


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

Elizabeth Marrett  · Winghan Jacqueline Kwong · Feride Frech · Chunlin Qian

Received: August 22, 2016 / Published online: October 4, 2016
© The Author(s) 2016. This article is published with open access at Springerlink.com

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

Enhanced content To view enhanced content for this article go to <http://www.medengine.com/Redeem/84E6F06069F22E1E>.

Electronic supplementary material The online version of this article (doi:[10.1007/s40122-016-0057-y](https://doi.org/10.1007/s40122-016-0057-y)) contains supplementary material, which is available to authorized users.

E. Marrett (✉) · W. J. Kwong · C. Qian
Daiichi Sankyo, Inc., Parsippany, NJ, USA
e-mail: emarrett@dsi.com

F. Frech
Spring, TX, USA

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.

Funding: Daiichi Sankyo, Inc.

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,

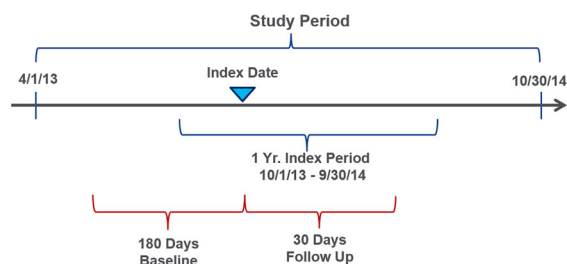


Fig. 1 Study timeline

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]).

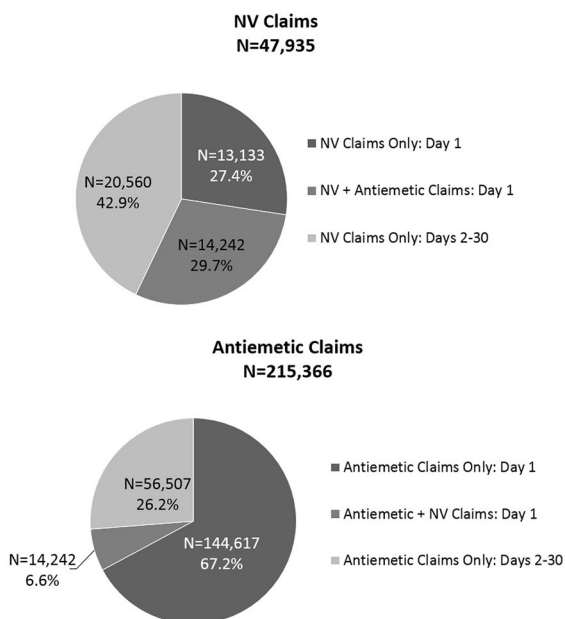


Fig. 2 Distribution of medical claims for nausea and/or vomiting and pharmacy claims for antiemetic agents over 30-day follow-up period. *NV* nausea and/or vomiting

Table 1 Baseline patient characteristics^{a,b}

Characteristic	NV (<i>n</i> = 45,790)	No NV (<i>n</i> = 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
Hydrocodone	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

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

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 (<i>n</i> = 45,790)	No NV (<i>n</i> = 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

