Predictors of Long-Term Opioid Use After Opioid Initiation at Discharge From Medical and Surgical Hospitalizations

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Opioid analgesics may be initiated following surgical and medical hospitalization or in ambulatory settings; rates of subsequent long-term opioid (LTO) use have not been directly compared. This retrospective cohort study of the Veterans Health Administration (VHA) included all patients receiving a new outpatient opioid prescription from a VHA provider in fiscal year 2011. If a new outpatient prescription was filled within 2 days following hospital discharge, the initiation was considered a discharge prescription. LTO use was defined as an episode of continuous opioid supply lasting a minimum of 90 days and beginning within 30 days of the initial prescription. We performed bivariate and multivariate analyses to identify the factors associated with LTO use following surgical and medical discharges. Following incident prescription, 5.3% of discharged surgical patients, 15.2% of discharged medical patients, and 19.3% of outpatient opioid initiators received opioids long term. Medical and surgical patients differed; surgical patients were more likely to receive shorter prescription durations. Predictors of LTO use were similar in medical and surgical patients; the most robust predictor in both groups was the number of days' supply of the initial prescription (odds ratio [OR] = 1.24 and 95% confidence interval [CI], 1.12-1.37 for 8-14 days; OR = 1.56 and 95% CI, 1.39-1.76 for 15-29 days; and OR = 2.59 and 95% CI, 2.35-2.86 for >30 days) compared with the reference group receiving ≤7days. Rates of subsequent LTO use are higher among discharged medical patients than among surgical patients. Characteristics of opioid prescribing within the initial 30 days, including initial dose and days prescribed, were strongly associated with LTO use. *Journal of Hospital Medicine* 2018;13:243-248. © 2018 Society of Hospital Medicine

While patients may be newly exposed to opioids during medical and surgical hospitalization and the prescription of opioids at discharge is common,[1-5] prescribers of opioids at discharge may not intend to initiate long-term opioid (LTO) use. By understanding the frequency of progression to LTO use, hospitalists can better balance postdischarge pain treatment and the risk for unintended LTO initiation.

Estimates of LTO use rates following hospital discharge in selected populations[1,2,4-6] have varied depending on the population studied and the method of defining LTO use.[7] Rates of LTO use following incident opioid prescription have not been directly compared at medical versus surgical discharge or compared with initiation in the ambulatory setting. We present the rates of LTO use following incident opioid exposure at surgical discharge and medical discharge and identify the factors associated with LTO use following surgical and medical discharge.

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METHODS

Data Sources

Veterans Health Administration (VHA) data were obtained through the Austin Information Technology Center for fiscal years (FYs) 2003 through 2012 (Austin, Texas). Decision support system national data extracts were used to identify prescription-dispensing events, and inpatient and outpatient medical SAS data sets were used to identify diagnostic codes. The study was approved by the University of Iowa Institutional Review Board and the Iowa City Veterans Affairs (VA) Health Care System Research and Development Committee.

Patients

We included all patients with an outpatient opioid prescription during FY 2011 that was preceded by a 1-year opioid-free period.[7] Patients with broadly accepted indications for LTO use (eg, metastatic cancer, palliative care, or opioid-dependence treatment) were excluded.[7]

Opioid Exposure

We included all outpatient prescription fills for noninjectable

TABLE 1. **Baseline Characteristics of Patients Initiating Outpatient Opioid Use Following Surgical or Medical Discharge**

