

ORIGINAL RESEARCH ARTICLES

The Prevalence, Severity, and Impact of Opioid-Induced Bowel Dysfunction: Results of a US and European Patient Survey (PROBE 1)

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ABSTRACT

Objective. This multinational, Internet-based survey was designed to assess the prevalence, frequency, severity, and impact of opioid-induced bowel dysfunction (OBD) in patients receiving opioid therapy for chronic pain and taking laxatives.

Design. In total, 322 patients taking daily oral opioids and laxatives completed the 45-item questionnaire. At the time of the survey, 45% of patients reported <3 bowel movements per week. The most prevalent opioid-induced side effects were constipation (81%) and straining to pass a bowel movement (58%). Those side effects considered most bothersome by patients were (in order of rank) constipation, straining, fatigue, small or hard bowel movements, and insomnia.

Results. Most of the OBD symptoms specified in the questionnaire were experienced by the majority of patients ≥ 4 times a week. Constipation was the OBD symptom that was most often reported as severe. Most patients reported that their OBD symptoms had at least a moderate negative impact on their overall quality of life and activities of daily living. A third of patients had missed, decreased or stopped using opioids in order to make it easier to have a bowel movement.

Conclusion. The survey findings confirm that OBD occurs frequently, despite the use of laxatives, in individuals taking daily oral opioids for chronic pain. These gastrointestinal symptoms add to the burden already experienced by chronic pain patients, negatively impacting quality of life and, in some cases, affecting opioid treatment itself.

Key Words. Opioid; Opioid-Induced Bowel Dysfunction (OBD); PROBE; Chronic Pain

Introduction

Opioids are the mainstay of chronic cancer pain treatment and are also important in the management of chronic non-cancer pain [1,2]. However, opioid therapy can be limited by side effects, including constipation and other gas-

trointestinal (GI) symptoms, nausea, vomiting, dry mouth, and sedation [1–3], of which constipation is the most common and persistent [2,4]. Constipation occurs as a result of the opioids binding to mu-opioid receptors in the GI system, which affects GI motility, secretion, fluid absorption and blood flow, and causes delayed colonic transit and inhibited defecation [2,5,6]. The spectrum of opioid-induced GI side effects is termed “opioid-induced bowel dysfunction” (OBD), and is characterized by hard, dry stools, straining to pass

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bowel movements, incomplete evacuation, bloating, abdominal distension, and increased gastric reflux [2].

Estimates of the prevalence of OBD, and its primary symptom, constipation, vary. A systematic review of randomized, placebo-controlled trials of opioid treatment for chronic noncancer pain found that, overall, 41% of oral opioid recipients reported constipation as an adverse event, compared with 11% of placebo recipients [7]. However, when actively questioned about side effects, studies have found that at least 90% of patients report constipation as a major side effect of their opioid regimen [8,9].

Opioid-induced side effects may be dose-limiting, thus affecting pain control, which together with the side effects themselves can reduce patients' quality of life (QoL) [4,10–12]. In particular, constipation is one of the most common reasons that patients avoid or stop using opioids, compromising effective analgesia [13]. Unlike many other opioid-induced side effects, such as nausea and sedation, patients rarely develop a tolerance to the GI side effects of opioid therapy [3,4]. Given this, laxatives are commonly used to manage OBD. However, this approach provides less than optimal symptom relief, possibly because laxatives do not specifically target the opioid-mediated mechanisms that cause constipation, such as those that result in delayed GI transit [2]. Furthermore, laxatives themselves are associated with a range of GI side effects, including bloating, increased gas, and abdominal fullness, which further limit the usefulness of this approach [2,14].

Here we describe results from the Patient Reports of Opioid-related Bothersome Effects

(PROBE) 1 survey, which was designed to assess the prevalence, frequency and severity of OBD symptoms in patients receiving opioid therapy for chronic pain who were taking laxatives. The survey assessed the impact of OBD on QoL and activities of daily living (ADL), and explored whether individuals alter their opioid regimen in order to avoid OBD.

