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Risk Factors for Prolonged Opioid Consumption in Lower Extremity Amputees

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Background: Extremity amputation is a common procedure performed to treat a variety of different problems and affects quality of life in a number of ways. In addition to acute postoperative pain, amputations have been shown to cause chronic pain that is often neuropathic in many amputees. This study sought to better characterize the role of opioids in postoperative pain control in lower extremity amputees.
Methods: Patients who underwent lower extremity amputation between 2010 and 2018 were identified in a national insurance-claims database using ICD-9, ICD-10, and CPT codes. Patient demographics, comorbidities, perioperative opioid use, and prolonged postoperative opioid use were then determined for both groups. Descriptive statistics and logistic regression analysis were utilized to evaluate the association of patient-related risk factors and neuropathic pain conditions with perioperative and prolonged postoperative opioid use.
Results: In total, 2247 opioid-naive lower extremity amputees were identified. An estimated 54.7% of patients utilized opioids in the perioperative period, and 44.6% were found to have prolonged opioid use. Younger age (ages 40–50 versus older), history of chronic pain, migraines, lower back pain, Charlson Comorbidity Index greater than 1, preoperative benzodiazepine, muscle relaxant, anticonvulsant, and antidepressant use were all significantly related to prolonged postoperative opioid use.
Conclusions: Prolonged postoperative opioid use is a problem that affects nearly half of lower extremity amputees and seems to be significantly related to the preoperative use of benzodiazepines, muscle relaxants, anticonvulsants, and antidepressants. Further research into the diagnosis and treatment of postamputation neuropathic pain is needed to prevent reliance on opioids in this patient population.
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INTRODUCTION

Limb amputation is a common surgical procedure that affects a number of individuals worldwide. In the United States alone, there are more than 185,000 individuals who undergo upper or lower extremity amputations each year.[1] Major causes of amputations include vascular disease, trauma, and cancer. It is estimated that currently about 1.6 million Americans are living with an amputation; almost 1 million of these patients are younger than 65 years. Furthermore, it is estimated that the number of people with an amputation is likely to double by 2050 secondary to the increasing rate of vascular disease and related sequelae.[1]

Although amputation profoundly affects almost all aspects of an amputees' life, the development of postamputation pain is one of the most significant impacts of these surgeries. Postamputation pain, which is a broad term that includes phantom pain and stump pain of various etiologies, is unfortunately a common complication for both upper and lower extremity amputees. Recent studies have shown the prevalence of phantom pain in up to 80% of patients postamputation, with higher prevalence among

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the lower extremity amputation population. Prior studies have shown that the impact of postamputation pain can be persistent and debilitating for variable amounts of time and is not limited to the immediate postoperative period[2,3] Although the exact mechanism is unknown, it is likely multifactorial and related to pathology that involves peripheral nerves, the spinal cord, and the somatosensory cortex.[4]

Current available treatments therefore target these multiple levels of pathology with variable success. Narcotic pain medications are often prescribed in the perioperative setting; however, prolonged narcotic pain medication use is not well studied in the amputee population. The goal of this study was to analyze patterns of postamputation narcotic use and risk factors for prolonged narcotic mediation use after lower extremity amputation. The secondary goal of the study was to investigate the relationship of postamputation pain, amputation-related nerve complications, and opioid medication usage.

Takeaways

Question: What is the role of opioids in postoperative pain control in lower extremity amputees, and what are the risk factors for prolonged opioid use in this population?

Findings: Using a national insurance-claims database, patient characteristics and postoperative opioid use were analyzed. Of the 2247 lower extremity amputees, 54.7% of patients utilized opioids in the perioperative period, and 44.6% were found to have prolonged opioid use. Risk factors for prolonged postoperative opioid use included younger age, history of chronic pain, migraines, lower back pain, Charlson Comorbidity Index greater than 1, preoperative benzodiazepine, muscle relaxant, anticonvulsant, and antidepressant.

Meaning: Prolonged postoperative opioid use is a problem that affects nearly half of lower extremity amputees and is associated with certain easily identifiable risk factors.

