Health Care Utilization and Costs Associated with Nausea and Vomiting in Patients Receiving Oral Immediate-Release Opioids for Outpatient Acute Pain Management

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ABSTRACT

Introduction: Nausea and vomiting (NV) are common side effects of opioid use and limiting factors in pain management. This study sought to quantify the frequency of antiemetic prescribing and the impact of NV on health care resource utilization and costs in outpatients prescribed opioids for acute pain. The perspective was that of a commercial health plan.

Methods: Medical and pharmacy claims from IMS PharMetrics Plus were used to identify patients initiating opioid therapy with a prescription for an oxycodone-, hydrocodone- or codeine-containing immediate-release product for acute use (≤15-day supply) between October 1, 2013 and September 30, 2014. Patients with a medical claim for NV (International Classification of Diseases, Ninth Revision, Clinical Modification codes 787.0x), with or without an antiemetic prescription fill, were compared with patients with no NV claim or antiemetic prescription fill to assess differences in all-cause health care utilization and costs over 1 month. Propensity score matching (PSM) was used to adjust for between-group differences in baseline patient characteristics.

Results: The co-prescribing of opioids with antiemetic agents was 10.2%. After PSM (n = 45,790 per group), patients with NV claims had significantly more hospitalizations (11.5% vs 4.2%), emergency department visits (65.0% vs 12.1%), and physician office visits (85.2% vs 64.5%) compared with patients with no NV claims (all P < 0.0001). Mean total health care costs were higher among patients with a NV claim versus those without evidence of the side effect ($6290 vs $2309; P < 0.0001). Among patients with a recent hospitalization, patients with NV claims had higher rates of 30-day rehospitalization than those with no NV claims (24.4% vs 3.0%; P < 0.0001).
Conclusions: Among outpatients prescribed opioids for management of acute pain, co-prescribing with antiemetics was low, and the economic burden associated with NV was high. Efforts to prevent NV in patients receiving opioid therapy may improve patient outcomes and provide cost savings to the health care system.

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Keywords: Acute pain; Analgesia; Analgesics; Antiemetics; Health care costs; Health care utilization; Rehospitalization; Opioid; Opioid-induced nausea and vomiting; Outpatient

INTRODUCTION

As the most common medical complaint in the United States, pain represents a significant public health burden, with estimated annual direct and indirect costs exceeding $600 billion [1]. Opioids are the most widely used analgesic and part of a multimodal pain management approach [2–5]. In 2012, health care professionals wrote more than 259 million prescriptions for opioid analgesics [6]. Careful monitoring and judicious use are warranted, as opioids are associated with life-threatening adverse events, such as respiratory depression, and there is also potential for diversion and misuse [7–12]. Opioid-induced nausea and vomiting (OINV), a common adverse event in patients using opioid therapy for acute pain, can be a significant barrier to effective pain management [13–17]. Published reports of OINV suggest that nausea develops in approximately 40% of patients and vomiting develops in approximately 20% of patients, both of which may have a higher incidence in clinical practice [18–23]. In a systematic review of opioid-related adverse events in postoperative patients, 31% reported gastrointestinal adverse events, such as nausea, vomiting, and constipation [24]. Gastrointestinal adverse events may be a contributing factor to treatment discontinuation [10]. Survey data have shown that, to reduce gastrointestinal-related adverse events, including nausea, vomiting, or constipation, 13% of patients with acute pain discontinued their opioid treatment, and 16% of patients with acute pain reduced their dose of opioids [25].

Inadequately treated acute pain has been associated with an increased risk of progression to chronic pain [10, 26–28]. In addition, studies have shown that inadequately treated acute pain may also result in problems ranging from sleep impairment to the development of depression or post-traumatic stress disorder [29, 30]. Thus, OINV may significantly compromise effective pain management increasing overall health care utilization and associated costs [10, 25, 31].

While there are ample data regarding the economic consequences of nausea and vomiting (NV) in the hospital setting [23, 32–35], corresponding data in the outpatient setting are limited. A previous study that examined the costs of gastrointestinal events in outpatients treated with immediate-release (IR) opioids for noncancer pain found that NV was associated with increased all-cause health care utilization and costs over a 3-month follow-up period [31]. However, as OINV typically occurs early in treatment and resolves as tolerance develops [36, 37], economic outcomes collected over this timeframe may not be applicable for shorter-term treatment. Although antiemetics are effective in preventing and alleviating
OINV, data pertaining to the rate of antiemetic co-prescribing are scarce.

