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Prolonged Opioid Use Among Opioid-Naive Women Undergoing Breast Reconstructive Surgery

Ankhita R. Samuel, MD[1] Laura Fuhr, BS[1] Brent R. DeGeorge Jr, MD, PhD[1] Jonathan Black, MD[1] Christopher Campbell, MD[1] John T. Stranix, MD[1]

[1] Department of Plastic Surgery, University of Virginia, Charlottesville, Virginia

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Address for correspondence John T. Stranix, MD, Department of Plastic Surgery, University of Virginia, Box 800376, Charlottesville, VA 22903 (e-mail: JTS3V@hscmail.mcc.virginia.edu).

Abstract

Background Patients that undergo mastectomy for breast cancer with reconstruction may be prone to prolonged opioid use. As risk factors are not well-established, this article sought to better understand the risk factors that may be associated with this.

Methods Patients that underwent breast reconstruction between 2010 and 2018 were identified in PearlDiver, a national insurance claims database. Patient demographics and comorbidities were elucidated, and various complications were then identified. Descriptive statistics as well as a multivariate analysis was used to evaluate the association of risk factors and complications.

Results Breast reconstruction patients of 24,765 were identified from this database. Obesity, tobacco use, benzodiazepine use, and anticonvulsant use were all associated with prolonged opioid prescriptions greater than 90 days after both alloplastic and autologous reconstruction.

Conclusion Prolonged opioid use continues to remain a topic of concern, and particularly in cancer patients that undergo breast reconstruction. Providers should be aware of potential risk factors for this to reduce this chance following breast reconstruction surgery.

Keywords
- prolonged opioid use
- breast reconstruction
- risk factors

The most recent wave of deaths secondary to opioid overdose has been secondary to synthetic opioids, both prescribed as well as illicitly manufactured.[1] Given the extent of harm that may arise, the burden of prescribing responsibly has never been greater. At the same time providers have a responsibility to manage their patients' pain, specifically among breast cancer patients who historically experience large amounts of pain.[2–4] Prolonged opioid use following mastectomy is a risk for those undergoing breast cancer curative surgery, even among those who are opioid-naive.[5,6] Additional risk factors include preoperative opioid use, daily oral morphine equivalent prescriptions at discharge, and patient demographics including younger age and psychiatric illness.[4] Additionally, as 24% of patients opt to undergo immediate reconstruction within 4 months and reconstruction is associated with improved quality of life after breast cancer surgery, understanding the risks associated with opioid use following the procedures as they become increasingly popular is paramount.[7–11] This study aims to build upon previous work looking at opioid usage among patients undergoing

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mastectomy with reconstruction by comparing autologous and alloplastic reconstruction following mastectomy with regards to risk for perioperative and prolonged opioid use. The purpose of this study was to elucidate the factors that may lead to postoperative opioid use across both alloplastic and autologous patient populations. We will also analyze other risk factors including patient demographics, comorbidities, and medications. Additionally, this study compares secondary outcomes of 30-day all-cause emergency department visits and hospital admissions between the two cohorts.

Methods

A commercially available, proprietary, national insurance claims-based database, PearlDiver Patients Records Database (www.pearldiverinc.com; PearlDiver Inc., Colorado Springs, CO) was used for this investigation. PearlDiver contains patient records, which are deidentified, 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. Accordingly, queries resulting in less than 11 patients are not indicated to protect patient privacy. The database contains patient demographics, comorbidities, diagnoses, procedures, and medications among numerous other data available for patients which may be queried via International Classification of Diseases, 9th revision (ICD-9) and 10th revision (ICD-10) and procedures or Current Procedural Terminology (CPT) codes. The database information spans all U.S. patients insured from 2010 to 2018, and patients can be tracked across all locations (inpatient, outpatient, etc.) throughout the database years, and contains approximately 20 million patients.

CPT codes for patients with a first instance of alloplastic or autologous breast reconstruction were collected (►**Supplementary Table S1**, available in the online version). Patients were filtered for the presence of valid age and gender and region information as well as the presence of claims data available for 6 months prior to 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 and 6 months prior to the operation. The month prior to the operation was not included to reduce the risk of identifying patients filling a prescription in advance in the setting of the planned surgical procedure. Additionally, patients with opioid use disorder or active methadone prescription were excluded from the cohort.

