)	68.3 (88.8)	83.8 (95.9)	64.0 (88.1)	80.6 (106.0)	65.0 (84.5)	73.2 (84.1)	57.8 (107.1)	66.0 (73.9)	147.2 (141.1)
Median (IQR)	40 (24.0–69.0)	40 (20.0–100.0)	30 (24.0–64.0)	39.5 (24.0–80.0)	40 (21.2–66.5)	44 (24.0–80.0)	24 (12.0–60.0)	42 (24.0–80.0)	92 (27.0–257.5)
Min, max	4.8, 580.0	4.8, 360.0	6.0, 580.0	6.4, 402.0	4.8, 580.0	6.0, 402.0	4.8, 580.0	6.0, 360.0	22.4, 402.0
Categories, N (%)									
20 mg or less	22 (17.5)	5 (16.7)	17 (18.5)	4 (13.3)	18 (19.6)	12 (13.3)	10 (32.3)	12 (14.6)	0 (0.0)
21 to 50 mg	54 (42.9)	11 (36.7)	41 (44.6)	15 (50.0)	37 (40.2)	38 (42.2)	13 (41.9)	35 (42.7)	3 (37.5)
51 to 80 mg	25 (19.8)	5 (16.7)	18 (19.6)	4 (13.3)	19 (20.7)	19 (21.1)	4 (12.9)	19 (23.2)	0 (0.0)
81 to 120 mg	11 (8.7)	4 (13.3)	7 (7.6)	3 (10.0)	8 (8.7)	10 (11.1)	1 (3.2)	8 (9.8)	2 (25.0)
Over 120 mg	14 (11.1)	5 (16.7)	9 (9.8)	4 (13.3)	10 (10.9)	11 (12.2)	3 (9.7)	8 (9.8)	3 (37.5)
Less than 20 mg	30 (23.8)	9 (30.0)	21 (22.8)	7 (23.3)	23 (25.0)	17 (18.9)	12 (38.7)	17 (20.7)	0 (0.0)
20 to 90 mg	72 (57.1)	13 (43.3)	55 (59.8)	16 (53.3)	52 (56.5)	53 (58.9)	15 (48.4)	49 (59.8)	4 (50.0)

Total daily morphine equivalent doses were calculated only for those patients who had data available for type of opioid, dose, and frequency. The following conversion ratios were used: buprenorphine:morphine, 0.5:1; codeine:morphine, 10:1; dihydrocodeine:morphine, 10:1; fentanyl:morphine, 0.2:1; methadone:morphine, 0.5:1; tapentadol:morphine, 2.5:1; tramadol:morphine, 10:1.

BFI = Bowel Function Index; IQR = interquartile range.

*Excludes 13 patients who did not complete the BFI questionnaire.

†Defined as patients who experienced frequent constipation before starting on opioids, excludes 13 patients whose previous constipation status was unknown.

‡Excludes 14 patients whose laxative use was unknown.

§Excludes 64 patients whose laxative use was unknown.

relief from bloating was the aspect of their laxative that they were least satisfied with [24].

Most patients had seen a primary care health care provider about their pain condition and/or constipation since starting their current treatment, suggesting that a proportion of the patients in our survey had inadequate pain control as well as constipation. There were also a number of secondary care visits: Approximately one-fifth of patients had required an overnight stay in the hospital, which would have had negative health care cost implications in addition to the burden on patients.

Patients' BFI scores provide the most compelling evidence that OIC does not respond to laxatives. In fact, patients who were using laxatives recorded a higher BFI score (i.e., they were more constipated) than those who did not use laxatives. BFI scores were not related to opioid strength, even though weak opioids are often prescribed over strong opioids as they are perceived to be "less constipating." Coyne et al. have previously shown that as the number of laxatives taken is increased, the proportion of patients with an inadequate response decreases [9]. We found that constipation appeared to worsen with increasing number of laxatives taken: 60% of patients who had never taken laxatives had a BFI score higher than 28.8, compared with all of those who were taking three or more laxatives. The proportion of patients who had a BFI score higher than 28.8 was similar to the proportion who reported that they had needed a laxative since starting their current opioid. Approximately one-quarter of patients said that they had a history of constipation before they started taking opioids, raising the possibility of a vulnerability to the condition. However, a post hoc analysis showed that their BFI scores were very similar to those of the total study cohort; therefore, these patients do not appear to have influenced the results.

