Costs of Gastrointestinal Events After Outpatient Opioid Treatment for Non-Cancer Pain

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BACKGROUND: Gastrointestinal (GI) adverse effects are common with oral opioid treatment.

OBJECTIVE: To estimate the costs associated with GI events after oral short-acting opioid treatment, from the payer perspective.

METHODS: Medical and pharmacy claims from the PharMetrics' Patient-Centric Database were used to identify opioid-naïve patients who received a new prescription for oxycodone- or hydrocodone-containing immediate-release oral products between 2002 and 2006. Health-care resource use and costs were determined for patients with claims associated with ICD-9 CM (International Classification of Diseases—9th Clinical Modification) codes for nausea/vomiting (787.0x), constipation (564.0x), bowel obstruction (560, 560.1, 560.3, 560.39, 564.81), or antiemetic and laxative prescriptions during the 3 months after opioid index prescription and compared with patients without these GI event medical or prescription claims. Resource use data were compared using negative binomial regression and cost data were compared using ordinary least squares confirmed by generalized gamma regression analysis while controlling for demographics, treatment duration, and comorbidities.

RESULTS: Data from 237,447 patients were analyzed. Patients with GI event claims had significantly more hospitalizations (adjusted mean 0.20 to 0.97 vs 0.17, respectively, $p < 0.001$), days in the hospital (1.12 to 12.05 vs 1.00 days, $p < 0.001$), emergency department visits (0.36 to 1.44 vs 0.25 visits, $p < 0.001$), outpatient office visits (5.68 to 11.81 vs 4.11 visits, $p < 0.001$), and prescription claims (7.46 to 8.21 vs 6.06 claims, $p < 0.001$) than did patients without any GI event claims in the 3 months after index opioid prescription. Compared with patients without any GI event claims, incremental adjusted mean total health-care costs for patients with any of the GI event claims ranged from $4,880 to $36,152 and were significant ($p < 0.001$).

CONCLUSIONS: The economic burden of GI events coincident with opioid treatment is significant for patients with a GI event recorded in claims. Reducing GI adverse effects has potential cost savings for the health-care system.

KEY WORDS: adverse effects, costs, economic, opioids.

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Pain affects at least 1 in 4 people in the US at any given time.[1] Opioids are frequently used to treat moderate-to-severe acute and chronic pain because of their established efficacy.[2-5] Market data show that 235 million opioid prescriptions were written in the US during 2005.[2] Despite the established efficacy of opioids, concerns about adverse effects have often limited their therapeutic potential.[3]

Mu-opioid receptors are present in the gastrointestinal (GI) tract; therefore, GI adverse effects are common with opioids. In a meta-analysis of randomized controlled trials of oral opioids, 80% of patients with chronic non-cancer pain reported at least 1 adverse event, with constipation (41%) and nausea (32%) being the most common adverse effects.[4] A recent US population-based survey confirmed the widespread prevalence of constipation (57%).[6] Although nausea and vomiting can subside as tolerance to opioids develops, constipation may persist despite laxative treatment, with only 46% of non-cancer opioid patients who used laxatives reporting the desired laxative results half of the time with continued opioid use.[7]

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Intolerable adverse effects can lead to dose reduction, patient nonadherence, and treatment discontinuation, resulting in undertreatment of pain, more health-care resource use, and productivity loss.[8-13] Patients with chronic non-cancer pain using opioids and experiencing opioid-induced constipation reported more severe pain and work and activity impairment than did opioid patients without constipation.[14] Primary care physicians have cited adverse effects (74%) and patient adherence (58%) as the major barriers to optimal pain control.[15] Balancing adverse effects with pain relief remains a major challenge in opioid therapy.

Despite the widespread prevalence of GI adverse effects with opioids, little is known about the costs of managing opioid GI adverse effects in outpatient settings, with a few studies suggesting that opioid adverse effects increase health-care resource utilization. Among US outpatients, a retrospective analysis of medical and prescription claims data found that patients with non-metastatic cancer who took opioids and experienced constipation were more likely to have inpatient admissions, emergency care, and outpatient visits than were patients without constipation.[12] A patient survey conducted in the US and Europe also showed increased outpatient visits for patients with opioid-induced constipation.[11] Information on the impact of nausea and vomiting is limited, especially for non-cancer outpatients.

Using medical and prescription claims data, the objective of this study was to assess the economic burden of 3 GI events (nausea/vomiting, constipation, bowel obstruction/ileus) associated with oral short-acting opioid treatment for non-cancer pain in the outpatient setting, from a US third-party payer perspective.

Methods

A retrospective analysis was performed, using the PharMetrics Patient-Centric Database, which consists of de-identified integrated medical and prescription claims of more than 80 health plans with more than 60 million patients in the US, in compliance with the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule. Because the database consists of de-identified data, no institutional review board review was required. The database is nationally representative of individuals covered by commercial health insurance. The integration of enrollment data with medical and outpatient prescriptions claims in the database allows longitudinal analyses of covered health-care services used by each patient. In the database, an Episode Treatment Group (ETG) is assigned to each medical or pharmacy claim, based on predefined proprietary algorithms[16] to determine the medical diagnosis associated with the claim. Each ETG is further grouped into 1 of 22 major practice categories (MPC) that represent a different body system and/or physician specialty. The database has been used in previous economic studies.[17-20]