METHODS

A commercially available, proprietary, national insurance-claims-based database, PearlDiver Patients Records Database (www.pearldiverinc.com; PearlDiver Inc., Colorado Springs, Colo.), was utilized in this study. The records available for analysis by the database are de-identified, anonymous, and compliant with the privacy rules of the Health Information Portability and Accountability Act and were therefore exempted from review by the institutional review board at our institution. The database contains patient demographics, comorbidities, diagnoses, procedures, and medications among numerous other data, which may be queried using International Classification of Diseases (ICD-9 and ICD-10) diagnosis or procedural codes, as well as current procedural terminology codes. The database information spans all US states and territories with all types of payers (commercial, Medicare, Medicaid, government, and cash) from 2010 to 2018. Patients can be tracked across all locations (inpatient, outpatient, pharmacy, etc.) as well. In total, the database contains approximately 20 million patient records.

Patients with a first-instance diagnosis of lower extremity amputation were identified using current procedural terminology codes. (**See table, Supplemental Digital Content 1,** which shows definitions of the codes. **http://links.lww.com/PRSGO/B887**.) Patients were filtered for the presence of valid age and gender information as well as the presence of claims data available for 6 months before or 6 months following the operation. Patients with a history of preoperative opioid use were excluded as defined by the presence of at least one filled opioid prescription between 1 month and 6 months before the operation. The month before the operation was not included to reduce the risk of excluding patients filling a prescription in advance in the setting of elective amputation management. (**See table, Supplemental Digital Content 1, http://links.lww.com/PRSGO/B887**.)

Prevalence of medical comorbidities of interest and risk factors for chronic pain and narcotic usage (including psychiatric and chronic pain conditions), as well as use of other medications of interest (including anticonvulsants, antidepressants, benzodiazepines, methadone, and muscle relaxants) were determined as reported in Supplemental, Digital Content 1. (**See table, Supplemental Digital Content 1, http://links.lww.com/PRSGO/B887**.) Demographic data on patient age, sex, and treatment region were reported by the database.

Perioperative opioid use was defined by the presence of a filled opioid prescription between 1 month before and 2 weeks following the operative procedure. Prolonged postoperative opioid use was defined as the presence of a filled opioid prescription between 90 days and 180 days following the operative amputation procedure. Opioid prescription information and opioid oral morphine milligram equivalent (MME) units were calculated as average daily MME per patient. To evaluate the impact of postamputation nerve-related pain with narcotic use, patients with a first-instance diagnosis of postoperative pain, phantom limb pain, amputation-related stump complications, or nerve-related pain in the range of 1–4 weeks, 4–12 weeks, and 12–26 weeks after amputation were identified within our previously identified group of lower extremity amputees (using ICD and current procedural terminology codes).

R Project for Statistical Computing software (https://www.r-project.org/), available through the PearlDiver database, was used for all statistical analyses. Epidemiologic data were analyzed to report descriptive statistics, including number, percentage, mean, median, and ranges as appropriate. Logistic regression analysis was utilized to evaluate the association of patient-related risk factors, including demographic variables and comorbidities with the reporting of perioperative and prolonged opioid prescriptions. Secondary endpoints included pain outcomes, all-cause 30-day emergency department visits, and hospital admissions. Odds ratios were calculated from the regression analysis, and a corresponding 95% confidence interval and *P*-value were also calculated for each patient-related risk factor. For all statistical calculations, a *P* value less than 0.05 was considered statistically significant.

RESULTS

A total of 2247 opioid-naive, first-time lower extremity amputees were identified within the database. The majority of patients were between 70 and 79 years old (52.96%), with 50- to 69-year-old patients as a close second largest population (42.73%). There were no notable differences between different genders. Numerous comorbidities were seen among the identified amputees, including depression (14.02%), hypertension (13.13%), chronic pain (10.81%), diabetes (10.10%), and low back pain (6.90%). Use of benzodiazepines (11.84%), muscle relaxants (10.50%), anticonvulsants (22.56%), and antidepressants (28.66%) were all noted to be prevalent among amputees (Table 1). In total, 19.5% of amputees developed an amputation-related complication of some type (4.4% phantom limb pain, 2.0% neuritis or neuralgia, 16.8% other amputation stump complication) (Table 2).

