Published in final edited form as:

J Am Acad Orthop Surg. 2019 May 01; 27(9): e423–e429. doi:10.5435/JAAOS-D-17-00663.

Prescription opioid type is not associated with increased likelihood of prolonged use in opiate-naïve patients after orthopaedic surgery

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Abstract

Introduction—A common belief is that some narcotic medications have a higher association with prolonged use. We assessed if the initial opiate type prescribed to post-operative, opiate-naïve orthopaedic trauma patients was associated with prolonged opioid use.

Methods—We studied 17,961 adult, opiate-naïve patients treated for an operative musculoskeletal injury. Discharge prescription in morphine milligram equivalents (MME, a standardized dosing unit that allows for comparison across opioid types) was calculated. Opioid prescribing beyond 90 days post-injury was defined as prolonged use.

Results—Initial analysis demonstrated a higher likelihood of prolonged use for patients discharged on hydromorphone or morphine versus hydrocodone. However, when we adjusted for discharge MME, only opioid quantity was predictive of prolonged use ($p < 0.001$). In addition, discharge MME was associated with opioid type ($p < 0.01$).

Discussion—Persistent opiate use was associated with discharge opioid quantity, not the opioid type. These results highlight the importance of calculating equivalence doses when selecting opioid types and considering amount of narcotics prescribed.

INTRODUCTION

Prescription opioids have contributed significantly to the rise in drug related deaths over the past decade.¹ They are among the most prescribed medications in the United States and

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American use accounts for at least 80% of the global supply. Orthopaedic surgeons are the third highest prescribers of opioids among US physicians.² While prescription opioids remain the standard of care of initial post-operative pain management in patients with traumatic musculoskeletal injuries, training on opioid prescribing for orthopaedic surgeons is limited.^{2,3} In addition, there is little published data to guide post-operative prescribing in this setting.^{3–6} As a result, the Centers for Disease Control, the US Department of Health and Human Services, and national orthopaedic societies have all highlighted the need for research to understand the variation in opioid prescribing to mitigate the risks of long-term use and addiction that are associated with initial opioid prescribing patterns.^{7–10}

A common belief is that some narcotic medications have a higher risk of long-term use than others.^{7,8} It is unclear based on the current literature if this is accurate or a myth.^{11,12} While the clinical literature suggests that opiate type and formulation are likely to have an effect on the risk of long-term use, the pharmacology literature suggests a more mixed picture. Some studies found no difference in risk by opiate type,¹¹ while others found evidence that the potency of some opioid types was related to the risk for long-term use.¹³

The aim of this study was to determine if the initial opiate type prescribed to post-operative, opiate-naïve orthopaedic trauma patients was associated with prolonged opioid use three months post-operatively using retrospective analysis of a clinical data warehouse cross-referenced to an orthopaedic trauma registry at two ACS Level I trauma centers. Our primary null hypothesis was that opiate type prescribed on discharge is not a factor that can be used to predict increased likelihood of prolonged opiate use. We also hypothesized that initial opioid quantity on discharge would be predictive of prolonged use. In addition, we examined the correlation between opioid type and initial opioid quantity on discharge.

METHODS

Ethics:

This study was approved by our institutional review board and they determined that individual patient and prescriber consent was not required.

Study Design:

Retrospective cohort study; Level III

Setting:

We identified operatively treated orthopaedic trauma patients at our two American College of Surgeons (ACS) Level 1 trauma centers between 2002 to 2015. Detailed demographic and clinical data, including initial opioid quantity on discharge, were matched to each patient using our institutions' Enterprise Data Warehouse (EDW) and Research Patient Data Registry (RPDR). Our institutions' EDW/RPDR is composed of over 6.5 million patients and over 2 billion records from patient encounters, medication prescribing history, laboratory and imaging studies, and other medical care. All patients have a unique identification number that is used to track any services or medications provided at all affiliated institutions.

Participants:

We restricted our sample to adult patients (age ≥ 18 years) who had a traumatic musculoskeletal injury, and underwent surgery within 14 days of presentation. To identify opiate-naïve patients, we excluded patients who were prescribed an opioid analgesic or opioid medication-assisted treatment in the 180 days prior to presentation, or those who had a documented opioid use history in their medical record. To limit the effect of small sample size, uncommon opioid types prescribed to fewer than 20 patients were excluded.