General comorbidity information, risk factors for postoperative pain, and medications, including anticonvulsants, antidepressants, benzodiazepines, and muscle relaxants, were collected as described in ►**Supplementary Table S1** (available in the online version). Demographic data on age, sex, and treatment region were reported by the database.

Perioperative opioid medications were defined by the presence of a filled opioid prescription between 1 month prior to and 2 weeks following the operative procedure (►**Table 1**). Prolonged postoperative opioid use was defined as the presence of a filled opioid prescription between 90 and 180 days following the operative procedure. Opioid prescription information and opioid oral morphine milligram equivalent (MME) units were calculated by daily average per patient.

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 then 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 prolonged opioid prescriptions in alloplastic and autologous

Table 1 Opioid prescribing patterns and utilization following breast reconstruction

Variable	Alloplastic ($n = 21,330$)	Autologous ($n = 3,435$)	*p*-Value
Perioperative opioids			
No. of patients (%)	13,729 (64.4)	2,126 (61.9)	0.005[a]
Average daily dose MME	127.39	116.69	
Average MME	357.34	408.95	
Average prescription days	6.97	7.42	
Prolonged postoperative opioids			
No. of patients (%)	10,021 (46.7)	1,739 (50.6)	< 0.001[a]
Average daily dose MME	140.26	129.82	
Average MME	808.88	871	
Average prescription days	15.63	15.71	

Abbreviation: MME, morphine milligram equivalent.
Note: 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.
[a]Statistically significant, $p < 0.05$.

Table 2 Multivariate logistic regression of prolonged opioid prescriptions

Factor	Alloplastic		Autologous	
	OR (95% CI)	*p*-Value	OR (95% CI)	*p*-Value
Demographics				
CCI > 1	0.94 (0.86–1.03)	0.19	1.75 (1.49–2.03)	< 0.001[a]
CCI > 3	0.93 (0.79–1.09)	0.35	1.08 (0.84–1.39)	0.52
Age > 65 y	1.15 (1.07–1.23)	<0.001[a]	1.77 (1.51–2.10)	< 0.001[a]
Age < 40 y	1.30 (1.18–1.44)	< 0.001[a]	1.83 (1.46–2.28)	< 0.001[a]
Comorbidities				
Diabetes	1.04 (0.97–1.10)	0.26	1.07 (0.95–1.20)	0.25
Hypertension	1.04 (0.98–1.09)	0.19	1.08 (0.97–1.21)	0.15
Obesity	1.12 (1.06–1.19)	< 0.001[a]	1.32 (1.18–1.47)	< 0.001[a]
Tobacco use	1.22 (1.16–1.30)	< 0.001[a]	1.18 (1.06–1.32)	0.003[a]
Medications				
Benzodiazepine	2.19 (2.08–2.31)	< 0.001[a]	1.33 (1.19–1.48)	< 0.001[a]
Anticonvulsant	1.46 (1.39–1.54)	< 0.001[a]	1.43 (1.29–1.59)	< 0.001[a]

Abbreviations: CCI, Charlson Comorbidity Index; CI, confidence interval; OR, odds ratio.
[a]Statistically significant, $p < 0.05$.

patients (►**Table 2**, ►**Fig. 1**). Odds ratios (ORs) were calculated from the regression analysis, and a corresponding 95% confidence interval (CI) and *p*-value was also calculated for each patient-related risk factor. For all statistical calculations, $p < 0.05$ was considered statistically significant.

Results

We identified 24,765 opioid-naive adult patients who underwent alloplastic or autologous breast reconstruction between 2010 and 2018 (►**Table 3**). The majority of patients within this database underwent alloplastic reconstruction ($n = 21,330$, 86%). The majority of patients across both patient populations fell under the ages of 40 to 59 at 12,472 (58%) for alloplastic and 2,297 for autologous (65%). Our univariate analysis demonstrated that patients who underwent autologous reconstruction had a significantly higher rate of diabetes, hypertension, tobacco use, and depression (►**Table 3**). Accordingly, patients who underwent autologous reconstruction had a higher Charlson Comorbidity Index (CCI; 3.38 vs. 2.54).

