Relationship Between Potential Opioid-Related Adverse Effects and Hospital Length of Stay in Patients Receiving Opioids After Orthopedic Surgery

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Study Objective. To determine whether there is an association between opioid-related adverse effects and postoperative hospital length of stay (p-LOS).

Design. Retrospective medical record review.

Setting. Large academic medical center.

Patients. Random sample of 402 patients (mean age 60.2 yrs, 50.3% female) who underwent orthopedic spine, hip, knee, or shoulder surgery during 2007 and received opioids during or after the procedure.

Measurements and Main Results. Potential opioid-related adverse effects were identified by using established criteria. Bivariate and multivariate analyses (generalized linear regression model, log transformed) were used to identify predictors of p-LOS. The model also estimated the effect of specific types of adverse effects and adverse-effect combinations on p-LOS. Mean ± SD p-LOS was 3.0 ± 2.1 days; median oral morphine equivalent postoperative dose was 60 mg/day. More than half of the patients (54.2%) experienced one or more adverse effects, 25.6% experienced two or more adverse effects, and 7.2% experienced three or more adverse effects. The composite of nausea and vomiting was experienced by 36.1% of study patients, and 12.6% had at least one emesis episode. Constipation and confusion were documented in 6.5% and 3.7% of patients, respectively. Constipation ($p<0.0001$), emesis ($p<0.001$), and confusion ($p<0.01$) were associated with increased p-LOS after adjusting for other significant variables. Patients with constipation had an adjusted 49% (95% confidence interval [CI] 25–77%) longer p-LOS (additional 1.4 days) compared with patients without constipation. Emesis and confusion significantly increased p-LOS by 25% (95% CI 10–42%) and 38% (95% CI 11–72%), respectively. Incremental increases in p-LOS for patients with two adverse effects ($p=0.02$), three adverse effects ($p<0.001$), and four adverse effects ($p<0.001$) versus patients with no adverse effects were 15%, 40%, and 82%, respectively.

Conclusion. Constipation, emesis, and confusion were associated with increased p-LOS in patients receiving opioids after orthopedic surgery. In addition, there was a significant linear relationship between the number of adverse effects/patient and increased p-LOS, and the strength of the association increased as the number of adverse effects increased. Although the

opioid dosages and adverse-effect rates were typical, these findings reinforce the need to balance pain management with risk of events.

Key Words: opioid, adverse effects, length of stay, orthopedic, postoperative care, health care utilization.

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Although opioid analgesics are the cornerstone of postoperative analgesia after orthopedic surgery,[1–5] knowledge about their adverse effects continues to emerge.[6–9] These adverse effects include nausea, emesis, constipation, ileus, urinary retention, pruritus, hypoxia, respiratory depression, hypotension, somnolence, confusion, and dizziness.[2, 8, 10]

The incidence of opioid-related adverse effects after orthopedic surgery is most often evaluated in randomized clinical trials, comparing opioid drugs and their routes of administration.[1, 7, 9, 11–14] In practice, however, patients are often exposed to more than one opioid drug administered through two or more routes; therefore, information from patient care settings about opioid-related adverse effects is needed so that practitioners can balance pain management with risk of adverse effects.

Despite this lack of real-world data, the potential for opioid-related adverse effects to lead to increased utilization of health care resources in the postoperative setting is widely accepted by clinicians and nurses who are on the front lines of postoperative patient care. Thus, the purported economic consequences of opioid-related adverse effects have spurred various emerging lines of research, including clinical and economic advantages of opioid sparing and opioid replacement,[10, 15] cost-effectiveness of prophylactic antiemetics in patients undergoing surgery,[16–20] and the value of treatment specifically indicated for opioid-induced adverse effects (e.g., methylnaltrexone).[21–27] Length of stay (LOS) is consistently used as a primary or secondary outcome measure in these studies, and any observed increase in LOS is often attributed to opioid-related adverse effects. However, the nature of the association between these adverse effects and LOS has received only modest attention.[8, 28] Past efforts examined the impact of adverse effects collectively, with no distinction between individual types of adverse effects.[8] Therefore, to our knowledge, the additive effect of multiple opioid-related adverse effects on LOS is unknown. Given the current and forecasted increases in the volume of joint replacement and spine surgeries performed each year in the United States,[29–31] any driver of extended LOS in these procedure groups poses economic and humanistic concern.

To address these gaps in the literature, we performed a retrospective medical record review to examine the incidence of opioid-related adverse effects among patients at an urban teaching hospital who underwent orthopedic surgeries of the hip, knee, shoulder, or spine. We examined the rates of potential opioid-related adverse effects, patterns of concurrent adverse effects, and the impact of adverse effects on postoperative LOS (p-LOS). An understanding of the relationship between adverse effects and LOS will allow the findings from this study to be applied to other institutions as well as to future economic evaluations of new opioids or treatments for opioid-related adverse effects.

Methods

This retrospective review of patient medical records (both paper and electronic versions) evaluated a stratified, random sample of patients who underwent orthopedic surgical procedures at one of two sites of an academic medical center in 2007. The study was approved by the Thomas Jefferson University Institutional Review Board; the requirement for written informed consent was waived.

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Study Population

Patients were identified for the study if they underwent a surgical procedure that was coded according to the *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) as one of 35 primary procedures. Patients were included if they were at least 18 years old; had undergone spine, hip, knee, or shoulder surgery; had a minimum LOS of 1 day; and had received opioids during or after the procedure. Trauma patients and patients with multiple operative procedures were excluded.

Data Collection

Data were collected on patient demographics, clinical characteristics (e.g., LOS), drug therapy, and opioid-related adverse effects. Three trained abstractors reviewed patients' medical records, including the nursing flow sheets. The flow sheets are used by nursing staff on a regular basis and include preformatted fields for each body system (e.g., gastrointestinal, respiratory) as well as specific fields for opioid-related adverse effects (e.g., nausea, emesis, and constipation). In addition, each patient's electronic medical record contains a medication administration record that lists administration dates and times, unit, doses, and route of administration for all drugs administered. For this study, we also reviewed patient-controlled analgesia (PCA) records that document dosing at 4-hour intervals. A final source for data on adverse effects was a standard form used by the acute pain management service to identify and score opioid-related adverse effects.[32] All data obtained from each of the different data sources were merged into one Microsoft Access database (Microsoft Corp., Redmond, WA).