PATIENT COHORT SELECTION

Patients who had an outpatient prescription claim for an oral immediate-release oxycodone- or hydrocodone-containing product between January 1, 2002, and December 31, 2005, were included in this analysis. Immediate-release oxycodone- and hydrocodone-containing products were the focus of this study because they are the most commonly prescribed opioids in the US.[21] The date on which a patient first filled an oxycodone- or hydrocodone-containing product during the study period was termed the opioid index date. Only patients who were continuously enrolled in plans in which their medical and pharmacy claims could be recorded in the database for the 90 days before and after the opioid index date were included in this analysis. Because nausea/vomiting usually develop early and sometimes resolve after tolerance to opioids develops, to ensure that we had captured these GI events following initiation of opioid treatment, we excluded patients who had filled a prescription for an opioid analgesic (eg, morphine, oxycodone, fentanyl, hydromorphone) of any formulation in the 90 days prior to the opioid index date. To examine the impact of adverse effects associated with use of opioids, we also excluded patients with underlying medical conditions in which GI adverse effects may not have been related to the use of opioids (ie, patients with claims for opioid treatment for gastroenterology- and/or cancer-related MPCs).

Medical claims of eligible patients were examined to identify patients who had a medical claim associated with ICD-9 CM (International Classification of Disease—9th Clinical Modification) codes of nausea/vomiting (787.0x), constipation (564.0x), or bowel obstruction (560, 560.1, 560.3, 560.39, and 564.81) during the 90 days following opioid index date. Prescription data were examined to identify patients who had a prescription claim of antiemetics and laxatives that are commonly used to manage opioid-induced GI adverse effects[22] (Appendix I) during the 90 days following opioid index date. Eligible patients were grouped into 7 mutually exclusive cohorts based on the absence and presence of GI event medical claims or use of relevant medications associated with treatment of nausea/vomiting and constipation during the 90-day follow-up period: (1) patients with no medical claims associated with any of the identified GI events and no pharmacy claims for relevant antiemetics and laxatives, (2) patients with nausea/vomiting medical claims only and no other relevant GI medical or pharmacy claims, (3) patients with constipation medical claims only and no other relevant GI medical or pharmacy claims, (4) patients with bowel obstruction medical claims only and no other relevant GI

medical or pharmacy claims, (5) patients with more than 1 GI event identified using medical claims and no other relevant GI pharmacy claims, (6) patients with a pharmacy claim for relevant antiemetics and no other relevant GI medical claims, and (7) patients with a pharmacy claim for relevant laxatives and no other relevant GI medical or pharmacy claims.

VARIABLES OF INTEREST

Health-care resource utilizations including hospitalizations, emergency department visits, outpatient visits, prescription drug claims, and their associated costs were examined in this study. The costs for inpatient services, emergency care, outpatient office visits, and pharmacy services were calculated by summing the insurer reimbursed payment amount (net of patient copay or coinsurance) associated with all medical or prescription claims during the 90-day follow-up period to estimate expenditures from the payer's perspective. Costs are presented in 2002–2006 prices, without any indexation to reflect medical cost inflation in the intervening period.

STATISTICAL ANALYSIS

Health-care resource use and cost data were compared between each cohort of patients with a GI event medical or pharmacy claim and those without any GI event claims. Multivariate analyses were used to take into account differences in any observable cohort characteristics that may have influenced the results. To allow transparency regarding the original data and the impact of multivariate adjustment, both observed and adjusted means are presented. Health-care resource use and cost data are typically skewed to the right, with a high proportion of patients with either no or limited service use while a small proportion of patients use services intensively. Although skewed data violate the assumptions of normality and homoscedasticity of the residuals of ordinary least squares (OLS) regression analysis, some researchers[23,24] found OLS analysis on raw costs data to be a satisfactory method for prediction when very large sample sizes are available. Others recommend alternative statistical models such as generalized linear modeling (GLM), with a log-link and gamma distribution of the error terms to take into account the skewness and non-normality of cost data.[25,26] We analyzed cost data with OLS regression and used GLM to confirm overall cost predictions. Health-care resource use data were analyzed as count data, using negative binomial regression.[27-29]

Covariates in the regression analyses included age, sex, number of opioid treatment days, index opioid prescription MPC, and comorbidities. The number of opioid treatment days was calculated by summing the number of days of supply associated with each opioid prescription claim during the 90 days following opioid index date. Because underlying pain conditions and comorbidities may affect health-care resource use differently, we included dummy variables to control for any possible differences among cohorts. The first group of dummy variables indicates the 6 most common MPCs associated with the index opioid prescriptions: (1) orthopedics and rheumatology, (2) isolated signs and symptoms, (3) dermatology, (4) urology, (5) neurology, and (6) cardiovascular. The remaining 17% of patients were included in the "other" category. To further control for comorbidities in all resource use and cost estimations, we included dummy variables for 30 comorbidity groups proposed by Elixhauser and colleagues (1998)[30] based on the ICD-9 CM codes of medical claims incurred during the 90 days before the opioid index date. In addition, the association of age, daily opioid dose, and days of opioid supply with the time to first GI event medical claim and time to first prescription claim for relevant antiemetics and laxatives during the 90-day follow-up period was examined using Cox regression analyses. Daily opioid dose was calculated using the following formula:

$$\frac{\Sigma \text{ Opioid product dose strength for prescription}_i \times \text{Units dispensed for prescription}_i}{\Sigma \text{ Days of supply for prescription}_i}$$

Analyses were performed using Statistical Analysis Software version 9.1.3 (SAS Institute, Cary, NC). An α

Table 1. Gastrointestinal Events in the 90 Days After Initial Oral Opioid Prescription

