The Relationship between the Pre- and Postoperative Use of Opioid Narcotics and Preoperative Patient-derived Functional Outcomes

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Abstract

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Background: Few studies have examined the relationship between pre- and postoperative opioid use and surgical treatment of cervical myelopathy.

Methods: A sub-analysis of opioid use was conducted in 300 of 401 patients with cervical myelopathy who underwent surgical decompression in a multicenter prospective study. Data on pre- and postoperative opioid use and preoperative patient-reported functional scores were analyzed. Three logistic regression models were compared to predict long-term opioid use.

Results: Patients using opioids preoperatively were more likely to be female and have comorbidities, frequent or debilitating headaches, and lower preoperative functional scores. Of 146 taking opioids preoperatively, 139 (95.2%) were still taking them more than 90 days post-surgery. The best predictor of postoperative opioid use was preoperative opioid use.

Conclusion: If surgeons consider myelopathic pain in the surgical decision-making process for cervical myelopathy, preoperative opioid use could have a confounding effect on outcomes due to their distortion of pain perception.

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1. Introduction

1.1 The History of Opium

The use and abuse of opium by humans has a long, colorful history. Images and artifacts from ancient cultures indicate that mankind first became aware of the unique effects of opium on the human brain over 6000 years ago. Pharaonic Egyptians used opium to provide analgesia for surgical procedures and to treat "excessive crying in children."[1] Prominent physicians from Hippocrates to William Osler extolled the benefits of opium. In fact, before the 20th century, opium might have been one of very few medications used by physicians that actually had any effect on symptoms.[1]

The British were among the first to exploit the addictive properties of opium. In the 19th century, smoking tobacco laced with opium became a popular recreational pastime in China,[1,2] The British East India Company controlled most of the opium production in the Middle East and conducted a profitable opium trade with China. In response to an alarming increase in addiction, Chinese officials tried to restrict the importation of British opium.[1,2] This conflict precipitated the "opium wars" of the 1840's between Britain and China, in which the British prevailed, largely due to their enormous advantage in naval power. One momentous outcome of this conflict was that the Chinese ceded Hong Kong to the British as a trading port. Ironically, the profit margins in the opium trade declined after China agreed to lift all restrictions on opium importation. [2]

Morphine has been in common use as a medication since it was first chemically derived from opium in 1804 by German pharmacist Friedrich Sertürner.[1,2] After Dr. Alexander Wood perfected the hypodermic syringe in 1853,[2] morphine came into common use for treatment of acute pain. It was found to be very effective, but also highly addictive, in treating war injuries. After the American civil war, opium addiction became known as "The Soldiers' Disease."[1] A surge in the development of opioid derivatives occurred in the late 19th century after the U.S. government began issuing drug patents. In 1898, Bayer laboratories developed heroin, promoting it as a treatment for morphine addiction.[1,2] It soon became evident that heroin was even more potent and addictive than morphine.

The medical profession was complicit in the rise of the use and abuse of opioids in the U.S. in the early 20th century, often ignoring the well-known long-term hazards of opioid use in favor of the short-term benefits.[1] The Harrison Act of 1914[1,2] and subsequent court rulings made opioid medications legally available only with a written doctor's prescription. A 1918 government report indicted inappropriate prescribing practices by physicians as a major cause of opioid dependence.[1] For the next 70 years, the common view of the medical profession was that prescribing opioids was appropriate only when clearly necessary to relieve cancer pain and the acute pain related to trauma or surgery.[1,2]

1.2 Sweeping Change in Attitudes

A sweeping change in the attitude of the medical profession toward the use of opioids for the treatment of pain occurred in 1995 after two physician groups, The American Pain Society and

the American Society of Anesthesiologists, sponsored a national campaign to address a perceived "under treatment" of pain.[3] One product of this crusade was the Veteran's Administration's "Pain As the 5th Vital Sign" program.[3] The Joint Commission also changed its standards, requiring hospitals to specifically address and treat pain.[3-5] For the first time, prescription opioid analgesics were considered appropriate treatment for any pain, including chronic non-cancer pain, despite a dearth of clear evidence of their safety or efficacy.[6] This disregard for the lessons of the past was not prompted by the development of any revolutionary new medications. Most of the opioids used today were developed a century or more ago.[1,2]

This policy transformation resulted in a dramatic increase in the prescription and consumption of opioids. Sales of prescription opioids in the U.S. increased 400% from 1999 to 2010.[3,7] Similar, though slightly less dramatic, trends were observed in the United Kingdom.[8] Two oral opioids developed in the early 1900's, oxycodone and hydrocodone, accounted for a large proportion of the prescriptions in the U.S. A new medical subspecialty, "Pain Management" was developed to manage "complex" pain.[9]

The recent increase in consumption of opioids has been paralleled by a predictable upsurge in physical dependence, addiction, and disability: the known complications associated with these medications. The combination of opioids with sedatives, including alcohol and benzodiazepines, has been found to be lethal in many cases.[10] One study reported a 90% increase in opioid-related deaths in the U.S. from 1999 to 2002.[3,7] Most of the patients who died of overdoses received their drugs through a legitimate physician's prescription.[10] Illegal trafficking of prescription

opioids has skyrocketed since 1995.[10] News reports of doctors being disciplined for inappropriate prescription practices are common.[7] Prescription fraud is also a major problem.[10-14]

The liberalization of opioid prescription has had effects that reach beyond the patients for whom the prescriptions are written. Doctors typically prescribe opioids in excessive quantities for minor procedures and conditions so they can be sure their patients have enough medication.[10] Unused portions of prescriptions are often either sold on the street or left in medicine cabinets and forgotten.[4,5,10] Naïve parents often do not realize that their children are familiar with these medications and use them for recreational purposes.[4,5,10] After the pills are gone, kids who become addicted sometimes turn to harder drugs including heroin.[10]

The medical profession's endorsement of the liberal use of opioids has also had unintended effects on the practice of medicine. In the U.S., reimbursement to physicians for office visits has declined over the past 20 years while expenses have increased.[15] Caught in a financial squeeze, primary care physicians struggle to make a living in private practice or choose to become employees of health care systems. In either case, they are pressured to see a certain number of patients per unit of time. Patients who are addicted to opioids typically are not receptive to counseling by physicians; they just want their prescriptions filled.[9] If the primary care physician does not give them what they want, they find another provider who will.[9] Counseling takes time that most primary care physicians do not have and is nearly always futile.[9] It is easier and less stressful to just write a prescription than it is to argue with a manipulative patient.[9,10] Moreover, patient satisfaction scores are a significant determinant of the compensation of employed physicians, and patients are often very dissatisfied when these drugs are not prescribed.[9,10]