Identification of Adverse Effects

The criteria used to identify specific adverse effects were developed with use of the published literature on opioids and reviewed by a clinical expert (EV) for face validity (Appendix 1). The medication administration record was not used to identify adverse effects (i.e., the administration of a specific therapy was not used to infer that an adverse effect had occurred). Nausea, emesis, constipation, urinary retention, pruritus, dizziness, respiratory depression, and confusion required documentation by a clinician that the symptom was present. For hypoxia to be considered, in addition to a clinician's documentation of the adverse effect, a second criterion was an oxygen saturation level less than 90%. Patients with a respiration rate of 10 breaths/minute or lower were identified as having a low respiration rate but were not classified as having respiratory depression unless respiratory rate was documented less than 8 breaths/minute. Nausea and emesis were recorded both separately and as a composite event.

The criteria were applied to potential adverse effects identified in the nursing flow sheets, the opioid-related adverse effect scoring sheet, and in the progress notes of attending clinicians. Once adverse effects were identified, the following data were captured: adverse effect date and time, specific adverse effect criterion used, and any clinician notes regarding the adverse effect or intervention. Each episode of a potential opioid-related adverse effect was recorded separately. Each note of an adverse effect was considered a separate episode, with the exception being a second clinician documenting the same event, as determined by the reviewer. Reviewer discretion was used to determine if the episode was a new episode, and consistency between reviewers on this issue was tested during a pilot study through a modified interrater reliability test. The adverse effects reported are only those observed after discharge from the postanesthesia care unit; investigators recognized that adverse effects caused by anesthesia would be difficult to distinguish from those caused by opioids.

Individual adverse effects were analyzed descriptively to assess the rate of each individual adverse effect (e.g., constipation, pruritus) and the rate of any adverse effect (i.e., at least one adverse effect of any type). In addition, the number of adverse effects/patient was examined. Use of antiemetics was analyzed across the entire study group and among patients who were experiencing nausea and emesis. Similarly, use of stool softeners and laxatives was analyzed across the entire study group and among patients with constipation.

Conversion to Morphine Equivalent Dose

The doses of all opioids administered were converted to oral morphine equivalencies.[33] Conversions of intraspinal doses were completed using conversion ratios from the literature.[34, 35] The total daily doses of opioids were summed across routes for each postoperative day. Opioid-tolerant patients were identified as those who were prescribed opioids prior to admission.

Length of Stay

The primary outcome of the study was the p-LOS, which was calculated by subtracting discharge date from procedure date. This approach excludes the number of days, if any, the patient was admitted before the surgical procedure. By this method, opioid-related adverse effects would only impact the LOS after the procedure. The cutoff used for each postoperative day was 12:00 A.M.; therefore, postoperative day 1 occurred at 12:00 A.M. the day after surgery.

Statistical Analysis

Statistical analyses were conducted using SAS, version 9.2. (SAS Institute Inc., Cary, NC). Patient demographics and clinical characteristics were analyzed across the entire study group. Means ± SDs are shown for continuous variables, whereas the number and percentage of patients are shown for categoric variables.

Bivariate analyses were conducted to assess the unadjusted effect of patient demographic characteristics, clinical characteristics (including postoperative complications and infections), and the presence or absence of individual opioid-related adverse effects on p-LOS. Multivariate analyses were used to isolate the effect of each adverse effect on p-LOS. Bivariate analyses examining the relationship between independent variables and p-LOS informed selection of variables for inclusion in the multivariate analyses. Because of the nonnormal distribution of p-LOS, a log-transformation, multivariate analysis was applied using a generalized linear regression model (ProcGenmod in SAS, version 9.2) with gamma distribution and a log link function. The exponent of the parameter estimate for each independent variable was interpreted as the increase in p-LOS compared with the reference case. For each adverse effect and comorbid condition, the reference case was "no adverse effect" and "no comorbid condition," respectively, and for each procedure group, the reference case was shoulder surgery. For the multivariate analyses, race-ethnicity was defined as either Caucasian (reference case) or non-Caucasian.

To account for the frequency of adverse effects, the same model used to estimate p-LOS was run a second time, substituting individual adverse effects for numbers of concurrent adverse effects experienced in each patient. This model compared the p-LOS of patients with no adverse effects with the p-LOS of patients with one, two, three, or four adverse effects.

All models controlled for procedure type, given that there were significant variations in p-LOS by procedure. Interactions between the most frequent adverse effects and procedure type were tested, but no significant interactions were detected. Therefore, the final models do not include interaction terms.

Results

Demographic and Clinical Characteristics

A total of 6204 patients were identified as having the procedures of interest during the study period (Figure 1). Of those, 455 patients were randomly selected, stratified equally from each of the four orthopedic surgery groups: spine, hip, knee, and shoulder. After accounting for those patients who were excluded, the final study population was 402 patients.

The majority of spine procedures were spinal fusions (48.5%), laminectomies and foraminotomies (28%), and discectomies (9%). Combinations of back procedures were common. Hip procedures were almost completely total hip arthroplasty (three were partial), and all patients undergoing knee surgery had total knee arthroplasties. Of the shoulder procedures, 52% of patients underwent a total shoulder arthroplasty, 14% received partial shoulder replacements, and

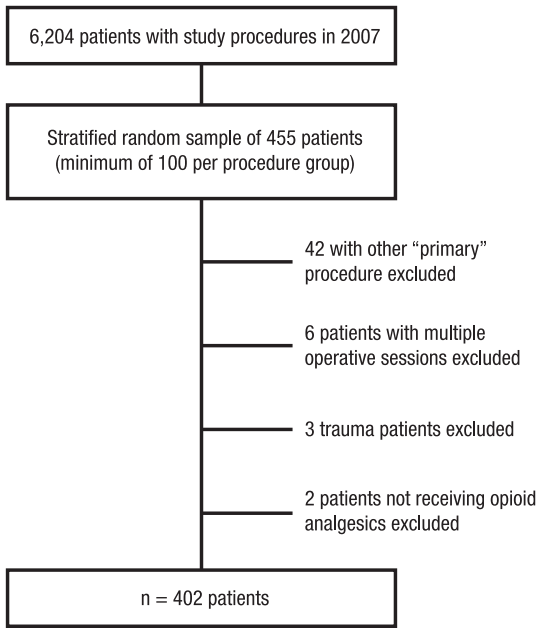

Figure 1. Schematic of the patient selection process.

the remainder underwent other orthopedic shoulder repairs.