Variables:

Our primary outcome variable was prolonged opioid use which we identified as the receipt of at least one opioid prescription within 90 days of injury presentation and another within 90–180 days post-operatively.^{14,15}

We defined the discharge prescription as the first outpatient prescription registered in the electronic medical record immediately after the index procedure for the identified injury. Discharge prescriptions were converted to total morphine milligram equivalent units per prescription (MME, a standardized unit of opioid dosage that allows for comparison across different opioid types) by multiplying quantity and dose, and applying standard conversion tables.⁷ MME units were summed across prescriptions in cases where more than one opioid prescription was prescribed on the same day. Opioid type was recorded as a separate indicator variable.

Injuries were originally classified using the AO/OTA fracture classification system and then grouped for analysis as upper extremity fracture, lower extremity fracture, or other. Polytrauma was defined as Injury Severity Score greater than 15. Patient comorbidity was defined using the count of unique medications for chronic conditions (hypertension, diabetes, etc.) in the prior 180 days, which is an accurate summary measure of patient comorbidity in trauma settings.¹⁶

Statistical Analysis:

We assessed association between prolonged opioid use and opioid type using multivariate logit regression, adjusting for patient age, gender, race, insurance status, injury location/type, and comorbidity; hydrocodone was the null type. We performed chi-squared tests of equality between coefficients of the nine included opioid types to assess if different opioid types were more likely to be associated with prolonged use. We tested association between opioid type and discharge MME using multivariate linear regression adjusting for similar patient- and injury-level co-variates. Two-sided p-values less than 0.05 were considered statistically significant. Stata, version 15 (StataCorp), was used for all analyses.

RESULTS**Characteristics of Patient Population**

Our sample consisted of 17,961 opiate-naïve patients with operatively treated traumatic musculoskeletal injuries. The mean age of our study cohort was 51.9 years, 50% were women, and 86.1% self-classified as white. Average ($\pm$ standard deviation) number of co-

morbidities was 0.68 (± 0.88). A majority of patients were on Medicare or privately insured; 7.76% were on Medicaid and 3% were self-pay. By broad anatomical location, 16.1 % of injuries were upper extremity long-bone fractures, 19.9% were lower extremity long-bone fractures, and other injuries were a combination of hand/foot fractures, spine fractures, and soft tissue injuries; 4.1% of patients sustained polytrauma. On average, patients were discharged on 556.8 MME; this is the equivalent of 74 tablets of oxycodone. Likelihood of use beyond three months was 20.65% (95% CI: 20.08% to 21.24%). The majority of opioid types were oxycodone, hydrocodone, or hydromorphone. Detailed demographic and clinical information for our patient sample are summarized in Supplement Table 1.

The relationship between prolonged opioid use, opioid type, and initial opioid quantity

Our initial multivariable analysis adjusted for all potential confounding variables except for initial opioid quantity (discharge MME). This approach simulates a scenario where discharge MME is not felt to represent a relevant confounding variable and is not considered by the discharging clinician. In this partially adjusted analysis, we found that patients discharged on hydromorphone ($p < 0.05$), morphine ($p < 0.05$), or multiple different opioid types ($p < 0.01$) had higher odds of prolonged use compared to patients who were discharged on hydrocodone (Table 1(1)), and the Chi-square test of equality among opioid types was rejected ($p = 0.030$).

We then performed the same analysis, but also adjusted for initial opioid quantity (discharge MME). This iteration simulates the scenario where discharge MME is a relevant confounding variable. After we controlled for discharge MME, we found that opioid type was no longer an associated factor for prolonged use and that only opioid quantity was predictive of prolonged use ($p < 0.001$; Chi-square test of equality among opioid types, $p = 0.435$; Table 1(2)). See Supplement Table 2 for details of regression analysis.

The relationship between opioid type and initial opioid quantity

Based on our previous analysis, we explored if the perceived association of opioid type on prolonged opioid use was directly confounded by the initial opioid quantity. To do this, we analyzed the relationship between discharge MME and opioid type using multivariable linear regression. We identified a significant association between opioid type and the average discharge MME prescribed (Table 2, $p < 0.01$; Detailed regression results in Supplement Table 3). Hydromorphone (coefficient = 417.7, $p < 0.001$) and morphine (coefficient = 863.1, $p < 0.001$) were associated with higher MME at discharge compared to hydrocodone. Figure 1 illustrates the average difference in discharge MME as compared to hydrocodone for all the opioid types included in this study.

