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Evaluation of Inpatient Opioid Prescribing Patterns and Adverse Events in General Medicine Patients with Chronic Non-Cancer Pain

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Abstract

Background: Chronic non-cancer pain is complex to manage and opioid prescriptions have been increasing in the past years. The objective of this study was to describe opioid prescribing patterns for general medicine inpatients and to identify risk factors that may predispose patients to opioid-related adverse events.

Methods and findings: This was a single center retrospective chart review at a tertiary academic medical center in Boston, Massachusetts from July 2016 to June 2017. Patients were included if at least 18 years of age, admitted to a general medicine unit, on opioids prior to admission, and had received one or more prespecified opioids during their admission. Patients with sickle cell disease, cancer-associated pain, use of peri-operative opioids, or opioid use disorder on methadone or buprenorphine/naloxone therapy were excluded. Of the 147 patients included in the analysis, 64.6% of patients had a change in the opioid regimen upon admission. There was a significant decrease in morphine milligram equivalents (MME) per day from PTA to inpatient ($p<0.001$) and a significant increase from inpatient to discharge ($p<0.003$). Change in MME per day was non-significant when comparing PTA regimens to discharge regimens ($p=0.53$). Ethnicity, age>65, gender, past medical history of substance use and psychiatric disorders, and institution primary care physician were not predictive of prescribing patterns. Upon evaluation of predisposing risk factors there was no difference in naloxone prescribing.

Conclusion: Results suggest that although opioid prescribing may change during admission, long-term management of the opioid regimen is generally deferred to the outpatient provider. The data also identifies a potential area for improvement with respect to naloxone prescribing.

Keywords: Opioid; Transitions of care; Naloxone

Introduction

The American Pain Society defines chronic non-cancer pain as pain that persists for more than three months, pain that lasts longer than a month or recurs after the healing of a lesion, or pain associated with a non-healing lesion [1]. This type of pain, a prevalent condition that occurs in upwards of 40% of the United States (US) population, accounts for approximately $600 billion of US health expenditure in 2010 [2]. The management of chronic non-cancer pain is challenging and many of these patients require frequent hospital visits for acute or inadequately treated pain [1,3]. Patients' outpatient pain regimens may be adjusted to better address their pain, improve quality of life, and reduce inpatient-associated healthcare costs.

Non-pharmacologic and non-opioid analgesic agents are preferred for initial management of patients with chronic non-cancer pain in most patients, however, the combination of necessary urgent pain control, the demonstrated effectiveness of opioids, and the limited therapeutic alternatives for chronic management has led to an increase in prescribing of opioids over the years [4]. In 2017, approximately 58 opioid prescriptions were written per every 100 Americans [5]. As a result, there has been an increase in opioid tolerance and dependence, the potential for misuse and abuse, the development of substance use disorders, drug diversion, and risk of overdose. From 1999 to 2016, the Centers for Disease Control and Prevention (CDC) reported the incidence of prescription opioid overdose-related deaths increased five-fold [6]. From 2001-2010, opioid prescribing patterns in the emergency department (ED), increased by 10.2% with no change in the prescribing of nonopioid analgesics [7]. Oxycodone and hydrocodone had the greatest increase in discharge prescriptions from 2005-2010. Prescribing patterns in the ED are variable based on the provider; so much so, that some studies cannot describe an over-arching pattern [8-10]. With regards to the primary care setting, a study in Kentucky found the top ten primary care provider (PCP) prescribers to account for 38.4% of scheduled two substances prescribed [11]. A study comparing primary care physicians in the United States and Japan found the rate of opioid prescribing to be higher in the United States and these respondents more often cited medical indications and

legal expectations as rationale for prescribing opioids [9]. In another study performed in 2016, 3000 primary care patients (>100 patients at 6 of the 36 clinics) were identified who received chronic opioid therapy and 71% had chronic non-cancer pain [12]. This data from the primary care setting suggests that while opioid prescribing is common throughout primary care setting, the highest rates of prescribing tends to be concentrated to a small number of providers. The authors of one study noted that initial prescription of opioids from the ED may provide enough "clinical inertia" for outpatient providers to "convert" patients to chronic long-term therapy [8].