Parameter	Pts.,[a] n (%)
No GI event medical or prescription claim	217,218 (91.48)
GI event medical claim only	8,730 (3.68)
nausea/vomiting	5,891 (2.48)
constipation	1,972 (0.83)
bowel obstruction	277 (0.12)
>1 GI event medical claim	590 (0.25)
nausea/vomiting + constipation	341 (0.14)
nausea/vomiting + bowel obstruction	150 (0.06)
constipation + bowel obstruction	55 (0.02)
nausea/vomiting + constipation + bowel obstruction	44 (0.02)
Antiemetic prescription claim[b,c]	8,196 (3.45)
Laxative prescription claim[b]	3,303 (1.39)
Any GI event medical or prescription claim	20,229 (8.52)
nausea/vomiting	14,622 (6.16)
constipation	5,715 (2.41)
bowel obstruction	526 (0.22)

GI = gastrointestinal.
[a]N = 237,447.
[b]Without GI event medical claim.
[c]127 patients in this group had pharmacy claims for both antiemetics and laxatives and no other relevant GI medical claims.

level of 0.05 was employed as a threshold for all statistical comparisons.

Results

Data from 237,447 patients were included in the analysis (Table 1). During the 90-day follow-up period, 8730 (3.68%) patients had medical claims associated with a GI event of interest. A total of 6426 (2.71%) patients were identified as having nausea/vomiting medical claims, 2412 (1.02%) patients had constipation claims, and 526 (0.22%) had bowel obstruction claims. Co-occurrence of nausea/vomiting with constipation or bowel obstruction was more common than co-occurrence of constipation with bowel obstruction. In the remainder of this article, patients with medical claims of more than 1 GI event are reported as a single group (>1 GI event). An additional 3.45% of patients were identified with a pharmacy claim for antiemetics without other relevant GI medical claims and 1.39% of patients were identified with a pharmacy claim for laxatives without other relevant GI medical or pharmacy claims.

Patients with medical claims for constipation only, patients with bowel obstruction medical claims only, or patients with claims for laxatives were older than patients with claims for nausea/vomiting only or patients using antiemetics; patients in the latter groups had a similar age distribution to patients without any GI event medical or prescription claims (Table 2). Cox regression analyses confirmed that younger patients were more likely to have a medical or prescription claim for nausea and vomiting while older patients were more likely to have a medical or prescription claim for constipation. Patients using a higher opioid dose ($p < 0.01$) also were more likely to have a GI event medical claim or relevant prescription claims. Patients using opioids for a greater number of days within the 90-day follow-up period were more likely to have constipation and bowel obstruction medical claims ($p < 0.001$); however, opioid treatment duration of patients with nausea and vomiting was significantly shorter than that of patients without any relevant GI event medical claims or prescription claims ($p < 0.001$).

Comorbidities were generally similar across patient cohorts except that patients in the GI event cohorts were more likely to have congestive heart failure, uncomplicated hypertension, fluid/electrolyte disorders, iron deficiency anemia, or depression than were patients without any GI event medical claim or prescription claim for relevant antiemetics and laxatives.

HEALTH-CARE RESOURCE USE

All cohorts of patients with a GI event medical claim had significantly more observed and adjusted mean inpatient and outpatient health-care utilization than did patients without relevant GI event medical claims or prescription claims for antiemetics or laxatives ($p < 0.001$; Table 3). Similarly, patients with prescription claims for antiemetics or laxatives who had no GI medical claims also used significantly more health-care resources than did patients without relevant GI event medical claims or prescription claims.

Inpatient Services

Patients with a GI event medical claim had increased hospital admissions (adjusted means: 0.35 to 0.97 vs 0.17/patient) and more days in hospital (adjusted means: 2.96 to 12.05 vs 1.00 per patient, $p < 0.001$) compared with patients without relevant GI event medical claims or prescription claims for antiemetics and laxatives (Table 3). Patients with prescription claims for laxatives and no other relevant GI medical or prescription claims had similarly increased hospital utilization as patients with constipation medical claims only when compared with patients with no relevant GI medical claims or prescription claims ($p < 0.001$; Table 3). Patients with prescription claims for antiemetics and no other relevant GI medical claims had similar hospital utilization compared with patients with no relevant GI medical claims or prescription claims.

Emergency Care Visits

Patients with a GI event medical claim had increased adjusted mean emergency care visits (0.62 to 1.44 vs 0.25 per patient) versus patients without relevant GI event medical or prescription claims ($p < 0.001$; Table 3). Patients identified as using antiemetics (0.36 visit per patient) or laxatives (0.37 visit per patient) without relevant GI event medical claims also had a significantly higher number of adjusted mean emergency care visits than did patients without relevant GI medical claims or prescription claims ($p < 0.001$), albeit with lower adjusted mean visits compared with patients with medical claims for nausea/vomiting or constipation.

Outpatient Office Visits

Patients with GI event medical claims or prescription claims for antiemetics and laxatives had increased adjusted mean outpatient office visits (5.68 to 11.81 vs 4.11 visits per patient) versus patients without relevant GI event medical or prescription claims ($p < 0.001$; Table 3). In common with patients who had medical claims for nausea/vomiting (7.43 per patient) or constipation (7.26 per patient), patients identified as using antiemetics (5.86 per patient) or laxatives (5.68 per patient) without relevant GI event medical claims also had more adjusted mean outpatient office visits than did patients without relevant GI medical or prescription claims ($p < 0.001$).

