Supportive Care in Cancer (2019) 27:687–696
https://doi.org/10.1007/s00520-018-4366-z

ORIGINAL ARTICLE

# Impact of opioid-induced constipation on healthcare resource utilization and costs for cancer pain patients receiving continuous opioid therapy

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Received: 5 April 2018 / Accepted: 18 July 2018 / Published online: 29 July 2018


## Abstract

**Purpose** Opioid therapy is often associated with adverse effects, including opioid-induced constipation (OIC), in patients receiving opioids for cancer pain. This retrospective observational cohort study evaluated healthcare utilization and costs during the first year after initiating opioid therapy among cancer patients with (cohort 1) and without (cohort 2) constipation.

**Methods** This study used administrative claims data from the HealthCore Integrated Research Environment between January 1, 2006, and April 30, 2014. Eligible patients included adults ≥ 18 years with a diagnosis of cancer who initiated continuous opioid therapy (≥ 30 days). Propensity scores were used to match patients with constipation in a 1:1 ratio to those without constipation. Generalized linear models were used to evaluate healthcare utilization and costs during the 12 months after initiating opioid therapy.

**Results** After matching, 1369 patients were included in each cohort. Patients with constipation were more than twice as likely as those without constipation to have an all-cause inpatient hospitalization (odds ratio [95% confidence interval (CI)], 2.47 [2.11–2.90]), or pain-related hospitalization (2.15 [1.82–2.54]) during the 12 months after initiating therapy. Mean unadjusted overall healthcare costs during the first 12 months post-index were $21,629 (95% CI, $14,850–$29,018) higher for patients with constipation than for those without constipation. For patients with constipation, total mean (SD) constipation-related costs were $9196 ($26,896).

**Conclusions** These results suggest that OIC is associated with significantly increased healthcare and economic burden in cancer pain patients and that early and ongoing recognition and management of OIC are unmet needs in this population.

**Keywords** Opioid-induced constipation · Cancer pain · Healthcare utilization · Costs

## Introduction

Pain is one of the most common and debilitating symptoms of cancer [1–3]. A recent meta-analysis showed that among patients with cancer who had undergone curative treatment, the pooled pain prevalence was 39.3%, while among patients undergoing anticancer treatment, the pooled pain prevalence was 55.0%; the pain prevalence was highest among patients with advanced, metastatic, or terminal cancer (66.4%) [1]. In that meta-analysis, moderate to severe pain was reported by 27.6% of patients who had undergone curative treatment, 32.4% of those undergoing anticancer treatment, and 51.9% of those with advanced, metastatic, or terminal cancer [1].

Although opioid analgesics are recommended for the management of moderate to severe cancer pain [4], opioid therapy is often associated with the development of side effects, particularly gastrointestinal side effects (e.g., constipation) [5–7], that may negatively impact patient outcomes or quality of life [7–9]. In a cross-sectional, observational study of 520 patients with cancer pain, 61.7% of patients reported problematic constipation and 85.7% of patients were considered to be constipated based on a physician-rated assessment [7]. In that same study, constipation in the setting of opioids was associated

**Electronic supplementary material** The online version of this article (https://doi.org/10.1007/s00520-018-4366-z) contains supplementary material, which is available to authorized users.

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with significant reductions in quality-of-life outcomes [7]. In a separate survey of patients receiving daily opioid therapy for cancer pain and experiencing constipation ($n = 31$), > 40% reported that their constipation moderately or completely interfered with achieving pain control with their opioid analgesic [8]. Furthermore, constipation in the setting of opioids may not respond to standard laxative therapy [10]. In one observational study of 274 patients receiving morphine for cancer pain, 72% of patients experienced constipation, and laxative therapy was inadequate for managing constipation in 89% of those patients [10].

Despite the prevalence of constipation among cancer patients receiving opioids, the impact of constipation in this population is often under-appreciated, and opioid-induced constipation (OIC) is often inadequately managed [10, 11]. The primary objective of this retrospective observational cohort study was to evaluate the impact of constipation in the setting of opioids on healthcare resource utilization and costs for cancer pain patients during the first year of continuous opioid therapy. Additional assessments in the current study included the characteristics (e.g., types, doses) of the opioids that were initiated for cancer pain, the dose of opioid used during the first year of treatment, patient characteristics among those with and without constipation, and, as a substudy, healthcare resource utilization and costs during the second year of continuous opioid treatment.

## Methods

### Data sources and study design

This study used administrative claims data from the HealthCore Integrated Research Database (HIRD; HealthCore Inc., Wilmington, DE). Additional information about the data source is included in the Supplemental material.

Data collected for this study dated from January 1, 2006, to September 30, 2015 (data collection period). This study included a 6-month pre-index period and a ≥ 12-month post-index period, unless the patient died during the 12 months after the index date (Fig. 1). The index date was defined as the fill date of the first continuous opioid therapy lasting for ≥ 30 days during the data collection period. Opioid treatment was considered continuous if an opioid prescription was filled within 30 days after the end of the days' supply covered by the prior prescription. The length of opioid therapy was defined as the time the prescription was first filled until the end of the days' supply covered by the last filled prescription during continuous therapy. Patients were followed from the index date to the end of 12 months after the index date or to the death date.