1.3 Long-term Use of Opioids and the Effect on Surgical Decision-Making

Long-term use of opioids results in up-regulation of receptors in the brain and a decreased response to a given dose. "Tolerance" is the clinical term used to describe this effect.[16] Patients and doctors sometimes mistake tolerance to a given daily dose of opioids that occurs normally over time, for a worsening of the painful condition. Surgeons often make decisions to perform invasive procedures, like spine surgery, as much on the basis of subjective complaints as objective findings because the pain generated by a given structural abnormality found on imaging studies, such as MRI scans, varies considerably from one patient to the next.[17-20] The true pain severity is difficult to assess in patients who are in various stages of opioid dependency.[21]

Surgeons have a strong financial incentive to perform procedures. They are typically ill-equipped to identify psychiatric disorders.[22] Psychiatric screening is neglected and surgical results reflect underlying psychopathology that manifests itself in poor outcomes and morbidity in proportion to the dosages of opioids.[10,23] Often, surgeons make decisions to operate during the first office visit because patients are anxious to have definitive treatment and the referring physicians have indicated that nonsurgical treatment has failed.[21] This is one factor that could explain the less than stellar reported results of spinal fusion performed for back pain in the developed world.[23,24]

Opioid-induced hyperalgesia is a recently recognized possible complication of opioid use.[21,25] It is defined as an increase in pain sensitivity despite an increasing dose of opioid medication.[21] In

humans, the evidence substantiating this phenomenon is mostly from case reports. Animal research indicates that the mechanism may be opioid-induced cell apoptosis associated with increased N-methyl, D-aspartate (NMDA) receptor activity and elevated levels of glutamate in the brain.[21] Although hyperalgesia and tolerance are different phenomena and have unique mechanisms, distinguishing between these two adverse effects can be difficult in the clinical setting.[21]

1.4 Cervical Myelopathy

Spondylosis is the term for age-related degeneration of the spine. Imaging studies have shown that the majority of individuals over the age of 50 have objective evidence of spondylosis but relatively few are symptomatic.[17-20] Spondylosis is characterized by loss of disk height, disk bulging, and pathologic changes in the facet and uncovertebral joints. Symptoms of cervical spondylosis can be divided into three main syndromes: axial neck pain, cervical radiculopathy, and cervical myelopathy. Axial neck pain can radiate to the shoulders but is not associated with spinal cord or nerve dysfunction. Cervical radiculopathy is caused by compression of spinal nerves and is manifested by pain and weakness in specific dermatomal and myotomal patterns. Cervical myelopathy is focal dysfunction of the cervical portion of the spinal cord due to extrinsic compression. The condition affects the neurologic function of both the upper and lower extremities. In clinical practice, patients present with a variable combination of elements of these three syndromes.[26] Pain is a primary symptom in axial pain syndrome and radiculopathy but is not as commonly reported in cervical myelopathy.[17-20]

Although congenital cervical stenosis and myelopathy have been reported in younger patients, including college[27] and professional football players,[28] in the vast majority of cases this condition is acquired and occurs in patients over the age of 60. In the group with acquired myelopathy, cord dysfunction typically occurs slowly and can be subtle in the early stages.

1.5 Pathophysiology of Cervical Myelopathy

The pathologic changes in the cervical spine that are associated with myelopathy are more advanced forms of normal age-related degeneration. Advanced degeneration of the cervical disks can result in instability of the spine and protrusion of disk material into the spinal canal as the disks lose their integrity and collapse. The ligamentum flavum can also fold inward toward the cord applying posterior compression. Hypertrophy of the facet and uncovertebral joints and calcification of the posterior longitudinal ligament are other sources of constriction of the cord. Calcification of the posterior longitudinal ligament is also a common finding in cervical myelopathy. Its cause is unknown.

A cross-section of the cervical spinal cord at any given level contains neurons (gray matter) in the center and bundles of axons of other nerve cells (white matter), on the periphery. The neurons are involved in modulation of motor function of the upper extremities. The axons provide communication between the brain and the lower extremities. Progressive compression of the cervical spinal cord results in apoptosis and death of neurons at the level of the compression and also interferes with conduction of nerve impulses in the white columns.[20] The effects of this compression are manifested in the signs and symptoms of cervical myelopathy.

Cervical myelopathy affects the neurologic function of the upper and lower extremities differently. Typical upper extremity symptoms reflect a decrement in fine motor skills such as handwriting and fastening buttons, caused by dysfunction of the spinal cord neurons at the level of the compression. Lower extremity symptoms include a shuffling gait and stiffness of the legs due to impaired function of the axons of the long tracts that transmit sensory input from the lower extremities to the brain.

Physical examination findings associated with compression of the long tracts include lower extremity hyperreflexia, clonus, and other pathologic signs including the Babinski reflex. A positive Lhermitte's sign—numbness in the upper extremities when the cervical spine is held flexed—indicates increased positional compression of the cervical spinal cord.[26] These signs are thought to be fairly sensitive for detecting myelopathy but their specificity has been questioned. They are absent in up to 20% of cases of cervical myelopathy.[20]

1.6 Diagnosis and Prognosis of Cervical Myelopathy

Diagnostic imaging is routinely used to confirm the diagnosis of cervical myelopathy although the interpretation of these studies is subjective and could vary significantly from one surgeon to another. Clinicians have observed considerable variation in the correlation between symptoms and the findings of plain radiographs, CT scans, and MRI. Symptoms can vary from minimal impairment to severe pain and dysfunction in patients with considerable constriction and deformity of the cervical spinal cord. Numerous efforts have been made to quantify and

categorize the extent and effects of the extrinsic compression of the cervical spine using imaging and electrodiagnostic studies.[20] Unfortunately there is no consensus in the literature on objective imaging or electrodiagnostic criteria for cervical myelopathy.[19]

The clinical course of cervical myelopathy also varies, with approximately 20% of patients experiencing steady worsening of their condition and the others progressing in stepwise fashion with long periods of apparent stable function.[29] Despite this variation, most investigators see cervical myelopathy as a progressive disorder and recommend surgical intervention in patients who have moderate to severe symptoms and corroborating imaging findings.[17-20] Surgery involves spinal decompression from either an anterior or posterior approach, usually followed by fusion of the decompressed segments.[30] Imaging studies are used to identify the extent and location of the pathology for planning the surgical approach (anterior versus posterior) and the number of levels to be decompressed.[17]

1.7 Outcome Measures

Traditionally, surgical outcomes reported in the medical literature have been based on the personal observations and opinions of surgeons. Patients' perspectives were often ignored or discounted.[29] Over the past two decades there has been a trend toward the use of patient-derived outcome measures as a more objective and meaningful measure of the effectiveness of various treatments. These assessments usually consist of questionnaires in which patients indicate their levels of physical and mental function. The results obtained before treatment are often compared to those recorded after treatment.