The objectives of this real-world study were to describe antiemetic usage and to estimate the economic burden associated with NV over a 30-day follow-up period among a large cohort of outpatients receiving IR opioids for the management of acute pain from the perspective of a US commercial health plan.

METHODS

Patient Eligibility and Study Design

A retrospective analysis was conducted using IMS PharMetrics Plus (IMS Health, Waltham, MA, USA) real-world data. The database consists primarily of US commercial preferred provider organization plans, enrolling approximately 95 million total patients with both medical and pharmacy benefits. The database contains deidentified patient records and complies with Health Insurance Portability and Accountability Act patient privacy safeguards. The IMS database provides a broad view of patient health status and utilization of health care via integrated medical and pharmacy claims. The reimbursable amounts for covered medical services and medications are also recorded allowing for the assessment of allowed (versus billed) costs. Due to the large number of covered lives, the IMS database is generally representative of the US commercially insured population.

Medical and pharmacy claims were used to identify patients initiating opioid therapy who were aged ≥18 years and who filled a short-term prescription (≤15-day supply) for any IR codeine-, hydrocodone-, or oxycodone-containing tablet or capsule from October 1, 2013 through September 30, 2014. The aforementioned analgesics were selected for this analysis as they represent the most commonly prescribed opioids for the treatment of acute pain in the outpatient setting. The date of this first prescription fill was considered the index date. Eligible patients were required to have continuous enrollment in the database for 180 days prior to the index date (baseline period) and for 30 days after the index date (follow-up period; Fig. 1). To ensure that patients were newly initiated to opioids and had not developed tolerance to NV, those prescribed any opioid-containing product during the baseline period were excluded from the study. Also excluded were patients with claims for medical conditions that may be associated with NV or antiemetic use unrelated to opioid use (cancer, vertigo, bulimia nervosa, intestinal infectious diseases, and food poisoning), patients with more than 1 opioid prescription fill on the index date and an index opioid claim that overlapped with an inpatient hospitalization. Eligible patients were assessed for nausea or vomiting medical claims based on International Classification of Diseases, Ninth Revision, Clinical Modification codes 787.0x, and pharmacy claims for antiemetic fills over the 30-day follow-up period. Antiemetics included aprepitant, diphenhydramine, granisetron, hydroxyzine, meclizine, ondansetron, prochlorperazine, promethazine, scopolamine, metoclopramide, trimethobenzamide, palonosetron, dolasetron,

Fig. 1 Study timeline
and thiethylperazine. This article does not involve any new studies of human or animal subjects performed by any of the authors.

**Study Outcomes**

Measures of all-cause health care resource utilization were hospitalizations (including 30-day readmission rates among a subgroup of patients), emergency department (ED) visits, and physician office visits. The prescribing rate of antiemetics was examined. All-cause health care costs (2013–2014 USD) were calculated for inpatient, outpatient, and pharmacy services using the allowed reimbursement payment amount (inclusive of patient copay).

**Statistical Analysis**

Patients with a medical claim for NV with or without a pharmacy claim for an antiemetic agent (NV group) were compared with patients having no medical claim for NV and no pharmacy claim for an antiemetic agent (no NV group). The incremental impact of NV on health care resource utilization and costs over the 30-day follow-up period was examined. The rate of antiemetic use in the overall study population was examined. In addition, rates of 30-day rehospitalization among the subgroup of patients who were hospitalized within 2 days of filling the index opioid prescription were compared between patients with and without a medical claim for NV during study follow-up. Antiemetics can be used for reasons other than NV, and therefore, patients with a pharmacy claim for an antiemetic agent, but no medical claim for NV were excluded from health care resource use and cost comparisons.

Descriptive data were compared using t-tests and Chi-squared tests for continuous and categorical variables, respectively. Propensity score matching (PSM) [38], using the Greedy method with a caliper of 0.01, was used to adjust for known differences in baseline patient characteristics. Patients were matched on age, gender, type of index opioid, health plan characteristics and baseline antiemetic claims, NV claims, total health care costs, and severity of comorbid conditions using the Charlson Comorbidity Index [39]. Health care resource utilization and costs were assessed using the propensity-matched cohorts.

Due to a residual imbalance between propensity-matched groups, regression analyses were conducted to generate adjusted cost ratios and their 95% confidence intervals (CI), accounting for differences in baseline antiemetic use. Generalized linear models (GLM) with log-link and gamma distribution were used to adjust pharmacy and total costs. Adjustment of inpatient and outpatient costs required the use of a two-part model, due to the large numbers of patients with zero costs; logistic regression was used to estimate the probability of having a positive cost, and GLM with log-link and gamma distribution was used to estimate the cost conditional on it being positive.

