ORIGINAL RESEARCH

Does the Association Between Psychosocial Factors and Opioid Use After Elective Spine Surgery Differ by Sex in Older Adults?

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Purpose: Psychosocial disorders have been linked to chronic postoperative opioid use and the development of postoperative pain. The potential interaction between sex and psychosocial factors with respect to opioid use after elective spine surgery in the elderly has not yet been evaluated. Our aim was to assess whether any observed association of anxiety or depression indicators with opioid consumption in the first 72 hours after elective spine surgery varies by sex in adults ≥65 years.

Patients and Methods: Secondary analysis of a retrospective cohort of 647 elective spine surgeries performed at Brigham and Women's Hospital, July 1, 2015–March 15, 2017, in patients ≥65. Linear mixed-effects models were used to test whether history of anxiety, anxiolytic use, history of depression, and antidepressant use were associated with opioid consumption 0–24, 24–48, and 48–72 post surgery, and whether these potential associations differed by sex.

Results: History of anxiety, anxiolytic use, history of depression, and antidepressant use were more common among women (51.3% of the sample). During the first 24 hours after surgery, men with a preoperative history of anxiety consumed an adjusted mean of 19.5 morphine milligram equivalents (MME) (99.6% CI: 8.1, 31.0) more than men without a history of anxiety; women with a history of anxiety only consumed an adjusted mean 2.9 MME (99.6% CI: −3.1, 8.9) more than women without a history of anxiety (P value for interaction between sex and history of anxiety <0.001). No other interactions were detected between sex and psychosocial factors with respect to opioid use after surgery.

Conclusion: Secondary analysis of this retrospective cohort study found minimal evidence that the association between psychosocial factors and opioid consumption after elective spine surgery differs by sex in adults ≥65.

Keywords: opioids, pain, psychosocial, sex anxiety, depression

Introduction

Spine procedures are among the most frequent surgeries performed in the United States and among the procedures requiring more pain management medication after surgery.[1] Postoperative pain following spine procedures is a common complaint, with persistent pain even after the immediate convalescent period, which can lead to negative impacts on health.[2,3] The adult population over 65 years has various comorbidities related to age, lifestyle and genetics; they are at notable risk for experiencing worth outcomes.[4] Indeed, this issue may become increasingly important, considering that

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the number of people in the United States aged 65 years and over was estimated to be 49.2 million in 2016 and it is projected to increase to 78.2 million people in 2035.[5]

Psychosocial conditions, including anxiety, depression, and catastrophizing have been linked to the development of persistent pain as well as opioid use postoperatively.[6–10] Recent studies suggest that elevated indices of distress such as anxiety, depression, catastrophizing, and enhanced sensitivity to pain are among the strongest predictors of persistent post-surgical pain and that these factors are stronger predictors than surgical variables.[6,9] Such findings suggest that persistent postoperative pain is associated with psychosocial factors that may promote pain sensitization.[8] Moreover, post-surgical pain is a risk factor for adverse opioid-related outcomes, including persistent opioid use and misuse.[11] Several risk factors have been recognized, but tools to identify high-risk patients and preventive interventions are lacking.[10,12] Therefore, even if physicians are encouraged to prescribe as few opioids as possible, it remains essential to properly control post-surgical pain, especially in the first 72 hours to prevent the development of chronic pain.

In spine surgery, opioid use has been associated with greater self-reported disability and poorer function for as long as 12 months following surgery.[13] Sex differences have emerged in risk factors for persistent pain and opioid use after surgery; for example, women have a higher prevalence of anxiety and depression than men and also reported more severe pain than men for a variety of clinical conditions.[14,15] However, in a recent study, preoperative anxiety and depression scores have demonstrated to be better predictors of severe postoperative pain among men compared to women.[16] Failure to control for these comorbid conditions may partially explain differences in pain experiences between men and women and the divergent findings among clinical studies investigating relationships between pain experience, opioid use and gender.

Recent reviews highlight the fact that known risk factors for poor outcomes after spine surgery (eg, preoperative anxiety, depression, opioid use) are unevenly distributed between men and women,[17] and given that we know relatively little about the potential interactions between sex and psychosocial factors with respect to postoperative opioid use, further study is warranted to understand whether men or women patients require greater doses of opioids to ameliorate pain from standard surgical procedures, especially in the geriatric population.

In this secondary analysis of a retrospective cohort study, our aim was to assess whether any observed association of anxiety or depression indicators (history of anxiety, history of depression, anxiolytic use, antidepressant use) with our primary outcome of opioid consumption 0–24, 24–48, and 48–72 hours after elective spine surgery varies by sex in adults 65 years and older. Secondary outcomes included highest pain severity and average pain severity 0–24, 0–24, 24–48, and 48–72 hours postoperatively. Our primary hypothesis was that the association of anxiety or depression indicators with opioid consumption 0–24, 24–48, and 48–72 hours after elective spine surgery differs by sex.