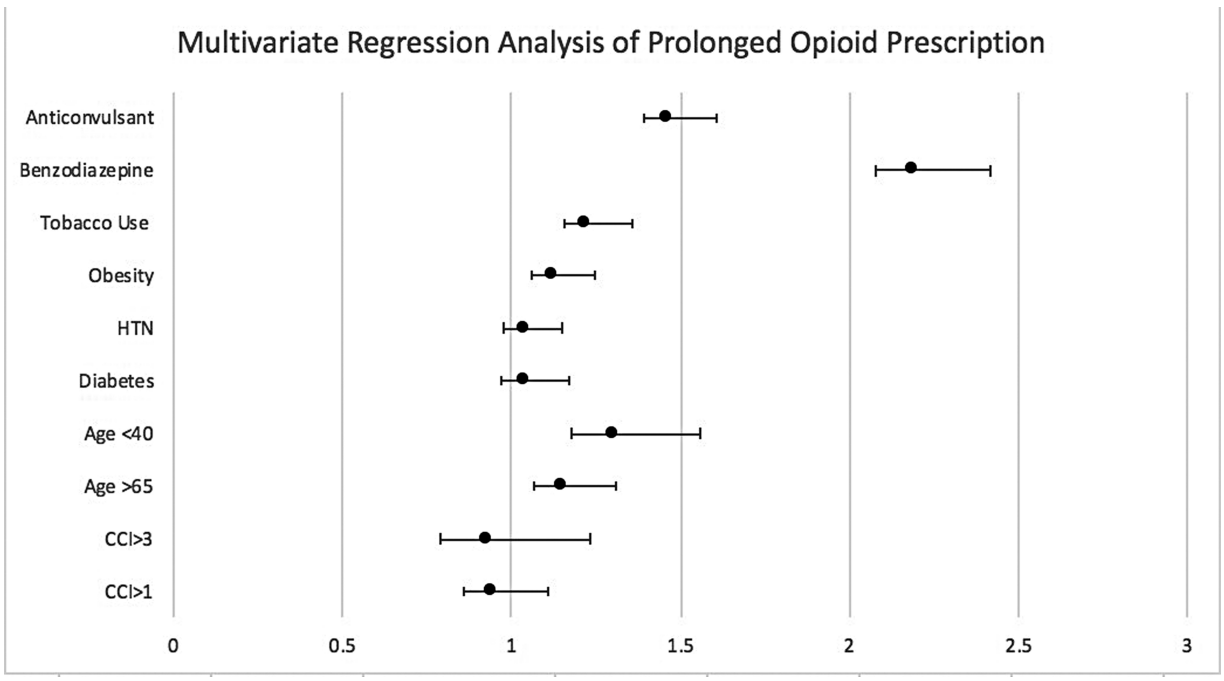

Fig. 1 Multivariate regression analysis of prolonged opioid prescription. HTN, hypertension; CCI, Charlson Comorbidity Index.

Table 3 Demographics and patient factors of opioid-naive breast reconstruction patients

Variable	Alloplastic ($n = 21,330$)	Autologous ($n = 3,435$)	*p*-Value
Age (y)			
< 40	3,039 (14.2)	462 (13.4)	
40–49	5,487 (25.7)	934 (27.2)	
50–59	6,985 (32.7)	1,293 (37.6)	
60–69	4,993 (23.4)	753 (21.9)	
70–79	1,744 (8.2)	146 (4.3)	
≥ 80	31 (0.1)	#	
Sex			
Male	8	7	0.001[a]
Female	21,322	3,428	
Region			
Midwest	5,158 (24.2)	820 (23.8)	0.69
Northeast	4,537 (21.3)	752 (21.9)	0.41
South	8,432 (39.5)	1,470 (42.8)	0.0003[a]
West	3,203 (15.0)	393 (11.4)	< 0.001[a]
Comorbidities			
Asthma	2,580 (12.1)	436 (12.7)	0.33
Congestive heart failure	738 (3.5)	140 (4.1)	0.08
Coronary artery disease	2,383 (11.2)	420 (12.2)	0.07
Chronic kidney disease	1,169 (5.5)	193 (5.6)	0.77
Chronic obstructive pulmonary disease	4,865 (22.8)	819 (23.8)	0.19
Diabetes mellitus	5,198 (24.4)	982 (28.6)	< 0.001[a]
Hypertension	10,568 (49.5)	1,819 (53.0)	0.002[a]
Obesity	5,783 (27.1)	1,169 (34.0)	< 0.001[a]
Tobacco use	4,486 (21.0)	794 (23.1)	0.006[a)]
Alcohol use	675 (3.2)	115 (3.3)	0.61
Depression	8,644 (40.5)	1,481 (43.1)	0.004[a]
Anxiety	5,652 (26.5)	856 (24.9)	0.05
Fibromyalgia	3,267 (15.3)	554 (16.1)	0.23
Back pain	5,430 (25.5)	869 (25.3)	0.86
Medications			
Benzodiazepine	13,024 (61.0)	1,951 (56.8)	< 0.001[a]
Muscle relaxant	10,773 (50.5)	1,755 (51.1)	0.54
Anticonvulsant	7,394 (34.7)	1,304 (38.0)	0.0002[a]
Antidepressant	12,613 (59.1)	2,011 (58.5)	0.53
Charlson Comorbidity Index	2.54 ± 2.83	3.38 ± 3.12	