### Study population

This study included patients who were ≥ 18 years of age at the start of the 6-month pre-index period. Eligible patients were required to have ≥ 1 cancer diagnosis, defined as having ≥ 2 medical claims ≥ 30 days apart with a diagnosis of the same type of cancer (breast, lung, colorectal, prostate, head and neck, liver, ovarian, gallbladder, thyroid, kidney, or pancreatic cancer; osteosarcoma; or multiple myeloma) any time during the 6 months prior to the index date, with ≥ 1 cancer diagnosis or metastasis within 30 days prior to the index date. Eligible patients were required to have ≥ 6 months of continuous health plan eligibility prior to the index date with a follow-up period of 12 months after the index date or until death. Patients also had to have had a claim for an opioid during the data collection period and to have used an opioid continuously for ≥ 30 days starting on the index date. Patients with any of the following during the overall study period were excluded: ≥ 1 diagnosis of brain cancer or hematologic cancer (e.g., leukemia), ≥ 1 filled methadone prescription with ≥ 1 associated medical claim for substance abuse or addiction, or ≥ 1 diagnosis of inflammatory bowel disease. Additional details of the exclusion criteria are summarized in the Supplemental material.

### Study cohorts

The study population was divided into two cohorts of patients who initiated opioid therapy during the data collection period and had ≥ 30 days of continuous opioid use: cohort 1 included patients with constipation that started or worsened during opioid use (consistent with the Rome IV definition of OIC), and cohort 2 included patients with no evidence of constipation during the 12-month post-index period. For cohort 1, constipation was confirmed by ≥ 1 medical claim with an International Classification of Diseases, 9th Revision (ICD-9) [12] diagnosis code for constipation, a pharmacy claim for a constipation medication, or a procedure related to constipation (Supplemental Table 1) at any time during opioid treatment or within 1 day's supply of discontinuation of opioid therapy. Patients in cohort 1 may have had a gap in their opioid therapy (i.e., a period of > 30 days beyond the supply days of an opioid prescription without filling an additional prescription) and still have experienced constipation during a separate use of opioid therapy during the post-index period. Study timing for cohorts 1 and 2 is summarized in Supplemental Fig. 1.

### Outcome measures

The primary outcome was healthcare resource utilization and associated costs during the post-index period. Healthcare resource utilization included the proportion and number of office visits, other outpatient visits, emergency room visits,

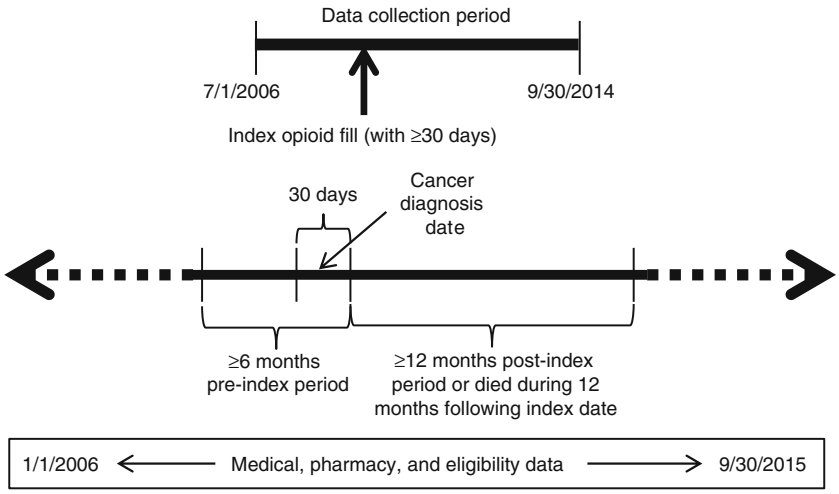


**Fig. 1** Study timing

inpatient stays (including length of stay), hospice care, and skilled nursing facility stays. Healthcare costs evaluated included medical and pharmacy costs. Medical costs were defined as the costs related to office visits, other outpatient visits, emergency room visits, hospice care, and inpatient visits and were evaluated by place of service and as total medical costs. Pharmacy costs were defined as the costs of all pharmacy claims during the period of interest.

All-cause, pain-specific, and constipation-specific healthcare resource utilization and associated costs were evaluated. Constipation-related resource utilization and costs were calculated only for patients with a constipation diagnosis during the post-index period. For constipation-related resource utilization and costs, events with ≥ 1 claim containing a diagnosis, procedure, or medication code for constipation were considered constipation-related events (Supplemental Tables 1 and 2). For pain-related resource utilization and costs, events with ≥ 1 claim containing a diagnosis, procedure, or medication code for pain were considered pain-related events.

Additional outcomes evaluated included characteristics of index opioids, patterns of opioid use during follow-up, and patient characteristics. Characteristics of the index opioids evaluated included opioid type and baseline dose. The following opioids were included in this analysis: codeine, tramadol, dihydrocodeine, tapentadol, hydrocodone, propoxyphene, fentanyl, hydromorphone, methadone, morphine, oxycodone, meperidine, oxymorphone, and levorphanol. Initial opioid dose was calculated as the average daily dose of opioid prescriptions during the first 30 days of continuous use to allow for changes during the titration period, and then converted to oral morphine-equivalent units (MEUs; Supplemental Table 3).