Methods

Study Design and Sample

The Internet-based PROBE 1 survey was performed in France, Germany, Spain, Italy, United Kingdom, and the United States in January 2006. Participants were recruited from individuals who had either completed a previous survey (the Consumer Health Sciences National Health and Wellness Survey; <http://www.nhwsurvey.com>) in 2005 and reported using opioids, or were members of consumer panels constructed by an online market research provider (Lightspeed Research; Chronic Illness and General panels, members of which had opted into the panel thereby providing consent to receive invitations to participate in online surveys; Table 1). Participation in the PROBE 1 survey was entirely voluntary; a small incentive was offered in the form of a points scheme under which panel members earned points for survey completion, which could be redeemed against a choice of products. No identifying information that could compromise confidentiality, such as name and address, was released by the panel provider.

At screening, patients currently suffering from self-reported long-term or persistent pain (includ-

Table 1 Subject disposition

	Total	National Health and Wellness Survey 2005*	Lightspeed Research Panels†
Invited	130,293	3,103	127,190
Responded‡	34,367 (26.4%)	1,485 (47.9%)	32,882 (25.9%)
Excluded on screening§	33,337	1,257	32,080
Excluded for other reasons¶	244	4	240
Did not complete main interview	83	17	66
Completed interview	703	207	496
Met inclusion criteria for analysis**	611	—	—
Daily oral opioids	322	—	—
Oral opioids 2–3 days/week	107	—	—
Oral opioids 4–6 days/week	96	—	—

* United States, United Kingdom, France, Germany; invitees restricted to subjects who reported opioid use in NHWS responses.

† Chronic Illness and general consumer panels; United States, United Kingdom, France, Germany, Italy, Spain. Chronic Illness panel invitees had reported pain in previous surveys, although treatment/opioid use history was not documented prior to screening for the current survey; general panel invitees were not pre-screened.

‡ Accessed link to enrol for screening.

§ Did not suffer from long-term/persistent pain; did not use any opioid ≥ 2 days/week; or did not use laxatives during periods when using opioids.

¶ Quit between screening and main interview, or exceeded sample quotas.

** Used <4 opioids and had a "main" opioid.

ing cancer-related and noncancer pain; duration not specified for screening purposes), who were taking opioids for ≥ 2 days per week and were taking laxatives, were eligible for inclusion and asked to complete the questionnaire.

Data Collection

Eligible patients completed a 45-item online questionnaire that included questions on their pain and pain-causing condition, opioid use, and side effect history. Pain intensity was assessed on an 11-point scale, where 0 = no pain at all, and 10 = severe pain. Patients were asked to select side effects/symptoms they had experienced while using their current opioid from a list of 28 symptoms. The list was composed primarily of symptoms typically associated with OBD (e.g., constipation, abdominal pain, straining) or related to upper GI tract function (e.g., reflux, decreased appetite), but also included a few more general opioid side effects (fatigue, insomnia and dyspnea). Respondents who reported more than five symptoms were then asked to select the five that they found most bothersome. For these five symptoms (or all symptoms reported if five or less were selected) patients were asked to indicate the frequency (daily, 4–6 times per week, 2–3 times per week, once per week or less) and severity (mild, moderate, or severe) with which they occurred. Patients were also asked to indicate the impact of these symptoms on QoL and ADL, rated on a 5-point scale, where 0 = no impact, and 4 = greatly impacts. Examples of ADL presented to patients in the questionnaire included going to work or school, going on holiday or planning trips out with family and friends, shopping, walking several blocks, driving a car, doing yardwork, preparing meals, bathing, and climbing stairs. Items for the survey were based on the review of the literature and clinician interviews. The initial survey was piloted in a small group of patients and minor changes were made.