Outpatient Prescription Drug Use

Patients with relevant GI event medical claims or prescription claims for antiemetics and laxatives had at least a

Table 2. Demographic and Clinical Characteristics

Characteristic	No GI Event Medical or Prescription Claim	Identified Using ICD-9 Code in Medical Claims				Identified Using Prescription Claims		All Pts.
		Nausea/ Vomiting	Constipation	Bowel Obstruction	>1 GI Event	Antiemetic	Laxative	
Age, y (mean ± SD)	46.4 ± 14.2	45.4 ± 14.8	53.7 ± 16.9	51.6 ± 13.7	52.5 ± 16.5	46.5 ± 14.3	55.3 ± 15.4	46.6 ± 14.3
Female, %	54	68	65	53	67	68	62	55
Duration of opioid treatment, days (mean ± SD)	15.1 ± 18.8	19.4 ± 21.2	24.2 ± 24.1	21.3 ± 19.7	25.3 ± 24.2	14.4 ± 17.0	22.4 ± 23.5	15.3 ± 19.0
Oxycodone IR users, %	52.2	44.5	50.1	48.4	47.5	56.6	52.1	52.1
Oxycodone dose/day, mg (median)[a]	33.33	33.33	33.33	34.53	37.5	37.5	33.33	33.33
Hydrocodone dose/day, mg (median)[a,b]	22.2	22.2	22.2	26.4	25.0	23.3	22.2	22.2
Pts., by index opioid MPC, %								
orthopedics	54.0	44.0	60.1	40.4	49.8	50.2	54.9	53.7
isolated signs and symptoms	8.3	0.8	0.4	0.7	0.0	4.4	3.3	7.8
dermatology	6.7	5.2	5.1	4.0	3.4	5.7	5.9	6.6
cardiovascular	5.2	6.2	7.6	8.0	7.1	5.3	8.7	5.3
urology	4.7	13.4	5.7	12.0	7.4	6.9	4.3	5.0
neurology	4.7	9.3	6.5	3.6	7.4	5.3	5.0	4.8
other	16.4	21.1	14.6	31.3	24.6	22.1	17.8	16.8
Comorbidities, %								
congestive heart failure	1.3	2.4	4.3	4.0	12.1	1.0	4.1	1.4
cardiac arrhythmias	0.1	0.2	0.4	0.7	0.0	0.1	0.2	0.1
valvular disease	0.2	0.3	0.4	0.0	3.7	0.1	0.5	0.2
pulmonary circulation disorder	0.0	0.1	0.0	0.0	0.0	0.0	0.0	0.0
peripheral vascular disorder	0.0	0.0	0.0	0.0	0.7	0.0	0.0	0.0
hypertension (uncomplicated)	10.8	15.9	20.1	18.5	64.6	12.9	19.2	11.3
paralysis	0.2	0.3	0.9	0.0	3.1	0.1	0.6	0.2
neurologic disorder	0.0	0.1	0.2	0.0	0.0	0.0	0.1	0.0
diabetes (uncomplicated)	0.0	0.0	0.1	0.0	0.0	0.0	0.0	0.0
diabetes (complicated)	0.3	0.8	0.7	0.4	0.3	0.3	0.6	0.3
hypothyroidism	0.0	0.1	0.1	0.0	0.0	0.1	0.0	0.0
liver disease	0.1	0.2	0.1	0.0	2.3	0.1	0.0	0.0
peptic ulcer disease	0.0	0.1	0.1	0.7	0.0	0.0	0.1	0.0
rheumatoid arthritis	0.0	0.1	0.1	0.4	0.0	0.0	0.0	0.0
coagulopathy	0.2	0.5	0.6	0.7	1.0	0.2	0.6	0.2
obesity	2.1	4.3	3.8	2.5	9.2	2.6	2.6	2.2
weight loss	0.0	0.0	0.1	0.0	0.0	0.0	0.1	0.0
fluid and electrolyte disorder	1.5	5.7	4.5	6.2	34.4	2.2	5.3	1.7
blood loss anemia	0.3	0.6	0.7	2.2	2.1	0.4	1.1	0.4
deficiency anemia	2.0	3.8	5.0	3.3	19.6	2.5	6.3	2.1

IR = immediate release; MPC = major practice category.

[a]Expressed in mg of oxycodone equivalent dose.

[b]Hydrocodone dose was converted into oxycodone equivalent dose, using conversion ratio: 100 mg oxycodone = 67.67 mg hydrocodone (www.globalrph.com/narcotic.cgi).

Table 3. Services Used[a]