* $P < 0.0001$

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

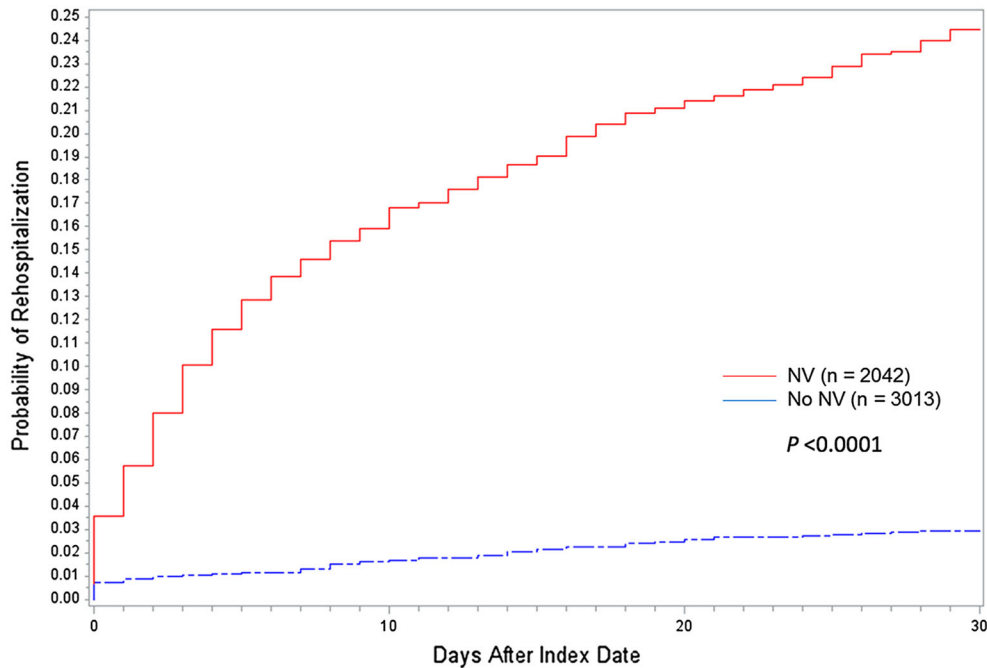


Fig. 3 Cumulative 30-day rehospitalization rates for patients with and without a medical claim for nausea and/or vomiting. *NV* nausea and vomiting

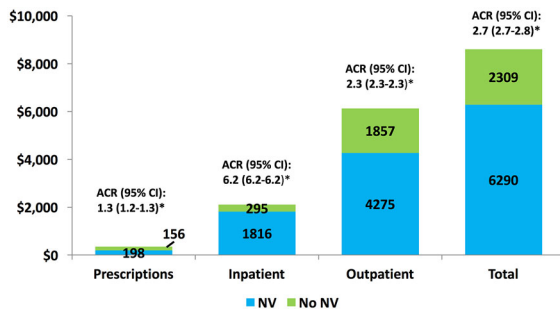


Fig. 4 Health care costs for patients with and without a medical claim for nausea and/or vomiting over 30-day follow-up period. *All $P < 0.0001$. *ACR* adjusted cost ratio, *CI* confidence interval *NV* nausea and/or vomiting

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

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 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.

ACKNOWLEDGMENTS

The study and article processing charges were sponsored by Daiichi Sankyo, Inc. Qiaoyi Zhang, MD, Ph.D., contributed to the study design. Writing assistance for this article was provided by Kathryn Leonard, B.Sc., of ETHOS Health Communications in Newtown, PA, USA, with financial support from Daiichi Sankyo, Inc, in compliance with international guidelines for Good Publication Practice.

All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this manuscript, take responsibility for the integrity of the work as a whole, and have given final approval to the

version to be published. All authors had full access to all of the data in this study and take complete responsibility for the integrity of the data and accuracy of the data analysis.

Disclosures. Elizabeth Marrett is an employee of Daiichi Sankyo, Inc. Wingham Jacqueline Kwong is an employee of Daiichi Sankyo, Inc. Chunlin Qian is an employee of Daiichi Sankyo, Inc. Feride Frech is a former employee of Daiichi Sankyo, Inc.

Compliance with Ethics Guidelines. This article does not involve any new studies of human or animal subjects performed by any of the authors.

Open Access. This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 International License (<http://creativecommons.org/licenses/by-nc/4.0/>), which permits any noncommercial use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made.