Note: Values are presented as the number (%) or mean ± standard deviation (SD).
[a]Statistically significant, $p < 0.05$.

The alloplastic patients (13,729, 64%) filled at least one perioperative prescription between 1 month prior and 2 weeks following the operative procedure (►**Table 1**). Of those that filled a prescription, the average daily dose MME was 127.39 for a prescription of 6.97 days on average. Of those undergoing autologous reconstruction, 2,126 (61.9%) filled at least one prescription with an average daily dose MME of 116.69 for an average of 7.42 prescription days. Additionally, 10,021 (46.7%) of alloplastic and 1,739 (50.6%) of autologous patients met the criteria for prolonged post-operative opioid use by filling a prescription between 90 and 180 days after the operation.

Table 4 Ninety-day all cause emergency department and hospital admissions

	Alloplastic ($n = 21,330$)	Autologous ($n = 3,435$)	*p*-Value
Emergency department visits	2,209 (10.4)	434 (12.6)	< 0.001[a]
Hospital admissions	1,149 (5.4)	361 (10.5)	< 0.001[a]

Note: Values are presented as the number of patients (%).
[a]Statistically significant, $p < 0.05$.

The measures of 90-day emergency department and hospital admissions are reported in ►**Table 4**. Of the 21,330 patients with alloplastic reconstruction, 2,209 (10.4%) visited the emergency department and 1,149 (5.4%) were admitted to the hospital. Of the 3,435 patients who had autologous reconstruction surgery, 434 (12.6%) visited the emergency department and 361 (10.5%) were admitted to the hospital.

Out of a cohort of over 30,000 patients, PearlDiver extracted the perioperative prescription data for 24,765 of those patients. Bearing this in mind, ►**Table 2** provides the adjusted odds of filling a prolonged opioid prescription among opioid-naive patients across alloplastic as well as autologous populations; this was done excluding patients with a current history of methadone prescription or a diagnosis of opioid use disorder. For the most part, alloplastic and autologous procedures had similar risk factors in requiring a prolonged opioid prescription. Such risk factors included hypertension ($p < 0.001$), tobacco use ($p = 0.003$), and active prescription of benzodiazepines ($p < 0.001$) as well as anticonvulsants ($p < 0.001$). With regard to opioid-naive alloplastic patients that required a prolonged opioid prescription, patients with an active benzodiazepine prescription had the highest ratio at 2.19 (95% CI, 2.08–2.31) (►**Table 2**). Analysis of patient demographics utilizing the CCI showed decreased odds of filling a perioperative opioid prescription with a CCI greater than 1 for autologous patients specifically (OR, 1.75; 95% CI, 1.49–2.03) but no significant effect with a CCI greater than 3 for either patient population.