Service Use	No GI Event Medical or Prescription Claim	Identified by ICD-9 Code in Medical Claim				Identified by Prescription Claims	
		Nausea/ Vomiting	Constipation	Bowel Obstruction	>1 GI Event	Antiemetic	Laxative
Hospital admissions							
pts. using service, %	13.5	33.9	36.4	82.2	69.3	13	28.1
service users, mean (95% CI)	1.13 (1.13 to 1.13)	1.45 (1.42 to 1.47)	1.37 (1.34 to 1.41)	1.46 (1.36 to 1.56)	1.66 (1.58 to 1.74)	1.21 (1.2 to 1.22)	1.25 (1.23 to 1.28)
all pts., mean (95% CI)	0.15 (0.15 to 0.15)	0.49 (0.47 to 0.51)	0.5 (0.46 to 0.54)	1.2 (1.09 to 1.31)	1.15 (1.06 to 1.24)	0.16 (0.15 to 0.17)	0.35 (0.33 to 0.38)
all pts., adjusted mean[b] (95% CI)	0.17 (0.15 to 0.19)	0.41 (0.35 to 0.47)	0.35 (0.29 to 0.42)	0.95 (0.76 to 1.17)	0.97 (0.72 to 1.29)	0.2 (0.17 to 0.23)	0.29 (0.24 to 0.34)
Days in hospital							
pts. using service, %	13.5	33.9	36.4	82.2	69.3	13	28.1
service users, mean (95% CI))	6.2 (6.15 to 6.24)	9.73 (9.33 to 10.13)	12.7 (11.68 to 13.71)	14.51 (11.42 to 17.59)	14.66 (13 to 16.32)	7.53 (7.3 to 7.77)	10.51 (9.64 to 11.39
all pts., mean (95% CI)	0.83 (0.81 to 0.85)	3.3 (3.03 to 3.56)	4.62 (3.95 to 5.29)	11.92 (9.05 to 14.8)	10.15 (8.66 to 11.64)	0.98 (0.88 to 1.08)	2.95 (2.46 to 3.44)
all pts., adjusted mean[b] (95% CI)	1 (0.74 to 1.56)	2.96 (2.01 to 5.12)	3.61 (2.29 to 6.7)	12 (5.78 to 29.28)	12.05 (4.02 to 45.59)	1.12 (0.76 to 1.91)	2.49 (1.63 to 4.45)
Emergency care visits							
pts. using service, %	18.4	69.5	42.5	60.4	77.4	24.8	24.7
service users, mean (95% CI)	1.32 (1.32 to 1.33)	1.86 (1.81 to 1.9)	1.66 (1.61 to 1.71)	1.55 (1.45 to 1.66)	2.15 (1.9 to 2.39)	1.5 (1.48 to 1.53)	1.61 (1.56 to 1.66)
all pts., mean (95% CI)	0.24 (0.24 to 0.25)	1.29 (1.25 to 1.33)	0.71 (0.66 to 0.76)	0.94 (0.81 to 1.06)	1.66 (1.43 to 1.89)	0.37 (0.35 to 0.39)	0.4 (0.36 to 0.43)
all pts., adjusted mean,[b] (95% CI)	0.25 (0.22 to 0.27)	1.08 (0.93 to 1.25)	0.62 (0.52 to 0.74)	0.84 (0.63 to 1.12)	1.44 (0.97 to 2.14)	0.36 (0.3 to 0.41)	0.37 (0.31 to 0.44)
Office visits							
pts. using service, %	78.7	96.4	98.6	98.5	99	87.7	91
service users, mean (95% CI)	5.14 (5.12 to 5.17)	8.17 (7.97 to 8.38)	9.28 (8.9 to 9.66)	11.01 (9.72 to 12.3)	13.32 (12.43 to 14.21)	6.61 (6.46 to 6.76)	7.66 (7.4 to 7.91)
all pts., mean (95% CI)	4.05 (4.02 to 4.07)	7.88 (7.68 to 8.08)	9.15 (8.77 to 9.53)	10.85 (9.56 to 12.14)	13.18 (12.29 to 14.07)	5.79 (5.64 to 5.94)	6.97 (6.71 to 7.22)
all pts., adjusted mean,[b] (95% CI)	4.11 (3.91 to 4.33)	7.43 (6.88 to 8.03)	7.26 (6.6 to 7.99)	10.53 (8.9 to 12.47)	11.81 (9.15 to 15.34)	5.86 (5.44 to 6.3)	5.68 (5.21 to 6.19)
Prescription claims							
pts using service, %	100	100	100	100	100	100	100
service users, mean (95% CI)	5.95 (5.93 to 5.97)	8.83 (8.68 to 8.99)	9.51 (9.23 to 9.78)	9.1 (8.44 to 9.76)	10.46 (9.97 to 10.96)	7.57 (7.45 to 7.69)	10.29 (10.07 to 10.51)
all pts., mean (95% CI)	5.95 (5.93 to 5.97)	8.83 (8.68 to 8.99)	9.51 (9.23 to 9.78)	9.1 (8.44 to 9.76)	10.46 (9.97 to 10.96)	7.57 (7.45 to 7.69)	10.29 (10.07 to 10.51)
all pts., adjusted mean,[b] (95% CI)	6.06 (5.89 to 6.23)	8.07 (7.73 to 8.42)	7.46 (7.07 to 7.86)	7.89 (7.17 to 8.68)	8.08 (7.01 to 9.33)	7.53 (7.22 to 7.84)	8.21 (7.83 to 8.61)

GI = gastrointestinal.

[a]Observed and adjusted mean (95% CI) number of service utilizations during the 90 days following index opioid prescriptions.

[b]Adjusted means were estimated using negative binomial regression analysis.

Table 4. Service Costs per Patient[a]

Service Cost, $ (range)	No GI Event Medical or Prescription Claim	Identified by ICD-9 Code				Identified by Drug in Prescription Claims	
		Nausea/ Vomiting	Constipation	Bowel Obstruction	>1 GI Event	Antiemetic	Laxative
Inpatient	1,356 (828–1,884)	7,025 (6,185–7,865)	7,220 (6,160–8,280)	28,715 (26,776–30,654)	33,985 (30,985–36,986)	2,397 (1,604–3,189)	4,121 (3,179–5,062)
Emergency care	141 (107–175)	880 (826–934)	382 (314–450)	540 (416–665)	871 (679–1063)	245 (194–296)	210 (150–271)
Office visit	1,933 (1,749–2,117)	3,671 (3,378–3,964)	3,327 (2,958–3,697)	3,132 (2,456–3,808)	4,065 (3,019–5,111)	5,555 (5,279–5,831)	3,526 (3,198–3,854)
Pharmacy	552 (456–647)	1,000 (847–1,153)	797 (604–990)	679 (327–1,031)	1,212 (666–1,757)	1,171 (1,027–1,315)	1,004 (833–1,175)
Overall	3,981 (3,385–4,577)	12,576 (11,627–13,524)	11,726 (10,529–12,923)	33,067 (30,877–35,256)	40,133 (36,745–43,521)	9,368 (8,473–10,263)	8,861 (7,798–9,924)
Difference[b]	*Reference*	8,595	7,745	29,086	36,152	5,387	4,880

GI = gastrointestinal.
[a]Adjusted mean (95% CI) health-care costs ($) per patient during the 90 days after opioid index date (2002–2005), estimated using ordinary least squares regression analysis.
[b]Compared with the No GI event medical or prescription claim cohort.