It might be expected that patients with a total BFI score higher than 28.8 would be taking higher morphine equivalent doses than those with scores lower than 28.8. It was clear, however, that constipation was not linked to opioid strength and dose, but it was anticipated that patients may lower their dose of opioid in an attempt to control their constipation, an observation that correlates with previous studies [3,7,9]. Patients with a history of constipation might be expected to be taking lower opioid doses than those without, but we found that the morphine equivalent doses were generally similar between these groups. Laxative use may be seen as an indicator that patients are taking higher doses of opioid, but our analysis gave conflicting results depending on whether the patients had ever taken a laxative since starting their current opioid or were currently using laxatives. Although not formally tested, the descriptive data suggested no clear relationship between increasing total daily morphine equivalent dose and constipation or laxative use; this emphasizes the need for patients to be assessed individually.

As this was a survey, patients self-reported their symptoms and laxative use, so there is the potential for inaccuracies and recall bias; this must be considered as a limitation of these data. However, by answering anonymously via the internet, patients may have felt able to give more truthful responses to sensitive questions about bowel function than if the survey was conducted face-to-face. It should be noted that the BFI is validated as a tool to be used by health care professionals during consultations with patients; it has not yet been validated in the context of patient self-reporting.

Although patients were asked how much opioid and laxative medication they were taking relative to the recommended daily dose, the survey did not collect information on compliance. It would have been interesting to see whether the negative effects of laxatives that patients described affected their dosing pattern, or whether patients had ever reduced or missed doses of their opioid medication to have a bowel movement (as has been documented by several other studies [7,8,9]).

By conducting a survey, we have obtained a "real world" perspective on prescribing, rather than a guideline-based one. The data reflect current practice and show that opioids are being used in a wide range of conditions (including headache) and in combination. These prescribing patterns emphasize the importance of recognizing and managing OIC.

Conclusions

Use of laxatives to treat OIC is often ineffective and associated with side effects that reflect their lack of specificity. Instead of relieving the burden of OIC, laxatives themselves have a negative impact: approximately half of the patients surveyed reported that laxatives interfere with their work or social lives. A number of treatments that target the underlying cause of OIC are now available or in development [22]. There is a need to develop evidence-based treatment guidelines, which, combined with better education for health care professionals and patients, would be likely to shift prescribing away from multiple courses of laxatives and toward these newer treatments.

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References

1 World Health Organization. Cancer Pain Relief: With a Guide to Opioid Availability, 2nd edition. Geneva:

World Health Organization. Available at: http://apps.who.int/iris/bitstream/10665/37896/1/9241544821.pdf (accessed December 2015).

2 Pappagallo M. Incidence, prevalence, and management of opioid bowel dysfunction. Am J Surg 2001; 182(suppl 5A):11S–8S.

3 Panchal SJ, Müller-Schwefe P, Wurzelmann JI. Opioid-induced bowel dysfunction: Prevalence, pathophysiology and burden. Int J Clin Pract 2007;61:1181–7.

4 Dorn S, Lembo A, Cremonini F. Opioid-induced bowel dysfunction: Epidemiology, pathophysiology, diagnosis, and initial therapeutic approach. Am J Gastroenterol Suppl 2014;2:31–7.

5 Kurz A, Sessler DI. Opioid-induced bowel dysfunction: Pathophysiology and potential new therapies. Drugs 2003;63:649–71.