### Substudy

A substudy evaluating the impact of constipation during the second year of treatment followed patients with health plan eligibility for ≥ 24 months after the index date; for that substudy, the follow-up period of interest was from 12 to 24 months after the index date or until the death date. Details of the substudy methods are presented in the Supplemental material.

### Statistical analyses

Patients were not recruited to meet a pre-specified sample size. Instead, all eligible patients from the general population who met the criteria for study inclusion were included.

To minimize selection bias, propensity scores were used to match patients in a 1:1 ratio, with the propensity score for each individual estimated as the probability of having constipation based on the observed baseline characteristics [13–15]. The following variables were used to balance the cohorts: index month and year, age, gender, geographic region, health plan type, Deyo-Charlson Comorbidity Index (DCI) score, cancer type, prescribing physician specialty, and pre-index healthcare resource utilization and costs. Logistic regression analyses were used to calculate the propensity scores, which were used to match each patient from cohort 1 to a patient from cohort 2 using a greedy nearest neighbor 1-to-1 matching technique without replacement [14]. Multivariable analyses were used to analyze differences in healthcare utilization, costs, and opioid treatment patterns between cohorts 1 and 2. Additional details of the statistical methods are included in the Supplemental material.

## Results

### Patient characteristics

Overall, 9201 patients were eligible for participation. Demographic and baseline characteristics prior to and after matching are shown in Supplemental Table 4. After matching

**Table 1** Baseline and demographic characteristics for matched cohorts

| Characteristic | Cohort 1: opioid users with constipation ($n = 1369$) | Cohort 2: opioid users without constipation ($n = 1369$) | Odds ratio (95% CI)[a] | *P* value |
|---|---|---|---|---|
| Age, years, mean (SD) | 63.2 (12.8) | 62.6 (12.6) | – | 0.277 |
| Gender, *n* (%) | | | | |
| Male | 679 (49.6) | 683 (49.9) | 0.99 (0.85–1.15) | 0.8785 |
| Female | 690 (50.4) | 686 (50.1) | 1.01 (0.87–1.18) | 0.8785 |
| Index cancer diagnosis, *n* (%) | | | | |
| Breast cancer | 331 (24.2) | 403 (29.4) | 0.76 (0.65–0.91) | 0.0019 |
| Lung cancer | 345 (25.2) | 316 (23.1) | 1.12 (0.94–1.34) | 0.1953 |
| Prostate cancer | 263 (19.2) | 282 (20.6) | 0.92 (0.76–1.11) | 0.3631 |
| Colorectal cancer | 197 (14.4) | 155 (11.3) | 1.32 (1.05–1.65) | 0.0165 |
| Head and neck cancer | 113 (8.3) | 134 (9.8) | 0.83 (0.64–1.08) | 0.1613 |
| Ovarian cancer | 87 (6.4) | 54 (3.9) | 1.65 (1.17–2.34) | 0.0043 |
| Pancreatic cancer | 83 (6.1) | 42 (3.1) | 2.04 (1.40–2.98) | 0.0002 |
| Multiple myeloma | 76 (5.6) | 63 (4.6) | 1.22 (0.87–1.72) | 0.2577 |
| Kidney cancer | 57 (4.2) | 52 (3.8) | 1.10 (0.75–1.62) | 0.6250 |
| Osteosarcoma | 51 (3.7) | 49 (3.6) | 1.04 (0.70–1.55) | 0.8385 |
| Thyroid cancer | 21 (1.5) | 30 (2.2) | 0.70 (0.40–1.22) | 0.2033 |
| Gallbladder cancer | 12 (0.9) | 3 (0.2) | 4.03 (1.13–14.30) | 0.0198 |
| Residence region, *n* (%) | | | | |
| Northeast | 317 (23.2) | 317 (23.2) | 1.00 (0.84–1.19) | 1.0000 |
| Midwest | 378 (27.6) | 390 (28.5) | 0.96 (0.81–1.13) | 0.6097 |
| South | 333 (24.3) | 323 (23.6) | 1.04 (0.87–1.24) | 0.6543 |
| West | 281 (20.5) | 286 (20.9) | 0.98 (0.81–1.18) | 0.8136 |
| Unknown | 60 (4.4) | 53 (3.9) | 1.14 (0.78–1.66) | 0.5012 |
| Plan type, *n* (%) | | | | |
| PPO | 1000 (73.0) | 970 (70.9) | 1.12 (0.94–1.32) | 0.2019 |
| HMO | 331 (24.2) | 375 (27.4) | 0.85 (0.71–1.00) | 0.0546 |
| CDHP | 38 (2.8) | 24 (1.8) | 1.60 (0.95–2.68) | 0.0721 |
| Index year, *n* (%) | | | | |
| 2006 | 684 (50.0) | 676 (49.4) | 1.02 (0.88–1.19) | 0.7598 |
| 2007 | 205 (15.0) | 209 (15.3) | 0.98 (0.79–1.21) | 0.8310 |
| 2008 | 137 (10.0) | 140 (10.2) | 0.98 (0.76–1.25) | 0.8492 |
| 2009 | 94 (6.9) | 99 (7.2) | 0.95 (0.71–1.27) | 0.7089 |
| 2010 | 73 (5.3) | 65 (4.7) | 1.13 (0.80–1.59) | 0.4846 |
| 2011 | 66 (4.8) | 68 (5.0) | 0.97 (0.69–1.37) | 0.8594 |
| 2012 | 50 (3.7) | 52 (3.8) | 0.96 (0.65–1.43) | 0.8401 |
| 2013 | 32 (2.3) | 30 (2.2) | 1.07 (0.65–1.77) | 0.7972 |
| 2014 | 28 (2.0) | 30 (2.2) | 0.93 (0.55–1.57) | 0.7907 |
| DCI score, mean (SD) | 6.3 (3.2) | 6.3 (3.3) | | 0.8861 |
| Comorbid pain conditions, *n* (%) | | | | |
| Chronic fatigue | 281 (20.5) | 256 (18.7) | 1.12 (0.93–1.36) | 0.2289 |
| Low back pain | 267 (19.5) | 237 (17.3) | 1.16 (0.95–1.40) | 0.1390 |
| Osteoarthritis | 175 (12.8) | 193 (14.1) | 0.89 (0.72–1.11) | 0.3132 |
| Rheumatoid arthritis | 25 (1.8) | 31 (2.3) | 0.80 (0.47–1.37) | 0.4179 |
| Other arthropathies and musculoskeletal pain | 549 (40.1) | 537 (39.2) | 1.04 (0.89–1.21) | 0.6392 |
| Migraine, headache | 119 (8.7) | 112 (8.2) | 1.07 (0.82–1.40) | 0.6303 |
| Fibromyalgia | 43 (3.1) | 43 (3.1) | 1.00 (0.65–1.54) | 1.0000 |
| Painful diabetic neuropathy | 30 (2.2) | 37 (2.7) | 0.81 (0.50–1.31) | 0.3866 |
| Radioculopathy (sciatica) | 27 (2.0) | 37 (2.7) | 0.72 (0.44–1.20) | 0.2059 |