Data Analysis

The analysis reported here includes data from patients taking daily oral opioids and laxatives. Patients who reported they were currently taking four or more opioids, did not have a “main” opioid that they took routinely, or did not take opioids on a daily basis were excluded from the main analysis. In addition, patients who used transdermal opioid patches as well as or instead of oral opioids were also excluded from the main analysis because we were unable to confirm the number of days per week that the patient actually used the patch. Data

from individual participating countries were pooled to create an overall analysis sample. The survey responses were summarized descriptively; no formal statistical analysis was performed. Data from the main analysis population of patients receiving daily opioids were compared with those for patients who used oral opioids 2–3 days per week and 4–6 days per week.

Results

Study Population

In total, 703 patients completed the questionnaire, of whom 611 were eligible for data analysis (taking < 4 opioids and had a “main” regular opioid; Table 1). Of these, 322 took opioids orally on a daily basis and are included in the main analysis presented here. More female than male patients participated in the survey, and the mean age of patients was 50 years. The most common primary cause of patients’ pain was back problems (36%), with cancer-related pain accounting for only 4% of the sample (Table 2). The majority of patients (89%) had been suffering from their primary pain condition for over a year, and less than 2% reported pain that had lasted less than 1 month. Most patients were taking one or two opioids, and

Table 2 Demographics and baseline characteristics for patients taking oral opioids (% of sample in each group)

Characteristic	Opioid Frequency		
	Daily (N = 322)	2–3 days/week (N = 107)	4–6 days/week (N = 96)
Gender			
Female	63	64	69
Male	37	36	31
Primary pain-causing condition			
Back problems	36	28	35
Joint problems	14	15	9
Surgical	8	7	3
Fibromyalgia	7	3	5
Dental	6	9	2
Neck problems	5	7	8
Muscle	5	5	11
Cancer	4	1	3
Migraine	2	23	10
Broken bones	2	2	2
Other*	16	10	9
Number of opioids per patient			
1	39	68	50
2	55	29	46
3	7	3	4
Longest duration on any opioid			
<1 month	4	9	6
1–12 months	19	33	38
1–5 years	43	36	30
>5 years	34	21	26

* Other includes rheumatoid/osteoarthritis, menstrual pain.

Table 3 Prevalence and “bothersomeness” rank of opioid-induced gastrointestinal side effects reported by $\geq 20\%$ of patients

OBD Symptom	Number of Patients (%) (N = 322)	Bothersomeness Rank*
Constipation	262 (81)	1
Straining (to pass a bowel movement)	188 (58)	2
Too small/hard bowel movement	161 (50)	4
Fatigue	160 (50)	3
Incomplete evacuation	144 (45)	6
Insomnia	128 (40)	5
Passing gas	111 (34)	7
Bloating	106 (33)	8
Lower abdominal discomfort	101 (31)	8
Heartburn	91 (28)	11
Nausea	83 (26)	10
Reflux/regurgitation [†]	83 (26)	11
Decreased appetite	76 (24)	16
Abdominal rumblings	75 (23)	20
False alarm [‡]	66 (20)	19
Upper abdominal pain/discomfort	65 (20)	13

* Bothersomeness ranked according to the relative number of respondents reporting side effect as bothersome.

[†] Presence of food or liquid in the mouth.

[‡] Feeling the need for a bowel movement, but no bowel movement on visiting the bathroom.

OBD = opioid-induced bowel dysfunction.

the majority had been receiving opioid therapy for ≥ 1 year; approximately one third of patients had been taking an opioid for >5 years (Table 2). The mean pain intensity score was 6.2.

All patients reported taking laxatives, the most common laxative classes being stimulants (33%), hyperosmotics (18%), and bulking agents (12%). Almost a half of patients (44%) reported using two or more different types of laxative in the preceding 3 months, and a similar proportion (48%) used a laxative on at least 5 days of the week. The majority of patients (226 individuals, 70%) reported

having ≥ 3 bowel movements per week prior to taking any treatment for their pain; 20% (64 patients) reported <3 bowel movements per week prior to receiving pain treatment (the remaining patients did not provide any information on prior bowel movement frequency). At the time of the survey (i.e., while taking oral opioids), the proportion of patients reporting ≥ 3 bowel movements per week had decreased to 55% (178 patients), and the proportion reporting <3 bowel movements per week had increased to 45% (144 patients).