20% increased adjusted mean number of prescription claims (7.46 to 8.08 vs 6.06 per patient) than did patients without relevant GI event medical or prescription claims ($p < 0.001$; Table 3).

HEALTH-CARE COSTS

Patients with a relevant GI event medical claim during the 90 days following index opioid prescription had significantly higher adjusted mean overall (total) health-care costs than did patients without relevant GI medical or prescription claims ($p < 0.001$; Table 4). Observed and adjusted mean costs estimated by OLS were generally similar (Figure 1). Patients identified through prescription claims for antiemetics or laxatives also had significantly higher overall cost compared with patients without GI medical or relevant prescription claims (Table 4; all comparisons $p < 0.001$). Compared with patients without any GI event claims, incremental adjusted mean total health-care costs for patients with any of the GI event claims ranged from $4880 to $36,152 and were significant ($p < 0.001$).

Patients with bowel obstruction medical claims only had the largest increase in adjusted mean inpatient cost compared with patients without relevant GI medical or prescription claims ($28,715 vs $1,356, $p < 0.001$; Table 4). Among the different GI adverse events, patients with nausea/vomiting medical claims only had the largest increase in other types of health-care costs versus patients without any relevant GI event medical or pharmacy claims: adjusted mean emergency care cost ($880 vs $141, $p < 0.001$); adjusted mean office visits cost ($3671 vs $1933; $p < 0.001$); adjusted mean pharmacy costs ($1000 vs $552; $p < 0.001$). Patients with prescription claims for antiemetics or laxatives and no relevant GI event medical claims also generally had increased adjusted mean health-care costs compared with patients without relevant GI event medical and prescription claims, except for adjusted mean inpatient cost for patients with prescription claims for antiemetics and adjusted mean emergency care cost for patients using laxatives, albeit with lower costs compared with patients with GI medical claims. Adjusted mean costs estimated from OLS and gamma linear regressions were similar.

Discussion

In this study we found that, for patients treated with oral opioids, nausea/vomiting, constipation, and bowel obstruction following opioid therapy significantly increased utilization and costs for inpatient and outpatient services. Contrary to the common perception that constipation is managed using over-the-counter laxatives, we observed significantly more hospitalizations, emergency department visits, office visits, and prescription drug use in patients with constipation medical claims. Having claims for 1 GI

event at least doubled the total cost of managing a patient without any relevant GI event medical or prescription claims during the 90 days following opioid therapy. A key strength of the study is that medical and prescription claims data represent actual health-care costs incurred by commercial insurers in real-life settings. However, analyses of claims data cannot rule out other causes of increased costs in the patients experiencing GI events. Although controlling for coexisting medical conditions in our analysis somewhat mitigated this concern, biases caused by other unobservable differences (eg, disease severity) among patient cohorts cannot be ruled out. Nevertheless, the significant association observed between opioid dose and treatment duration with the incidence of GI medical claims or relevant prescription claims is supportive.

The incidence rate of bowel obstruction in this study (0.22%) was similar to estimates reported in previous studies,[31,32] but the incidence rates for nausea/vomiting (6.16%) and constipation (2.41%) identified by medical claims and prescription claims for antiemetics and laxatives in this study were much lower than those reported in clinical trials and population-based surveys in which 23–32% of patients reported nausea and 36–57% reported constipation.[4,6] It is possible that patients experiencing nausea/vomiting and constipation may not seek medical care and self-manage these opioid adverse effects using nonprescription medications.[33] However, it is also possible that these events are undercoded in medical claims. Therefore, the costs of nausea/vomiting and constipation following opioid therapy observed in this study are representative only of patients with GI events that were recorded in medical claims or when antiemetic or laxative use was used as a proxy. Our results may overestimate the costs for patients who did not seek care for GI events and underestimate the costs for patients whose medical encounters for GI events were not coded properly. Notwithstanding the limitations, results from this study are consistent with previous findings that opioid adverse effects resulted in more health-care resource use.[11-13]

This study was limited to health-care costs from commercial insurance claims. The US commercially insured population available for analyses includes fewer elderly people who are covered by Medicare. Nonreimbursable items such as over-the-counter medications and phone calls to physicians regarding opioid adverse effects were not available in this analysis. It is possible that the small proportion of patients who were identified as using laxatives may have used these prophylactically rather than to address opioid-induced constipation, but we were unable to determine this based on the pharmacy claims data. Similarly, we did not have information on the use of over-the-counter laxatives either for prophylaxis or for treatment of opioid-induced constipation. Furthermore, because some antiemetic medications, such as diphenhydramine, have multiple therapeutic uses, we were also unable to confirm whether the medication was prescribed