The mean ± SD age of patients was 60.2 ± 4.8 years, with an even distribution between males and females (Table 1). Overall, patients reported 1.6 ± 1.4 comorbid conditions, of which the top four conditions were arthritis (47.5%), hypertension (46.8%), gastroesophageal reflux disease (27.4%), and diabetes mellitus (14.2%). The mean ± SD total LOS and p-LOS were comparable, 3.2 ± 2.4 and 3.0 ± 2.1 days, respectively, which reflects the current practice of admitting patients on the day of surgery. The distribution for p-LOS was skewed to the right, ranging from 1–22 days.

Opioid Management

Table 2 contains descriptive statistics on opioid use in the study population. Approximately one fifth of the study group reported preadmission opioid use; more than half (53%) were patients undergoing spinal procedures. Only 21.4% of patients received intraspinal opioids by epidural or intrathecal routes. The majority (70.7%) were placed on a PCA pump in the perioperative or postoperative setting. The transition from intravenous to oral opioids occurred generally between postoperative days 1 and 2, or 24–48 hours after the surgery. Approximately one half (51%) of all patients were receiving oral opioids by postoperative day 1, and 78% by postoperative day 2. Only 8% of patients were still receiving intravenous opioids on postoperative day 3. Among the entire study group, the median oral morphine equivalent postoperative dose was 60 mg/day and 274.6 mg over the entire postoperative course.

Adverse Effects

More than half (54.2%) of the patients experienced at least one adverse effect (Table 3). Nearly one (18.4%) of five patients in the sample experienced two adverse effects and 7.2% experienced three or more. There was no significant difference between procedure subgroup and rate of adverse effect.

The composite of nausea and vomiting (or emesis) was the most common adverse effect,

Table 1. Baseline Demographic and Clinical Characteristics of the 402 Study Patients

Characteristic	Spine Surgery (n=101)	Hip Surgery (n=99)	Knee Surgery (n=102)	Shoulder Surgery (n=100)	Total (N=402)
Age, yrs (mean ± SD)	54.3 ± 15.1	61.7 ± 13.8	65.5 ± 9.9	59.4 ± 17.4	60.2 ± 14.8
Sex, no. (%)					
Male	54 (53.5)	49 (49.5)	36 (35.3)	61 (61.0)	200 (49.8)
Female	47 (46.5)	50 (50.5)	66 (64.7)	39 (39.0)	202 (50.2)
Race-ethnicity, no. (%)					
African-American	7 (6.9)	7 (7.1)	12 (11.8)	7 (7.0)	33 (8.2)
Asian	0 (0)	0 (0)	0 (0)	1 (1.0)	1 (0.2)
Caucasian	92 (91.1)	91 (91.9)	86 (84.3)	72 (72.0)	341 (84.8)
Hispanic	0 (0)	0 (0)	1 (1.0)	0 (0)	1 (0.2)
Hispanic, other	0 (0)	0 (0)	0 (0)	1 (1.0)	1 (0.2)
Unknown	2 (2.0)	1 (1.0)	3 (2.9)	19 (19.0)	25 (6.2)
Body mass index, kg/m^2 (mean ± SD)	28.6 ± 6.5	28.8 ± 6.4[a]	32.3 ± 7.1	28.8 ± 5.3[b]	29.7 ± 6.6[c]
Smoking, no. (%)					
Current smoker	18 (17.8)	16 (16.2)	11 (10.8)	14 (14.0)	59 (14.7)
Ex-smoker	33 (32.7)	24 (24.2)	45 (44.1)	11 (11.0)	113 (28.1)
Comorbidities, no. (%)					
Arthritis	22 (21.8)	74 (74.7)	87 (85.3)	8 (8.0)	191 (47.5)
Hypertension	38 (37.6)	43 (43.4)	67 (65.7)	40 (40.0)	188 (46.8)
GERD	34 (33.7)	26 (26.3)	48 (47.1)	2 (2.0)	110 (27.4)
Diabetes mellitus	12 (11.9)	12 (12.1)	19 (18.6)	14 (14.0)	57 (14.2)
Depression	14 (13.9)	16 (16.2)	16 (15.7)	4 (4.0)	50 (12.4)
Asthma	8 (7.9)	11 (11.1)	12 (11.8)	11 (11.0)	42 (10.4)
Heart disease	5 (5.0)	10 (10.1)	14 (13.7)	2 (2.0)	31 (7.7)
LOS, days (mean ± SD)	3.7 ± 3.7	3.3 ± 1.8	4.1 ± 1.9	1.8 ± 0.7	3.2 ± 2.4
Taking opioids on admission, no. (%)	42 (41.6)	18 (18.2)	12 (11.8)	8 (8.0)	80 (19.9)

GERD = gastroesophageal reflux disease; LOS = total hospital length of stay.
[a]Data were available for 98 patients.
[b]Data were available for 97 patients.
[c]Data were available for 398 patients.

Table 2. Opioid Use in the 402 Study Patients

Characteristic	No. (%) of Patients
Taking opioid at home	80 (19.9)
Route of administration	
Intraspinal	86 (21.4)
Oral	358 (89.1)
PCA	284 (70.7)
Intravenous	326 (81.1)
Opioid drug[a]	
Codeine	24 (6.0)
Fentanyl	332 (82.6)
Hydrocodone	165 (41.1)
Hydromorphone	129 (32.1)
Meperidine	24 (6.0)
Morphine	292 (72.6)
Oxycodone	166 (41.3)
Propoxyphene	68 (16.9)
Remifentanil	45 (11.2)
Sufentanil	13 (3.2)
PCA opioid	
Fentanyl	138/284 (48.6)
Hydromorphone	49/284 (17.3)
Morphine	151/284 (53.2)

PCA = patient-controlled analgesia.
[a]Patients may have received more than one opioid during hospitalization.