For the subgroup analysis of patients hospitalized within 2 days of filling index opioid prescription, Kaplan–Meier curves were generated to estimate 30-day rehospitalization rates. All $P$ values were considered to be significant at $P < 0.05$. Analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC, USA).

**RESULTS**

Study eligibility was met by 2,120,806 patients (Table S1). Of the total cohort of eligible patients receiving an IR opioid prescription, 2.3% ($n = 47,935$) had a medical claim for NV.
within 30 days of index opioid prescription, with the majority of these patients (57.1%, \( n = 27,375 \)) having an NV claim occurring on the index date (Fig. 2). Of patients with an NV claim on the same day as the index opioid prescription, 52.0% \( (n = 14,242) \) were also co-prescribed an antiemetic.

Among all eligible patients receiving an IR opioid prescription, 10.2% \( (n = 215,366) \) filled an antiemetic prescription within 30 days after the index opioid prescription, and most of these patients (73.7%, \( n = 158,859 \)) received the antiemetic on the same day as the index opioid prescription. Among patients who filled an antiemetic prescription on the same date as the index opioid prescription, 9.0% \( (n = 14,242) \) also had an NV claim on the index date (Fig. 2).

Among patients with an NV claim, 2145 were excluded from further analyses due to having negative cost data. Baseline characteristics for 45,790 patients with a medical claim for NV, with or without an antiemetic claim, and 1,835,228 patients, with no medical claim for NV and no pharmacy claim for an antiemetic, are shown in Table 1. Compared with patients without NV claims, patients with medical claims for NV were younger and more likely to be female. They were also more likely to be treated with oxycodone, have previous claims for NV or antiemetic use, have a greater comorbidity burden, and have higher baseline total health care costs. Baseline patient characteristics after PSM were similar, with the exception of baseline antiemetic use, which remained significantly higher among patients with a medical claim for NV versus no NV claim (12.5% vs 11.8%; \( P = 0.002 \); Table S2).

**Health Care Resource Utilization**

Patients with a claim for NV had significantly more hospitalizations (11.5% vs 4.2%), ED visits (65.0% vs 12.1%), and physician office visits (85.2% vs 64.5%) in the 30 days following the index opioid prescription compared with patients having no NV claim (all \( P < 0.0001 \); Table 2). The unadjusted mean (standard deviation [SD]) number of hospital days over the 30-day follow-up period was 3.8 (3.7) days for patients with an NV medical claim versus 1.9 (2.2) days for patients without an NV claim, corresponding to 0.43 (1.73) per-member-per-month (PMPM) days for patients with a medical claim for NV versus 0.08 (0.59) PMPM days for patients with no evidence of NV. The unadjusted mean (SD) number of ED visits was 1.3 (0.6) for patients with NV claims versus 1.1 (0.4) for patients without NV claims. Patients with NV claims also had higher unadjusted mean (SD) number of physician office visits (3.2 [2.3]) than patients without a NV claim (2.6 [2.2]).
Among patients with NV claims, 4.5% (n = 2042) had a hospitalization within 2 days of the index opioid prescription, compared with 6.6% (n = 3013) among patients with no claim for NV. The rate of 30-day rehospitalization was significantly higher for those with a NV claim than for those without such a claim (24.4% vs 3.0%; P < 0.0001; Fig. 3).

### Health Care Costs

Patients with a medical claim for NV had higher unadjusted mean inpatient ($1816 vs $295), outpatient ($4275 vs $1857), pharmacy ($198 vs $156), and total costs ($6290 vs $2309) compared with patients with no NV claim (all P < 0.0001; Fig. 4). After adjustment for baseline antiemetic use, cost ratios for patients with compared to without a NV claim were 6.2 (95% CI 6.2–6.2), 2.3 (2.3–2.3), 1.3 (1.2–1.3), and 2.7 (2.7–2.8) for inpatient, outpatient, pharmacy, and total costs, respectively. In both groups, the majority of the expenditures were for outpatient visits (68.0% in patients with a NV claim and 80.4% in patients with no NV claim); however, the greatest cost differential was for inpatient services.