Patient Demographics	Surgery N = 26,476	Medicine N = 16,551	χ^2; DF; P
Age, years			558; 5; <.001
18-34	997 (3.8%)	956 (5.8%)	
35-49	2270 (8.6%)	1814 (11.0%)	
50-64	12,099 (45.7%)	7644 (46.2%)	
65-79	9178 (34.7%)	4315 (26.1%)	
≥80	1748 (6.6%)	1685 (10.2%)	
Unknown	184 (0.7%)	137 (0.8%)	
Gender			38; 1; <.001
Male	24,669 (93.2%)	15,665 (94.6%)	
Female	1807 (6.8%)	886 (5.4%)	
Race			194; 2; <.001
White	18,089 (68.3%)	10,841 (65.5%)	
Black	4178 (15.8%)	3451 (20.9%)	
Other/unknown	4209 (15.9%)	2259 (13.6%)	
Residence			90; 3; <.001
Isolated	2267 (12.5%)	1176 (7.1%)	
Small rural	1991 (7.5%)	1075 (6.5%)	
Large rural	3316 (8.6%)	1795 (10.8%)	
Urban	18,902 (71.4%)	12,505 (75.6%)	
Mental health characteristics			
Mental health clinic visit			386; 1; <.001
At least 1 in prior year	7287 (27.5%)	6045 (36.5%)	
None	19,189 (72.5%)	10,506 (63.5%)	
Substance abuse diagnosis			819; 1; <.001
Present	3152 (11.9%)	3687 (22.3%)	
Not present	23,324 (88.1%)	12,864 (77.7%)	
Anxiety disorder diagnosis			56; 1; <.001
Present	1961 (7.4%)	1561 (9.4%)	
Not present	24,515 (92.6%)	14,990 (90.6%)	
Benzodiazepine use			472; 2; <.001
Active at opioid start	1743 (6.6%)	2044 (12.3%)	
Use within last year	1257 (4.8%)	988 (6.0%)	
No recent use	23,476 (88.7%)	13,519 (81.7%)	
Depressive disorder diagnosis			157; 1; <.001
Documented	2362 (8.9%)	2104 (12.7%)	
Not documented	24,114 (91.1%)	14,447 (87.3%)	
Antidepressant use			514; 1; <.001
Active at opioid start	4838 (18.3%)	4560 (27.6%)	
Not active at opioid start	21,638 (81.7%)	11,991 (72.4%)	

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dosage forms of butorphanol, fentanyl, hydrocodone, hydromorphone, levorphanol, meperidine, methadone, morphine, oxycodone, oxymorphone, pentazocine, and tramadol. Consistent with the Centers for Disease Control and Prevention and VA/Department of Defense guidelines, LTO use was defined conceptually as regular use for >90 days. Operationalizing this definition to pharmacy refill data was established by using a cabinet supply methodology,[7] which allows for the construction of episodes of continuous medication therapy by estimating the medication supply available to a patient for each day during a defined period based on the pattern of observed refills. LTO use was defined as an episode of continuous opioid supply for >90 days and beginning within 30 days of the initial prescription. While some studies have defined LTO use based on onset within 1 year following surgery,[5] the requirement for onset within 30 days of initiation was applied to more strongly tie the association of developing LTO use with the discharge event and minimize various forms of bias that are introduced with extended follow-up periods.

Clinical Characteristics

Patients were classified as being medical discharges, surgical discharges, or outpatient initiators. Patients with an opioid in-

TABLE 1. **Baseline Characteristics of Patients Initiating Outpatient Opioid Use Following Surgical or Medical Discharge (continued)**

Patient Demographics	Surgery N = 26,476	Medicine N = 16,551	χ^2; DF; P
Pain-related characteristics			
Chronic pain diagnosis			157; 1; <.001
Present in prior year	10,982 (41.5%)	5861 (35.4%)	
Not present	15,494 (58.5%)	10,690 (64.6%)	
Nonopioid analgesic use, days in prior year			1; 1; .315
>90	4265 (16.1%)	2727 (16.5%)	
≤90	22,211 (83.9%)	13,824 (83.5%)	
Muscle relaxant use			297; 2; <.001
Active at opioid start	1190 (4.5%)	1415 (8.5%)	
Use within prior year	1348 (5.1%)	868 (5.2%)	
None	23,938 (90.4%)	14,268 (86.2%)	
Opioid prescription characteristics at index			
Opioid prescribed			4310; 3; <.001
Hydrocodone	16,612 (62.7%)	8041 (48.6%)	
Oxycodone	8660 (32.7%)	4281 (25.9%)	
Tramadol	540 (2.0%)	3073 (18.6%)	
Other	664 (2.5%)	1156 (7.0%)	
Morphine equivalents, mg per day			534; 3; <.001
≤15	6714 (25.4%)	5577 (33.7%)	
15.01 to ≤30	11,416 (43.1%)	7190 (43.4%)	
30.01 to ≤45	4963 (18.7%)	2099 (12.7%)	
> 45	3383 (12.8%)	1685 (10.2%)	
Days' supply of first prescription			1286; 3; <.001
≤7	7805 (29.5%)	5842 (35.3%)	
8-14	9888 (37.3%)	4072 (24.6%)	
15-29	3949 (14.9%)	1802 (10.9%)	
≥30	4834 (18.3%)	4835 (29.2%)	