Health outcomes surveys can be either general or disease-specific. General surveys typically include a range of mental and physical health assessments. Disease-specific measures focus on the known physical and mental effects of a given disease or condition.

Third party payers use patient-derived measurements to assign relative values to different treatments and make health care decisions.[29] Treatment protocols are increasingly based on the results of patient surveys in addition to other accepted objective criteria.[29] Most published studies of surgical outcomes now include the results of patient-derived measures.[31]

Patient-derived outcome measures have a long history in cervical myelopathy. Developed in the early 1970s, the Japanese Orthopaedic Association scoring system has become a standard scale for measuring outcomes of treatment of cervical myelopathy. The original Japanese version has been modified for patients who use Western eating utensils.[32] The modified Japanese Orthopaedic Association (mJOA) scale has four sets of questions with a total of 22 choices. The sections include upper extremity motor dysfunction, lower extremity motor dysfunction, sensory dysfunction, and sphincter dysfunction. The first choice in each section is given a value of 0 and indicates the greatest severity of the disease. Completely normal function is given the highest possible score of 18. Functional disability is divided into three categories and graded as mild (mJOA score of >12), moderate (mJOA score 9-12) and severe (mJOA score <9).[31-33]

Introduced in 1976, the Nurick Functional Disability Scale is still used in most cervical myelopathy outcome studies.[33,34] The scale is relatively simple with six grades from 0 to 5. A

grade of 0 indicates no evidence of spinal cord disease. Patients who are chair bound or bed ridden are graded 5. The scale does not include measures of upper extremity or mental dysfunction.

The Neck Disability Index (NDI) is based on a questionnaire with a total of 10 sections.[35] It was designed to be applied to a variety of cervical spine conditions. The sections cover both mental and physical aspects of disability from cervical dysfunction. Each section has 6 possible responses numbered from 0 to 5. The level of dysfunction increases from 0 to 5 in each section. The largest possible raw value is 50. The outcome is measured as a percentage with the raw score divided by 50 and then multiplied by 100. A score greater than 40% indicates severe cervical cord dysfunction .[35,36]

Originally developed by the Rand corporation think tank, the SF-36 is one of the most widely used general patient-derived outcome surveys.[29] Its 36 questions are designed to cover three main areas: functional ability, wellbeing, and overall health. The survey is divided into 8 parts called domains or subscales. **(Table 1)** The number of items varies from one domain to the next, with physical functioning having the largest number. The results of the SF-36 are often divided into physical and mental components that are reported separately.[29]

Table 1: Short Form-36 Subscales

SF-36 Subscales: Number of Items and Questions in Each Subscale		
Subscale	**Items**	**Questions**
Physical Functioning	10	3-12
Role		

Physical	4	13-16
Emotional	3	17-19
Pain	2	21, 22
General Health	5	1, 33-36
Vitality	4	23, 27, 29, 31
Social Functioning	2	20, 22
Emotional Well-Being	5	24-26, 28, 30

In a recent prospective cohort study of the largest series of cervical myelopathy cases reported to date, Fehlings et al. used patient-derived outcomes measures to show that surgical decompression for cervical myelopathy is effective in improving function and quality of life.[37] In a subsequent study, the same group used the same measures to demonstrate that diabetes does not diminish the benefits of decompressive surgery for cervical myelopathy.[38]

The Walk Test is a quantitative functional measure of gait dysfunction.[39] It requires subjects to walk 30 meters as quickly as possible. Both times and number of steps are recorded. This test has been shown to be valid and reproducible in cervical myelopathy.[39]

2. Materials and Methods

The subjects for this study were part of a multicenter prospective cohort of patients from twelve North American institutions. The participating centers were members of the AOSpine North America Clinical Research Network. Patients had clinically and radiographically confirmed cervical myelopathy and underwent surgical treatment from November 2005 to August 2010. The criteria for inclusion in the study were symptomatic myelopathy, objective evidence of compression by MRI, no prior surgical treatment for myelopathy, and no evidence of lumbar

spinal stenosis. The study enrolled 401 patients meeting these criteria. Data regarding opioid use was available for 300 of these patients.

Descriptive statistics were used to investigate potential differences in relevant covariates between patients who used and did not use pain medications at baseline (defined as use within 90 days of surgery), and between patients who did and did not use pain medications long-term (defined as more than 90 days after surgery). Continuous covariates were compared using t-tests, while categorical covariates were compared using Fisher's exact test.

2.1 Predictive Modeling of Long-term Pain Medication Use

Using patient data with complete covariate and outcome information, three logistic regression models were investigated for their ability to predict the long-term use of pain medications more than 90 days after surgery. Model 1 included use of pain medications at baseline as the only covariate, while Model 2 added baseline NDI score. Model 3 included covariates selected by stepwise regression using AIC values (using the step AIC function in the MASS package in R) from the predictors listed in Table 4. The sample was split randomly into a training dataset of 60%, used for model development, and a validation dataset of 40%, used to assess model performance. The discriminatory ability of each predictive model, including sensitivity and specificity, was evaluated on a randomly selected validation dataset consisting of 40% of the sample. The calibration of each model was examined for purposes of internal validity. **(Figure 1)**