Prevalence, Frequency, and Severity of the Symptoms of OBD

The most frequently reported opioid-induced GI side effects are summarized in Table 3. The most common side effects were constipation (81%) and straining to pass a bowel movement (58%). The majority of patients reported between two and 10 side effects (72%); a further 22% reported >10 side effects, whereas only 2% (six patients) reported none. When patients were asked to indicate the five side effects that they found most bothersome, those most commonly cited (in order of rank) were constipation, straining, fatigue, small or hard bowel movements, and insomnia (Table 3).

The frequency of the most common symptoms of OBD is illustrated in Figure 1. For most symptoms, the majority of patients who reported them experienced the symptom ≥ 4 times a week. The exceptions were hard bowel movements and straining, which the majority of patients experienced ≤ 3 times a week. Bloating and passing gas were experienced daily by over half (67%) of those who reported these symptoms. Symptoms were most commonly reported as moderate or severe (Figure 2). The symptoms most frequently

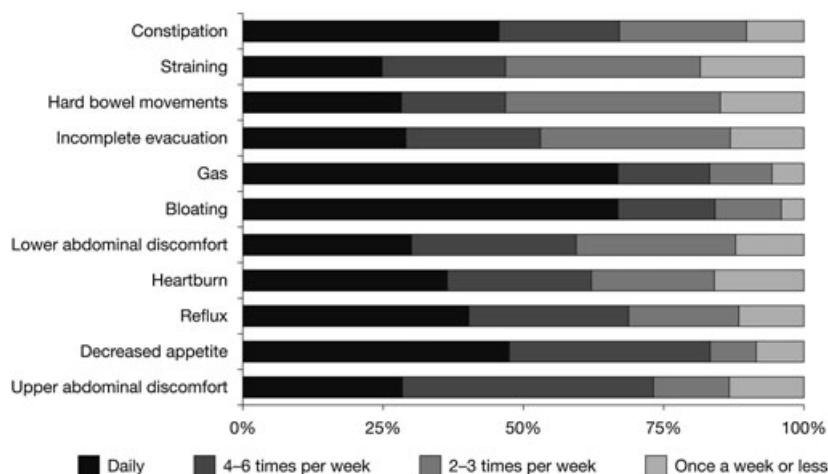


Figure 1 Frequency of the most common symptoms of OBD: the majority of patients experienced most symptoms ≥ 4 times a week.

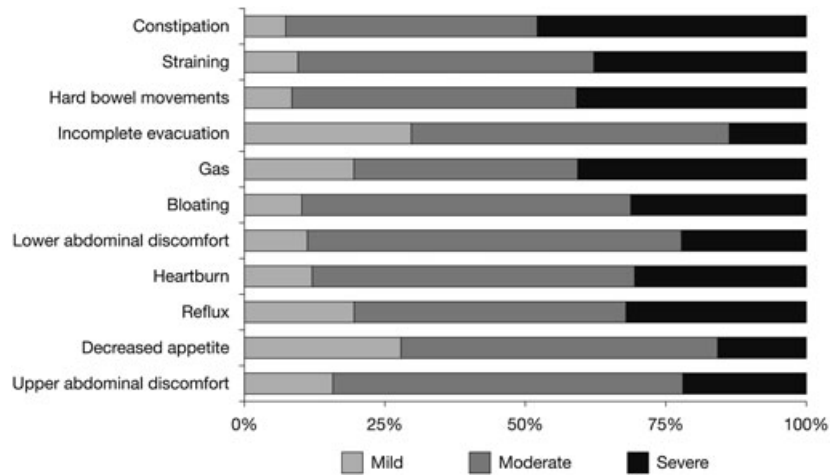


Figure 2 Severity of the most common symptoms of opioid-induced bowel dysfunction: symptoms were rated as moderate or severe by most patients.

reported as severe were constipation (48%), gas (41%), hard bowel movements (41%), and straining (38%).