Materials and Methods
Samples
This research was a secondary analysis of a retrospective cohort study that assessed the association between perioperative variables and the development of delirium in 716 men and women 65 years of age and older who underwent cervical, thoracic, lumbar, or sacral/pelvic spine surgery at the Brigham and Women's Hospital between July 1, 2015, and March 15, 2017.[18]

The current study analyzed the subset of 647 patients from this cohort who underwent elective surgery and had all exposure variables of interest recorded. All patients underwent general anesthesia. Regional anesthesia was not provided to any patients. The Mass General Brigham Institutional Review Board (IRB) approved this study of existing medical records and waived the need for patient consent. This manuscript was written in accordance with the STROBE statement[19] and complies with the Declaration of Helsinki.

Measures
Our four exposures of interest were preoperative history of anxiety, anxiolytic use, history of depression, and anti-depressant use as documented in the pre-admission anesthesia evaluation note. Preoperative history was defined as any

point in the patient's lifetime, based on the patient report during the pre-admission anesthesia evaluation or as documented in the electronic medical record. History of anxiety, anxiolytic use, history of depression, and antidepressant use were systematically asked to all patients during the pre-op visit, regardless of gender. Patient sex, as documented in the medical record, was tested for interactions with these anxiety and depression indicators. Additional patient and surgical characteristics included as model covariates were age, BMI, American Society of Anesthesiologist (ASA) Physical Status Classification Index (a risk-stratifying system used to help predict preoperative risks; the system is used to assess a patient's preoperative comorbid conditions and assigns a class ranging from 1 to 6), surgical invasiveness category (defined following the classification developed by Armaghani et al for surgical invasiveness[20,21] with tier 1: microdiscectomy, tier 2: lumbar laminectomy, anterior cervical procedures, or minimally invasive spinal fusions, tier 3: standard or complex lumbar fusion, emergency surgery following trauma, or posterior cervical fusion procedures, and tier 4: surgeries to ameliorate tumor, infection, or deformity, or combined anterior and posterior cervical procedures), reoperation, and preoperative opioid use. The primary study outcome was opioid consumption expressed in intravenous morphine milligram equivalents (MME) 0–24, 24–48, and 48–72 hours postoperatively. Secondary outcomes included highest numeric rating scale (NRS) pain score (0 to 10 scale) and average NRS pain score 0–24, 24–48, and 48–72 hours postoperatively.

Statistical Analysis

The magnitude and direction of differences in patient and surgical characteristics between patients with and without each of the four anxiety and depression indicators and between men and women were quantified as standardized differences.[22] Standardized differences with a magnitude greater than or equal to 0.1 were taken to indicate a notable difference between groups.[23] Linear mixed-effects models were used to test whether the four preoperative anxiety or depression indicators of interest were associated with opioid consumption (primary outcome) or the highest or average pain severity (secondary outcomes) at 0–24, 24–48, and 48–72 hours post spine surgery, and whether these associations differed by sex (ie, whether there were any interactions between sex and anxiety or depression indicators with respect to these outcomes). Mixed-effects models were employed to account for the correlation between repeated outcome measurements on the same patient. Each mixed-effects model included a random intercept for patient ID with a first-order autoregressive (AR[1]) correlation structure. A set of four models separately tested the association of each of the four preoperative anxiety and depression indicators with postoperative opioid consumption assuming these psychosocial factors have the same effect on outcomes across both sexes. These models included terms for preoperative history of anxiety (except when testing anxiolytic use), anxiolytic use (except when testing history of anxiety), history of depression (except when testing antidepressant use), antidepressant use (except when testing history of depression), age, BMI, ASA physical status, surgical invasiveness tier, reoperation, preoperative opioid use, postoperative timepoint, and an interaction between one of the anxiety or depression indicators and postoperative timepoint. To test whether the associations of preoperative anxiety and depression indicators with postoperative opioid consumption differ by sex, a second set of four models expanded upon the first set to include all two-way interactions between sex/anxiety or depression indicator/postoperative timepoint as well a three-way interaction term for sex by anxiety or depression indicator by postoperative timepoint. The potential interaction between sex and each of the four anxiety and depression indicators with respect to postoperative opioid consumption was tested at each of the three postoperative time points, resulting in 12 comparisons. The secondary outcomes of the highest and average NRS pain scores were evaluated in an identical manner to the opioid consumption primary outcome. All multivariable model residuals were approximately normally distributed. To account for 12 comparisons of interest per outcome, all hypothesis tests were evaluated at a Bonferroni-corrected two-sided alpha level of 0.05/12 = 0.004. All statistical analyses were performed using SAS software version 9.4 (SAS Institute, Cary, NC).