Risk factors predisposing patients to opioid overdose include use of opioids with other sedating medications, comorbid psychiatric illnesses, male gender, older age, and use of >50 morphine milligram equivalents (MMEs) per day [13,14]. Many general medicine patients who are prescribed opioids have at least one or a combination of these risk factors which increases their risk of opioid-related adverse drug events (ADEs) and overdose [15]. The majority of data regarding opioid prescribing patterns for patients with chronic non-cancer pain originates from the primary care and emergency department settings, leaving a paucity of published data surrounding opioid prescribing patterns in the general medicine inpatient setting. Transitions of care is imperative and gaining increased awareness, it is therefore important to assess this population and understand if changes to outpatient regimens during admission are significantly impacting discharge regimens. A better understanding of opioid prescribing patterns in this patient population may aid in identifying high risk patient attributes, reducing inappropriate prescribing, decreasing rates of opioid-related ADEs, and decreasing overall healthcare costs related to the treatment of non-cancer pain. The objective of this study was to describe opioid prescribing patterns for chronic non-cancer pain in general medicine inpatients and to identify risk factors that may predispose patients to opioid-related adverse events.

Methods

Study design and patient selection

A single center retrospective chart review of general medicine patients admitted to a tertiary academic medical center in Boston, Massachusetts was conducted between July 2016 to June 2017. This study was approved by the Brigham and Women's Hospital Institutional Review Board. A computer-generated report from the electronic health record system was utilized to identify patients admitted to one of four pre-specified general medicine units during this time. Patients were included in the analysis if they were of 18 years of age or older and had at least one opioid listed on their prior to admission (PTA) medication list for the treatment of chronic non-cancer pain that was reordered upon inpatient admission. All patients were exposed to or continued at least one of the following opioids during their admission: oxycodone, hydrocodone, morphine, hydromorphone, fentanyl, codeine, methadone, or meperidine. Excluded patients included those with documented sickle cell disease, cancer-associated pain, use of peri-operative opioids, or opioid use disorder currently on methadone or buprenorphine/naloxone therapy.

Endpoints

Given the descriptive nature of this analysis, the following four questions were intended to be answered upon study completion: 1) How does the patients' inpatient admission affect their opioid regimen on discharge?; 2) Are there baseline characteristics or other concurrently prescribed medications that influence a patients' opioid regimen in the hospital and on discharge; 3) Does multimodal therapy affect the opioid regimen during admission?; and 4) Is naloxone being prescribed appropriately to patients who meet criteria for initiation?

Endpoints identified included: median opioid dose during admission, percent of patients with a change in their opioid regimen at three different transition periods (PTA to inpatient, inpatient to discharge, and PTA to discharge), and hospital length of stay (LOS). Regarding to the second question, data collected included ethnicity, age, gender, history of psychiatric or substance use disorder, and management of their opioid regimen by an institution-affiliated PCP or by a pain specialist at any institution. The third question was evaluated by looking at the number of multimodal agents and the change in MME/day on discharge. To answer the fourth question, naloxone prescribing patterns were evaluated with respect to the following patient characteristics that place a patient at high risk of opioid-related adverse events: use of >50 MME/day, an increase in MME/day on discharge, history of psychiatric or substance use disorder, and discharge with concomitant sedating agents. Medications that were identified as sedating included: gabapentin, pregabalin, muscle relaxants, benzodiazepines, zaleplon, doxepin, topiramate, dronabinol, zolpidem, zaleplon, tramadol, and trazodone. Pain scores were not obtained for this study as baseline pain scores we not readily available to compare against. The Chi Square statistical test was utilized for categorical data and the Mann-Whitney U statistical test was used for nonparametric continuous data. A multivariable regression was performed to assess if ethnicity, age, gender, history of psychiatric or substance use disorder, and management of a patient's opioid regimen by an institution-affiliated PCP or by a pain specialist at any institution affected the opioid regimen.

Results

Patient selection

Of the 275 patients identified, 147 were included in the final analysis. Of the 128 patients excluded, 105 patients were using opioids for cancer-associated pain, 17 patients were using opioids for sickle cell disease, 5 patients were on methadone or buprenorphine/naloxone for substance use disorder maintenance therapy, and 1 patient was administered opioids during the peri-operative period (**Figure 1**).

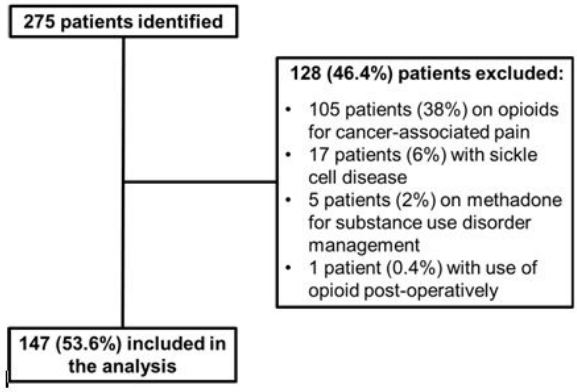

Figure 1: Buprenorphine/naloxone for substance use disorder maintenance therapy.