Table 3. Potential Opiod-related Adverse Effects in the 402 Study Patients

Adverse Effect	No. (%) of Patients
Composite of nausea and vomiting (emesis)	145 (36.1)
Nausea	123 (30.6)
Emesis	50 (12.4)
Dizziness	44 (11.0)
Pruritus	44 (11.0)
Hypoxia	27 (6.7)
Constipation	26 (6.5)
Urinary retention	19 (4.7)
Confusion	15 (3.7)
Respiration rate < 8 breaths/min[a]	10 (2.5)
Any adverse effect	218 (54.2)
No. of adverse effects	
0	184 (45.8)
1	115 (28.6)
2	74 (18.4)
3	21 (5.2)
4	8 (2.0)

[a]Respiration rate < 8 breaths/min was used to indicate respiratory depression.

occurring in 36.1% of patients. These patients experienced a mean ± SD of 1.9 ±1.2 episodes (range 1–8 episodes). The rate of this composite event increased from 16.7% on the day of surgery to a peak of 21.1% on postoperative day 1. The rate decreased to 12.9% and 6.3% on postoperative days 2 and 3, respectively. The decline in the rate closely followed the decline in intravenous opioid use and total daily morphine equivalent dose. Emesis occurred in 50 patients (12.6%), and 32.0% experienced more than one episode. Approximately one in four patients who reported nausea also reported an emesis episode.

Patients received a mean ± SD of 1.0 ± 1.8 antiemetic (range 0–15), regardless of whether they experienced the composite of nausea and vomiting. Patients with nausea received 2.0 ± 1.9 antiemetics, whereas patients with emesis received 2.8 ± 2.6 (range 0–15 antiemetics for both effects). Forty-three patients (> 10% of the entire study population) were administered an antiemetic at least 3 times. Ondansetron was the most common antiemetic administered, followed by metoclopramide and promethazine.

The rate of constipation (documented by a clinician) was 6.5%. A mean ± SD of 4.7 ± 5.1 stool softeners (range 0–39) were administered to the 402 patients. For patients who reported constipation, the mean ± SD number of stool softener administrations increased to 8.1 ± 6.7 (range 1–27). The mean ± SD number of laxatives administered to patients with constipation was 1.3 ± 1.8 (range 0–6).

Effect of Individual Adverse Effects on Postoperative Length of Stay

The results of the generalized linear regression model analyzing the effect of individual adverse effects on p-LOS are shown in Table 4. Constipation ($p<0.0001$), confusion ($p=0.0038$), and emesis ($p=0.0008$) remained significantly associated with increased p-LOS after adjusting for other significant predictors of p-LOS. Procedure subgroup, complication or infection developed after surgery, age, and sex remained significantly associated with p-LOS, as did the following comorbid conditions: Parkinson's disease, COPD and hypertension. Constipation and urinary retention reported on admission also remained significant.

Constipation had the strongest effect on p-LOS among the adverse effects. Patients with constipation had a 49% (95% confidence interval [CI] 25–77%) longer p-LOS compared with patients without constipation. If compared with the mean LOS of the patients without constipation, the effect translates to an additional 1.4 days (range 0.7–2.2 days) of p-LOS due to constipation. Confusion and emesis significantly increased p-LOS by 38% (95% CI 11–72%) and 25% (95% CI 10–42%), respectively. Confusion added 1.1 days (range 0.3–2.1 days) in p-LOS compared with patients without confusion, and emesis added 0.7 day (range 0.3–1.2 days) in p-LOS compared with patients without emesis.

Table 4. Results from a Generalized Linear Regression Model of the Impact of Individual Adverse Effects on Postoperative Length of Stay in the 402 Study Patients

Independent Variable	Parameter Estimate	Exponent of Parameter Estimate (95% CI)	p Value
Adverse effect			
Constipation	0.3966	1.49 (1.25–1.77)	<0.0001
Confusion	0.3242	1.38 (1.11–1.72)	0.0038
Emesis	0.2220	1.25 (1.10–1.42)	0.0008
Urinary retention	0.1441	1.15 (0.94–1.42)	0.1659
Respiration rate ≤ 8 breaths/min	0.1081	1.11 (0.84–1.47)	0.4481
Dizziness	0.0746	1.08 (0.94–1.23)	0.2775
Hypoxia	0.0695	1.07 (0.91–1.27)	0.4169
Nausea	−0.0052	0.99 (0.91–1.09)	0.9133
Pruritus	−0.0126	0.99 (0.86–1.13)	0.8577
Demographic and clinical characteristics			
Knee procedure	0.7307	2.08 (1.79–2.41)	<0.0001
Complication or infection[a]	0.6041	1.83 (1.26–2.66)	0.0015
Hip procedure	0.5559	1.74 (1.51–2.01)	<0.0001
Spine procedure	0.5069	1.66 (1.47–1.87)	<0.0001
Female	0.0884	1.09 (1.00–1.19)	0.0391
Age	0.0073	1.01 (1.00–1.01)	<0.0001
Comorbid conditions[b]			
Parkinson's disease	0.8964	2.45 (1.04–5.75)	0.0394
COPD	0.3350	1.40 (1.08–1.80)	0.0099
Hypertension	0.1073	1.11 (1.01–1.22)	0.0247
Pneumonia	0.2714	1.31 (0.95–1.81)	0.0959
Heart disease	0.1594	1.17 (0.85–1.62)	0.3350
Anemia	0.0652	1.07 (0.88–1.29)	0.5067
GERD	0.0353	1.04 (0.94–1.14)	0.4814
Arthritis	−0.0970	0.91 (0.81–1.02)	0.0944
Symptoms[b]			
Urinary retention	0.4251	1.53 (0.99–2.35)	0.0530
Constipation	0.2026	1.22 (1.02–1.46)	0.0258
Impaired cognition	0.2870	1.33 (0.87–2.05)	0.1904

CI = confidence interval; COPD = chronic obstructive pulmonary disease; GERD = gastroesophageal reflux disease.
[a]Complication or infection developed after surgery.
[b]Present on admission.

The additional p-LOS for patients with constipation, confusion, and emesis is presented graphically in Figure 2.

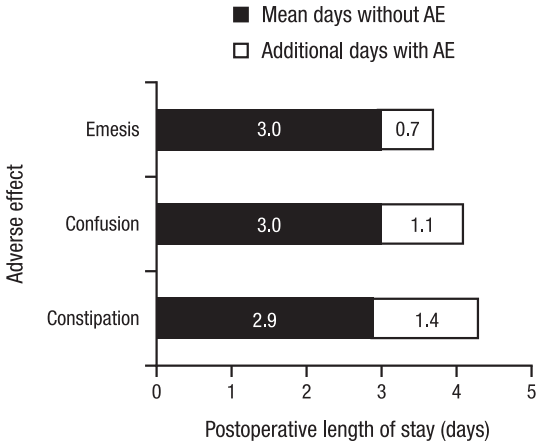

Figure 2. Additional postoperative days due to specific adverse effects (AEs). Emesis, confusion, and constipation were associated with a significantly prolonged postoperative length of stay (p=0.0008 for emesis, p=0.0038 for confusion, and p<0.0001 for constipation). Mean number of days without each AE was calculated from the average postoperative length of stay among patients who did not experience the specific AE. The AEs observed during postoperative opioid treatment are defined in Appendix 1. Of the 402 study patients, 26 (6.5%) experienced constipation, 15 (3.7%) confusion, and 195 (48.5%) emesis or composite of nausea and vomiting (emesis).