Adjusted odds were calculated for prolonged opioid prescriptions. Factors associated with the highest ORs of prolonged opioid prescriptions included benzodiazepine medication for both alloplastic (OR, 2.19; 95% CI, 2.08–2.31), as mentioned previously, as well as autologous (OR, 1.33; 95% CI, 1.19–1.48). Anticonvulsant medications were also associated with an increased risk of filling a prolonged opioid prescription for both alloplastic (OR, 1.46; 95% CI, 1.39–1.54) as well as autologous (OR, 1.43; 95% CI 1.29–1.59). Obesity was statistically significant for having a prolonged opioid prescription for alloplastic (OR, 1.12; 95% CI, 1.06–1.19) and autologous (OR, 1.32; 95% CI, 1.18–1.47) reconstruction as was tobacco use (OR, 1.22; 95% CI, 1.16–1.30; OR, 1.18; 95% CI, 1.06–1.32).

Discussion

Both bilateral mastectomy with and without immediate breast reconstruction have the highest pain ratings reported among all breast surgery procedures.[12,13] However, past research has been inconclusive as to whether immediate reconstruction increases risk for prolonged opioid use compared with bilateral mastectomy alone; Woeste et al[4] reported that extent of surgery was not predictive of long-term opioid use, but Shen et al[14] found mastectomy with reconstruction to have higher rates of prolonged opioid use, with 38% of patients who underwent reconstruction and 15% of patients who only underwent mastectomy meeting the criteria for prolonged opioid use. With regard to breast reconstruction, when comparing alloplastic (i.e., implant-based) and autologous (i.e., flap-based) reconstructions, implant-based reconstruction has been associated with higher pain levels and narcotic use in the postoperative hospitalization time period compared with autologous flap-based patients.[7,15–17] Research has shown that higher levels of acute pain following breast reconstruction are associated with higher chronic pain levels and long-term analgesic consumption.[18,19] Marcusa et al[5] previously reported that 10% of opioid-naive women between 2010 and 2014 undergoing immediate breast reconstruction met the criteria for prolonged opioid use, and women with free flap reconstruction were less likely to use opioids at the 90-day benchmark. However, there is also some evidence that long-term pain following breast reconstruction may not be surgically induced, given the high preoperative as well as postoperative pain ratings.[2] The paucity of research in the current literature into the factors, particularly those surrounding specific surgical interventions, creates a gap in the current understanding of what specifically leads to high rates of prolonged opioid use in this patient population. Given that patients who undergo immediate reconstruction are most commonly white, married, and from the Northeast, Midwest, and South where the opioid epidemic has been particularly severe this additional risk stratification by procedure type may provide additional guidance to best serve these patients and minimize risk of prolonged opioid use and/or dependence.[11,20] Breast surgery, especially breast reconstruction, has been associated with chronic pain and high rates of prolonged opioid use as over half of individuals using opioids at the 90-day mark are still using opioids after 5 years.[5,7,14,17–19,21] Our study is particularly relevant given the resurgence of tissue expander placement surgeries; this could change the outcomes for the cohort of patients within the expander pool. Thus, this study aims to identify and compare autologous and alloplastic patients' risk for perioperative and prolonged opioid use following surgery.

Of the 24,765 opioid-naive individuals who underwent breast reconstruction procedures, 74% filled a perioperative opioid prescription and 47% filled an opioid prescription between 90 and 180 days following the operation. Per our univariate analysis, a significant population of patients had comorbidities including diabetes, hypertension, obesity, tobacco use, depression, and used benzodiazepines or anticonvulsants. Although both surgery types were associated with increased odds of meeting the criteria for prolonged opioid prescriptions when controlling for other demographic and comorbidity factors, the risk was fairly consistent among both groups. When controlling for the variables previously listed, it was found that obesity, tobacco use, benzodiazepines, and anticonvulsants were significantly associated with increased risk of prolonged opioid use. These findings suggest that the type of reconstruction performed is not the biggest driver in predicting long-term opioid use. Rather, patient demographics, comorbidities, and concurrent medication use are better predictors of who is most likely to fill an opioid prescription 90 to 180 days after surgery.

These findings are consistent with previous research demonstrating a high association between comorbid conditions and prolonged opioid use across other surgical disciplines including elective orthopaedic surgeries and spinal surgeries.[22,23] Patients with additional comorbidities may have more touchpoints with the medical system and additional indications for chronic pain management, although it is notable that this cohort was limited to opioid-naive individuals. Thus, these patients were not utilizing opioid prescriptions to manage chronic pain prior to their reconstruction procedure.