Just over half (54.65%) of amputees filled perioperative opioid prescriptions; average daily MME was 114.92. Almost half of the amputees had prolonged postoperative opioid use (44.59%) with average daily MME of 116.18 (Table 3).

With regard to prolonged postoperative opioid use, patients between the ages of 40 and 50 years had the highest odds ratio of 2.51 ($P = 0.008$). Overall, patients with more significant comorbidities (Charlson Comorbidity Index > 1) were also at increased risk of prolonged opioid use with an odd ratio of 1.97. Chronic pain ($P = 0.011$), migraine ($P = 0.022$), and back pain ($P = 0.023$) were all associated with increased risk of prolonged narcotic use postoperatively. History of medications (including benzodiazepines, muscle relaxants, anticonvulsants, and antidepressants) were all significant factors that were associated with the increased risk of both perioperative and prolonged postoperative narcotic pain medication use ($P < 0.001$) (Table 4). Of note, amputation-related complications, specifically phantom limb pain, amputation stump complications, and amputation neuroma, were not specifically associated with a higher incidence of either perioperative opioid use or prolonged postoperative opioid use (Table 4).

Table 1. Demographics and Comorbidities in Opioid-naive Lower Extremity Amputees

Patients	N = 2247	%
Age (y)		
Less than 40	18	0.80
40–49	59	2.63
50–59	337	15.00
60–69	623	27.73
70–79	1190	52.96
80 and over	20	0.89
Gender		
Men	1056	47.00
Women	1191	53.00
Region		
Northeast	427	19.00
Midwest	697	31.02
South	793	35.29
West	326	14.51
Comorbidities		
Asthma	*	
Congestive heart failure	39	1.74
Coronary artery disease	97	4.32
Chronic kidney disease	74	3.29
Chronic obstructive pulmonary disease	52	2.31
Diabetes mellitus	227	10.10
Hypertension	295	13.13
Obesity	44	1.96
Osteoarthritis	142	6.32
Rheumatoid arthritis	30	1.34
Tobacco use	34	1.51
Alcohol use	61	2.71
Drug abuse	*	
Anxiety	96	4.27
Fibromyalgia	55	2.45
Chronic pain	243	10.81
Opioid use or dependence	41	1.82
Migraine	17	0.76
Low back pain	155	6.90
Medications		
Methadone	23	1.02
Benzodiazepine	266	11.84
Muscle relaxant	236	10.50
Anticonvulsant	507	22.56
Antidepressant	644	28.66
Charlson Comorbidity Index	3.87±3.44	

*Cannot be revealed due to less than 11 patients.

DISCUSSION

Over 185,000 patients undergo upper or lower extremity amputation each year in the United States secondary to various conditions, including peripheral vascular disease, diabetes, trauma, and malignancy. Unfortunately, these procedures can lead to many complications, including chronic postamputation pain. Prior literature suggests that a significant portion of amputees experience such pain, with prevalence of phantom limb pain ranging from 42% to as high as 85% in some studies.[5–8] Furthermore, such pain continues even decades after amputation and interferes with amputees' daily lives. Pain management in these patients can be difficult and require implementation of multiple modalities, including pharmacologic agents, surgical procedures including stump revision or neurectomy, CNS stimulation, and other adjuvant therapies such as transcutaneous nerve stimulation, biofeedback, and massage.[9] Studies suggest that lower extremity amputees are at a higher risk of developing chronic pain, as well as suffering opioid overdose.[2,10] Despite such significant risks of prolonged use, narcotic pain medication use patterns and risk factors after lower extremity amputation are not very well studied. This study therefore sought to better characterize perioperative and prolonged postoperative opioid use, as well as the risk factors for prolonged postoperative use in amputee population.

Among the group of lower extremity amputees that were identified in this study, almost half were found to have prolonged postoperative narcotic pain medication use. This obviously represents a substantial portion of the population,

Table 2. One-year Postamputation Stump and Nerve-related Complications

	N	%
Patients	2247	100
Any amputation-related complication	439	19.54
Phantom limb pain	99	4.41
Postamputation neuroma	*	NA
Postamputation neuritis or neuralgia	44	1.96
Amputation stump complication	378	16.82

*Cannot be revealed due to less than 11 patients.