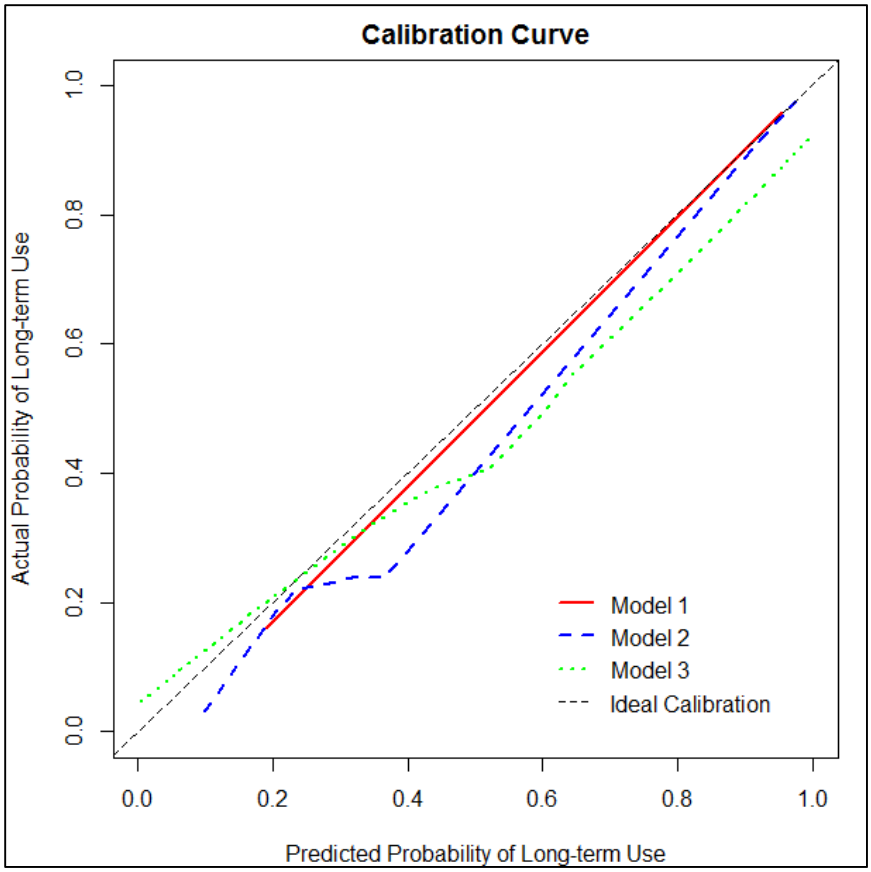

Figure 1: Calibration Plot Using Validation Dataset (N = 150), for Each Predictive Model

Receiver Operating Characteristic curves were plotted for the proposed models and the AUC (or C-statistic) calculated to quantify discrimination among models.[40] **(Figure 2)**

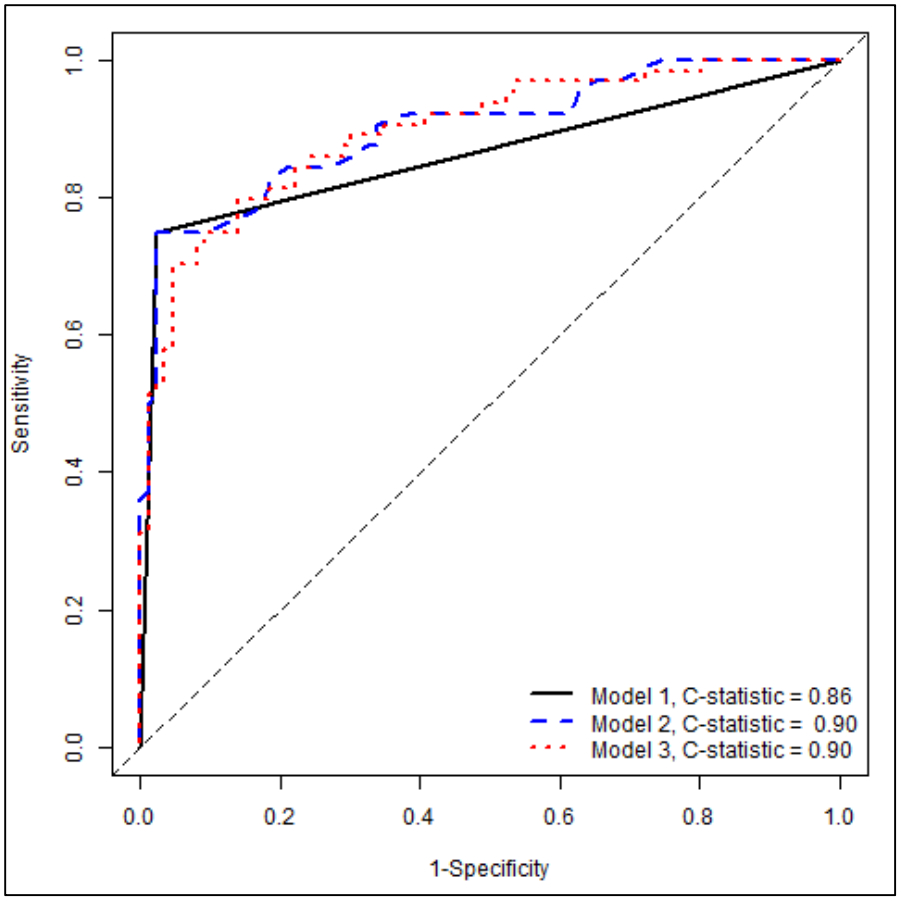

Figure 2: Receiver Operating Characteristic Curves for Prediction Analysis, Using Validation Dataset (N = 150)

Final model estimates were obtained using the entire dataset. All analyses were done using R for Windows Version 3.1.1.[41]

2.2 Results

A number of differences were observed in patients who did and did not use opioids at baseline. **(Table 2)**

Table 2: Demographic Characteristics of Study Participants by Baseline Pain Medication Use (N = 401)