**Table 1** (continued)

| Characteristic | Cohort 1: opioid users with constipation ($n = 1369$) | Cohort 2: opioid users without constipation ($n = 1369$) | Odds ratio (95% CI)[a] | *P* value |
|---|---|---|---|---|
| Post-herpetic neuralgia | 4 (0.3) | 5 (0.4) | 0.80 (0.21–2.98) | 1.0000 |
| Post-traumatic neuralgia | 6 (0.4) | 8 (0.6) | 0.75 (0.26–2.16) | 0.5920 |

*CDHP*, consumer-driven health plan; CI, confidence interval; *DCI*, Deyo-Charlson Comorbidity Index; *HMO*, health maintenance organization; *PPO*, preferred provider organization; *SD*, standard deviation

[a] Odds ratios were used for categorical variables

and balancing for prespecified variables, 1369 patients were included in each cohort. Baseline and demographic characteristics were generally similar across cohorts (Table 1). Hypertension was the most common comorbidity and was reported by 43.2% (592/1369) and 46.5% (636/1369) of patients in cohorts 1 and 2, respectively. In the unmatched overall population ($n = 9201$), the top physician specialties prescribing opioids to patients with cancer pain in the unmatched overall population were hematology (15.9% [1462/9201]), surgery (12.2% [1118/9201]), oncology (10.4% [953/9201]), and primary care (internal medicine, 10.0% [916/9201]; family/general medicine, 7.2% [660/9201]).

## Index opioid use

The types and strengths of opioids that were being used at the index date were similar across both cohorts (Table 2). Patients could be using more than one opioid at index; at index, the most commonly used opioids in both cohorts included oxycodone (cohort 1, 30.7% [420/1369]; cohort 2, 32.5% [445/1369]) and hydrocodone (cohort 1, 35.4% [485/1369]; cohort 2, 34.0% [466/1369]). The mean (SD) baseline opioid dose in MEUs was 77.5 (100.8) mg in cohort 1 and 79.3 (134.1) mg in cohort 2.

## 12-month post-index opioid dosing, healthcare resource utilization, and costs

During the 12-month post-index period, the mean (SD) opioid dose was 77.5 (100.8) MEU in cohort 1 (patients with constipation) and 79.3 (134.1) MEU in cohort 2 (patients without constipation). In cohorts 1 and 2, the mean (SD) opioid dose was 27.8 [7.2] and 26.7 [8.2] MEU, respectively, in the lowest quartile and 156.0 [136.4] and 180.4 [209.8] MEU, respectively, in the highest quartile.

During the first 12 months after the index date, 72.5% (993/1369) of patients with constipation and 51.6% (707/1369) of patients without constipation had ≥ 1 inpatient hospitalization for any reason (odds ratio [OR; 95% confidence interval (CI)], 2.47 [2.11–2.90]; Table 3). Compared with patients without constipation, patients with constipation were approximately 1.6 times more likely to have an emergency room visit and skilled nursing facility stay for any reason and were approximately twice as likely to require hospice care for any reason (Table 3). In addition, the risk of all-cause death was approximately 1.7 times higher for patients with constipation than for those without (Table 3). For patients with constipation and those without, respectively, 39.2% (536/1369) and 23.0% (315/1369) of patients had ≥ 1 pain-related inpatient hospitalization (OR [95% CI], 2.15 [1.82–2.54]). Patients with constipation had a 1.4 times higher risk of pain-related outpatient/office visits and a 1.5 times higher risk of pain-related emergency room visits than those without (Table 3). Of the patients with constipation, 35.4% (485/1369) had ≥ 1 constipation-related outpatient/office visit, 30.2% (413/1369) had ≥ 1 constipation-related inpatient hospitalization, and 9.9% (136/1369) had ≥ 1 constipation-related emergency room visit (Table 3).