Incremental Effect of Multiple Adverse Effects

The results of the model analyzing the incremental impact of multiple adverse effects are presented in Table 5. There was a significant linear relationship between the number of adverse effects/patient and increased p-LOS. The strength of the association and size of the effect increased as the number of adverse effects experienced increased. Patients with one adverse effect did not experience a significantly longer p-LOS than patients with no adverse effects. However, p-LOS increased by 15% in patients with two adverse effects (p=0.02), by 40% in patients with three adverse effects (p<0.001), and by 82% in patients with four adverse effects (p<0.001). The relationships between number of adverse effects experienced and the attributed increase in p-LOS are shown in Figure 3.

Nausea was the most common concurrent adverse effect. Among patients with two or more adverse effects, 71.8% complained of nausea. Similarly, in patients who had three or more adverse effects, 79.3% had nausea. Of those patients with constipation, 73.0% had at least one other adverse effect and 30.8% had two or more concurrent adverse effects. The most common concurrent adverse effects among patients with constipation were pruritus (26.9%) and nausea (23.1%). Likewise, 74.0% of patients with emesis had at least one other adverse effect, and 32.0% had two or more concurrent adverse effects. The most common concurrent adverse effects in patients with emesis were nausea (56.0%), pruritus (28.0%), and dizziness (12.0%). Half of the patients with confusion had

Table 5. Results from a Generalized Linear Regression Model of the Effects of the Number of Adverse Effects on Postoperative Length of Stay in 402 Study Patients

Independent Variable	Parameter Estimate	Exponent of Parameter Estimate (95% CI)	p Value
No. of adverse effects			
1	0.0652	1.07 (0.97–1.18)	0.1884
2	0.1417	1.15 (1.03–1.29)	0.0166
3	0.3349	1.40 (1.15–1.69)	0.0006
4	0.5989	1.82 (1.33–2.49)	0.0002
Demographic and clinical characteristics			
Knee procedure	0.7255	2.07 (1.78–2.40)	<0.0001
Complication or infection[a]	0.6989	2.01 (1.39–2.91)	0.0002
Spine procedure	0.5771	1.78 (1.58–2.01)	<0.0001
Hip procedure	0.5699	1.77 (1.54–2.03)	<0.0001
Age	0.0084	1.01 (1.01–1.01)	<0.0001
Female	0.0681	1.07 (0.98–1.17)	0.1170
Comorbid conditions[b]			
Parkinson's disease	0.9204	2.51 (1.10–5.73)	0.0290
COPD	0.3189	1.38 (1.06–1.78)	0.0157
Pneumonia	0.3171	1.37 (0.99–1.90)	0.0547
Hypertension	0.1175	1.12 (1.02–1.24)	0.0156
GERD	0.0452	1.05 (0.95–1.16)	0.3728
Heart disease	0.1072	1.11 (0.80–1.54)	0.5212
Anemia	0.0664	1.07 (0.88–1.30)	0.5098
Arthritis	–0.1194	0.89 (0.79–0.99)	0.0405
Symptoms[b]			
Constipation	0.2613	1.30 (1.08–1.56)	0.0046
Urinary retention	0.3998	1.49 (0.96–2.31)	0.0722
Impaired cognition	0.3286	1.39 (0.90–2.15)	0.3195

CI = confidence interval; COPD = chronic obstructive pulmonary disease; GERD = gastroesophageal reflux disease.
[a]Complication or infection developed after surgery.
[b]Present on admission.

at least one other adverse effect; 27.0% experienced nausea and 20.0% had constipation.

Discussion

Previous studies have examined postoperative opioid-related adverse effects and their effect on opioid utilization.[8, 28] Although the opioid dosages and potential opioid-related adverse effects observed in our population were typical, the study distinctly examined the independent as well as the combined influence of these events on inpatient p-LOS, adjusting for procedure type.

The most common postoperative adverse effect in our study was the composite measure of nausea and vomiting (emesis). Published rates of this composite event range widely, from 1%[8] to 67%,[7] reflecting the diversity of methods used to observe

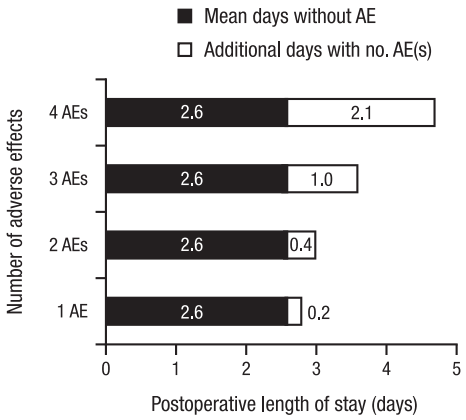

Figure 3. Additional postoperative days due to numbers of adverse effects (AEs) experienced by each patient. Mean number of days without each AE was calculated from the average postoperative length of stay among patients without the specific number of AEs. The AEs observed during postoperative opioid treatment are defined in the Appendix. Of the 402 study patients, 115 patients (28.6%) experienced one AE, 74 patients (18.4%) had two, 21 patients (5.2%) had three, and 8 patients (2.0%) had four.

and classify this event as a potentially opioid-related adverse effect. Postoperative nausea or vomiting is most often studied in patients undergoing ambulatory surgery.[36–40] In this study, nausea and vomiting episodes that occurred in the postanesthesia care unit were not included, although they did occur often. Despite this exclusion, our rate for the composite of nausea and vomiting was still 36.1% and, thus, within the range reported in the previously published studies.

The association between opioid-related adverse effects and increased LOS was determined in one study.[8, 28] This study estimated that patients with opioid-related adverse effects experienced a 10.3% increase in LOS (equating to 0.47 day/patient).[8] However, the findings were based on patients with any adverse effect compared with those with no adverse effects (as opposed to analysis of individual adverse effects); and the investigators found that only 1.8% of patients experienced an opioid-related adverse effect (low percentage compared with other studies).[8] Our study also found these significant associations, but specific to type of adverse effect and combinations of adverse effects.