6 Walsh DT. Prevention of opioid side effects. J Pain Symptom Manage 1990;5:362–7.

7 Bell TJ, Panchal SJ, Miaskowski C, et al. The prevalence, severity, and impact of opioid-induced bowel dysfunction: Results of a US and European patient survey (PROBE 1). Pain Med 2009;10:35–42.

8 Cook SF, Lanza L, Zhou X, et al. Gastrointestinal side effects in chronic opioid users: Results from a population-based survey. Aliment Pharmacol Ther 2008;27:1224–32.

9 Coyne KS, Margolis MK, Yeomans K, et al. Opioid-induced constipation among patients with chronic noncancer pain in the United States, Canada, Germany, and the United Kingdom: Laxative use, response, and symptom burden over time. Pain Med 2015;16:1551–65.

10 Choi YS, Billings JA. Opioid antagonists: A review of their role in palliative care, focusing on use in opioid-related constipation. J Pain Symptom Manage 2002;24:71–90.

11 Penning-van Beest FJ, van den Haak P, Klok RM, et al. Quality of life in relation to constipation among opioid users. J Med Econ 2010;13:129–35.

12 Candrilli SD, Davis KL, Iyer S. Impact of constipation on opioid use patterns, health resource utilization, and costs in cancer patients on opioid therapy. J Pain Palliat Care Pharmacother 2009;23:231–41.

13 Morlion B, Clemens KE, Dunlop W. Quality of life and healthcare resource in patients receiving opioids for chronic pain: A review of the place of oxycodone/naloxone. Clin Drug Invest 2015;35:1–11.

14 Kwong WJ, Diels J, Kavanagh S. Costs of gastrointestinal events after outpatient opioid treatment for non-cancer pain. Ann Pharmacother 2010;44: 630–40.

15 Hjalte F, Berggren A-C, Bergendahl H, Hjortsberg C. The direct and indirect costs of opioid-induced constipation. J Pain Symptom Manage 2010;40: 696–703.

16 Iyer S, Davis KL, Candrilli S. Opioid use patterns and health care resource utilization in patients prescribed opioid therapy with and without constipation. Manag Care 2010;19:44–51.

17 Wan Y, Corman S, Gao X, et al. Economic burden of opioid-induced constipation among long-term opioid users with noncancer pain. Am Health Drug Benefits 2015;8:93–102.

18 Rentz AM, Yu R, Müller-Lissner S, Leyendecker P. Validation of the Bowel Function Index to detect clinically meaningful changes in opioid-induced constipation. J Med Econ 2009;12:371–83.

19 Ueberall MA, Müller-Lissner S, Buschmann-Kramm C, Bosse B. The Bowel Function Index for evaluating constipation in pain patients; definition of a reference range for a non-constipated population of pain patients. J Int Med Res 2011;39:41–50.

20 Rentz AM, van Hanswijck de Jonge P, Leyendecker P, Hopp M. Observational, nonintervention, multicentre study for validation of the Bowel Function Index for constipation in European countries. Curr Med Res Opin 2011;27:35–44.

21 Abramowitz L, Béziaud N, Caussé C, et al. Further validation of the psychometric properties of the Bowel Function Index for evaluating opioid-induced constipation (OIC). J Med Econ 2013;16:1434–41.

22 Webster LR. Opioid-induced constipation. Pain Med 2015;16:S16–21.

23 Argoff CE, Brennan MJ, Camilleri M, et al. Consensus recommendations on initiating prescription therapies for opioid-induced constipation. Pain Med 2015;16:2324–37.

24 Emmanuel A, Quigley EMM, Simrén M, et al. Factors affecting satisfaction with treatment in European women with chronic constipation: An internet survey. United European Gastroenterol J 2013;1:375–84.

25 Chau D, Walker V, Pai L, Cho LM. Opiates and elderly: Use and side effects. Clin Interv Aging 2008; 3: 273–8.