Table 3. Incidence of Perioperative and Prolonged Postoperative Opioid Prescriptions

	Total (n)	%
Patients	2247	100
Perioperative opioids		
Patients	1228	54.65
Average daily dose MME	114.92	
MME per prescription	851.51	
Prolonged postoperative opioids		
Patients	1002	44.59
Average daily dose MME	116.18	
MME per prescription	1518.13	

Perioperative opioids = at least one prescription between 1 month before and 2 weeks after the operation.
Prolonged postoperative opioids = at least one prescription between 90 and 180 days after the operation.

suggesting that many amputees continue to have significant pain related to their amputation well beyond the expected perioperative recovery period. The average daily MME consumption for these patients in this prolonged postoperative time period (116.18 mg) was also substantial and actually slightly higher than the average daily use during the immediate perioperative period (114.92 mg). Again, this is likely evidence that almost half of amputees continue to have pain that is equal or greater in severity during perioperative period for up to 6 months after their index amputation. Despite recent interest in multimodal pain management—including NSAIDs, gabapentinoids, NMDA antagonists, and antidepressants—our data may also suggest that these patients are not receiving effective multimodal pain control regimens and are thus left to rely on opioids. Interestingly, none of the stump-related complications or conditions associated with neuropathic stump pain (phantom limb pain, neuroma) were significant predictors of prolonged postoperative narcotic use. Of the 2247 study subjects, only 4.4% received a diagnosis of phantom limb pain after their index amputation, and less than 0.5% were diagnosed with neuroma. Both of these figures are less than what has been reported in prior literature, and therefore suggest that these conditions (phantom limb pain, neuroma) are often undiagnosed or misdiagnosed, which can lead to inappropriate or inadequate treatment with prolonged opioid agents. If properly identified, these patients may benefit from multimodal pain medication regimens targeting neuropathic pain or surgical interventions, including targeted muscle reinnervation (TMR) or regenerative peripheral nerve interface.[11–13]

Table 4. Multivariate Logistic Regression of Perioperative and Prolonged Postoperative Opioid Prescriptions

	Perioperative Opioid Prescriptions		Prolonged Postoperative Prescriptions	
Factors	Odds Ratio (95% CI)	*P*	Odds Ratio (95% CI)	*P*
Demographic factors				
Age less than 40	1.32 (0.43–4.47)	0.636	1.3 (0.42–4.11)	0.645
Age 40–50	1.5 (0.78–2.95)	0.229	2.51 (1.29–5.02)	0.008*
Age 50–60	1.27 (0.94–1.72)	0.122	1.92 (1.41–2.62)	<0.001*
Age 60–70	1.26 (1–1.59)	0.050*	1.66 (1.31–2.11)	<0.001*
Men	0.9 (0.74–1.1)	0.320	0.81 (0.66–1)	0.055
Comorbidities				
Asthma	1.47 (0.66–3.45)	0.363	1.34 (0.61–2.97)	0.472
Congestive heart failure	1.04 (0.62–1.74)	0.881	1.2 (0.71–2)	0.497
Coronary artery disease	1.26 (0.8–2)	0.320	1.61 (1.01–2.57)	0.046
Chronic kidney disease	0.89 (0.57–1.39)	0.596	0.65 (0.41–1.03)	0.069
Chronic obstructive pulmonary disease	0.97 (0.61–1.55)	0.901	0.9 (0.56–1.45)	0.674
Diabetes	0.91 (0.57–1.44)	0.681	1.05 (0.65–1.68)	0.855
Hypertension	0.67 (0.32–1.4)	0.288	0.58 (0.28–1.23)	0.157
Obesity	1.16 (0.75–1.8)	0.519	1.52 (0.98–2.36)	0.063
Osteoarthritis	1.81 (0.94–3.52)	0.077	1.26 (0.65–2.42)	0.496
Rheumatoid arthritis	1.84 (0.98–3.57)	0.062	1.47 (0.8–2.73)	0.221
Specific risk factors				
Tobacco use	1.01 (0.63–1.63)	0.973	0.89 (0.55–1.44)	0.641
Alcohol use	1 (0.72–1.4)	0.996	1.39 (0.98–1.96)	0.061
Drug use	1.24 (0.73–2.14)	0.432	0.93 (0.55–1.59)	0.790
Anxiety	0.78 (0.6–0.99)	0.045*	0.8 (0.62–1.04)	0.096
Fibromyalgia	1.08 (0.81–1.45)	0.600	0.99 (0.74–1.33)	0.947
Chronic pain	1.18 (0.94–1.47)	0.144	1.34 (1.07–1.68)	0.011*
Opioid use dependence	1.11 (0.75–1.67)	0.604	1.24 (0.83–1.86)	0.302
Migraine	1.55 (0.89–2.83)	0.136	1.96 (1.12–3.55)	0.022*
Back pain	0.98 (0.8–1.2)	0.818	1.27 (1.03–1.57)	0.023*
Charlson Comorbidity Index				
CCI greater than 1	1.33 (0.95–1.88)	0.101	1.97 (1.39–2.8)	<0.001*
Preoperative medication history				
Methadone	1.84 (0.99–3.68)	0.068	1.53 (0.85–2.85)	0.165
Benzodiazepines	1.87 (1.52–2.31)	<0.001*	2.28 (1.85–2.81)	<0.001*
Muscle relaxants	1.77 (1.43–2.19)	<0.001*	1.95 (1.57–2.42)	<0.001*
Anticonvulsants	2.02 (1.65–2.47)	<0.001*	2.17 (1.76–2.68)	<0.001*
Antidepressants	2.59 (2.07–3.25)	<0.001*	2.29 (1.81–2.9)	<0.001*
Amputation complications				
Phantom limb pain	1.12 (0.73–1.73)	0.604	1.08 (0.7–1.67)	0.734
Amputation stump complications	0.88 (0.51–1.5)	0.632	0.85 (0.5–1.46)	0.561
Amputation neuroma	0.84 (0.16–6.47)	0.844	4.13 (0.55–89.69)	0.238
Neuritis or neuralgia	0.87 (0.52–1.47)	0.611	0.85 (0.51–1.45)	0.560
Any amputation complication	1.02 (0.58–1.79)	0.951	1.07 (0.6–1.89)	0.822