REFERENCES

1. Institute of Medicine Committee on Advancing Pain Research, Care, and Education. *Relieving Pain in America: a blueprint for transforming prevention, care, education, and research*. Washington, DC: The National Academies Press; 2011.
2. Fornasari D. Pain pharmacology: focus on opioids. *Clin Cases Miner Bone Metab*. 2014;11(3):165–8.
3. Kehlet H, Dahl JB. The value of “multimodal” or “balanced analgesia” in postoperative pain treatment. *Anesth Analg*. 1993;77(5):1048–56.
4. Manchikanti L, Singh A. Therapeutic opioids: a ten-year perspective on the complexities and complications of the escalating use, abuse, and nonmedical use of opioids. *Pain Physician*. 2008;11(2 Suppl):S63–88.
5. National Pharmaceutical Council and Joint Commission on Accreditation of Healthcare Organizations. *Pain: current understanding of assessment, management, and treatments*. <http://www.npcnow.org/system/files/research/download/Pain-Current-Understanding-of-Assessment-Management-and-Treatments.pdf>. Accessed April 11, 2016.
6. Centers for Disease Control and Prevention. CDC VitalSigns: opioid painkiller prescribing. <http://www.cdc.gov/vitalsigns/opioid-prescribing/>. Accessed May 16, 2016.
7. US Food and Drug Administration. Fact Sheet—FDA opioids action plan. <http://www.fda.gov/NewsEvents/Newsroom/FactSheets/ucm484714.htm>. Accessed April 11, 2016.
8. Jarzyna D, Jungquist CR, Pasero C, et al. American Society for Pain Management Nursing guidelines on monitoring for opioid-induced sedation and respiratory depression. *Pain Manag Nurs*. 2011;12(3):118–45.
9. Duensing L, Eksterowicz N, Macario A, Brown M, Stern L, Ogbonnaya A. Patient and physician perceptions of treatment of moderate-to-severe chronic pain with oral opioids. *Curr Med Res Opin*. 2010;26(7):1579–85.
10. Sinatra R. Causes and consequences of inadequate management of acute pain. *Pain Med*. 2010;11(12):1859–71.
11. Centers for Disease Control and Prevention. New CDC opioid prescribing guidelines: improving the way opioids are prescribed for safer chronic pain treatment. http://www.wha.org/pdf/CDCguidelines_factsheet_opioids.pdf. Accessed May 27, 2016.
12. Dart RC, Surratt HL, Le Lait MC, et al. Diversion and illicit sale of extended release tapentadol in the United States. *Pain Med*. 2015;17(8):1490–6.
13. Gregorian RS Jr, Gasik A, Kwong WJ, Voeller S, Kavanagh S. Importance of side effects in opioid treatment: a trade-off analysis with patients and physicians. *J Pain*. 2010;11(11):1095–108.
14. Chung F, Lane R, Spraggs C, et al. Ondansetron is more effective than metoclopramide for the treatment of opioid-induced emesis in post-surgical adult patients. *Eur J Anaesthesiol*. 1999;16(10):669–77.
15. Smith HS, Laufer A. Opioid induced nausea and vomiting. *Eur J Pharmacol*. 2014;722:67–78.