### DISCUSSION

In this study of patients newly treated with an IR opioid prescribed for acute pain, NV coincident with opioid use was associated with a significant economic burden. Total adjusted health care costs were more than 1.5 times higher for patients with a NV claim compared with those with no NV claim, and for inpatient services, the adjusted costs were more than five times higher over the 30-day follow-up period. Furthermore, in the subgroup of patients with a recent hospitalization, 30-day hospital readmission rates were more than seven times higher for patients with a NV claim compared with those with no NV claim.

| Characteristic          | NV (n = 45,790) | No NV (n = 1,835,228) |
|-------------------------|-----------------|------------------------|
| Age (%)                 |                 |                        |
| 18–35 years             | 37.9            | 31.2                   |
| 36–45 years             | 22.5            | 20.1                   |
| 46–55 years             | 21.7            | 23.9                   |
| >55 years               | 17.9            | 24.7                   |
| Median (years)          | 41              | 45                     |
| Female (%)              | 64.2            | 52.5                   |
| Region (%)              |                 |                        |
| East                    | 22.8            | 23.0                   |
| Midwest                 | 27.4            | 31.0                   |
| South                   | 44.6            | 39.9                   |
| West                    | 5.2             | 6.1                    |
| Health plan type (%)    |                 |                        |
| Commercial              | 61.7            | 63.6                   |
| Self-insured            | 34.3            | 33.5                   |
| Other/unknown           | 4.0             | 2.9                    |
| Plan product type (%)   |                 |                        |
| PPO                     | 82.7            | 82.2                   |
| HMO                     | 9.1             | 9.3                    |
| POS                     | 4.7             | 4.6                    |
| Traditional\(^c\)       | 1.8             | 2.1                    |
| Other/unknown           | 1.6             | 1.7                    |
| Index drug (%)          |                 |                        |
| Codeine                 | 4.5             | 8.6                    |
| Hydrocodeine            | 67.9            | 72.5                   |
| Oxycodone               | 27.6            | 19.0                   |
| Baseline antiemetic use (%) | 12.5         | 4.7                    |
| Baseline NV event (%)   | 20.5            | 3.0                    |
| CCI (%)                 |                 |                        |
| 0                       | 75.4            | 81.9                   |
| 1–2                     | 21.6            | 15.8                   |
| >3                      | 3.1             | 2.4                    |
| Mean (SD) baseline total health care costs, USD | 5772 (88) | 4301 (10) |

CCI Charlson Comorbidity Index, HMO health maintenance organization, NV nausea and/or vomiting, POS point of service, PPO Preferred Provider Organization, SD standard deviation, USD US dollars

\(^a\) Patients with negative cost data were excluded from comparative analyses

\(^b\) All comparisons P < 0.0001

\(^c\) Traditional, indemnity/fee-for-service
higher for patients with a medical claim for NV compared with patients without such a claim. While patients may seek medical attention for the symptoms of NV, health care resource use may also occur for conditions that are a consequence of the patient having experienced NV and secondary reduction or interruption of opioid therapy, resulting in insufficient analgesia [10]. Uncontrolled pain in itself may contribute to increased health care costs as affected patients seek additional care and treatment for their pain [10]. Medical complications of uncontrolled pain may also result in additional health care costs. For example, unrelieved postoperative pain may reduce patient mobility, leading to complications, such as deep vein thrombosis, pulmonary embolism, or pneumonia, any of which may add to the cost of care [40].

The direction of our results is consistent with an earlier study that examined the costs of gastrointestinal events in outpatients treated with IR opioids for noncancer pain [31]. In that study, total health care costs over a three-month follow-up period were more than 200% higher in patients with a medical claim for NV ($12,576) compared with patients with no medical claim for a gastrointestinal event ($3981), primarily driven by hospital costs ($7025 vs $1356, respectively). It is possible that differences in the total cost ratios may be due to differences in timing of data collection relative to the index date (1 vs 3 months) or cohort selection definitions (e.g., patients with no medical claims for NV vs patients with no medical claims for an opioid-related gastrointestinal event).