	Did not use pain meds at baseline (N = 255)	Used pain meds at baseline (N = 146)	p-value
Age (years)			0.22
Mean (SD)	57.9 (12.1)	56.4 (11.1)	
Age (categorical)			0.63
≤ 40	19 (7.5)	10 (6.8)	
41-50	50 (19.6)	38 (26.0)	
51-60	82 (32.2)	47 (32.2)	
61-70	64 (25.1)	32 (21.9)	
> 70	40 (15.7)	19 (13.0)	
Sex			0.0007
Female	89 (34.9)	77 (52.7)	
Male	166 (65.1)	69 (47.3)	
Race/ethnicity			0.16
White	205 (80.4)	126 (86.3)	
Black	23 (9.0)	11 (7.5)	
Native American	1 (0.4)	1 (0.7)	
Asian	19 (7.5)	3 (2.1)	
Other	5 (2.0)	5 (3.4)	
Marital status			0.013
Married	192 (75.3)	89 (61.0)	
Single	20 (7.8)	11 (7.5)	
Separated/divorced	25 (9.8)	26 (17.8)	
Widowed	17 (6.7)	16 (11.0)	
Other	1 (0.4)	4 (2.7)	
Years of education completed			0.23
≤ 8 years	24 (9.4)	21 (14.4)	
9-12 years	71 (27.8)	42 (28.8)	
≥ 13 years	148 (58.0)	75 (51.4)	
Missing	12 (4.7)	8 (5.5)	
Insurance status			0.44
Private	17 (6.7)	9 (6.2)	
Public/state	64 (25.1)	30 (20.5)	
Other	1 (0.4)	1 (0.7)	
Missing	173 (67.8)	106 (72.6)	
Current smoker			0.10
No	193 (75.7)	99 (67.8)	
Yes	62 (24.3)	47 (32.2)	
Comorbidities			0.0006
No	88 (34.5)	27 (18.5)	
Yes	167 (65.5)	119 (81.5)	
Cardiovascular comorbidities			0.83
No	126 (49.4)	69 (47.3)	
Yes	129 (50.6)	77 (52.7)	
Respiratory comorbidities			0.55
No	221 (86.7)	123 (84.2)	
Yes	34 (13.3)	23 (15.8)	

Gastrointestinal comorbidities			> 0.99
No	241 (94.5)	136 (93.2)	
Yes	14 (5.5)	10 (6.8)	
Renal comorbidities			> 0.99
No	254 (99.6)	145 (99.3)	
Yes	1 (0.4)	1 (0.7)	
Endocrine comorbidities			> 0.99
No	195 (76.5)	111 (76.0)	
Yes	60 (23.5)	35 (24.0)	
Psychological comorbidities			< 0.0001
No	213 (83.5)	91 (62.3)	
Yes	42 (16.5)	55 (37.7)	
Mild severity	30 (71.4)	41 (74.5)	
Moderate severity	2 (4.8)	2 (3.6)	
Severity NA	10 (23.8)	12 (21.8)	
Rheumatologic comorbidities			0.12
No	240 (94.1)	131 (89.7)	
Yes	15 (5.9)	15 (10.3)	
Neurological comorbidities			0.59
No	234 (91.8)	131 (89.7)	
Yes	21 (8.2)	15 (10.3)	
Headaches			0.001
No headaches	97 (38.0)	41 (28.1)	
Slight headaches infrequently	58 (22.7)	30 (20.5)	
Moderate headaches infrequently	37 (14.5)	17 (11.6)	
Moderate headaches frequently	25 (9.8)	18 (12.3)	
Severe headaches frequently	13 (5.1)	16 (11.0)	
Headaches almost all the time	7 (2.7)	19 (13.0)	
NA	18 (7.1)	5 (3.4)	
Number of ICU days			0.34
0 days	234 (91.8)	131 (89.7)	
1 day	9 (3.5)	9 (6.2)	
≥ 2 days	9 (3.5)	6 (4.1)	
BMI, mean	28.3 (5.7)	29.6 (6.7)	0.047
BMI, median	27.4 (24.5-31.1)	28.7 (25.1-32.3)	
BMI (categorical)			0.19
< 18.5	4 (1.6)	0 (0.0)	
18.5-25	74 (29.0)	35 (24.0)	
25-30	99 (38.8)	55 (37.7)	
≥ 30	76 (29.8)	55 (37.7)	
Baseline Nurick score			0.44
Grade I	11 (4.3)	4 (2.7)	
Grade II	53 (20.8)	22 (15.1)	
Grade III	115 (45.1)	63 (43.2)	
Grade IV	55 (21.6)	40 (27.4)	
Grade V	17 (6.7)	15 (10.3)	
Grade VI	3 (1.2)	2 (1.4)	
Baseline MJOA score	12.9 (2.7)	12.3 (2.4)	0.034
Baseline NDI score	35.5 (19.7)	48.7 (20.7)	< 0.0001
Baseline SF-36 aggregate physical subscore	35.7 (10.1)	32.4 (9.1)	0.0014

Baseline SF-36 aggregate mental subscore	43.7 (13.1)	36.8 (14.4)	< 0.0001
Baseline SF-36 Bodily Pain score	38.3 (11.5)	32.1 (9.5)	< 0.0001
Baseline SF-36 EM score	43.5 (12.5)	36.7 (13.4)	< 0.0001
Baseline SF-36 EN score	42.7 (11.1)	38.4 (11.4)	0.0003
Baseline SF-36 General Health score	44.5 (10.3)	41.1 (10.8)	0.0025
Baseline SF-36 Physical Functioning score	33.4 (12.6)	30.2 (11.1)	0.01
Baseline SF-36 Role-Emotional score	37.4 (16.2)	31.4 (16.2)	0.0006
Baseline SF-36 Role-Physical score	33.1 (12.4)	28.4 (10.6)	0.0001
Baseline SF-36 Social Functioning score	38.7 (12.6)	31.4 (12.9)	< 0.0001
Baseline walk test score, mean	30.2 (9.7)	32.6 (15.0)	0.38
Baseline walk test score, median	29.3 (22.7-35.2)	28.7 (24.3-38.0)	

Categorical covariates are N (%); continuous covariates are Mean (SD), or Median (IQR) where noted.
p-value from t-test or Fisher's exact test, as appropriate
Baseline use defined as use of pain medication 90 days or fewer before surgery.

Patients using opioids were more likely to be female, and have comorbidities, especially psychological comorbidities, and less likely to be married. They were also more likely to suffer from frequent or debilitating headaches. Patients using opioids at baseline had lower baseline scores on a wide range of patient-derived functional measures, including the NDI score and all subscores of the SF-36. Of the 146 patients who used opioids at baseline, 139 (95.2%) were still taking them more than 90 days after surgery. In measures confined to lower extremity function, both patient-reported (Nurick) and observer measured (the Walk Test), no significant difference was found between patients who did and did not use opioids preoperatively.