When the results for patients who used opioids daily were compared with those who used them for 4–6 days per week or for 2–3 days per week, the pattern of opioid-induced side effects reported was similar. However, the prevalence of the most common side effects declined with decreased opioid use. For example, constipation and straining to pass a bowel movement declined from 81% and 58% for daily opioid use to 59% (57 of 96 patients) and 47% (45 of 96 patients), respectively, in patients who used opioids 4–6 days per week, and to 46% (49 of 107 patients) and 30% (32 of 107 patients), respectively, in patients who used opioids only 2–3 days per week. Although a difference in prevalence of side effects was seen with opioid dosing frequency,

there were no consistent trends in how often patients experienced side effects during the week or symptom severity.

Impact on QoL and Activities of Daily Living

The majority of patients reported that the symptoms of OBD had at least a moderate negative impact on their QoL or overall well-being (Figure 3). More than half of patients who experienced them rated the impact on QoL of constipation, passing gas, and bloating as 3 or 4 (moderate-to-great or great impact). The majority of patients also reported that the symptoms of OBD had at least a moderate impact on ADL (Figure 4). The symptoms most often reported as having a moderate-to-great or great impact on ADL were upper abdominal pain, bloating, passing gas, lower abdominal pain, reflux, and heartburn. However, overall, the proportion of

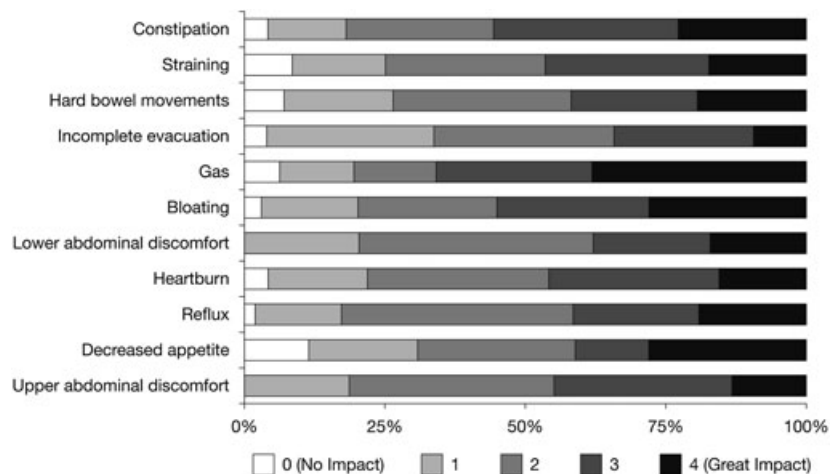


Figure 3 Impact of the most common symptoms of opioid-induced bowel dysfunction on quality of life: the majority of patients reported at least a moderate negative impact on quality of life of opioid-induced bowel dysfunction symptoms.

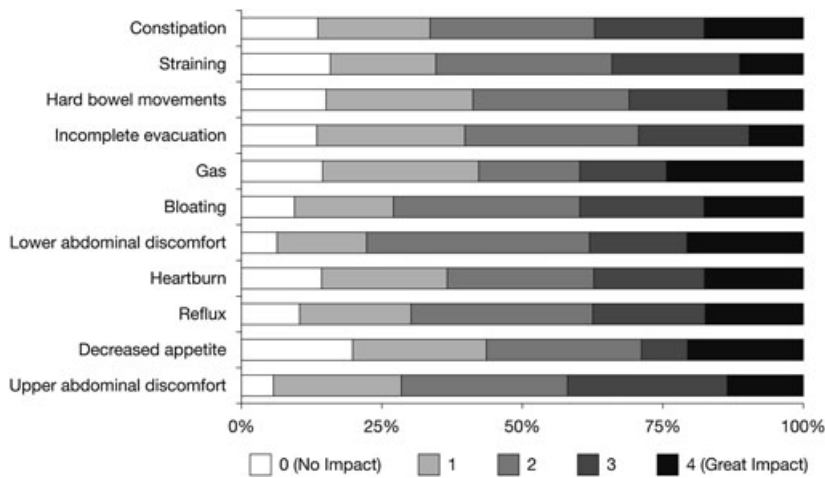


Figure 4 Impact of the most common symptoms of opioid-induced bowel dysfunction on activities of daily living: opioid-induced bowel dysfunction symptoms generally had at least a moderate impact on activities of daily living.

patients considering that individual symptoms had a moderate-to-great or great impact on ADL was lower than for QoL.