DISCUSSION

A common belief is that some narcotic medications have a higher association with long-term use than others,^{7,8} but it is unclear if this is accurate.^{11,12} In this cohort of opiate-naïve orthopaedic surgery patients, we found that the likelihood of prolonged opiate use was not associated with the opioid type initially prescribed, but rather the overall MMEs prescribed at discharge. We then demonstrated that average discharge MME was associated with opioid

type. Opioid types associated with higher discharge MME (morphine, hydromorphone) are the same opioid types that initially appear to be associated with higher odds of prolonged use. Thus, we suggest that the common belief that some opioid types (e.g. Dilaudid®/hydromorphone) have a higher propensity for subsequent prolonged use is due to selection bias¹⁷ whereby the opioid type is more accurately a reflection of the average MMEs typically provided at discharge.

Opioid medications are the mainstay of pain management in orthopaedic trauma, but formal validated training on opioid prescribing for orthopaedic surgeons is limited and there is limited data to guide balanced post-operative prescribing.^{3–6} Our results contribute to the existing literature on analgesia in musculoskeletal trauma by utilizing an institutional dataset with sufficient size and prescribing detail to address how opioid type and initial opioid quantity are related to the likelihood of prolonged use in this population.

Recent studies have demonstrated that initial prescribing practices can influence the risk of long-term use.^{18,19} One recent study found that some opioid types were associated with the risk of long-term use, but were unable to control for opioid quantity prescribed on discharge due to their study design. In contrast, other studies in the pharmacology literature found very little difference between opioid type and pharmacologic effect when opioid dose was held constant.¹¹ Our analysis supports the importance of considering discharge MME, instead of opioid type, when discharging patients after operative orthopaedic trauma.

Major national and state opioid prescribing guidelines advocate starting at a low and “effective” initial dose of opioids and titrating up if needed.^{2,7,20,21} Several recent papers have proposed reasonable “start points” for orthopaedic upper extremity injuries and common general surgical procedures.²² Typically, these initial recommended doses are reported in terms of pill quantity for a specific opioid type (e.g. oxycodone). This analysis builds upon those results by highlighting the importance of proper equivalence conversions in settings where patients require a different opioid type due to allergy or adverse effect.¹¹ For example, existing literature recommends an initial dose of 20 tablets of 5 mg oxycodone (150 MME) as the initial prescription for operative extra-articular distal radius fractures in opiate-naïve patients.^{23,24} Suppose a patient was instead discharged on hydromorphone (strength: 4 mg/pill) because they could not tolerate oxycodone. In this setting, the equivalent number of pills to prescribe the same initial opioid quantity (150 MME) would be 9 pills. This can be calculated using the appropriate MME conversion factors (Table 3) in the equivalence equation for switching opioid types (See equation below).

$$\text{Number of Pills}_{\text{alternateOpioidType}} = \frac{\left(\text{Number of Pills}_{\text{initialOpioidType}}\right) * \left(\text{Strength per pill}_{\text{initialOpioidType}}\right) * \left(\text{MME conversion factor}_{\text{initialOpioidType}}\right)}{\left(\text{Strength per pill}_{\text{alternateOpioidType}}\right) * \left(\text{MME conversion factor}_{\text{alternateOpioidType}}\right)}$$

If the equivalence calculation was not performed when converting from oxycodone to hydromorphone and the patient was simply prescribed the same number of pills as when prescribing oxycodone (20 pills), the patient would have received 320 MME which

represents a dose increase of 142% in terms of initial opioid quantity. In this scenario, failure to properly calculate an equivalence dose when switching opioid types would place the patient at higher odds for prolonged use based on our data and the current literature.^{18,19}

Limitations

Our study has several limitations. Our investigation was limited to two academic ACS level I trauma centers that are regionally close to each other, but other work suggests that our results are likely to be similar in different locations.²⁵ We used an institutional dataset because national and state databases do not report the quantity of initial prescribed opiate for individual patients with sufficient follow-up and injury-level detail. Our results apply to those who are opiate-naïve as we excluded those with prior opioid use within 180 days of injury in this study. We identified prolonged opioid use as receipt of at least one opioid prescription within 90 days of injury presentation, and another 90–180 days post-operatively. Since prescription of opioids is not identical to measurement of opioid intake, our estimate of prolonged use may be an over-estimate if patients are prescribed opioids but not using them.^{14,15} In contrast, our method for identifying prior opioid use and opioid naïve patients may be an underestimate since our data spans a time period not completely covered by the Massachusetts Prescription Monitoring Program. However, our incidence rate of prolonged use is consistent with prior reports that used state registries monitoring prescription fulfillment suggesting that these measurement errors do not significantly affect our findings.