Similar differences in preoperative patient-derived measures were seen in patients who used opioids long-term postoperatively compared to those who did not use opioids long-term. **(Table 3)**

Table 3: Demographic Characteristics and Patient Derived Outcomes of Study Participants by Post-operative Pain Medication Use (N = 401)

	Long-term pain medication use (N = 185)	No long-term pain medication use (N = 216)		p-value
		Baseline use of pain meds (N = 7)	No baseline use of pain meds (N = 209)	
Age (years)				0.076
Mean (SD)	56.2 (11.4)	54.4 (10.0)	58.4 (12.1)	
Age (categorical)				0.54
≤ 40	16 (8.6)	0 (0.0)	13 (6.2)	
41-50	43 (23.2)	4 (57.1)	41 (19.6)	
51-60	59 (31.9)	1 (14.3)	69 (33.0)	
61-70	45 (24.3)	1 (14.3)	50 (23.9)	
> 70	22 (11.9)	1 (14.3)	36 (17.2)	
Sex				0.0011
Female	93 (50.3)	4 (57.1)	69 (33.0)	
Male	92 (49.7)	3 (42.9)	140 (67.0)	
Race/ethnicity				0.064
White	161 (87.0)	5 (71.4)	165 (78.9)	
Black	15 (8.1)	1 (14.3)	18 (8.6)	
Native American	1 (0.5)	0 (0.0)	1 (0.5)	
Asian	4 (2.2)	0 (0.0)	18 (8.6)	
Other	4 (2.2)	1 (14.3)	5 (2.4)	
Marital status				0.002
Married	111 (60.0)	5 (71.4)	165 (78.9)	
Single	16 (8.6)	0 (0.0)	15 (7.2)	
Separated/divorced	35 (18.9)	2 (28.6)	14 (6.7)	
Widowed	19 (10.3)	0 (0.0)	14 (6.7)	
Other	4 (2.2)	0 (0.0)	1 (0.5)	
Years of education completed				0.28
≤ 8 years	26 (14.1)	0 (0.0)	19 (9.1)	
9-12 years	51 (27.6)	6 (85.7)	56 (26.8)	
≥ 13 years	97 (52.4)	1 (14.3)	125 (59.8)	
Missing	11 (5.9)	0 (0.0)	9 (4.3)	
Insurance status				0.31
Private	14 (7.6)	1 (14.3)	11 (5.3)	
Public/state	37 (20.0)	1 (14.3)	56 (26.8)	
Other	1 (0.5)	0 (0.0)	1 (0.5)	
Missing	133 (71.9)	5 (71.4)	141 (67.5)	
Current smoker				0.056
No	126 (68.1)	4 (57.1)	162 (77.5)	
Yes	59 (31.9)	3 (42.9)	47 (22.5)	
Comorbidities				0.0002
No	36 (19.5)	2 (28.6)	77 (36.8)	
Yes	149 (80.5)	5 (71.4)	132 (63.2)	
Cardiovascular comorbidities				0.56
No	87 (47.0)	5 (71.4)	103 (49.3)	
Yes	98 (53.0)	2 (28.6)	106 (50.7)	
Respiratory comorbidities				0.13
No	152 (82.2)	6 (85.7)	186 (89.0)	
Yes	33 (17.8)	1 (14.3)	23 (11.0)	

Gastrointestinal comorbidities				0.33
No	173 (93.5)	7 (100.0)	197 (94.3)	
Yes	12 (6.5)	0 (0.0)	12 (5.7)	
Renal comorbidities				> 0.99
No	184 (99.5)	7 (100.0)	208 (99.5)	
Yes	1 (0.5)	0 (0.0)	1 (0.5)	
Endocrine comorbidities				0.55
No	136 (73.5)	6 (85.7)	164 (78.5)	
Yes	49 (26.5)	1 (14.3)	45 (21.5)	
Psychological comorbidities				< 0.0001
No	121 (65.4)	5 (71.4)	178 (85.2)	
Yes	64 (34.6)	2 (28.6)	31 (14.8)	
Mild severity	47 (73.4)	0 (0.0)	24 (77.4)	
Moderate severity	1 (1.6)	1 (50.0)	2 (6.5)	
Severity NA	16 (25.0)	1 (50.0)	5 (16.1)	
Rheumatologic comorbidities				0.16
No	166 (89.7)	7 (100.0)	198 (94.7)	
Yes	19 (10.3)	0 (0.0)	11 (5.3)	
Neurological comorbidities				0.66
No	169 (91.4)	6 (85.7)	190 (90.9)	
Yes	16 (8.6)	1 (14.3)	19 (9.1)	
Headaches				0.0005
No headaches	50 (27.0)	2 (28.6)	86 (41.1)	
Slight headaches infrequently	38 (20.5)	3 (42.9)	47 (22.5)	
Moderate headaches infrequently	26 (14.1)	1 (14.3)	27 (12.9)	
Moderate headaches frequently	22 (11.9)	0 (0)	21 (10.0)	
Severe headaches frequently	19 (10.3)	0 (0)	10 (4.8)	
Headaches almost all the time	22 (11.9)	0 (0)	4 (1.9)	
NA	8 (4.3)	1 (14.3)	14 (6.7)	
Number of ICU days				0.21
0 days	168 (90.8)	6 (85.7)	191 (91.4)	
1 day	11 (5.9)	0 (0.0)	7 (3.3)	
≥ 2 days	6 (3.2)	1 (14.3)	8 (3.8)	
BMI, mean	29.3 (6.5)	31.3 (6.6)	28.2 (5.7)	0.08
BMI, median	28.2 (25.0-31.9)	28.7 (28.1-34.2)	27.3 (24.4-30.5)	
BMI (categorical)				0.37
< 18.5	1 (0.5)	0 (0.0)	3 (1.4)	
18.5-25	46 (24.9)	1 (14.3)	62 (29.7)	
25-30	67 (36.2)	3 (42.9)	84 (40.2)	
≥ 30	70 (37.8)	3 (42.9)	58 (27.8)	
Baseline Nurick score				
Grade I	5 (2.7)	0 (0.0)	10 (4.8)	
Grade II	33 (17.8)	1 (14.3)	41 (19.6)	
Grade III	80 (43.2)	3 (42.9)	95 (45.5)	
Grade IV	48 (25.9)	2 (28.6)	45 (21.5)	
Grade V	16 (8.6)	1 (14.3)	15 (7.2)	
Grade VI	3 (1.6)	0 (0.0)	2 (1.0)	0.80
Baseline MJOA score	12.6 (2.5)	11.9 (1.6)	12.7 (2.8)	0.58