NOTE: Abbreviation: DF, degrees of freedom.

dex date within 2 days following discharge were designated based on discharge bed section; additionally, if patients had a surgical bed section during hospitalization, they were assigned as surgical discharges. Demographic, diagnosis, and medication exposure variables that were previously associated with LTO use were selected.[8,9] Substance use disorder, chronic pain, anxiety disorder, and depressive disorder were based on *International Classification of Diseases, 9th Revision* (ICD-9) codes in the preceding year. The use of concurrent benzodiazepines, skeletal muscle relaxants, and antidepressants were determined at opioid initiation.[10] Rural or urban residence was assigned by using the Rural-Urban Commuting Area Codes system and mapped with the zip code of a veteran's residence.[11]

Analysis

Bivariate and multivariable relationships were determined by using logistic regression. The multivariable model considered all pairwise interaction terms between inpatient service (surgery versus medicine) and each of the variables in the model. Statistically significant interaction terms ($P < .05$) were retained, and all others were omitted from the final model. The main effects for variables that were involved in a significant interaction term were not reported in the final multivariable model; instead, we created fully specified multivariable models for surgery service and medicine service and reported odds ratios (ORs) for the main effects. All analyses were conducted by using SAS version 9.4 (SAS Institute Inc, Cary, North Carolina).

RESULTS

During FY 2011, 43,027 patients received an incident opioid prescription at discharge from a VHA hospital, including 26,476 surgical discharges and 16,551 medical discharges. Discharged veterans differed on nearly all the examined characteristics (Table 1). A lower proportion of surgical patients used VA mental health services, had a substance use disorder, anxiety, or depression diagnosis, or had active benzodiazepine or antidepressant prescriptions. A higher proportion of surgical patients had a chronic pain diagnosis. At discharge, a larger proportion of surgical patients (62.7%) than medical patients (48.6%) received hydrocodone and daily doses of ≥45 mg per day of

TABLE 2. **Demographic, Clinical, and Prescription Characteristics Associated with LTO Use Following Hospital Discharge**