The magnitude of the impact of each adverse effect on p-LOS should be considered as a combination of the rate of the adverse effect and the size of its impact isolated in the model. Although we did not find the composite of nausea and vomiting to be a p-LOS driver, we found the rate of emesis in the inpatient setting to be a significant driver. Twelve percent of patients in our study population vomited between discharge

from the postanesthesia care unit and discharge from the hospital. This was the most common adverse effect among those adverse effects found to have a significant impact on p-LOS. Patients with emesis were administered an average of three antiemetics, usually ondansetron, followed by metoclopramide if the former agent was unsuccessful. Regardless of whether emesis or even the composite of nausea and vomiting occurred, we found utilization of antiemetics for the prevention or treatment of the composite to be common in this population. In addition, these data suggest that although nausea in and of itself does not appear to be a significant contributor to increase p-LOS, it is a commonly occurring adverse effect and when it occurs with constipation, confusion, or emesis, it may have an additive effect on the impact of the adverse effects on LOS.

Of all the adverse effects examined in this study, patient complaints of constipation had the greatest effect on p-LOS. Patients with constipation were found to have an approximately 50% longer p-LOS than patients without constipation. Whether the constipation was an adverse effect is difficult to examine and is dependent on how well the situation was recorded, whether the constipation existed before admission, and whether prophylaxis was given (e.g., stool softeners, laxatives). Overall, we observed a low rate of constipation. We suspect that the low rate is due to prophylactic use as well as the fact that the types of the procedures examined do not involve bowel manipulation. In the multivariate analysis examining predictors of p-LOS, we accounted for constipation in two ways: preoperative constipation reported in the records, and constipation, as defined in the Appendix, reported during postoperative opioid use. Therefore, we independently examined the effect of each of these constipation occurrences on LOS. We think that this approach was acceptable for addressing the primary study question.

Opioid-related adverse effects may lead to a longer LOS for several reasons. First, patients experiencing an opioid-induced adverse effect have been shown in other studies to have a longer recovery time.[41] Adverse effects may lead to delays in patient time to ambulation,[42–44] time to first oral intake,[42, 44] and time to first bowel movement.[44] Although not a primary outcome evaluated in our study, we observed that delays in physical therapy were often attributed to opioid-related adverse effects by the clinician or therapist (e.g., six patients had physical therapy delayed due to the composite of nausea and vomiting).

Although our findings indicate that constipation, emesis, and confusion have independent statistically significant effects on p-LOS, the data also show that combinations of adverse effects have an even stronger impact. In fact, the data suggest that these three adverse effects rarely occur alone. Thus a considerably large proportion of patients in our study may have been opioid intolerant and had numerous adverse effects throughout their hospitalization, the combination of which significantly increased their p-LOS.

This study focused on the outcome of hospital LOS as opposed to a clinical outcome (e.g., pain score); however, post hoc, we descriptively examined pain scores using the electronic medical record data. We found the mean pain score (10-point numeric rating scale, with higher scores indicating more severe pain) by procedure to be as follows: discectomy 5.58, hip replacement 3.25, knee replacement 3.75, laminectomy and foraminectomy 4.13, and spinal fusion 5.02. The differences in reported pain scores may have contributed to the amount and type of opioid prescribed, as well as potential opioid-related adverse effects and hospital LOS. It is assumed that inclusion of the procedure types as covariates in the regression model adjusted for the differences in pain experienced by the patients.

Several limitations should be considered when interpreting the results of this study. First, coadministration of other postoperative drugs known to potentiate the adverse effects of opioids (e.g., anticholinergics, antispasmodics, sedatives) was not addressed. Second, although significant detail was gathered from the patient medical records, the rates of the adverse effects examined were low, calling to question whether our sample size of 402 patients was large enough to sufficiently examine individual adverse effects. Although our analysis revealed certain adverse effects to be significant predictors of p-LOS, larger sample sizes might have enabled us to more robustly examine this relationship. Third, although the adverse effects captured in this study are all known to be associated with the use of opioids, there is no way to establish causation in retrospect, and even during clinical practice, establishing causation is not practical. A review of studies examining postoperative opioid-related adverse effects noted that some suspected opioid-related adverse effects may be due to other factors in the patient's postoperative

course and not necessarily from the opioid exposure.[6] Regardless of etiology, the adverse effects examined in this study have all been linked to opioid use,[45, 46] and clinicians commonly associate them with opioid use in the postoperative setting. Given that many patients in this study were discharged on the second postoperative day, it was not possible to apply the accepted definition of constipation (3 days without a bowel movement); instead, we relied on clinical documentation of constipation in the nursing notes. Therefore, our reported rate of constipation (7%) may underestimate the true incidence in this population.

In modeling the effect of each adverse effect on cost, we included comorbid conditions that were found to have a significant bivariate relationship with p-LOS. A comorbidity index would have been preferred to assessing individual adverse effects; however, no index could be identified that was appropriate for this population. Preliminary models did assess the effect of the sum of comorbid conditions on p-LOS, but the variable was not significant.

Because the study was a retrospective medical record review, we were limited to observing only what was documented. Any adverse effects not documented by a clinician were not captured. Likewise, we could not account for any confounding causes of additional p-LOS not documented by a clinician.

Conclusion

This study examined the effect of potential opioid-related adverse effects on p-LOS. Our findings suggest that constipation, emesis, and confusion were potential opioid-related adverse effects resulting in statistically significant increases in p-LOS. In addition, the number of adverse effects/patient significantly contributed to increased p-LOS. Although significant differences were noted, the clinical relevance of our findings ultimately needs to be determined by health care providers and administrators. Increasing rates of orthopedic surgical procedures in the United States point to the need for further examination of potential opioid-related adverse effects on efficiency measures such as LOS.

