

Opioid-Induced Gastrointestinal Dysfunction (OGD): A Questionnaire Survey of Chronic Opioid Users

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Abstract

In order to gain insight into the symptoms of opioid-induced gastrointestinal dysfunction, we conducted a questionnaire survey among 119 daily prescription-opioid users, also to understand how they deal with the dysfunction, with or without physician assistance, using the abundantly available, over-the-counter constipation remedies. Almost 80% had constipation, as opposed to almost 20% before taking opioids, and more than 60% had constipation despite the use of constipation remedies. More than half had bowel movements 1 to 3 times per week, which was the case in slightly over 20% before taking opioids. Despite the use of constipation remedies, straining, incomplete evacuation, rectal impaction, and hard stool were common. Of these symptoms, hard stool was considered to be the most bothersome, followed by flatulence, abdominal discomfort/pain, false alarm, and abdominal bloating. Relatively serious complications of the constipation, such as hemorrhoids, anal fissures, rectal impaction, and rectal prolapse, were reported by 20% to 40% of patients. Of the stomach symptoms per se, anorexia and acid reflux were relatively common, warranting the term opioid-induced gastrointestinal dysfunction.

Keywords: Opioids; Constipation; Hard stool; Abdominal symptoms; Flatulence; Acid reflux; Nausea

Introduction

Opioid receptors are extensively present in the central nervous system and in the gastrointestinal tract. Their extensive presence in the gastrointestinal tract causes the profound gastrointestinal dysfunction often seen in chronic opioid users. Constipation is generally the most prominent consequence of opioid-induced gastrointestinal dysfunction but hardly the only one. The focus on constipation has generated such terms as opioid-induced constipation (OIC) and opioid-induced bowel dysfunction (OBD), the latter also encompassing bowel-dysfunction consequences other than constipation, such as abdominal bloating, discomfort or pain, cramping, and flatulence. Opioid-induced gastrointestinal dysfunction (OGD) is probably a better term, also covering the gastric symptoms often seen with chronic opioid use, such as anorexia, nausea, acid reflux, and vomiting. It also encompasses the consequences of bowel dysfunction at the other end of the gastrointestinal tract, such as hemorrhoids, anal fissures, fecal impaction in the rectum (rectal impaction), and rectal prolapse.

In order to gain insight into the symptoms of opioid-induced gastrointestinal dysfunction, we conducted a questionnaire survey among 119 daily prescription-opioid users, also to understand how they deal with dysfunction, with or without physician assistance, using the abundantly available, over-the-counter constipation remedies.

Methods

Our questionnaire consisted of 6 sections. The first section asked about daily opioid use and requested only those who were taking opioid analgesics on a daily basis to complete the questionnaire. It proceeded to inquire about age, gender, weight, height, duration of daily opioid use (<1 month; 1-3 months, 4-12 months, >1 year) and the main reason for opioid use. Section 2 asked about the opioids used, including information to allow for the calculation of the average daily doses. It also inquired about constipation before daily opioid use, whether the prescribing physician had recommended the use of constipation remedies, and whether constipation is present without the use of stool softeners or laxatives or despite their use.

Section 3 asked about the average number of bowel movements per week before daily opioid use (0-1, 2-3, 4-5, 6-7, >7) and the average

number of bowel movements per week, even when using stool softeners or laxatives. It proceeded to inquire about the percentage of bowel movements (less or more than 25%) with incomplete evacuation, straining, stool stuck in the rectum (rectal impaction), requiring manual assistance, and producing small, hard pellets or hard, lumpy stool (Types 1 and 2, respectively, of the Bristol Stool Scale). Finally, it asked to rate the intensity as absent, mild, moderate, severe, or very severe of the following symptoms in the last 2 weeks, with or without the use of constipation remedies: stool too hard, discomfort/pain in the abdomen, cramping in the abdomen, inability to pass stool when feeling the urge ("false alarm"), difficulty breathing because of pressure in the abdomen, passing gas, decreased appetite, bloating, acid reflux due to the constipation, nausea, and vomiting, and which symptom is most bothersome.