Characteristic	Distribution N (column %)	Frequency of LTO Use n (row %)	LTO Use Bivariate Models OR (95% CI)	LTO Use Multivariate Model[a] OR (95% CI)
Inpatient service				
Medicine	16,551 (38.5)	2509 (15.2)	3.18 (2.97-3.41)	Not applicable[a]
Surgery	26,476 (61.5)	1408 (5.3)	Reference	
Patient demographics				
Age, years				
18-34	1953 (4.5)	175 (9.0)	0.77 (0.65-0.90)	0.72 (0.61-0.86)
35-49	4084 (9.5)	438 (10.7)	0.94 (0.84-1.04)	0.91 (0.81-1.02)
50-64	19,743 (45.9)	2246 (11.4)	Reference	Reference
65-79	13,493 (31.4)	852 (6.3)	0.53 (0.48-0.57)	0.59 (0.54-0.65)
≥80	3433 (8.0)	186 (5.4)	0.45 (0.38-0.52)	0.41 (0.35-0.49)
Missing	321 (0.8)	20 (6.2)	0.52 (0.33-0.82)	0.49 (0.31-0.79)
Sex				
Male	40,334 (93.7)	3721 (9.2)	Reference	Reference
Female	2693 (6.3)	196 (7.3)	0.77 (0.67-0.90)	0.73 (0.63-0.86)
Race				
White	28,930 (67.2)	2727 (9.4)	Reference	Interaction[a]
Black	7629 (17.7)	693 (9.1)	0.96 (0.88-1.05)	$\chi^2 = 7.9$; DF = 2; $P = .019$
Other/unknown	6468 (15.0)	497 (7.7)	0.80 (0.72-0.88)	
Residence				
Isolated	3443 (8.0)	453 (8.9)	0.97 (0.85-1.10)	1.02 (0.92-1.14)
Small rural	3066 (7.1)	331 (10.8)	1.22 (1.08-1.38)	1.29 (1.14-1.47)
Large rural	5111 (11.9)	301 (8.7)	0.98 (0.88-1.09)	1.02 (0.90-1.17)
Urban	31,407 (73.0)	2832 (9.0)	Reference	Reference
Mental health characteristics				
Mental health clinic visit				
At least 1 in prior year	13,332 (31.0)	1601 (12.0)	1.61 (1.51-1.73)	0.98 (0.89-1.07)
None	29,695 (69.0)	2316 (7.8)	Reference	Reference
Substance abuse diagnosis				
Documented ICD in prior year	6839 (15.9)	992 (14.5)	1.93 (1.79-2.08)	Interaction[a]
Not documented	36,188 (84.1)	2925 (8.1)	Reference	$\chi^2 = 10.7$; DF = 1; $P = .001$
Anxiety disorder diagnosis				
Documented ICD in prior year	3522 (8.2)	456 (13.0)	1.55 (1.40-1.72)	1.07 (0.95-1.21)
Not documented	39,505 (91.8)	3461 (8.8)	Reference	Reference
Benzodiazepine use				
Active at opioid start	3787 (8.8)	678 (17.9)	2.45 (2.23-2.68)	1.56 (1.41-1.73)
Use within prior year	2245 (5.2)	210 (9.4)	1.16 (0.99-1.34)	0.84 (0.72-0.98)
No use in prior year	36,995 (86.0)	3029 (8.2)	Reference	Reference
Depressive disorder diagnosis				
Documented ICD in prior year	4466 (10.4)	571 (12.8)	1.54 (1.40-1.70)	0.92 (0.82-1.03)
Not documented	38,561 (89.6)	3346 (8.7)	Reference	Reference
Antidepressant use				
Active at opioid start	9398 (21.8)	1291 (13.7)	1.88 (1.75-2.02)	1.26 (1.16-1.37)
Not active at opioid start	33,629 (78.2)	2626 (7.8)	Reference	Reference

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morphine equivalents (12.8% vs 10.2%). Medical patients were more likely to receive an initial supply of ≥30 days.

The rate of LTO initiation was higher in medical patients (15.2%) than in surgical patients (5.3%; OR = 3.18; 95% confidence interval [CI], 2.97-3.41; Table 2). For reference, the rate of subsequent LTO initiation among outpatients was 19.3% (93,076 of 483,472). LTO use was most common among patients ages 50 to 64 years. Relative to urban areas, LTO risk was higher among residents of small, rural areas (OR = 1.29; 95% CI, 1.14-1.47). The interaction between inpatient service and

TABLE 2. **Demographic, Clinical, and Prescription Characteristics Associated with LTO Use Following Hospital Discharge (continued)**