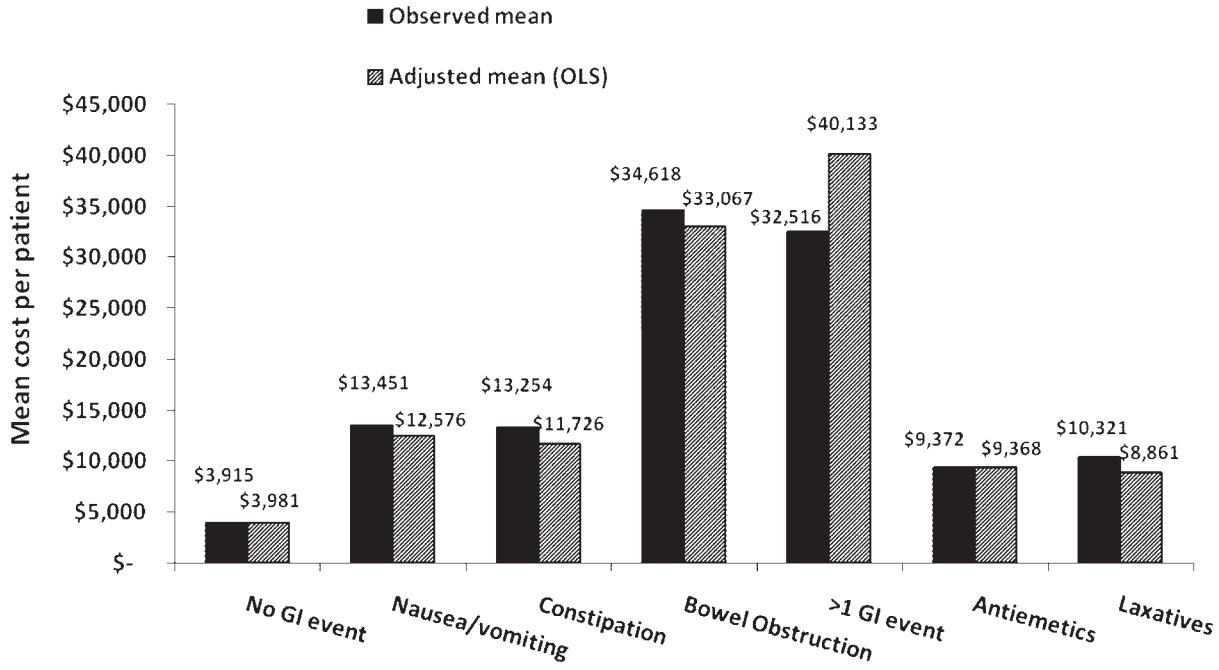

Figure 1. Comparison of mean overall observed and adjusted mean cost per patient (2002–2005 $) in the 90-day period following initial opioid prescription. GI = gastrointestinal; OLS = ordinary least squares.

for the treatment of nausea or other symptoms (eg, pruritus).

Opioid GI adverse effects also negatively affect function and productivity,[11,34,35] which are not captured in claims databases. Incremental costs due to the different GI events estimated by this study may be conservative for 2010, as estimates based on 2002–2005 data were not indexed to take into account medical care cost inflation in the intervening period (annual medical price index change from 4.0% to 4.4% between 2002 and 2005).[36] It should not be viewed as a comprehensive assessment of the economic burden of opioid GI adverse effects. It is also noteworthy that this study examined direct medical costs associated with opioid use of no more than 90 days and that it did not address the costs of GI events associated with chronic opioid therapy longer than 90 days.

US guidelines recommend that opioid therapy balance benefits relative to harms.[5] Despite the widespread incidence of opioid GI adverse effects reported by patients in clinical trials and surveys, the low incidence rates recorded in claims in this study suggest that payers and clinicians may underrecognize the occurrence of these opioid adverse effects. Programs that facilitate patient-physician communication, prevention, and treatment of opioid adverse effects are needed.

Future research using alternative sources, such as patient surveys or clinic studies, is needed to further identify the impact of GI events on pain management from both a payer and a patient perspective. Similarly, data from populations beyond the commercially covered population, such as the elderly, would be useful.

Summary

The economic burden of GI events following opioid treatment is substantial, with significantly increased utilization of inpatient, outpatient, and pharmacy services. Despite opioids' perceived efficacy in pain relief, their benefits are somewhat offset by the substantial additional costs of GI adverse events. The broad costs of pain management should be considered when evaluating the cost-effectiveness of treatment.

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Appendix I. Antiemetics and Laxatives Examined in this Study[a]

Antiemetics	Laxatives
Aprepitant	Bisacodyl
Diphenhydramine	Calcium polycarbophil
Dolasetron	Casanthranol
Dronabinol	Cellulose powder
Granisetron	Docusate
Hydroxyzine	Glycerin
Meclizine	Lactulose
Ondansetron	Magnesium citrate
Palonosetron	Magnesium hydroxide
Prochlorperazine	Methylcellulose
Promethazine	Mineral oil
Scopolamine	Polyethylene glycol
Thiethylperazine	Psyllium
	Senna
	Senosides
	Sodium phosphates

[a]Some medications reported by Herndon[22] (eg, haloperidol, naloxone) have indications that are unrelated to gastrointestinal events; they were used infrequently in the patient cohorts and were excluded from this study.

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Costos de Eventos Gastrointestinales Después de Tratamiento con Opioides para Pacientes que no Tienen Cáncer

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Ann Pharmacother 2010;44:630-40.

EXTRACTO

TRASFONDO: Los efectos secundarios gastrointestinales con comunes con el tratamiento oral con medicamentos derivados de opio.

objetivo: Estimar los costos asociados con eventos gastrointestinales después de tratamiento oral con opioides de corta duración utilizando la perspectiva del pagador.