Total mean adjusted overall healthcare costs, including medical and pharmacy costs, during the first 12 months post-index were $21,629 (95% CI, $14,850–$29,018) higher for patients with constipation than for those without (Table 4). Total mean adjusted overall plan-paid costs were $21,065 (95% CI, $14,262–$28,515) higher, and total mean adjusted overall patient-paid costs were $563 ($294–$854) higher for patients with constipation than for those without (Supplemental Table 5). For patients with constipation compared with those without, total mean adjusted pain-related costs (medical and pharmacy) were $7546 (95% CI, $5450–$9918) higher, pain-related medical costs were $7019 ($4554–$9917) higher, and pain-related pharmacy costs were $527 ($378–$691) higher (Table 4). For patients using opioids who had constipation, total mean (SD) constipation-related costs were $9196 ($26,896; Table 4), total mean (SD) plan-paid costs were $9004 ($26,656), and total mean (SD) patient-paid costs were $192 ($679).

## Substudy: Healthcare resource utilization and costs from 12 to 24 months post-index

A total of 116 matched patients (cohort 1, $n = 33$; cohort 2, $n = 83$) were included in the substudy evaluating resource utilization and costs from 12 to 24 months after the index date. Similar trends in opioid dosing, resource utilization, and costs

**Table 2** Index opioid characteristics

| Characteristic | Cohort 1: opioid users with constipation ($n = 1369$) | Cohort 2: opioid users without constipation ($n = 1369$) | Odds ratios or differences in means (95% CI)[a] | *P* value |
|---|---|---|---|---|
| Index opioid type, *n* (%) | | | | |
| Hydrocodone | 485 (35.4) | 466 (34.0) | 1.06 (0.91–1.24) | 0.4457 |
| Oxycodone | 420 (30.7) | 445 (32.5) | 0.92 (0.78–1.08) | 0.3041 |
| Fentanyl | 164 (12.0) | 166 (12.1) | 0.99 (0.78–1.24) | 0.9065 |
| Propoxyphene | 88 (6.4) | 99 (7.2) | 0.88 (0.66–1.19) | 0.4046 |
| Morphine | 97 (7.1) | 87 (6.4) | 1.12 (0.83–1.52) | 0.4453 |
| Tramadol | 89 (6.5) | 90 (6.6) | 0.99 (0.73–1.34) | 0.9384 |
| Hydromorphone | 64 (4.7) | 54 (3.9) | 1.19 (0.83–1.73) | 0.3467 |
| Codeine | 55 (4.0) | 53 (3.9) | 1.04 (0.71–1.53) | 0.8443 |
| Meperidine | 12 (0.9) | 8 (0.6) | 1.50 (0.61–3.69) | 0.3693 |
| Methadone | 10 (0.7) | 4 (0.3) | 2.51 (0.79–8.03) | 0.1079 |
| Baseline opioid dose, MEU | | | | |
| Mean (SD) | 77.5 (100.8) | 79.3 (134.1) | − 1.79 (− 10.68–7.10) | 0.693 |
| Range, *n* (%) | | | | |
| 0–200 | 1306 (95.4) | 1304 (95.3) | 1.03 (0.73–1.47) | 0.8563 |
| ≥ 200 | 37 (2.7) | 34 (2.5) | 1.09 (0.68–1.75) | 0.7183 |
| ≥ 400 | 10 (0.7) | 10 (0.7) | 1.00 (0.42–2.41) | 1.0000 |
| ≥ 600 | 8 (0.6) | 8 (0.6) | 1.00 (0.37–2.67) | 1.0000 |
| ≥ 800 | 6 (0.4) | 5 (0.4) | 1.20 (0.37–3.94) | 0.7626 |
| ≥ 1000 | 2 (0.1) | 8 (0.6) | 0.25 (0.05–1.17) | 0.0573 |

*CI*, confidence interval; *MEUs*, morphine-equivalent units; *SD*, standard deviation

[a] Odds ratios were used for categorical variables and difference in means were used for continuous variables

were observed from month 12 to 24 post-index as during the initial 12-month post-index period. Detailed results are presented in the Supplemental material.

## Sensitivity analyses

Sensitivity analysis 1 evaluated data for the subset of patients with constipation identified via a constipation diagnosis or constipation-related procedure, while sensitivity analysis 2 evaluated data for patients with constipation and ≥ 80% of the first post-index year covered by an opioid medication. For both substudies, the patterns of healthcare utilization during the 12-month post-index period were generally comparable to that in the primary analysis; however, for sensitivity analysis 1, the pattern of healthcare utilization was generally more pronounced and for sensitivity analysis 2, the differences in resource utilization between the cohorts were not as pronounced in some cases. Detailed results are presented in the Supplemental material.