Section 4 asked whether any of the following constipation-relieving products were used in the past week and the number of doses taken: stool softeners, stimulant laxatives, mineral oil, enema, polyethylene glycol, psyllium, milk of magnesia, and other. It proceeded to inquire whether taking stool softeners or laxatives provided adequate constipation relief. Section 5 inquired whether the constipation was ever discussed with the prescribing physician, whether it was ever considered to decrease the opioid dose because of the constipation, whether the physician ever switched opioids because of the constipation, whether the opioid dose was actually ever decreased because of the constipation, and whether side effects were ever a deterrent for taking constipation remedies. Section 6 asked about the constipation complications of hemorrhoids, anal fissures, rectal impaction, and rectal prolapse and, if present, before taking opioids without change, before taking opioids with worsening, or newly developed after taking opioids.

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The answers to the questionnaires were entered on an Excel spreadsheet and imported into SPSS. Morphine-equivalent doses were determined using the opioid analgesic calculator as provided by www.globalrph.com; oral fentanyl 400 mcg was considered equivalent to 15 mg morphine equivalents, transdermal fentanyl 25 mcg/hour equivalent to 100 mg morphine equivalent, and 100 mg tramadol equivalent to 22.2 mg morphine equivalent. The Fisher exact test was used to analyze 2x2 contingency tables; otherwise, the Chi-square test was used.

Results

A total of 119 prescription-opioid users completed the questionnaire, 57 (47.9%) men and 62 (52.1%) women; their age averaged 53.9 ± 9.5 (S.D.) years, with a range of 27 to 84 (median: 53.0). Their BMI was 29.9 ± 7.3 kg/m² with a range of 16.3 to 52.6 (median: 29.0). Almost all of them (93.3%) had been taking opioids on a daily basis for longer than 1 year and, hence, were chronic opioid users. Almost half of them (47.2%) were taking opioids for chronic low-back pain, followed by osteoarthritis hip or knee pain (20.8%), and fibromyalgia (6.6%), while 22.6% were taking opioids for a variety of other pain conditions, and 2.8% for addiction. The opioids they were taking included oxycodone in 77 (64.7%) (Table 1); 39 (32.8%) were taking two opioids and 7 (5.9%) three. The mean daily opioid dose in terms of morphine equivalents was 142.7 ± 153.1 mg, with a range of 4 to 744 mg (median: 68.0 mg); the distribution was very much skewed to the left.

Of the opioid users, 23 (19.3%) acknowledged constipation before taking opioids on a daily basis. On the daily opioids, 93 (78.2%) indicated to be constipated without the use of constipation remedies (p<0.0001 versus before taking opioids) and 62 (52.1%) even when taking those remedies (p<0.0001 versus without constipation remedies). Before the daily use of opioids, 26 (21.8%) indicated to have bowel movements, on average, 1 to 3 times per week; while on the daily opioids and even with the use of constipation remedies, this number was 61 (51.3%) (Figure 1,

p<0.0001). Even with constipation remedies and related to more than 25% of the bowel movements, 79 (66.4%) acknowledged moderate or severe straining, 70 (58.8%) incomplete evacuation, 55 (46.2%) the feeling that stool is stuck in the rectum (rectal impaction), 42 (35.3%) small, hard pellets (Bristol Stool Scale Type 1) or hard, lumpy stool (Type 2), and 12 (10.1%) the use of manual assistance. The intensity of the gastrointestinal symptoms as experienced by the opioid users in the last 2 weeks, with or without constipation remedies, is presented in Table 2. Of these symptoms, 31 (26.1%) indicated the stool being too hard as the most bothersome one, 20 (16.8%) the flatulence, 19 (16.0%) the abdominal discomfort/pain, 17 (14.3%) the false alarm, and 14 (11.8%) the abdominal bloating; dyspnea and vomiting were indicated least often as the most bothersome (<1.0%).

Sixty eight (57.1%) of the opioid users indicated that the prescribing physician had also recommended them to take a constipation remedy. Only 15 (12.6%) did not take anything for the constipation, 52 (43.7%) took one remedy in the past week, 30 (25.2%) two remedies, 17 (14.3%) three, and 5 (4.2%) four. Sixty three (52.9%) took stool softeners (7.1 ± 4.0 doses/week), 46 (38.7%) stimulant laxatives (4.8 ± 4.4 doses/week), 35 (29.4%) osmotic laxatives (5.5 ± 4.1 doses/week), 13 (10.9%) fiber (5.3 ± 3.5 doses/week), 10 (8.4%) enema (2.2 ± 1.7 doses/week), 6 (5.0%) mineral oil (3.8 ± 2.0 doses/week), and 10 (8.4%) other constipation remedies (6.4 ± 2.6 doses/week). Forty eight (40.3%) indicated obtaining adequate relief from the constipation remedies; 54 (45.4%) acknowledged experiencing side effects.