Baseline characteristics

Patients included in the final analysis were primarily Caucasian (68%), female (68%), and with a mean age of 60.4 years+14.8. With regards to past medical history, 67.3% had a history of a psychiatric disorder, 23.8% chronic kidney disease, 17% insomnia, and 17% substance use disorder. Approximately one-fourth of patients were admitted for acute pain not related to their underlying chronic non-cancer pain whereas only 12% of patients were admitted for acute exacerbation of chronic non-cancer pain. The majority of patients' home opioid regimens were managed by an institution-affiliated PCP and only small percentages (8%) were managed by a pain specialist. See **Table 1** for more details.

Table 1: Demographics and Baseline Characteristics. A=Data represented as mean+SD.

Variable	Patients (n=147)
Age (years)A	60.4+14.8
Age>65 years, n (%)	59 (40.1)
Gender: female, n (%)	100 (68.0)
Weight (kg)A	80.4+25.7
Ethnicity (n, %)	
Caucasian	100 (68.0)
African American	24 (16.3)
Hispanic	19 (13.0)
Other	4 (2.6)
Admission Diagnosis, n (%)	
Other	60 (41.0)
Acute pain	38 (25.8)
Infection	35 (23.8)
Pulmonary	25 (17.0)
Chronic non-cancer pain	18 (12.2)
Past Medical History (PMH), n (%)	
Psychiatric disease	99 (67.3)
Depression	49 (33.3)
Anxiety	34 (23.0)
Bipolar disorder	8 (5.4)
Post-traumatic stress disorder	5 (3.4)
Schizophrenia	3 (2.0)
Chronic kidney disease	35 (23.8)
Insomnia	25 (17.0)
Substance use disorder	25 (17.0)
Opioid use disorder	12 (7.5)
Peripheral neuropathy	23 (15.6)
Opioid Prescriber, n (%)	
Primary care provider at the institution	65 (44.2)
Pain specialist	13 (8.8)

Results

In analyzing inpatient admissions, the median MME/day PTA was 64 mg (IQR 32-120), 37.4 mg (14.25-122) during hospital stay, and 60 mg (30-128) upon discharge. Upon admission, 64.6% (n=95) patients had a change in their opioid regimen. The change in MME/day was significant from PTA to inpatient (p=0.0001) and from inpatient to discharge (p=0.0024), however, was not found to be significant when analyzing PTA to discharge regimens (p=0.53). Upon discharge, 74% (n=109) of patients had their PTA opioid regimen resumed without any changes. There was no difference in hospital LOS when specifically analyzing patients with an increase in MME/day on admission (p=0.32) or for admission with chronic non-cancer pain (p=0.32).

The specific factors to assess prescribing patterns included in the multivariable analysis were ethnicity, age, gender, history of psychiatric or substance use disorder, and management of the patient's opioid regimen by an institution-affiliated PCP or by a pain specialist. All characteristics were found to be to be non-significant (p>0.09) at all three transition periods (PTA, inpatient admission, upon discharge).

Patients' charts were evaluated for use of multimodal agents in conjunction with opioid regimens in an attempt to identify a causal relationship. The data demonstrated that an increase in the number of multimodal agents upon discharge was not associated with a change in MME/day upon discharge (p=0.938). The mean number of multimodal agents used PTA was 2.75+1.72, upon inpatient admission was 2.88+1.63, and upon discharge was 2.57+1.66.

Of the 147 patients included in the analysis, 9 patients received a new prescription for naloxone upon discharge. The opioid regimens upon prescribing of naloxone ranged from 45-372 MME/day (average 180 MME/day, SD 118) (**Table 2**). There was no significant difference in naloxone prescribing with respect to the use of >50 MME/day (p=0.0059), an increase in

MME/day on discharge (p=0.88), history of psychiatric (p=0.55) or substance use disorder (p=0.77), and discharge with concomitant sedating agents (p=0.47) (**Table 3**).

Table 2: Patients with use of opioid agent (n=147).

	Prior to Admission, n (%)	Inpatient, n (%)	Outpatient, n (%)
Oxycodone IR	95 (64.6)	101 (68.7)	91 (61.9)
Oxycodone ER	13 (8.8)	11 (7.5)	12 (8.2)
Hydrocodone	3 (2)	1 (0.7)	1 (0.7)
Morphine IR	13 (8.8)	30 (20.4)	13 (8.8)
Morphine ER	9 (6.1)	8 (5.4)	10 (6.8)
Hydromorphone	34 (23.1)	60 (40.8)	32 (21.8)
Fentanyl	20 (13.6)	20 (13.6)	19 (12.9)
Codeine	1 (0.7)	1 (0.7)	1 (0.7)
Meperidine	0 (0)	0 (0)	0 (0)
Methadone	6 (4.1)	6 (4.1)	6 (4.1)

Table 3: Patients with use of multimodal agent (n=147).