# Discussion

Constipation is a common and burdensome side effect associated with opioid use in patients with cancer pain [7, 8]. As noted in the 2017 update of the National Cancer Center Network's guidelines on Adult Cancer Pain, opioid side effects occur frequently and should be anticipated and treated aggressively in patients receiving opioids for cancer pain. These guidelines also note that although most opioid-related side effects improve over time, constipation generally persists [16]. There are limited data on the economic burden of constipation in cancer patients receiving opioids. This retrospective observational cohort study, which included 2738 matched patients, represents (to the best of our knowledge) the largest real-world study of the impact of constipation in the setting of opioids on healthcare resource utilization and costs in patients with cancer pain.

Patient baseline and demographic characteristics in the current study were generally comparable to those in previous studies of constipation in patients with cancer pain receiving opioids, suggesting that this population was a representative sample of patients with cancer pain [8, 17]. The cancer types identified in the current study are also consistent with expectations based on the prevalence of cancer and cancer types that have the potential to result in related pain conditions. The average DCI score was higher in the current analysis than in a previous database analysis of constipation in patients with cancer pain receiving opioids; however, the mean age in the current study (~ 63 years) was also higher than in the previous

**Table 3** Healthcare resource utilization during the 12 months post-index

| Resource utilization | Cohort 1: opioid users with constipation ($n = 1369$) | Cohort 2: opioid users without constipation ($n = 1369$) | Odds ratios or differences in means (95% CI)[a] | *P* value |
|---|---|---|---|---|
| All-cause resource utilization | | | | |
| Inpatient hospitalizations | | | | |
| 1 hospitalization, *n* (%) | 993 (72.5) | 707 (51.6) | 2.47 (2.11–2.90) | < 0.0001 |
| Number of hospitalizations, mean (SD)[b] | 2.4 (1.7) | 1.8 (1.3) | 0.55 (0.39–0.72) | < 0.0001 |
| Length of stay, days, mean (SD)[b] | 14.9 (16.4) | 10.8 (14.6) | 4.03 (2.71–5.48) | < 0.0001 |
| Emergency room visits | | | | |
| 1 visit, *n* (%) | 547 (40.0) | 398 (29.1) | 1.62 (1.39–1.90) | < 0.0001 |
| Number of visits, mean (SD)[b] | 1.8 (1.3) | 1.5 (1.2) | 0.31 (0.13–0.50) | < 0.0001 |
| Outpatient and office visits | | | | |
| 1 visit, *n* (%) | 1368 (99.9) | 1367 (99.9) | 2.00 (0.18–22.10) | 1.0000 |
| Number of visits, mean (SD)[b] | 83.8 (60.7) | 67.1 (52.7) | 16.67 (12.17–21.43) | < 0.0001 |
| Skilled nursing facility stays | | | | |
| 1 stay, *n* (%) | 79 (5.8) | 50 (3.7) | 1.62 (1.12–2.32) | 0.0089 |
| Hospice care | | | | |
| 1 hospice intervention, *n* (%) | 146 (10.7) | 79 (5.8) | 1.95 (1.47–2.59) | < 0.0001 |
| Patients who died during follow-up, *n* (%) | 562 (41.1) | 399 (29.1) | 1.69 (1.44–1.98) | < 0.0001 |
| Constipation-related resource utilization | | | | |
| Inpatient hospitalizations | | | | |
| 1 visit, *n* (%) | 413 (30.2) | – | – | – |
| Number of visits[b] | 1.2 (0.5) | – | – | – |
| Length of stay, days, mean (SD)[b] | 9.7 (10.2) | – | – | – |
| Emergency room visits | | | | |
| 1 visit, *n* (%) | 136 (9.9) | – | – | – |
| Number of visits, mean (SD)[b] | 1.1 (0.4) | – | – | – |
| Outpatient and office visits | | | | |
| 1 visit, *n* (%) | 485 (35.4) | – | – | – |
| Mean (SD) number of visits[b] | 2.6 (4.0) | – | – | – |
| Hospice care | | | | |
| 1 hospice intervention, *n* (%) | 2 (0.1) | – | – | – |
| Pain-related resource utilization | | | | |
| Inpatient hospitalizations | | | | |
| 1 visit, *n* (%) | 536 (39.2) | 315 (23.0) | 2.15 (1.82–2.54) | < 0.0001 |
| Number of visits, mean (SD)[b] | 1.5 (0.8) | 1.3 (0.8) | 0.16 (− 0.01–0.34) | 0.0583 |
| Length of stay, days, mean (SD)[b] | 12.3 (15.8) | 11.0 (15.8) | 1.32 (− 0.24–3.10) | 0.1018 |
| Emergency room visits | | | | |
| 1 visit, *n* (%) | 205 (15.0) | 141 (10.3) | 1.53 (1.22–1.93) | 0.0002 |
| Number of visits, mean (SD)[b] | 1.2 (0.6) | 1.3 (0.8) | − 0.05 (− 0.26–0.21) | 0.6771 |
| Outpatient and office visits | | | | |
| 1 visit, *n* (%) | 1023 (74.7) | 921 (67.3) | 1.44 (1.22–1.70) | < 0.0001 |
| Number of visits, mean (SD)[b] | 10.5 (16.7) | 9.4 (12.2) | 1.14 (0.19–2.18) | 0.0181 |
| Hospice care | | | | |
| 1 hospice intervention, *n* (%) | 1 (0.1) | 3 (0.2) | 0.33 (0.04–3.20) | 0.6247 |