When data on the impact of the symptoms of OBD on QoL and ADL were compared between patients who used oral opioids daily, and those who used them for 4–6 days per week, or for 2–3 days per week, there were no clear differences in impact associated with the frequency of opioid use.

Pain Relief and Avoidance of Opioid-Induced Side Effects

When questioned, about a third of patients (114 patients, 35%) reported that they had missed, decreased, or stopped using opioids in order to obtain relief from opioid-induced side effects, and over a quarter (89 patients, 28%) had used a lower dose than desired in order to avoid side effects. A third of patients (105 patients, 33%) reported that they had missed, decreased, or stopped using opioids specifically in order to make it easier to have a bowel movement.

As might be expected, the majority of patients who had decreased or stopped using opioids due to OBD symptoms reported that they had experienced increased pain after doing so (125 of 136 patients, 92%). Most of these patients then reported that the increased pain had a moderate-to-great or great impact on QoL (107 of 125 patients, 86%) and ADL (107 of 125 patients, 86%).

Discussion

The PROBE 1 survey is one of the first large-scale patient surveys to investigate the prevalence, fre-

quency and severity of OBD symptoms in individuals taking oral opioids for chronic pain, and the impact of these side effects on QoL and ADL. The survey results confirm that OBD occurs frequently in this patient population, despite the use of laxatives. While a trend was noted in the survey sample toward a reduction in the number of bowel movements per week after starting opioid treatment, this finding is partly based on patients' recall of bowel movement frequency before starting opioid treatment. More specific questioning on the side effects that patients experienced while using opioids demonstrated that constipation (81% of patients) and straining to pass a bowel movement (58% of patients) were the most prevalent opioid-induced side effects. Constipation was also the side effect considered most bothersome by patients, and most often reported as severe. Generally, patients experienced OBD symptoms frequently, with most patients reporting suffering ≥ 4 times a week, and bloating and passing gas occurring most frequently in those who experienced them. Most patients reported that their OBD symptoms had at least a moderate negative impact on their overall QoL and ADL. A key finding of the survey was that approximately a third of patients had missed, decreased, or stopped using opioids either in order to obtain relief from opioid-induced side effects (35%) or specifically in order to make it easier to have a bowel movement (33%), and 28% had used a lower dose than desired in order to avoid side effects. Of these patients who altered their opioid dose to avoid OBD, over 90% reported an increase in pain, which in turn had a negative impact on QoL.

The prevalence of constipation in this sample of patients with chronic pain and taking oral opioids

is consistent with the findings of previous studies that used active questioning to elicit information on opioid side effects. In patients with cancer pain and in those with chronic low back pain, at least 90% of patients reported constipation as a major side effect of their opioid therapy [8,9]. Furthermore, as the majority of the patients in the survey sample had been using opioids for ≥ 1 year, the results would seem to confirm that patients rarely develop tolerance to the constipating effects of opioid therapy [4]. Thus, for patients who experience constipation as a result of the disease process or medication (such as patients with cancer), opioid therapy may add to the burden of illness of this GI symptom and make it more difficult to manage [2]. In extreme cases, complications of uncontrolled constipation can include fecal impaction and fecal incontinence, anorexia, nausea, vomiting and inadequate absorption of oral drugs due to bowel obstruction [15], which can significantly add to patients' pain and may also lengthen hospital stays and increase health-care resource use [15].