Other studies that have evaluated the economic impact of NV associated with opioid use have largely been conducted in the inpatient setting. In a retrospective study of adult surgical patients, median total health care costs were increased by 7.6% and median length of hospital stay was increased by 10.3% in patients who experienced opioid-related adverse drug events (ADEs) versus matched controls who did not experience such events [35]. Of note, NV accounted for approximately

| Table 2  | Health care resource utilization among patients with and without nausea and/or vomiting over 30-day follow-up period |
|----------|-------------------------------------------------------------------------------------------------------------|
| Health care resource utilization | NV (n = 45,790) | No NV (n = 45,790) |
| Any hospitalization (%)* | 11.5 | 4.2 |
| PPPM hospitalization days, mean (SD) | 0.43 (1.7) | 0.08 (0.6) |
| PTPPM hospitalized days, mean (SD) | 3.8 (3.7) | 1.9 (2.2) |
| Any ED visit (%)* | 65.0 | 12.1 |
| PPPM ED visit, mean (SD) | 0.83 (0.8) | 0.14 (0.4) |
| PTPPM ED visit, mean (SD) | 1.3 (0.6) | 1.1 (0.4) |
| Any office visit (%)* | 85.2 | 64.5 |
| PPPM office visit, mean (SD) | 2.8 (2.4) | 1.7 (2.2) |
| PTPPM office visit, mean (SD) | 3.2 (2.3) | 2.6 (2.2) |

ED emergency department, NV nausea and vomiting, PPPM per-patient-per-month, PTPPM per-treated-patient-per month, SD standard deviation

* P < 0.0001
50% of all opioid-related ADEs in this study. In another study among hospitalized patients who received oral opioids, those who received medication for nausea, vomiting, or constipation were hospitalized 1.36 days longer than those who did not receive any such medication, at an additional cost of $2223 per patient (both $P < 0.0001$) [41]. Medication for nausea, vomiting, or constipation was also associated with a longer hospital length of stay and greater costs per patient among patients who received injectable (including epidural) opioids in that study [41].

The prevalence of NV claims coincident with short-term opioid use in this study was much lower (2.3%) than rates of OINV reported spontaneously in the previous clinical trials [18–22], suggesting the underreporting of these side effects to treating providers. In a retrospective survey of oral opioid users with acute pain, 77% of patients with nausea and 65% with vomiting did not inform their physician of these side effects [13]. Of patients who experienced nausea (vomiting), 2% (4%) visited the ED, 4% (12%) visited their doctor, 18% (19%) called their doctor, and 17% (27%) took a prescription medication to alleviate their symptoms, as reported over a 3-month recall period. It is possible that NV is under-recognized as a side effect of opioid use, and therefore, patient reporting to their

Fig. 3 Cumulative 30-day rehospitalization rates for patients with and without a medical claim for nausea and/or vomiting. NV, nausea and vomiting.

Fig. 4 Health care costs for patients with and without a medical claim for nausea and/or vomiting over 30-day follow-up period. *All $P < 0.0001$. ACR, adjusted cost ratio; CI, confidence interval; NV, nausea and/or vomiting.
physician is low. However, even when NV is disclosed by the patient, providers may not code for these conditions in submitted medical claims.

Concomitant use of antiemetic agents was low (~10%), with three-quarters of prescription fills occurring on the index date. Among patients with opioid and antiemetic claims at index who also had an NV claim recorded over the follow-up period, over 70% of such NV claims occurred on the index date, suggesting that antiemetic prescribing may have been in response to episodes of OINV rather than for the prevention of the side effect. The need to minimize the troublesome side effects of opioids to optimize pain management and curtail-associated health care costs suggests a potentially important role for antiemetic co-prescribing. Prophylactic use of antiemetics may improve patient outcomes, including quality of life, and reduce the burden on caregivers, providers, and the health care system [16, 31, 32, 42].

Strengths of this real-world study include its large sample size, the integration of medical and pharmacy claims information, and reimbursed cost data that represent the US managed care perspective. However, this study has several limitations that are typical of retrospective claims analyses. Causal relationships cannot be established, and episodes of NV identified by medical claims cannot be definitively attributed to opioid use. In addition, it is unknown whether patients took their prescription medications as directed. It could not be determined whether antiemetics were prescribed for the prevention or treatment of NV. PSM and multivariate regression modeling can only adjust for known confounding variables; therefore, residual bias may be present. As NV is likely underreported by the patient or under-coded by the physician, there is potential for differential misclassification of exposure. If only the most severe cases of NV were recorded in the medical claims, then the economic impact associated with NV may be biased.

Future research to improve pain management might include the identification of patient risk factors that increase the likelihood of OINV to help clinicians identify patients who would benefit from antiemetic prophylaxis. Comparative studies of preventive versus reactive antiemetic prescribing strategies could also provide relevant insights related to clinical and economic outcomes.

CONCLUSIONS

Among outpatients managed with IR opioids for acute pain, use of concomitant antiemetics was low and the economic burden associated with NV was high. Efforts to prevent NV associated with opioid use may improve patient outcomes and provide cost savings to the health care system.

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