*CI*, confidence interval; *SD*, standard deviation

[a] Odds ratios were used for categorical variables and difference in means were used for continuous variables

[b] Only analyzed among those with ≥ 1 event of interest

study (~ 53 years) [17]. Results of this study showed that patients with cancer pain who were taking opioid analgesics and experienced constipation during the first year after initiating opioid therapy had significantly more all-cause and pain-

**Table 4** Healthcare costs during the 12 months post-index

| Costs, USD, mean (SD) | Cohort 1: opioid users with constipation ($n = 1369$) | Cohort 2: opioid users without constipation ($n = 1369$) | Differences in means (95% CI) | *P* value |
|---|---|---|---|---|
| All-cause costs | | | | |
| Total medical costs | 79,763 (98,369) | 58,471 (83,094) | 21,292 (14,250–29,015) | <0.0001 |
| Inpatient hospitalization | 29,144 (56,667) | 16,799 (44,931) | 12,345 (7630–17,971) | <0.0001 |
| Emergency room | 999 (2906) | 579 (1623) | 420 (257–615) | <0.0001 |
| Outpatient/office visit | 48,785 (67,719) | 40,557 (62,971) | 8228 (3740−13,171) | 0.0002 |
| Skilled nursing facility | 287 (1939) | 204 (1642) | 82 (32–144) | 0.0007 |
| Hospice care | 547 (2692) | 332 (2365) | 216 (117–336) | <0.0001 |
| Total pharmacy costs | 2306 (3392) | 1968 (2970) | 337 (170–518) | <0.0001 |
| Total (medical + pharmacy) costs | 82,068 (98,542) | 60,439 (83,217) | 21,629 (14,850–29,018) | <0.0001 |
| Constipation-related costs | | | | |
| Total medical costs | 9144 (26,904) | – | – | – |
| Inpatient hospitalization | 8310 (26,588) | – | – | – |
| Emergency room | 146 (801) | – | – | – |
| Outpatient/office visit | 672 (3667) | – | – | – |
| Skilled nursing facility | 15 (310) | – | – | – |
| Hospice care | 2 (81) | – | – | – |
| Total pharmacy costs | 52 (130) | – | – | – |
| Total (medical + pharmacy) costs | 9196 (26,896) | – | – | – |
| Pain-related costs | | | | |
| Total medical costs | 16,521 (47,102) | 9502 (34,310) | 7019 (4554–9917) | <0.0001 |
| Inpatient hospitalization | 12,373 (38,792) | 7007 (31,845) | 5366 (3008–8280) | <0.0001 |
| Emergency room | 253 (1152) | 172 (792) | 80 (38–131) | <0.0001 |
| Outpatient/office visit | 3778 (25,866) | 2236 (10,023) | 1542 (984–2198) | <0.0001 |
| Skilled nursing facility | 117 (1080) | 87 (875) | 30 (11–54) | 0.0015 |
| Hospice care | 1 (23) | 14 (425) | −13 (−13–13) | <0.0001 |
| Total pharmacy costs | 1503 (2911) | 977 (2341) | 527 (378–691) | <0.0001 |
| Total (medical + pharmacy) costs | 18,025 (47,286) | 10,479 (34,426) | 7546 (5450–9918) | <0.0001 |

*CI*, confidence interval; *SD*, standard deviation

related inpatient hospitalizations, all-cause and pain-related emergency room visits, all-cause hospice care, pain-related outpatient/office visits, all-cause skilled nursing facility stays, and all-cause costs and pain-related costs than matched patients without constipation. Results of this study also showed substantial constipation-related healthcare utilization and costs for patients with cancer pain who were receiving opioids and were experiencing constipation. OIC may be indicative of poor opioid tolerability, which may lead patients to lower their opioid dose, leading to inadequate pain control; this may, in part, explain the difference in all-cause and pain-related resource utilization and costs between patients with and without constipation.

Results of a substudy evaluating healthcare resource utilization and costs associated with constipation during the second year after initiating opioid therapy supported the main analysis, showing higher rates of inpatient hospitalizations and higher total healthcare costs in patients taking opioids who experienced constipation than in those without constipation. In sensitivity analyses in a subset of patients with constipation identified via a constipation diagnosis or constipation-related procedure and a subset of patients with constipation and ≥ 80% of the first post-index year covered by an opioid medication, the pattern of healthcare utilization was relatively comparable to that in the primary analysis.

Results of the current study are consistent with those of a 2009 analysis of the burden of constipation in patients with cancer pain receiving opioids [17]. In that previous retrospective database analysis of data for patients with a diagnosis of cancer and a prescription for opioid analgesics (matched patients, $n = 1642$), a significantly higher proportion of patients with constipation had ≥ 1 inpatient hospital admission, ≥ 1 emergency room visit, ≥ 1 office visit, ≥ 1 nursing home stay, and ≥ 1 hospice service compared with those without constipation ($P < 0.03$ for all comparisons) [17].