Characteristic	Distribution N (column %)	Frequency of LTO Use n (row %)	LTO Use Bivariate Models OR (95% CI)	LTO Use Multivariate Model[a] OR (95% CI)
Pain characteristics				
Chronic pain diagnosis				
Documented ICD in prior year	16,843 (39.1)	1759 (10.4)	1.30 (1.22-1.39)	1.18 (1.04-1.21)
Not documented	26,184 (61.9)	2158 (8.2)	Reference	Reference
Nonopioid analgesic use				
>90 days in prior year	6992 (16.2)	1014 (14.5)	1.94 (1.79-2.09)	Interaction[a]
≤90 days in prior year	36,035 (83.8)	2903 (8.1)	Reference	χ^2 = 7.1; DF = 1; *P* = .008
Muscle relaxant use				
Active at opioid start	2605 (6.1)	539 (20.7)	2.94 (2.66-3.26)	1.69 (1.52-1.89)
Use within prior year	2216 (5.2)	265 (12.0)	1.53 (1.34-1.75)	1.17 (1.01-1.35)
No use within prior year	38,206 (88.8)	3113 (8.2)	Reference	Reference
Opioid use characteristics				
Opioid prescribed at index				
Hydrocodone	24,653 (57.3)	1766 (7.2)	Reference	Reference
Oxycodone	12,941 (30.1)	1077 (8.3)	1.18 (1.09-1.27)	0.96 (0.88-1.05)
Tramadol	3613 (8.4)	746 (20.7)	3.37 (3.07-3.70)	1.55 (1.39-1.72)
Other	1820 (4.2)	328 (18.0)	2.85 (2.50-3.24)	1.23 (1.05-1.45)
Morphine equivalents, mg per day				
≤15	12,291 (28.6)	1219 (9.9)	Reference	Reference
15.01 to ≤30	18,606 (43.2)	1537 (8.3)	0.82 (0.76-0.89)	1.11 (1.02-1.21)
30.01 to ≤45	7062 (16.4)	540 (7.6)	0.75 (0.68-0.84)	1.18 (1.05-1.33)
> 45	5068 (11.8)	621 (12.3)	1.27 (1.15-1.41)	1.70 (1.49-1.94)
Days' supply, index prescription				
≤7	13,647 (31.7)	882 (6.5)	Reference	Reference
8-14	13,960 (32.4)	932 (6.7)	1.04 (0.94-1.14)	1.24 (1.12-1.37)
15-29	5751 (13.4)	502 (8.7)	1.38 (1.24-1.55)	1.56 (1.39-1.76)
≥30	9669 (22.5)	1601 (16.6)	2.87 (2.63-3.13)	2.59 (2.35-2.86)

[a]The multivariable model considered all pairwise interaction terms between inpatient service (medicine versus surgery) and each of the other variables in the model. Significant interactions were observed for 3 variables: race, substance abuse diagnosis, and nonopioid analgesic use. All nonsignificant interaction terms were omitted from the final multivariable model. Because the main effects of the variables involved in a statistical interaction term cannot be independently interpreted, these estimates were omitted. In order to describe these relationships, we performed separate multivariable analyses for medicine service and surgery service patients. For medicine service patients, the associations between race and LTO use were OR of 0.77 (95% CI, 0.69-0.87) for black race and OR of 0.89 (95% CI, 0.78-1.02) for other races relative to white race. For surgical service patients, these associations were OR of 0.96 (95% CI, 0.83-1.13) and OR of 0.78 (95% CI, 0.66-0.92), respectively. Substance abuse diagnosis was associated with increased risk for LTO use but to a greater extent in surgical patients (OR = 1.56; 95% CI, 1.34-1.81) than in medicine patients (OR = 1.14; 95% CI, 1.02-1.27). Similarly, the risk for LTO use associated with prior nonopioid analgesic use was greater in surgical patients (OR = 1.83; 95% CI, 1.60-2.08) than medicine patients (OR = 1.44; 95% CI, 1.29-1.62).

NOTE: Abbreviations: CI, confidence interval; DF, degrees of freedom; ICD, *International Classification of Diseases*; LTO, long-term opioid; OR, odds ratio.

race (χ^2 = 7.9; degrees of freedom = 2; *P* = .019) was significant; black race was associated with a reduced risk for LTO use in medicine service patients (OR = 0.77; 95% CI, 0.69-0.87) but not surgical patients (OR = 0.96; 95% CI, 0.83-1.13; Table 2).