Of the opioid users, 85 (71.4%) had discussed the constipation with the prescribing physician; only 9 (7.6%) reported that the physician switched to a different opioid because of the constipation. The constipation made 32 (26.9%) consider decreasing the amount of opioid medication taken, while 25 (21.0%) had actually decreased the amount.

In terms of complications of the constipation, 30 (25.2%) of the

Opioid	N (%)	Mean daily dose	Median daily dose	Daily dose range
Oxycodone	77 (64.7%)	41.3 ± 57.6 mg	25.0 mg	10-400 mg
Morphine	20 (16.8%)	100.4 ± 67.8 mg	67.5 mg	30-300 mg
Hydrocodone	18 (15.1%)	23.8 ± 13.4 mg	20.0 mg	4-60 mg
Fentanyl	17 (14.2%)	67.6 ± 39.3 mcg	50.0 mcg	25-175 mcg
Methadone	18 (15.1%)	68.2 ± 42.7 mg	60.0 mg	6-140 mg
Tramadol	12 (10.1%)	220.8 ± 125.2 mg	200.0 mg	50-400 mg
Hydromorphone	8 (6.7%)	12.7 ± 9.2 mg	13.5 mg	1-24 mg
Other	4 (3.4%)	NA	NA	NA

Table 1: Opioids taken daily by the opioid users (N=106).

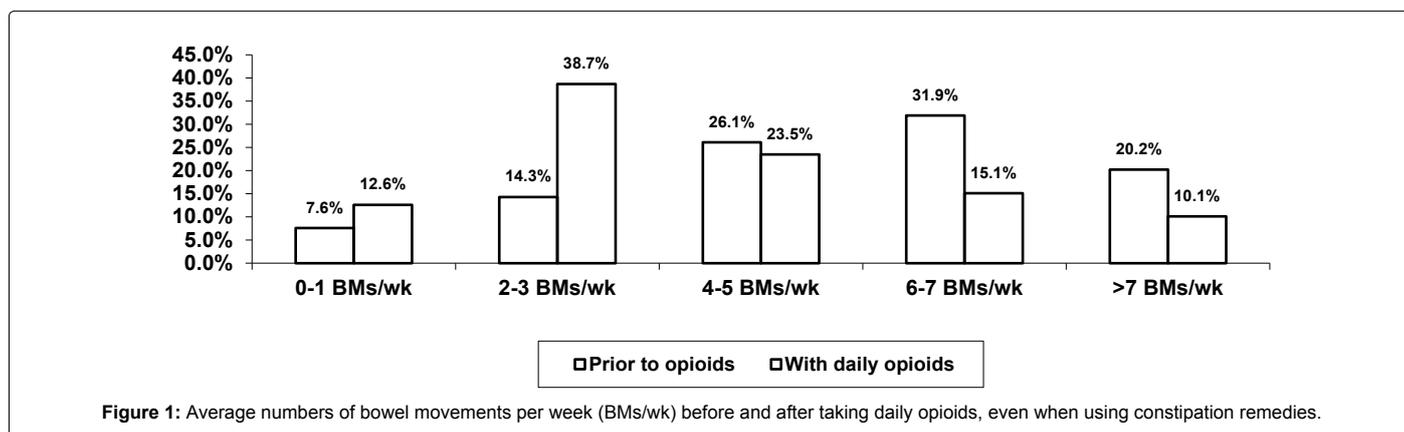


Figure 1: Average numbers of bowel movements per week (BMs/wk) before and after taking daily opioids, even when using constipation remedies.