Baseline NDI score	47.5 (20.2)	41.7 (12.1)	34.0 (20.0)	< 0.0001
Baseline SF-36 aggregate physical subscore	32.4 (8.8)	37.8 (8.5)	36.2 (10.4)	0.0001
Baseline SF-36 aggregate mental subscore	37.8 (14.0)	33.2 (13.1)	44.4 (13.2)	< 0.0001
Baseline SF-36 Bodily Pain score	32.2 (9.1)	38.0 (13.2)	39.3 (11.7)	< 0.0001
Baseline SF-36 EM score	37.7 (13.1)	35.5 (11.2)	44.0 (12.8)	< 0.0001
Baseline SF-36 EN score	38.7 (10.9)	40.1 (14.4)	43.3 (11.3)	< 0.0001
Baseline SF-36 General Health score	41.1 (10.6)	42.8 (10.2)	45.2 (10.3)	0.0002
Baseline SF-36 Physical Functioning score	30.6 (10.8)	32.5 (15.2)	33.7 (13.1)	0.011
Baseline SF-36 Role-Emotional score	32.0 (16.0)	27.4 (11.4)	38.3 (16.4)	0.0004
Baseline SF-36 Role-Physical score	28.8 (10.4)	31.1 (11.9)	33.6 (12.9)	0.0001
Baseline SF-36 Social Functioning score	32.4 (12.9)	30.5 (11.7)	39.4 (12.7)	< 0.0001
Baseline walk test score, mean	32.3 (13.9)	46.3 (NA)	29.8 (9.8)	0.36
Baseline walk test score, median	30.0 (23.8-37.0)	46.3 (46.3-46.3)	29.3 (21.7-35.0)	

Categorical covariates are N (%); continuous covariates are Mean (SD), or Median (IQR) where noted.
p-value from t-test or Fisher's exact test, as appropriate
Long-term pain medication use defined as use of pain medication 90 days or greater after surgery.
p-value compares patients with long-term use and those who did not use long-term (regardless of baseline use).

Table 4 presents details of comorbidity categories among patients using opioids at baseline. The most common comorbidities were hypertension (45.2%), followed by psychiatric (37.7%), gastrointestinal (28.8%), and endocrine/diabetes (24.0%).

Table 4: Comorbidities Among Participants Using Pain Medications at Baseline (N = 146)

Comorbidity	**N**	**%**
Cardiovascular System	77	52.7
Myocardial Infarct	5	3.4
Angina	11	7.5
Congestive Heart Failure	4	2.7
Arrhythmias	5	3.4
Hypertension	66	45.2
Venous Disease	2	1.4
Peripheral Arterial Disease	3	2.1
Respiratory System	23	15.8
Gastrointestinal System	42	28.8
Hepatic	2	1.4
Stomach/Intestine	28	19.2
Pancreas	0	0

Renal System	7	4.8
Endocrine/Diabetes	35	24.0
Psychiatric	55	37.7
Rheumatologic	15	10.3
Neurological System	15	10.3
Stroke	4	2.7
Paralysis	0	0
Neuromuscular	5	3.4

The performances of three possible models were compared to predict the long-term (i.e., 90 days or more post-surgery) use of pain medications. The covariates of the three models are shown in **Table 5**.

Table 5: Covariates Selected for Inclusion in Predictive Models

Covariate	**Model 1**	**Model 2**	**Model 3**
Age (continuous)			
Age (categorical)			X
Race			
Sex			X
Education			
Marital status			
Height			X
Weight			
Indicator of any comorbidity			
Indicator of baseline cardiovascular comorbidities			
Indicator of baseline respiratory comorbidities			
Indicator of baseline gastrointestinal comorbidities			
Indicator of baseline renal comorbidities			
Indicator of baseline endocrine comorbidities			
Indicator of baseline psychiatric comorbidities			
Indicator of baseline rheumatologic comorbidities			X
Indicator of baseline neurological comorbidities			
Prior cervical operation (for something other than CSM)			
Patient on supplemental oxygen			
Current smoker			
Number of ICU days (0, 1, or ≥ 2 days)			
CSM duration			
Baseline pain medication use (90 or fewer days before surgery)	X	X	X
Baseline Nurick score			
Baseline MJOA score			
Baseline SF-36 Bodily Pain (BP) score			X
Baseline SF-36 General Health (GH)			X
Baseline SF-36 Physical Functioning (PF)			

Baseline SF-36 Role-Emotional (RE)			
Baseline SF-36 Role-Physical (RP) score			
Baseline SF-36 Social Functioning (SF)			
Baseline EM score			
Baseline EN score			
Baseline Neck Disability Index (NDI) score		X	
C-statistic	0.86	0.90	0.90

In a validation dataset consisting of 40% of subjects, Model 1 had a C-statistic of 0.86, while Models 2 and 3 both had a C-statistic of 0.90. **(Figure 2)** The difference in the ability to predict postoperative opioid use was minimal between the relatively simple Model 2 using only preoperative opioid use and baseline NDI score and Model 3 which incorporated over 30 covariates. Calibration of each predictive model was assessed graphically using the validation dataset. **(Figure 1)**

After evaluation of each predictive model, final parameter estimates were obtained using the full dataset. The predicted probability of long-term pain medication use more than 90 days after surgery is equal to $\frac{e^Y}{1+e^Y}, where$

For Model 1:

$Y = -1.51 + 4.50 * I(baseline\ pain\ med\ use)$

For Model 2:

$Y = -2.35 + 4.51 * I(baseline\ pain\ med\ use) + 0.021 * BL\ NDI\ score$

For Model 3:

$$Y = -5.16 - 0.57 * I(male) + 0.11 * height + 0.97 * I(rheumatologic\ comorbidities) + 4.81 * I(baseline\ pain\ med\ use) - 0.052 * BL\ BP\ score - 0.024 * BL\ GH\ score - 0.80 * I(age\ 40-50) - 0.70 * I(age\ 50-60) - 0.34 * I(age\ 60-70) - 1.29 * I(age\ 70-100)$$

Thus, a 45-year-old woman who was 65 inches tall, with a baseline SF-36 BP and GH score of 30, and a baseline NDI score of 45, who did not have rheumatologic comorbidities, but did use pain medications at baseline, would have a predicted probability of long-term use of 0.95, 0.96, and 0.98 under Models 1, 2, and 3, respectively. The prediction under each model differed only slightly, since the most important characteristic—use of opioids at baseline—was included in all predictive models.