*$P < 0.05$.

Some of the significant comorbidities that predicted higher likelihood of prolonged narcotic pain medications included history of chronic pain, migraine, back pain, and a Charlson Comorbidity Index greater than 1 (a surrogate for overall increasing severity of comorbidity burden). First-time lower extremity amputees in this study were mostly patients of age 50 and over. This finding is consistent with prior literature and is attributable to the chronicity of diabetes and peripheral vascular disease, the two most common causes of lower extremity amputation. Younger patients (ages 40–50) had higher risk of prolonged narcotic use compared with older ages (70 or older), which was previously shown in other studies.[11] Interestingly, certain conditions commonly thought to be associated with chronic pain (including osteoarthritis, rheumatoid arthritis, fibromyalgia, and opioid use dependence) did not increase the risk of prolonged narcotic use. This finding provides evidence that although patients may carry these prior diagnoses, if they fulfill the definition of "opioid naive," (no filled narcotic prescription between 1 and 6 months before surgery), they are not at any increased risk of having prolonged opioid use. Prescription history of benzodiazepines, muscle relaxants, anticonvulsants, and antidepressants was a significant predictor of both perioperative and prolonged postoperative narcotic pain medication use. Interestingly, while use of these medications clearly shows increased risk, some of the conditions treated by these medications (such as fibromyalgia, anxiety) were not implicated in increased risk of prolonged postoperative opioid use on their own. This finding strongly suggests that the prescription history of the previously mentioned medications, rather than having the diagnosis of chronic pain that is treated non-pharmacologically or with homeopathic modalities, is linked to prolonged postoperative opioid use. Given this, preoperative screening of patients' prior preoperative medication profile rather than past medical history would be more predicative of risk of prolonged postoperative narcotic pain medication use.