Symptom	Absent or mild	Moderate	Severe or very severe
Stool too hard	37 (31.1%)	40 (33.6%)	42 (35.3%)
Abdominal bloating	43 (36.1%)	35 (29.4%)	41 (34.5%)
Abdominal discomfort/pain	42 (35.3%)	40 (33.6%)	37 (31.1%)
Abdominal cramping	55 (46.2%)	31 (26.1%)	33 (27.7%)
False alarm ¹	48 (40.3%)	40 (33.6%)	31 (26.1%)
Flatulence	36 (30.3%)	48 (40.3%)	35 (29.4%)
Dyspnea ²	77 (64.7%)	25 (21.0%)	17 (14.3%)
Anorexia	61 (51.3%)	33 (27.7%)	25 (21.0%)
Acid reflux ²	67 (56.3%)	31 (26.1%)	21 (17.6%)
Nausea	82 (68.9%)	25 (21.0%)	12 (10.1%)
Vomiting	111 (93.3%)	6 (5.0%)	2 (1.7%)

¹Feeling to have to pass stool but unable to do so; ²Due to constipation

Table 2: Symptoms of opioid-induced gastrointestinal dysfunction (N=119).

opioid users reported the worsening or occurrence of hemorrhoids, 22 (18.5%) that of anal fissures, 50 (42.0%) rectal impaction, and 24 (20.2%) rectal prolapse.

Discussion

The prescription-opioid users who completed the questionnaire were mostly long-term users for chronic non-cancer pain related to the musculoskeletal system. They were taking opioids on a daily basis, often one or two and almost two-third were taking oxycodone. The range of daily morphine equivalents was 4 mg to 744 mg with a median of 68.0 mg, with the conversion mostly based on www.globalrph.com. Almost 80% had constipation with the daily use of opioids as opposed to almost 20% before taking opioids; more that 60% had constipation despite using constipation remedies. More than half had bowel movements 1 to 3 times per week, which was slightly over 20% before taking opioids. Despite the use of constipation remedies, straining, incomplete evacuation, rectal impaction, and hard stool were common. Of these symptoms, hard stool was considered to be the most bothersome, followed by flatulence, abdominal discomfort/pain, false alarm, and abdominal bloating.

In more than half had the prescribing physician recommended constipation remedies and almost 90% had taken something in the past week, mostly stool softeners and/or laxatives. However, only 40% indicated to obtain adequate relief and almost half experienced side effects. More than two-third had discussed the constipation with the prescribing physician, which had resulted in a dose decrease in slightly over 20% and switching to a different opioid in less than 10%. Relatively serious complications of the constipation, such as hemorrhoids, anal fissures, rectal impaction, and rectal prolapse, were reported by 20% to 40% of patients. Of the stomach symptoms per se, anorexia and acid reflux were relatively common, warranting the term opioid-induced gastrointestinal dysfunction.

Researching the literature, three similar surveys of opioid-induced gastrointestinal dysfunction were found, published since 2008. The survey by Cook et al. [1] was population based, used a Web-based panel, and involved US adults who used opioid medication on a chronic basis for pain unrelated to cancer. A total of 2055 met their eligibility criteria and they found that those who responded to their invitation had characteristics similar to the general US population with a few exceptions. Back problems were most commonly noted (63%) and hydrocodone and oxycodone were the most frequently used opioid medications (56% and 28%, respectively). Approximately half were using one opioid currently (51%), 31% two, and 18% three or more; 60% were taking opioids for more than 12 months and, hence,

were chronic users. In response to the question, have you ever had constipation that began or became worse after using current opioids, 57% responded affirmatively. Increased gas was acknowledged by 34%, nausea by 31%, abdominal discomfort/pain by 30%, bloating by 29%, heartburn by 24%, reflux by 23%, and anorexia by 20%. They indicated their most bothersome symptoms to be constipation, followed by nausea, abdominal discomfort/pain, and gas. Of those who reported gastrointestinal symptoms, 73% had not changed the dose or frequency of opioid intake and of those who reported new or worsening constipation, 72% had used at least one non-prescription laxative and 12% a prescription laxative. Approximately one-quarter reported dissatisfaction with the available laxatives and when using a laxative, approximately 45% reported diarrhea or urgency.