MÉTODOS: Las reclamaciones médicas y de farmacia del banco de datos de la compañía PharMetrics se utilizaron para identificar pacientes que no habían usado medicamentos derivados de opio que obtuvieron una receta para productos orales de acción inmediata que contenían oxicodona o hidrocodona entre el 2002 y el 2006. El uso de recursos y los costos fueron determinados para los pacientes con códigos de ICD-9 para nausea/vómito (787.0x), estreñimiento (564.0x), obstrucción intestinal (560, 560.1, 560.3, 560.39 y 564.81) o recetas para laxantes o antieméticos durante un período de 3 meses después de la receta índice de opioide, y se comparó con pacientes que no habían tenido estos tipos de eventos médicos o recetas para laxantes o antieméticos. Los datos de uso de recursos se compararon usando regresión binomial negativa y los datos de costos con mínimos cuadrados ordinarios confirmados por análisis de regresión gama controlando por variables demográficas, duración de tratamiento y co morbilidades.

RESULTADOS: Datos de un total de 237,447 pacientes fueron analizados. Pacientes con reclamaciones por eventos gastrointestinales tuvieron significativamente más hospitalizaciones (media ajustada 0.20 a 0.97 vs 0.17, respectivamente, $p < 0.001$), días en el hospital (1.12 a 12.05 vs 1.00 días, $p < 0.001$), visitas a sala de emergencia (0.36 a 1.44 vs 0.25 visitas, $p < 0.001$), visitas ambulatorias (5.68 a 11.81 vs. 4.11 visitas, $p < 0.001$) y reclamaciones de recetas (7.46 a 8.21 vs. 6.06 reclamaciones, $p<0.001$) que los pacientes sin eventos gastrointestinales en los 3 meses después de la receta índice de opioide. Comparado con los pacientes sin ninguna reclamación de eventos gastrointestinales, la media ajustada de costos incrementales de salud para pacientes con alguna reclamación por eventos gastrointestinales fluctuó entre $4,880 y $36,152 ($p < 0.001$).

CONCLUSIONES: La carga económica de eventos gastrointestinales que ocurrieron durante el tratamiento con medicamentos derivados de opio fue significativa para pacientes con un evento gastrointestinal en las reclamaciones. La reducción de efectos secundarios gastrointestinales tiene el potencial de ahorros en costos para el sistema de salud.

Traducido por Homero A Monsanto

Coûts des Événements Gastro-Intestinaux Reliés à l'Utilisation d'Opioïdes pour le Traitement de la Douleur Non Cancéreuse en Milieu Ambulatoire

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RÉSUMÉ

HISTORIQUE: Les effets indésirables gastro-intestinaux (GI) sont fréquents avec l'utilisation d'opioïdes pour usage thérapeutique.

OBJECTIF: Estimer les coûts associés aux événements GI après l'utilisation d'opioïdes à courte durée d'action selon la perspective du tiers payeurs.

MÉTHODOLOGIE: Les réclamations médicales et pharmaceutiques de la base de données «PharMetrics Patient-Centric Database» ont été utilisées pour identifier les patients qui n'ont jamais reçu d'opioïdes par le passé et ont obtenu une nouvelle ordonnance pour un médicament oral à libération immédiate contenant de l'oxycodone ou de l'hydromorphone entre 2003 et 2006. Les ressources en soins de santé et les coûts ont été déterminés pour les réclamations associées aux codes de l'ICD-9 de nausées/vomissements (787.0x), constipation (564.0x), obstruction intestinale (560, 560.1, 560.39 et 564.81) ou des ordonnances pour des antiémétiques et laxatifs durant la période de 3 mois suivant la délivrance de l'ordonnance d'opioïdes et comparées aux données des patients sans réclamation médicale ou pharmaceutique reliées à des événements GI. Les données en ressources de la santé utilisées ont été comparées utilisant une régression binominale négative et les données concernant les coûts ont été comparées en utilisant la méthode des moindres carrés et confirmées par une analyse de régression gamma généralisée avec contrôle pour les données démographiques, la durée de traitement et les comorbidités.

RÉSULTATS: Les données de 237,447 patients ont été analysées. Les patients avec des réclamations pour des événements GI avaient significativement plus d'hospitalisation (moyenne ajustée 0.20 à 0.97 vs 0.17, respectivement, $p < 0.001$), durée de séjour à l'hôpital (1.12 à 12.05 vs 1.00 jours, $p < 0.001$), visites à la salle d'urgence (0.36 à 1.44 vs 0.25 visite, $p<0.001$), visites aux cliniques externes (5.56 à 11.81 vs 4.11 visites, $p<0.001$) et réclamations d'ordonnances pharmaceutiques (7.46 à 8.21 vs 6.06 réclamations, $p<0.001$) que les patients sans réclamation pour des événements GI durant la période de 3 mois suivant la délivrance d'une ordonnance pour des opioïdes. En comparaison avec les patients sans réclamations pour des événements GI, le total des coûts moyens incrémentiels ajustés en soins de santé pour les patients avec des réclamations pour des événements GI se situait entre $4,880 et $36,152 et était significativement plus élevé ($p < 0.001$).

CONCLUSIONS: Le fardeau économique occasionné par les événements GI coïncidant avec un traitement par des opioïdes est significatif pour les patients avec des événements GI enregistrés dans les réclamations. La réduction des effets indésirables GI pourrait engendrer des économies pour le système des soins de la santé.

Traduit par Chantal Guévremont