	Prior to Admission, n (%)	Inpatient, n (%)	Outpatient, n (%)
Tylenol scheduled	19 (12.9)	28 (19)	25 (17)
Tylenol as needed	50 (34)	81 (55.1)	49 (33.3)
NSAIDs scheduled	12 (8.2)	10 (6.8)	8 (5.4)
NSAIDs as needed	17 (11.6)	19 (12.3)	14 (9.5)
COX-2 Inhibitors	4 (2.7)	1 (0.7)	2 (1.4)
Tricyclic antidepressants	12 (8.2)	10 (6.8)	11 (7.5)
Gabapentin	63 (42.9)	61 (41.5)	59 (40.1)
Pregabalin	10 (6.8)	13 (8.8)	12 (8.2)
Muscle relaxant	30 (20.4)	22 (14.9)	27 (18.4)
Benzodiazepine	47 (31.9)	54 (36.7)	42 (28.6)
Lidocaine (topical)	32 (21.8)	37 (25.2)	35 (23.8)
Trazodone	34 (23.1)	35 (23.8)	34 (23.1)
Duloxetine	24 (16.3)	23 (15.6)	23 (15.6)
Venlafaxine	8 (5.4)	7 (4.8)	8 (5.4)
Zolpidem	11 (7.5)	11 (7.5)	12 (8.2)
Zaleplon	1 (0.7)	1 (0.7)	1 (0.7)
Tramadol	3 (2)	3 (2)	4 (2.7)
Capsaicin	3 (2)	1 (0.7)	2 (1.4)
Dronabinol	1 (0.7)	0 (0)	0 (0)
Ketamine	0 (0)	1 (0.7)	0 (0)

Discussion

Results of our analysis demonstrate that admission to a general medicine inpatient unit at our institution did not significantly affect opioid regimens at discharge. Additionally, pre-defined patient characteristics and use of multimodal therapy did not significantly influence opioid regimens. While it would seem that a significant change occurs between transitions of care opioid regimens, the effect is likely overestimated due to calculation of MME/day being based on assumed maximum utilization of as needed opioid regimens. This is further supported by the lack of statistical significance seen when comparing MME/day from PTA to discharge. Although this is a major limitation of our study, it brings light to the difficulty of assessing changes in opioid consumption during transitions of care as it can be difficult to retrospectively obtain accurate outpatient opioid consumption information.

Upon admission, the usage of hydromorphone greatly increased as our institution commonly uses intravenous hydromorphone first line for rapid control of acute pain. Regarding multimodal agents, there was a slight decrease in the mean number of agents upon discharge. It is thought that this may be due to medication reconciliation upon admission and removal of agents no longer being used. Based on the data collected, it appears that opioid regimens are adjusted during admission to acutely control pain however upon discharge, PTA regimen are resumed with minimal to no change.

A potential area of improvement with regards to naloxone prescribing was identified. There was no significant difference in naloxone prescribing with respect to pre-specified indications, however, this may be explained by a low number of patients who received a new prescription for naloxone on discharge. Additionally, many patients who were candidates for naloxone therapy were not prescribed it.

Two other limitations were identified. This study was a retrospective single center study at a tertiary teaching hospital in Boston, Massachusetts. While this data describes patients admitted specifically to this institution, it may not be generalizable to all inpatient general medicine patient populations. Second, limitations to the chart and ICD coding may lead to inaccurate or incomplete past medical history.

Conclusion

The management of chronic non-cancer pain is complex and adjustments to opioid regimens do not come without risk. We have learned that it is difficult to compare the prescribing patterns in different areas of healthcare; however, this data helps to provide a more complete picture. The results of this study supplement the picture and suggest that opioid prescribing may change during the admission but the long-term management of the opioid regimen is generally deferred to the outpatient provider as many patients were found to be

discharged on their PTA opioid regimen without change. Results identified a potential need for provider education regarding indications for naloxone prescribing in an effort to decrease risk of overdose and opioid-related adverse events. Although limited in terms of sample size and determination of accurate outpatient opioid utilization, this study provides a basis for further research regarding opioid prescribing patterns and risk factors for opioid related adverse events in the general medicine inpatient population.

Declarations

The authors have nothing to disclose.

Acknowledgements

Results of this trial were presented at the American Society of Health-System Pharmacists Eastern States Conference, Hershey PA: 2018 as a short platform presentation. A methods poster was presented at the Vizient University Health System Consortium Orlando, FL: 2017.

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