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References

1. **Blumenthal S, Min K, Marquardt M, Borgeat A.** Postoperative intravenous morphine consumption, pain scores, and side effects with perioperative oral controlled-release oxycodone after lumbar discectomy. Anesth Analg 2007;105:233–7.
2. **American Society of Anesthesiologists Task Force on Acute Pain Management.** Practice guidelines for acute pain management in the perioperative setting: an updated report by the American Society of Anesthesiologists Task Force on Acute Pain Management. Anesthesiology 2004;100:1573–81.
3. **Rosenquist RW, Rosenberg J.** Postoperative pain guidelines. Reg Anesth Pain Med 2003;28:279–88.
4. **Gordon DB, Dahl JL, Miaskowski C, et al.** American Pain Society recommendations for improving the quality of acute and cancer pain management: American Pain Society Quality of Care Task Force. Arch Intern Med 2005;165:1574–80.
5. **Agency for Health Care Policy and Research.** Acute pain management: operative or medical procedures and trauma. Clinical Practice Guideline No.1. AHCPR Pub. No. 92-0032. Rockville, MD: AHCPR, 1992.
6. **Wheeler M, Oderda GM, Ashburn MA, Lipman AG.** Adverse events associated with postoperative opioid analgesia: a systematic review. J Pain 2002;3:159–80.
7. **Hong D, Flood P, Diaz G.** The side effects of morphine and hydromorphone patient-controlled analgesia. Anesth Analg 2008;107:1384–9.
8. **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;41:400–6.
9. **Hutchison RW, Chon EH, Tucker WF, et al.** A comparison of a fentanyl, morphine, and hydromorphone patient-controlled intravenous delivery for acute postoperative analgesia: a multicenter study of opioid-induced adverse reactions. Hosp Pharm 2006;41:659–63.
10. **Philip BK, Reese PR, Burch SP.** The economic impact of opioids on postoperative pain management. J Clin Anesth 2002;14:354–64.
11. **Illgen RL, Pellino TA, Gordon DB, Butts S, Heiner JP.** Prospective analysis of a novel long-acting oral opioid analgesic regimen for pain control after total hip and knee arthroplasty. J Arthroplasty 2006;21:814–20.
12. **Minkowitz HS, Rathmell JP, Vallow S, Gargiulo K, Damaraju CV, Hewitt DJ.** Efficacy and safety of the fentanyl iontophoretic transdermal system (ITS) and intravenous patient-controlled analgesia (IV PCA) with morphine for pain management following abdominal or pelvic surgery. Pain Med 2007;8:657–68.
13. **Viscusi ER.** Patient-controlled drug delivery for acute postoperative pain management: a review of current and emerging technologies. Reg Anesth Pain Med 2008;33:146–58.
14. **Rathmell JP, Wu CL, Sinatra RS, et al.** Acute post-surgical pain management: a critical appraisal of current practice. Reg Anesth Pain Med 2006;31:1–42.
15. **Kehlet H.** Postoperative opioid sparing to hasten recovery: what are the issues? Anesthesiology 2005;102:1083–5.
16. **Hill RP, Lubarsky DA, Phillips-Bute B, et al.** Cost-effectiveness of prophylactic antiemetic therapy with ondansetron, droperidol, or placebo. Anesthesiology 2000;92:958–67.
17. **Watcha MF, Smith I.** Cost-effectiveness analysis of antiemetic therapy for ambulatory surgery. J Clin Anesth 1994;6:370–7.
18. **Tang J, Watcha MF, White PF.** A comparison of costs and efficacy of ondansetron and droperidol as prophylactic antiemetic therapy for elective outpatient gynecologic procedures. Anesth Analg 1996;83:304–13.
19. **White PF, Watcha MF.** Postoperative nausea and vomiting: prophylaxis versus treatment. Anesth Analg 1999;89:1337–9.
20. **Kovac AL.** Prevention and treatment of postoperative nausea and vomiting. Drugs 2000;59:213–43.
21. **Bates JJ, Foss JF, Murphy DB.** Are peripheral opioid antagonists the solution to opioid side effects? Anesth Analg 2004;98:116–22.
22. **Berde C, Nurko S.** Opioid side effects–mechanism-based therapy. N Engl J Med 2008;358:2400–2.

23. **Thomas J, Karver S, Cooney GA, et al.** Methylnaltrexone for opioid-induced constipation in advanced illness. N Engl J Med 2008;358:2332–43.
24. **Slatkin N, Thomas J, Lipman AG, et al.** Methylnaltrexone for treatment of opioid-induced constipation in advanced illness patients. J Support Oncol 2009;7:39–46.
25. **Rosow CE, Gomery P, Chen TY, Stefanovich P, Stambler N, Israel R.** Reversal of opioid-induced bladder dysfunction by intravenous naloxone and methylnaltrexone. Clin Pharmacol Ther 2007;82:48–53.
26. **Shaiova L, Rim F, Friedman D, Jahdi M.** A review of methylnaltrexone, a peripheral opioid receptor antagonist, and its role in opioid-induced constipation. Palliat Support Care 2007;5:161–6.
27. **Viscusi ER, Goldstein S, Witkowski T, et al.** Alvimopan, a peripherally acting mu-opioid receptor antagonist, compared with placebo in postoperative ileus after major abdominal surgery: results of a randomized, double-blind, controlled study. Surg Endosc 2006;20:64–70.
28. **Oderda GM, Evans RS, Lloyd J, et al.** Cost of opioid-related adverse drug events in surgical patients. J Pain Symptom Manage 2003;25:276–83.
29. **Reinberg S.** Joint replacement soars as number of docs fall. US News & World Report. Available from http://health.usnews.com/health-news/family-health/pain/articles/2009/02/26/joint-replacement-soars-as-number-of-docs-falls. Accessed October 25, 2011.
30. **Fehring TK, Iorio R, Odum S.** Joint Replacement Access in 2016: A Supply Side Crisis. Poster Presentation Number: P043. American Academy of Orthopedic Surgeons, 2009 Annual Meeting Poster Presentations, 2009.
31. **Cowan JA Jr, Chandler WF.** Changing trends in the use and costs of procedures performed by neurosurgeons in the United States. Clin Neurosurg 2007;54:209–11.
32. **Correll DJ, Viscusi ER, Grunwald Z, Moore JH Jr.** Epidural analgesia compared with intravenous morphine patient-controlled analgesia: postoperative outcome measures after mastectomy with immediate TRAM flap breast reconstruction. Reg Anesth Pain Med 2001;26:444–9.
33. **Brunton L, Lazo J, Parker K.** Goodman and Gilman's the pharmacologic basis of therapeutics. New York, NY: McGraw-Hill Companies, 2006.
34. **Krames ES.** Intraspinal opioid therapy for chronic nonmalignant pain: current practice and clinical guidelines. J Pain Symptom Manage 1996;11:333–52.
35. **Sylvester RK, Lindsay SM, Schauer C.** The conversion challenge: from intrathecal to oral morphine. Am J Hosp Palliat Care 2004;21:143–7.
36. **Gan TJ, Sinha AC, Kovac AL, et al.** A randomized, double-blind, multicenter trial comparing transdermal scopolamine plus ondansetron to ondansetron alone for the prevention of postoperative nausea and vomiting in the outpatient setting. Anesth Analg 2009;108:1498–504.
37. **Kovac AL, Pearman MH, Khalil SN, et al.** Ondansetron prevents postoperative emesis in male outpatients. S3A-379 Study Group. J Clin Anesth 1996;8:644–51.
38. **Fortney JT, Gan TJ, Graczyk S, et al.** A comparison of the efficacy, safety, and patient satisfaction of ondansetron versus droperidol as antiemetics for elective outpatient surgical procedures. S3A-409 and S3A-410 Study Groups. Anesth Analg 1998;86:731–8.
39. **Skledar SJ, Williams BA, Vallejo MC, et al.** Eliminating postoperative nausea and vomiting in outpatient surgery with multimodal strategies including low doses of nonsedating, off-patent antiemetics: is "zero tolerance" achievable? ScientificWorldJournal 2007;7:959–77.
40. **Birmingham SD, Mecklenburg BW, Lujan E, Dacanay RG, Boyle PK, Green R.** Dolasetron versus ondansetron as single-agent prophylaxis for patients at increased risk for postoperative nausea and vomiting: a prospective, double-blind, randomized trial. Mil Med 2006;171:913–6.
41. **Michaloliakou C, Chung F, Sharma S.** Preoperative multimodal analgesia facilitates recovery after ambulatory laparoscopic cholecystectomy. Anesth Analg 1996;82:44–51.
42. **Ramirez-Ruiz M, Smith I, White PF.** Use of analgesics during propofol sedation: a comparison of ketorolac, dezocine, and fentanyl. J Clin Anesth 1995;7:481–5.
43. **Sukhani R, Vazquez J, Pappas AL, Frey K, Aasen M, Slogoff S.** Recovery after propofol with and without intraoperative fentanyl in patients undergoing ambulatory gynecologic laparoscopy. Anesth Analg 1996;83:975–81.
44. **Stahlgren LR, Trierweiler M, Tommeraasen M, et al.** Comparison of ketorolac and meperidine in patients with postoperative pain–impact on health care utilization. Clin Ther 1993;15:571–80.
45. **Roberts GW, Bekker TB, Carlsen HH, Moffatt CH, Slattery PJ, McClure AF.** Postoperative nausea and vomiting are strongly influenced by postoperative opioid use in a dose-related manner. Anesth Analg 2005;101:1343–8.
46. **Zhao SZ, Chung F, Hanna DB, Raymundo AL, Cheung RY, Chen C.** Dose-response relationship between opioid use and adverse effects after ambulatory surgery. J Pain Symptom Manage 2004;28:35–46.