Adjuvant medications have been suggested as means to reduce the need for opioid analgesics through alternative pain management.[24] Specifically, the use of muscle relaxants has been previously suggested as a means to effectively manage pain following breast reconstruction and reduce the need for opioid analgesics.[25] Our study's findings did not indicate an association between muscle relaxants and prolonged opioid use, and thus muscle relaxants could be considered as part of adjuvant therapy at the provider's discretion. On the other hand, anticonvulsants—particularly gabapentin—have also been previously suggested as adjuvant pain medication therapy; the significantly increased risk of prolonged opioid use in patients also taking anticonvulsant medications in our study is a point of concern.[26]

Given that autologous reconstruction is a bigger initial surgical procedure, the findings of no significant difference in perioperative prescriptions or average daily dose MME was somewhat surprising.[17] However, this reduced perioperative opioid usage did not translate to sustained reduction in risk of prolonged opioid use. Although this study did not specifically compare pain ratings among the two cohort groups, lower perioperative prescription filling among the autologous reconstruction cohort is consistent with research demonstrating higher pain scale ratings and postoperative narcotic consumption in the inpatient setting among alloplastic reconstruction patients.[27] Of note, autologous reconstruction was significantly associated with increased odds of all-cause hospital admission in the 30 days following surgery. This finding warrants further exploration as cause of admission was not captured in this data set.

Finally, although neither reconstruction type was significantly associated with a greater increased risk for prolonged opioid use, the overall rate of prolonged postoperative opioid use was 47% of the entire patient cohort. This rate is comparable to the 38% reported by Shen et al but much higher than the 10% rate of prolonged opioid use beyond 3 months reported by Marcusa et al.[5,14] Given that 64% of the patients filled perioperative prescriptions, this data suggests that most patients who initially filled a perioperative prescription for pain management do not cease filling prescriptions by the 90-day benchmark, a concerning finding. It is possible that the patients with prolonged opioid use had higher rates of complications following surgery or could be indicative that opioids were prescribed for other causes including adjuvant therapy treatment or management of medical comorbidities.

Despite its strengths, our study has many of the limitations that one might expect from a retrospective, databased analysis. The data we captured demonstrates that 74% filled a perioperative opioid prescription and 47% filled an opioid prescription between 90 and 180 days following the operation. These results suggest significantly lower perioperative opioid prescription usage than previously reported in past studies.[4,13,28] This is likely because not all prescriptions provided during an inpatient stay will show up in the claims. Second, this data set did not include pain outcomes at either the immediate postoperative or prolonged stage which could have been used to identify if reported pain levels were consistent with the amount of opioid prescribed immediately following surgery as well as if higher postoperative acute pain was associated with increased risk of prolonged opioid use. The use of regional anesthesia techniques was also not captured and may have had an impact on the observed differences in postoperative pain medication requirements.

Additionally, we were not able to control for adjuvant treatments—such as chemotherapy or radiation—that the patients in the study may have received for the treatment of their breast cancer which could have increased their pain levels following surgery and necessitated chronic pain management. As mentioned prior, the cause of emergency department visits and hospitalizations was not captured and necessitates further investigation to elucidate and strengthen some of the correlations observed in this study. Lastly, we operated under the assumption that the opioid prescriptions filled were indicative of opioid use, but this does not account for the chance the medications were filled but not taken, diverted, or filled for management a separate condition in the case of the prolonged opioid use case.

In this study, we observed that no significant difference was identified between the reconstruction types with regards to prolonged opioid use among opioid-naive patients. Given that both groups had relatively high rates of prolonged opioid use and there were significant associations between several comorbidities and increased risk of prolonged postoperative opioid use, prescribers should be aware of the high risk among

the patient population and employ alternative chronic pain management strategies when possible.

Author Contributions

Conceptualization: A.R.S. and J.T.S. Data curation: A.R.S., J. T.S. Formal analysis: A.R.S., J.T.S. Methodology: J.T.S. Project administration: A.R.S. Visualization: A.R.S. and J.T.S. Writing - original draft: A.R.S. and L.F. Writing - review and editing: L.F., B.R.D.Jr, J.B., C.C., J.S.

Conflict of Interest

None declared.

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