Retrospective database analyses evaluating OIC in patients taking opioids for cancer pain are associated with certain challenges in terms of patient selection. For database analyses

evaluating OIC in patients with non-cancer pain, patients are first identified as receiving chronic opioid therapy and then those with recent cancer diagnosis are excluded [18, 19]. For analyses of OIC in patients with cancer pain, database analyses need to select for a population receiving opioids for pain that is associated with cancer. Furthermore, the pain associated with cancer may not be present at the initial cancer diagnosis. To address these issues, the current study included only patients with ≥ 2 medical claims for a cancer diagnosis and a new opioid prescription within close temporal proximity. This differs from the previously described retrospective database analysis [17], which included patients with ≥ 1 cancer diagnosis and a new prescription for an opioid after that diagnosis. Using these criteria, the number of patients selected was highest in the first year of the data collection period (2006) and declined in the subsequent calendar years. This may have been related to the patient selection criteria, which selected for new cases of opioid use, as well as the approach of multimodal pain therapies to complement opioid prescriptions [16]. In addition, this study was associated with challenges in terms of balancing baseline characteristics across the cohorts of patients with and without constipation, as shown by the unmatched data in Supplemental Table 4. Propensity score matching was conducted to balance the cohorts and minimize any potential bias that could influence the results. These matched cohorts of patients with and without constipation were similar in terms of baseline and demographic characteristics and in terms of the type and dose of opioid used at baseline.

As a retrospective database analysis, the current study was subject to certain limitations. First, administrative claims data are subject to potential coding error and are not collected for research purposes; missing values or data may result in exclusion from the analysis. In addition, these types of observational analyses may be subject to residual confounding due to unmeasured variables. Although the matched cohorts were similar in terms of baseline and demographic characteristics, there were significant differences in the proportions of patients with certain cancer diagnoses between patients with constipation and those without. A significantly higher proportion of patients with constipation had diagnoses of colorectal, pancreatic, ovarian, and gallbladder cancer than without constipation, while a significantly higher proportion of patients without constipation had breast cancer than with constipation. These differences could have contributed, in part, to the differences in outcomes (e.g., all-cause death) observed between the two cohorts. Furthermore, the database used in the current study included only patients who were covered by commercial health plans in the USA; thus, the findings of this study may not be applicable to the patient populations who were not represented in this database (e.g., patients covered by Medicare or Medicaid). Although average opioid doses were evaluated at baseline and during the 12-month follow-up period, changes in opioid dosing over time and doses of constipation medication were not assessed in this study. Patients with brain and hematologic cancers were excluded because these patients were likely to have limitations related to treatment options for OIC (e.g., peripherally-acting opioid receptor antagonists, brain cancer) or opioids for pain (hematologic cancer); however, exclusion of these patients was unlikely to confound the study results. There is no diagnosis code for OIC, and constipation could have resulted from other causes related to the patients' underlying disease or treatments. In addition, the use of ≥ 1 medical claim with an ICD-9 diagnosis code for constipation or a pharmacy claim for constipation medication to confirm constipation may not have captured OIC because of unreliable coding or co-prescription of prophylactic constipation medication with opioid prescriptions, even in patients without constipation. Nevertheless, data from this study are highly suggestive of a comorbidity of constipation associated with opioid usage. The pharmacy cost data did not include over-the-counter analgesics or laxatives and, thus, may have underestimated the costs related to pain and constipation related to opioids in this population.

## Conclusions

Results of the current analysis are consistent with those of previous analyses of the burden of constipation in the setting of opioids [20–23] and indicate a substantial healthcare and economic burden for constipation in patients with cancer pain. Pain is often a chronic condition for cancer survivors and patients undergoing treatment for active cancer; however, there is a lack of data on side effects of opioid therapy (including OIC) when used for the management of chronic cancer-related pain. There is a need for additional registry and prospective trials, including the development and analysis of a clinical database, to evaluate the incidence of bowel dysfunction, including OIC, and its impact on patient outcomes in patients with cancer pain. Further analyses incorporating other factors that could potentially affect OIC, such as opioid or constipation medication dosing over time, could also be considered in patients with cancer pain. Although the severity of OIC or adequacy of its management were not assessed in this study, the increase in resource utilization in patients with constipation suggests that there may be a need for early and ongoing management of constipation among patients with cancer-related pain receiving opioid analgesics in order to reduce the burden and increased costs associated with constipation in this setting.

**Acknowledgments** The authors thank Megan Knagge, PhD, of MedErgy (Yardley, PA, USA) for providing medical writing support, which was in accordance with Good Publication Practice (GPP3) guidelines and funded by AstraZeneca (Wilmington, DE, USA).

**Funding information** This study was supported by AstraZeneca Pharmaceuticals, LP (Wilmington, DE).

## Compliance with ethical standards

For this retrospective study based on administrative data, formal consent was not required. All procedures were performed in accordance with the ethical standards of the institutional and/or national research committee and with the Declaration of Helsinki.

**Conflict of interest** P.G.F. is on the Board of Directors of Magellan Health, and he has received consulting fees from AstraZeneca Pharmaceuticals, Capital Caring, and Endo Pharmaceuticals within the last 36 months. Y.-W.C. is an employee of HealthCore, Inc. E.W. and C.D. are employees of AstraZeneca.

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