16. Anastassopoulos KP, Chow W, Ackerman SJ, Tapia C, Benson C, Kim MS. Oxycodone-related side effects: impact on degree of bother, adherence, pain relief, satisfaction, and quality of life. *J Opioid Manag.* 2011;7(3):203–15.
17. Varrassi G, Muller-Schwefe GH. The international CHANGE PAIN physician survey: does specialism influence the perception of pain and its treatment? *Curr Med Res Opin.* 2012;28(5):823–31.
18. Chang DJ, Desjardins PJ, Bird SR, et al. Comparison of rofecoxib and a multidose oxycodone/acetaminophen regimen for the treatment of acute pain following oral surgery: a randomized controlled trial. *Curr Med Res Opin.* 2004;20(6):939–49.
19. Kalso E, Edwards JE, Moore RA, McQuay HJ. Opioids in chronic non-cancer pain: systematic review of efficacy and safety. *Pain.* 2004;112(3):372–80.
20. Daniels S, Casson E, Stegmann JU, et al. A randomized, double-blind, placebo-controlled phase 3 study of the relative efficacy and tolerability of tapentadol IR and oxycodone IR for acute pain. *Curr Med Res Opin.* 2009;25(6):1551–61.
21. Park YB, Ha CW, Cho SD, et al. A randomized study to compare the efficacy and safety of extended-release and immediate-release tramadol HCl/acetaminophen in patients with acute pain following total knee replacement. *Curr Med Res Opin.* 2015;31(1):75–84.
22. Musclow SL, Bowers T, Vo H, Glube M, Nguyen T. Long-acting morphine following hip or knee replacement: a randomized, double-blind and placebo-controlled trial. *Pain Res Manag.* 2012;17(2):83–8.
23. Pizzi LT, Toner R, Foley K, et al. Relationship between potential opioid-related adverse effects and hospital length of stay in patients receiving opioids after orthopedic surgery. *Pharmacotherapy.* 2012;32(6):502–14.
24. Wheeler M, Oderda GM, Ashburn MA, Lipman AG. Adverse events associated with postoperative opioid analgesia: a systematic review. *J Pain.* 2002;3(3):159–80.
25. Moskovitz BL, Benson CJ, Patel AA, et al. Analgesic treatment for moderate-to-severe acute pain in the United States: patients' perspectives in the Physicians Partnering Against Pain (P3) survey. *J Opioid Manag.* 2011;7(4):277–86.
26. Pergolizzi JV Jr, Raffa RB, Taylor R Jr. Treating acute pain in light of the chronification of pain. *Pain Manag Nurs.* 2014;15(1):380–90.
27. Shipton EA. The transition from acute to chronic post surgical pain. *Anaesth Intensive Care.* 2011;39(5):824–36.
28. Swegle JM, Logemann C. Management of common opioid-induced adverse effects. *Am Fam Physician.* 2006;74(8):1347–54.
29. Moeller-Bertram T, Keltner J, Strigo IA. Pain and post traumatic stress disorder—review of clinical and experimental evidence. *Neuropharmacology.* 2012;62(2):586–97.
30. Brennan F, Carr DB, Cousins M. Pain management: a fundamental human right. *Anesth Analg.* 2007;105(1):205–21.
31. Kwong WJ, Diels J, Kavanagh S. Costs of gastrointestinal events after outpatient opioid treatment for non-cancer pain. *Ann Pharmacother.* 2010;44(4):630–40.
32. Eberhart L, Koch T, Kranke P, Rusch D, Torossian A, Nardi-Hiebl S. Activity-based cost analysis of opioid-related nausea and vomiting among inpatients. *J Opioid Manag.* 2014;10(6):415–22.
33. Kane-Gill SL, Rubin EC, Smithburger PL, Buckley MS, Dasta JF. The cost of opioid-related adverse drug events. *J Pain Palliat Care Pharmacother.* 2014;28(3):282–93.
34. Oderda GM, Evans RS, Lloyd J, et al. Cost of opioid-related adverse drug events in surgical patients. *J Pain Symptom Manag.* 2003;25(3):276–83.
35. Oderda GM, Said Q, Evans RS, et al. Opioid-related adverse drug events in surgical hospitalizations: impact on costs and length of stay. *Ann Pharmacother.* 2007;41(3):400–6.
36. Coluzzi F, Pappagallo M, National Initiative on Pain Control. Opioid therapy for chronic noncancer pain: practice guidelines for initiation and maintenance of therapy. *Minerva Anestesiol.* 2005;71(7–8):425–33.
37. Smith HS, Smith JM, Seidner P. Opioid-induced nausea and vomiting. *Ann Palliat Med.* 2012;1(2):121–9.
38. Coca-Perraillon M. Local and global optimal propensity score matching. *SAS Global Forum 2007, April 16–19, 2007, Orlando, FL.*
39. Quan H, Sundararajan V, Halfon P, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Med Care.* 2005;43(11):1130–9.
40. Wells N, Pasero C, McCaffery M. Improving the quality of care through pain assessment and

-
- management. In: Hughes RG, editor. Patient safety and quality: an evidence-based handbook for nurses. Rockville: Agency for Healthcare Research and Quality; 2008. p. 469–97.
41. Suh DC, Kim MS, Chow W, Jang EJ. Use of medications and resources for treatment of nausea, vomiting, or constipation in hospitalized patients treated with analgesics. *Clin J Pain.* 2011;27(6):508–17.
42. Lapane KL, Quilliam BJ, Benson C, Chow W, Kim MS. Gastrointestinal events after opioid treatment in nonmalignant pain: correlates of occurrence and impact on health-related quality of life. *J Opioid Manag.* 2013;9(3):205–16.