In a previous study looking at persistent opioid consumption following major limb amputation population at a single center, it was also shown that preoperative use of neuropathic medications, benzodiazepines, and lower extremity amputation was associated with increased risk of prolonged opioid use, with about 20% population developing persistent postoperative opioid usage (opioid use up to 24 months postamputation).[12] Our study reflects this trend in a larger, multi-institutional, nationally representative patient population with a lower extremity amputee population. Higher rate of prolonged narcotic use in our study may be secondary to narrower definition of prolonged postoperative opioid use (up to 6 months versus 24 months postamputation), but it may also be due to our focus on lower extremity amputees, which is known to be a risk factor for developing chronic pain and opioid overdose. Our study further confirms that postamputation pain is a common and significant complication that can affect one's quality of life. Multimodal pain control strategies or pharmacologic treatments that more specifically target neuropathic pain may decrease these patients' prolonged postoperative reliance on narcotics and decrease their risk for grave complications such as opioid addiction and overdose.

In addition to targeted pharmacologic interventions, surgical treatments have also been shown in recent years to be promising in the treatment of postamputation pain. TMR is a novel nerve transfer technique that was initially developed to allow for intuitive myoelectric upper limb prosthetic control.[13] Interestingly, TMR was found to also help reduce postamputation / phantom limb pain / and neuroma pain in limb amputees.[14,15] A recent prospective, randomized control study showed significantly decreased phantom limb pain in patients who received TMR versus traditional neurectomy.[16] Another promising surgical intervention for postoperative neuroma and phantom limb pain is the use of regenerative peripheral nerve interface.[17] Medications attempt to manage the postamputation pain without solving the underlying etiology of the pain; however, surgical interventions are designed to address the pain at its root cause, the peripheral neuroma, and may be performed at the time of the index amputation for primary prevention or in a delayed fashion to treat an established neuroma.

Both the strength and limitations of the study arise from the fact that this is a study based on a national registry. PearlDiver contains more than 122 million distinct patient records from all US states and territories and can extract data from various clinical settings, including inpatient, outpatient, and pharmacy settings with all types of payers. This study provides by far the largest volume of data for this specific patient population. Unfortunately, national registry comes with its own set of limitations, including the quality of the data and the accuracy of procedural reporting. The use of opioid-naive patients was selected to provide the cleanest analysis of postoperative opioid utilization; however, many patients undergoing amputation may not be opioid-naive before surgery. Using this certain database, trying to clearly distinguish pre-existing opioid prescription from postoperative opioid prescription would not be possible. However, future studies including patients with history of opioid use before surgery and analyzing their opioid use postamputation would be of value. Pain is subjective, and as such, many psychosocial factors, physician prescribing preferences, and cultural/regional norms play a role in its recognition and ultimately its treatment in the form of opioid medications. The prescribing of opioids does not guarantee the possibility of opioid use, and the possibility of diversion or secondary gain remains. In addition, the indication for the prescriptions was not specifically addressed, only the timing related to the index amputation procedure, and presumably a given patient could be consuming opioids for an indication not directly related to the amputation in the perioperative or postoperative period. Because the patients analyzed in this study were limited to lower extremity amputees, the findings presented here may not be readily applicable to upper extremity amputees. The majority of upper limb amputations are of fingertip, digit, and metacarpal levels as opposed to wrist disarticulation or even more proximal

amputation, which would not be a suitable comparison to BKA or AKA. As mentioned previously, based on our data analysis and review of the prior literature, we feel that it is likely that many patients identified in our database search likely had undiagnosed postamputation phantom limb pain or neuroma, which decreased the apparent significance of these conditions in prolonged postoperative opioid use. Alternatively, it is possible that our ability to identify patients with confirmed postamputation pain diagnoses was limited due to our choice of search terms. Either way, future studies to determine how well and how often amputees are diagnosed with these conditions would be useful. Development of enhanced recovery after surgery protocols directed specifically at amputees with incorporation of nonnarcotic pain control modalities should also be investigated in future research endeavors.

CONCLUSIONS

In this study we observed prolonged postamputation opioid use in almost half of lower extremity amputees identified in a large, national patient population. Based on the data presented here, prolonged opioid prescribing is associated with younger age at the time of amputation, as well as the preoperative use of benzodiazepines, muscle relaxants, anticonvulsants, and antidepressants. Prolonged opioid prescriptions are not associated with the incidence of phantom limb or neuroma-related pain in this study. However, based on prior literature, we suspect that development of these conditions may contribute to increased prolonged postoperative opioid use; however, the incidence of these confounding conditions is often under-reported.

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