Concurrent use of benzodiazepines, antidepressants, and muscle relaxants and chronic pain diagnosis (but not mental health clinic use and anxiety and depressive disorders) were associated with LTO use. Interactions with inpatient services were observed for substance use disorder diagnoses and prior nonopioid analgesic use; the magnitude of the association was higher among surgical service patients than in the medical patients model (Table 2).

Days' supply was associated with LTO use in a dose-dependent fashion relative to the reference category of ≤7 days: OR of 1.24 (95% CI, 1.12-1.37) for 8 to 14 days; OR of 1.56 (95% CI, 1.39-1.76) for 15 to 29 days; and OR of 2.59 (95% CI, 2.35-2.86) for ≥30 days (Table 2). LTO risk was higher among patients with an estimated dose of ≥15 morphine equivalents per day (MED) compared with those with doses of <15 equivalents (OR = 1.11; 95% CI, 1.02-1.21); patients who received >45 MED were at the greatest risk (OR = 1.70; 95% CI, 1.49-1.94).

DISCUSSION

Our observed LTO use rate of 5.3% among surgical patients compares with rates of 0.12% to 1.41%[5] and 5.9% to 6.5%[12] in privately insured samples and 4.1% among discharges in a single US hospital that included both medical and surgical patients in the United States.[1] The LTO use rate of 15.2% among medical-

ly discharged patients more closely resembles the rates found among outpatient initiators[13] and lacks robust comparators.

The observation that subsequent LTO use occurs more frequently in discharged medical patients than surgical patients is consistent with the findings of Calcaterra et al.[1] that among patients with no surgery versus surgery during hospitalization, opioid receipt at discharge resulted in a higher adjusted OR (7.24 for no surgery versus 3.40 for surgery) for chronic opioid use at 1 year. One explanation for this finding may be an artifact of cohort selection in the study design: patients with prior opioid use are excluded from the cohort, and prior use may be more common among surgical patients presenting for elective inpatient surgery for painful conditions. Previous work suggests that opioid use preoperatively is a robust predictor of postoperative use, and rates of LTO use are low among patients without preoperative opioid exposure.[6]

Demographic characteristics associated with persistent opioid receipt were similar to those previously reported.[5,8,9] The inclusion of medication classes indicated in the treatment of mental health or pain conditions (ie, antidepressants, benzodiazepines, muscle relaxants, and nonopioid analgesics) resulted in diagnoses based on ICD-9 codes being no longer associated with LTO use. Severity or activity of illness, preferences regarding pharmacologic or nonpharmacologic treatment and undiagnosed or undocumented pain-comorbid conditions may all contribute to this finding. Future work studying opioid-related outcomes should include variables that reflect pharmacologic management of comorbid diagnoses in the cohort development or analytic design.

The strongest risk factors were potentially modifiable: days' supply, dose, and concurrent medications. The measures of opioid quantity supplied are associated with subsequent ongoing use and are consistent with recent work based on prescription drug–monitoring data in a single state[14] and in a nationally representative sample.[15] That this relationship persists following hospital discharge, a scenario in which LTO use is unlikely to be initiated by a provider (who would be expected to subsequently titrate or monitor therapy), further supports the potential to curtail unintended LTO use through judicious early prescribing decisions.

We assessed only opioids that were supplied through a VA pharmacy, which may lead to the misclassification of patients as opioid naive for inclusion and an underestimation of the rate of opioid use following discharge. It is possible that differences in the rates of non-VA pharmacy use differ in medical and surgical populations in a nonrandom way. This study was performed in a large, integrated health system and may not be generalizable outside the VA system, where more discontinuities between hospital and ambulatory care may exist.

CONCLUSION

The initiation of LTO use at discharge is more common in veterans who are discharged from medical than surgical hospitalizations, likely reflecting differences in the patient population, pain conditions, and discharge prescribing decisions. While patient characteristics are associated with LTO use, the strongest associations are with increasing index dose and days' supply; both represent potentially modifiable prescriber behaviors. These findings support policy changes and other efforts to minimize dose and days supplied when short-term use is intended as a means to address the current opioid epidemic.

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