The survey by Bell et al. [2] was a multinational, internet-based survey and involved 703 opioid users of whom 611 were eligible for data analysis, based on taking less than 4 opioids and having a "main" regular opioid. Of those, 322 were taken opioids daily, 36% for back problems and 14% for joint problems, with 39% taking one opioid and 55% two, 77% for 1 year or longer. Of the 322 daily opioid users, 81% reported constipation, 58% straining, 50% too small/hard bowel movements, 45% incomplete evacuation, 34% passing gas, 33% bloating, 31% lower-abdominal discomfort/pain, 28% heartburn, 26% nausea, 26% reflux, 24% anorexia, 23% borborygmus, 20% false alarm, and 20% upper-abdominal discomfort/pain. All of them indicated taking laxatives, most commonly stimulants (33%), hyperosmotics (18%), and bulking agents (12%); 44% used two or more laxatives and 48% used a laxative at least 5 days per week. With opioid use, the proportion with three or more bowel movements per week decreased from 70% to 55% and the proportion with less than three bowel movements per week increased from 20% to 45%. A third of them (33%) reported that they had missed, decreased, or stopped using opioids specifically to make it easier to have a bowel movement, with 92% acknowledging increased pain after doing so.

The third survey by Abramowitz et al. [3] dealt, in contrast to ours and the two above, with cancer pain patients and involved a cross-sectional study conducted in France. It involved 520 patients but 68% of them presented at the time of the study also with factors other than opioid treatment likely to cause constipation. Hence, it is not clear how much of their gastrointestinal symptomatology is caused by opioids and, in addition, the duration of their opioid treatment was relatively short, that is, 4.4 months on average. On the basis of the Knowles Eccersley Scott Symptom (KESS) questionnaire, 62% of the patients were considered constipated. Of these patients, 55% had bloating, 51% anorexia, 43% flatulence, 36% straining, 26% pelvic discomfort, 24% pain during defecation, 13% epigastric discomfort, and 12% reflux;

85% took laxatives and 51% almost on a daily basis. Three-quarter of the constipated patients experienced pain from the condition, with 37% reporting the pain as moderate or severe and 19% considering a change in opioid treatment if the pain persisted. The gastrointestinal symptoms had already led to a decrease in opioid dose in 10%, decrease in frequency of intake in 7.5%, and discontinuation in 5%. When the opioid treatment was, indeed, altered, it led to increased pain in at least 86%.

In the context of our survey and the surveys reviewed, a study of interest is the one by Epstein et al. [4], focusing on the question, which of their many symptoms patients with opioid-induced constipation viewed as most important to be improved upon. The study was a cross-sectional, geographically dispersed, online, self-reported survey of adults with self-reported chronic non-cancer pain, on a chronic course of opioid medications, and having at least two active symptoms of opioid-induced constipation. Of the 513 participants, only 11% considered themselves to be in "very good" or "excellent" health, with 80% taking opioids for back pain, 70% for joint pain, and 50% headache (the majority seems to have multiple pain issues). The aspects of the constipation most ($\geq 80\%$) would prefer to improve were: 1. Being able to have a bowel movement without pain (88%); 2. Being able to have soft stool that is not loose or watery (87%); 3. Not experiencing rectal straining due to the constipation (83%); 4. Feeling less bloated (83%); 5. Being more comfortable using opioid medication without fear of being constipated (82%); 6. Worrying less about being able to have a bowel movement (80%); and 7. Having less pain in the stomach area (80%).

In summary and based on our survey and the surveys reviewed, 60% to 80% of (daily) opioid users for cancer or non-cancer pain have constipation, while up to 20% may have had constipation prior to the opioid use. Of those who are constipated, 70% to 100% take constipation remedies, such stool softeners or laxatives, generally non-prescription,

often on a daily or almost daily basis, and relatively commonly with unsatisfactory results or side effects such as diarrhea. In one-fifth to one-third, the constipation and/or relative lack of the constipation remedies leads to downward alterations of the opioid treatment, with worsening of the pain in as much as 90%. Apart from constipation, the list of gastrointestinal symptoms with opioids is long, affecting both the upper- and lower-gastrointestinal tract, that is, stomach and colon, impacting quality of life and, as the cancer survey revealed, causing pain in and by itself. In addition, the aspect of the constipation that was number one on the improvement wish list of the patients with opioid-induced constipation was being able to have a bowel movement without pain! Hence, a double, pain-relief appeal seems to emerge from the surveys, that is, relief of the pain of the painful, cancer or non-cancer condition and relief of the pain of the opioid-induced gastrointestinal dysfunction.

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