Given our study design, we cannot identify casual relationships between discharge MME, opioid type, and long-term use since other unobservable characteristics, such as pain catastrophization or pain anxiety, may be associated with increased opioid quantity and increased likelihood of prolonged use.^{26,27} Our estimate of the rate of prior and long-term use may be underestimated if patients received subsequent opioid prescriptions outside of the healthcare network we studied or convert to illicit or “street” opioids such as heroin; however, our estimates are consistent with prior studies. We also did not explore associations between opioid types and non-narcotic analgesic medication selection.

An alternate explanation for our results is that some opioid types are preferentially prescribed for more painful injuries, and hence receive a higher initial opioid quantity. If this were the case, we would expect higher discharge MME or preferential prescribing of some opioid types (like hydromorphone) for more painful injuries in our dataset. We tested this by analyzing if the distribution of opioid types was different by fracture location or morphology (as classified using the AO/OTA fracture classification), since some fractures are known to be more painful than others.^{23,24} We did not find significant differences in discharge MME by fracture morphology or in the distribution of some opioid types for different fracture types (Supplemental Analysis), suggesting that opioid types are not selectively prescribed based on injury type or severity.

Conclusion

Our study found that the likelihood of persistent opioid use was related to the quantity of initial opioid prescribed (discharge MME) and was not associated with the initial opioid type

that was selected. Our analysis suggests that the notion that some opioid types are intrinsically more dangerous than others is a myth. Our results also highlight the importance of calculating equivalent opioid dosing when switching opioid types to avoid inadvertently prescribing patients significantly higher MME. In summary, current beliefs about the mechanism of prolonged use may be confounded. Our findings highlight how further research, accurate registries, and outcome assessment based on opioid use are critical toward developing a better understanding of the relationship between opioid prescribing patient use, and long-term sequelae.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

FUNDING & ACKNOWLEDGEMENTS

The content of this article is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute on Aging or the National Institutes of Health. Mr. Basilico is supported by a pre-doctoral Fellowship in Aging and Health Economics (NIA T32 AG 51108) from the National Institute on Aging. We thank David Cutler, PhD, Nihar Shah, and Michael Weaver, MD and Mark Vrahas, MD for helpful comments.

Dr. Heng or an immediate family member serves as a board member, owner, officer, or committee member of the New England Orthopaedic Society. None of the following authors or any immediate family member has received anything of value from or has stock or stock options held in a commercial company or institution related directly or indirectly to the subject of this article: Mr. Basilico, Dr. Bhashyam, and Dr. Harris.

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Figure 1:

Average difference in discharge MME as compared to hydrocodone for all opioid types

Table 1:

Prolonged use by opioid type; (1) Unadjusted for initial opioid quantity (discharge MME), (2) Adjusted for initial opioid quantity (discharge MME); *p<0.05, **p<0.01, ***p<0.001

	(1) No Dosing Control Persistent Use	(2) Dosing Control Persistent Use
Initial Opioid Quantity (discharge MME)		0.00023±0.00003***
Hydrocodone	---	---
Oxycodone	0.111 ± 0.065	0.054 ± 0.067
Hydromorphone	0.200 ± 0.090*	0.100 ± 0.092
Morphine	0.725 ± 0.310*	0.521 ± 0.319
Multiple	0.253 ± 0.075***	0.0516 ± 0.082
Demographic/Injury Controls	Y	Y
Model	Logit (N=17961)	Logit (N=17961)
Pseudo R ²	0.00918	0.0114

Table 2:

Initial opioid quantity (discharge MME) by opioid type; *p<0.05, **p<0.01, ***p<0.001

Initial opioid quantity (discharge MME)	
Hydrocodone	---
Oxycodone	243.1 ± 5.0 ***
Hydromorphone	417.7 ± 18.6***
Morphine	863.1 ± 134.3***
Multiple	841.5 ± 14.6***
Demographic/Injury Controls	Y
R ²	0.271
Model	Linear (N=17961)

Table 3:

Opioid morphine milligram equivalent (MME) conversion factors (<https://www.cms.gov/Medicare/Prescription-Drug-Coverage/PrescriptionDrugCovContra/Downloads/Opioid-Morphine-EQ-Conversion-Factors-April-2017.pdf>)

Opioid type (strength units)	MME conversion factor
Oxycodone (mg)	1.5
Hydrocodone (mg)	1
Hydromorphone (mg)	4
Codeine (mg)	0.15
Tramadol (mg)	0.1
Morphine (mg)	1
Fentanyl (mcg)	7.2