Appendix. Study Definitions for Potential Opioid-Related Adverse Effects

Adverse Effect	Study Definition
Nausea and vomiting	Documentation of the following within the progress notes or supplemental forms of the medical record during course of opioid treatment: N/V (term documented) Nausea (term documented) Vomiting (term documented) Emesis (term documented) Retching (term documented) Note of administration of antiemetic during and after discharge from PACU

(continued)

Appendix. (continued)

Adverse Effect	Study Definition
Constipation	Documentation of the following within the progress notes or supplemental orms of the medical record during course of opioid treatment: Constipation (term documented) Note of an order for or administration of a laxative Note of an order for or administration of a stool softener Note of an order for or administration of an enema First post-operative bowel movement does not occur within 2 days of surgery Note of fecal impaction, w/o bowel movement and decreased/absent bowel sounds Note of gas distention, w/o bowel movement and decreased/absent bowel sounds Note of incomplete evacuation, w/o bowel movement and decreased/absent bowel sounds Note of abdominal cramping, w/o bowel movement and decreased/absent bowel sounds
Ileus	Documentation of the following within the progress notes or supplemental forms of the medical record during course of opioid treatment: Ileus (term documented) First bowel movement > 3 days post-operation Note of an order for or administration of a radiological test on the abdomen w/ notation of bowel dysfunction Presence of nasogastric tube (NG tube; excluding NG tube administered in the operating room or immediately following the surgical procedure) Note of "re-insertion" of NG Tube
Pruritus	Documentation of the following within the progress notes or supplemental forms of the medical record during course of opioid treatment: Pruritus (term documented) Patient complaint of itching, scratching Note of order for or administration of antihistamine w/ notation of patient complaint Note of order for or administration of steroidal cream w/ notation of patient complaint
Respiratory depression[a]	Documentation of the following within the progress notes or supplemental forms of the medical record during course of opioid treatment: Respiratory depression (term documented) Inferred respiratory depression, defined as: Respiratory rate < 10 bpm Use of naloxone as an indication of "attempt to treat" Evidence of apneic episode Note of order for or administration of intubation Note of order for or administration of ventilation
Hypoxia	Documentation of the following within the progress notes or supplemental forms of the medical record during course of opioid treatment: Note of hypoxia Oxygen saturation < 90%
Hypotension	Documentation of the following within the progress notes or supplemental forms of the medical record during course of opioid treatment: Hypotension (term documented) Inferred hypotension, defined as: Systolic arterial pressure of < 100 mmHg and/or greater than 20% decrease in arterial pressure (baseline = pre-op) OR Administration of fluid bolus w/ notation of arterial pressure concern (excluding OR and PACU) OR Transfusion of red blood cells w/ notation of arterial pressure concern (excluding OR and PACU)
Urinary retention	Documentation of the following within the progress notes or supplemental forms of the medical record during course of opioid treatment: Urinary retention (term documented) Note of patient being unable to urinate (excluding OR and PACU)
Confusion	Documentation of the following terms within the progress notes or supplemental forms of the medical record during course of opioid treatment: Confused Disoriented

(continued)

Appendix. (continued)

Adverse Effect	Study Definition
Dizziness	Documentation of the following terms within the progress notes or supplemental forms of the medical record during course of opioid treatment: Dizziness Lightheaded
Sleeplessness	Documentation of patient having difficulty sleeping or unable to sleep within the progress notes or supplemental forms of the medical record during course of opioid treatment
Euphoria/dysphoria	Documentation of euphoria or dysphoria in the progress notes or supplemental forms of the medical record during course of opioid treatment
Patient falls	Note of patient fall

[a]Only clinically significant respiratory depression, defined as < 8 breaths/minute, was included in the analysis.