When considering the results of the survey, it is important to bear in mind several limitations of the study design. This was an Internet-based survey, introducing potential bias against individuals without Internet access; however, the impact of this is expected to be limited in countries with high levels of Internet use, such as the United States and Western European countries. As patients were free to choose whether or not to participate in the survey, there may be a bias in the survey sample toward individuals who were experiencing side effects from their opioid therapy; it is also unlikely that individuals who were severely unwell responded to the survey. Furthermore, as no independent verification of the patients' diagnosis or treatment was made, it is possible that misclassification bias occurred. All patients included in the analysis were taking laxatives as well as oral opioid therapy; therefore, it is possible that the GI side effects that can occur with laxative treatment were a confounding factor. In particular, this may partly explain the high frequency of bloating and passing gas in those who experienced these symptoms, as these are known to be side effects of laxative use [14]. In addition, patients may be taking other medications, have limited mobility, or have dietary habits that can contribute to the occurrence of constipation. Therefore, it may not be certain that the prevalence of OBD symptoms found in this study are only related to opioids. Finally, it should be noted that the rating scale used to assess the

impact of side effects on patients' QoL and ADL was not a validated instrument.

However, it is clear that the survey findings confirm that OBD symptoms occur frequently in individuals taking daily oral opioids for chronic pain, despite the use of laxatives. This finding has important implications for patients' QoL. Given the burden of illness already experienced by patients with chronic cancer and noncancer pain, the additional effects of OBD on QoL and ADL are not insignificant. The most prevalent opioid-induced side effect in the survey sample, constipation, was also one of the OBD symptoms most frequently reported as having a great impact on QoL and ADL. This finding is consistent with existing evidence from studies using a range of disease-specific and generic questionnaires to measure health-related QoL, which suggests that constipation of any cause results in reduced QoL, compared with that of the general population [16,17]. Persistent constipation in patients with advanced cancer has also been shown to be associated with deteriorating performance status [10]. Interestingly, in the current survey sample, passing gas rather than constipation was the symptom of OBD reported as having a great impact on QoL and ADL by the largest proportion of those experiencing it. Again, as all patients included in the survey were taking laxatives as well as oral opioid therapy, it is possible that this finding reflects the side effects of laxative treatment as well as those of oral opioids. Further research into the impact of laxative side effects on patients with OBD is warranted.

As demonstrated by the survey findings, patients with chronic pain may choose to limit or discontinue opioid therapy in order to avoid the symptoms of OBD; this may be a particular problem if physicians fail to anticipate opioid side effects [13,18]. Thus, OBD can compromise pain control: 92% of patients in the survey sample who had decreased or stopped using opioids due to OBD reported that they had experienced increased pain after doing so, with consequent negative impacts on QoL and ADL. In addition to influencing patients' decisions about opioid therapy, concerns about side effects may also mean that physicians are reluctant to prescribe opioids [1].

Although the proportion of patients who reported the most common side effects was seen to reduce with decreased opioid dosing frequency, about 50% of patients continued to experience constipation, even where opioid dosing was as infrequent as 2 or 3 times a week. Furthermore,

for those patients experiencing opioid-related GI symptoms, the negative impact of these side effects on QoL and ADLs was similar regardless of the frequency of opioid use. The survey did not collect sufficient data on opioid dosages to permit robust assessment of a possible relationship between opioid load and occurrence of side effects. However, the data on dosing frequency suggest that, while opioid-sparing strategies are an option for physicians managing patients experiencing side effects, GI symptoms remain a problem.

Summary

The findings of the PROBE survey confirm that OBD occurs frequently, despite the use of laxatives, in individuals taking daily oral opioids for chronic pain. Most patients reported that their OBD symptoms had at least a moderate negative impact on their overall QoL and ADL, adding to the burden already experienced by chronic pain patients. The survey also demonstrated the potential for OBD to compromise opioid therapy, with as many as one-third of patients reporting that they missed or reduced doses to alleviate side effects. As opioids remain the mainstay of treatment for moderate to severe chronic pain, there is a clear need to manage OBD effectively to ensure that GI side effects are not a burden to patients or a barrier to optimal pain management.

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