Under Model 1:

Y = -1.51 + 4.50 = 2.99

$\frac{e^{2.99}}{1+e^{2.99}} \approx 0.95$ probability

Under Model 2:

Y = -2.35 + 4.51 + 0.021*45 = 3.11

$\frac{e^{3.11}}{1+e^{3.11}} \approx 0.96$ probability

Under Model 3:

Y = -5.16 + 0.11*65 + 4.81 - 0.052*30 – 0.024*30 – 0.80 = 3.72

$\frac{e^{3.72}}{1+e^{3.72}} \approx 0.98$ probability

The difference in the ability to predict postoperative opioid use was minimal between the relatively simple Model 2 using only preoperative opioid use and baseline NDI score and Model 3 which incorporated over 30 covariates. Both had a C statistic of .90 in the validation data set.

2.3 Discussion

A number of studies have analyzed the role opioid medications play in determining the outcomes of both surgical and nonsurgical treatment of spine problems. Lee et al.[3] prospectively examined data from patient-derived outcomes from the Vanderbilt Spine Registry on 593 patients who underwent cervical, thoracolumbar and lumbar procedures. The measures they analyzed included the SF12 Physical Component Score, SF12 Mental Component Score, Oswestry Disability Index, Neck Disability Index, and EQ-5D. Linear regression analysis of the data revealed a negative relationship between the size of the daily dose of preoperative opioids and the self-reported outcomes. A subsequent study involving the same cohort found that patients on large dosages of opioids preoperatively, compared to those not on large dosages preoperatively, were less likely to be opioid independent 12 months after surgery than those not on opioids.[42] These investigators recommended that patients who are taking large dosages of opioids preoperatively should consider "decreasing or eliminating" opioid use prior to surgery.

Opioids have been found to have a large impact on outcomes and costs for workers' compensation.[43-47] Bernacki et al. reported a dramatic increase in the use of opioids to treat chronic pain in injured workers in the Louisiana Workers' Compensation System from 1999 to 2009. Much of the increase was attributed to an increase in prescription of long-acting opioids.[43]

Franklin et al. found little correlation between increasing dosage and improvement in pain or function in a small percentage of patients from the Washington State Workers' Compensation System with work-related low back pain who were taking opioids one year after their injuries.[46] The authors did not report which patients, if any, underwent surgical treatment. In addition, the authors found only 25% of prescribing physicians provided appropriate documentation to justify continuing or increasing opioid dosages.[45] These same investigators observed a marked decrease in the prescription of long-acting opioids after new guidelines were implemented in 2007.[45-48]

Few studies have examined the relationship between opioid narcotics and treatment of cervical myelopathy. In the medical literature, pain is not usually listed as one of the classic hallmarks of cervical myelopathy. When describing this condition, most investigators focus on functional neurological deficits and corroborating findings on imaging studies. However, because the pathologic process that leads to cervical myelopathy is the same as that for typically painful cervical disorders, it is possible that pain is an underreported symptom.[19] The 36% prevalence of opioid use preoperatively in this study is only about 10 to 20% less than that found in multiple other analyses of outcomes of surgical treatment of a variety of degenerative spinal conditions that are usually associated with pain.[3] In one series, 81% of patients diagnosed with cervical

myelopathy included pain as one of their symptoms. The only symptom that was more common was upper extremity numbness.[48]

Tetreault et al. developed a predictive model for outcomes in patients with cervical myelopathy undergoing surgical treatment.[49] In their study, logistic regression modeling revealed that psychological comorbidities, baseline mJOA scores, age, impairment of gait, smoking, symptom duration, and area of cord in mm^2 on imaging studies all were significant factors in the outcome. Although pain levels and opioid use were not included in this analysis, the finding of a correlation with psychological comorbidities could imply a role for opioid medications. Narcotic dependency is more common in patients with mental illnesses, because patients with mental illness sometimes find that opioids ease their symptoms.[50]

Our analysis was limited to the relationship between the pre- and postoperative use of opioid narcotics and preoperative patient-derived functional outcomes. Our results could have been confounded by the presence of other painful conditions that we did not gather information on for which opioids were used both pre- and postoperatively. However, the finding of a low preoperative prevalence of a broad range of comorbidities that are associated with pain in this group mitigates the likelihood of this effect.

A large sample size and the prospective design are the main strengths of this study. Unfortunately, detailed data on the opioid dosages and the daily morphine equivalent amounts were not recorded in this series. Still unknown is the effect, if any, surgery had on the total amount of opioid medication taken postoperatively. In addition, the postoperative prevalence of

opioid use was only reported at three months after surgery. It is possible that at least some of the patients who were using opioids at that time subsequently experienced improvement in their pain and discontinued use.

The surgical procedures used to treat cervical myelopathy typically involve spinal decompression and fusion, using an anterior or posterior approach. Because these are major procedures that can have serious complications,[37] it behooves both patients and surgeons to consider surgical treatment only when it is clearly necessary. The diagnosis of cervical myelopathy and the choice of treatment for this condition are usually made by the treating surgeon and are based on mostly subjective findings. It is not clear from most reported analyses of surgical treatment of cervical myelopathy whether or not pain was a factor in the decision-making process.[29] If surgeons consider pain in making decisions, the preoperative use of opioids could have a confounding effect on outcomes by virtue of their well-known ability to distort the perception of pain. Unfortunately, the data available for this study did not allow for determination of whether or not pain was a significant factor in the clinical decision to do surgery.

In this investigation, the patient-reported preoperative functional and psychological scores were significantly different between patients who were taking opioid narcotics preoperatively and those who were not. Surgical treatment for cervical myelopathy had minimal effect on the prevalence of use of opioid analgesics in this group of patients. Surgeons should consider this finding, especially if they are using pain as one of the indications for performing major surgery for cervical myelopathy. The findings of this study raise the question of whether or not

decreasing or eliminating opioid use before surgical decompression and fusion for cervical myelopathy could obviate the need for surgery in some cases. Future studies should examine this possible factor in more detail.

The state of opioid use in the U.S. in 2015 is all too reminiscent of 1910.[1] Nearly 20 years after the liberalization of opioid prescription laws, it remains unclear that chronic non-cancer pain can be treated effectively and at acceptable risk with the opioid narcotics available today.[6] Preoperative opioid use should be considered a potential confounder in the outcome of any surgical procedure performed to relieve pain.

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