Results

A total of 753 patients over 65 years of age were identified who underwent spine surgery at Brigham and Women's Hospital between July 1, 2015, and March 15, 2017. After exclusions, the final sample included 647 patients, including 51.3% women (Figure 1). Table 1 compares patient and surgical characteristics between patients with versus without
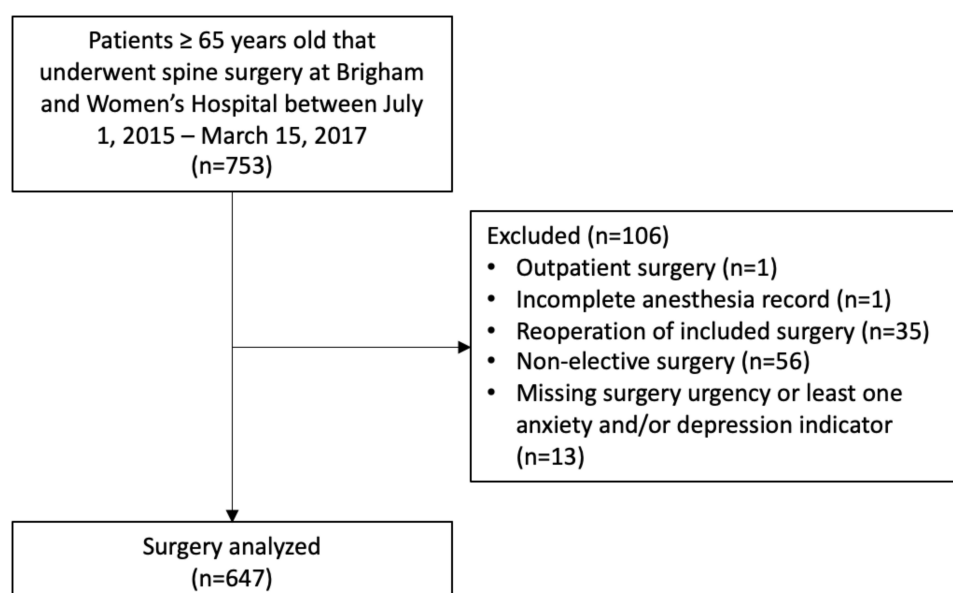
Figure 1 Patient inclusion flow diagram.

each of the four anxiety and depression indicators and Supplementary Table 1 compares these characteristics between women and men. Patients with preoperative anxiety or depression indicators tended to be younger, women, and take opioids preoperatively (Table 1, Supplementary Table 1).

Preoperative History of Anxiety

Preoperative history of anxiety was associated with an adjusted mean (99.6% confdence interval [CI]) 6.6 (1.1, 12.0) MME greater opioid consumption in men and women combined 0–24 hours post-surgery (Supplementary Table 2). No associations were detected between the preoperative history of anxiety and postoperative opioid consumption at 24–48 or 48–72 hours post-surgery, or with the highest or average pain severity at any postoperative time point (Supplementary Tables 2–4) In the subgroup analysis by sex, no association was detected between the preoperative history of anxiety and opioid consumption at 0–24 hours among women (adjusted difference in means [99.6% CI]: 2.9 [−3.1, 8.9] MME), but there was a strong association between preoperative history of anxiety and opioid consumption at 0–24 hours among men (adjusted difference in means [99.6% CI]: 19.5 [8.1, 31.0] MME) (Table 2 and Figure 2). When directly compared, the adjusted difference in mean opioid consumption (99.6% CI) between patients with and without a history of anxiety for women vs men was −16.6 (−29.2, −4.0) (P < 0.001 for the interaction between sex and history of anxiety) (Table 2 and Figure 2). No interactions between sex and history of anxiety with respect to postoperative opioid consumption at 24–48 or 48–72 hours post-surgery, or with the highest or average pain severity were detected at any postoperative time point (Tables 2–4).

Preoperative Anxiolytic Use

No associations were detected between preoperative anxiolytic use and postoperative opioid consumption, highest pain severity, or average pain severity at any postoperative time point (Supplementary Tables 2–4). No interactions were detected between sex and preoperative anxiolytic use with respect to opioid consumption, highest pain severity, or average pain severity at any postoperative time point (Tables 2–4).

Preoperative History of Depression

Preoperative history of depression was associated with an adjusted mean (99.6% CI) 5.0 (0.3, 9.7) MME greater opioid consumption in men and women combined 0–24 hours post-surgery (Supplementary Table 2). No associations were

Table 1 Patient and Surgical Characteristics by Anxiety and Depression Indicators

Characteristic	History of Anxiety		Standardized Difference	Anxiolytic Use		Standardized Difference
	Yes (n=78)	No (n=569)		Yes (n=146)	No (n=501)	
Age (years), mean ± SD	72.7 ± 5.8	73.7 ± 5.9	−0.170	72.2 ± 5.5	73.9 ± 6.0	−0.309
BMI (kg/m^2), mean ± SD	29.9 ± 6.0	28.9 ± 5.3	0.179	29.0 ± 5.8	29.0 ± 5.3	−0.004
Women, n (%)	64 (82.1)	268 (47.1)	0.785	93 (63.7)	239 (47.7)	0.326
ASA, n (%)			0.084			0.066
2	26 (33.3)	203 (35.7)		48 (32.9)	181 (36.1)	
3	49 (62.8)	360 (63.3)		96 (65.8)	313 (62.5)	
4	3 (3.8)	6 (1.1)		2 (1.4)	7 (1.4)	
Reoperation, n (%)	7 (9.0)	32 (5.6)	0.129	17 (11.6)	22 (4.4)	0.270
Surgical invasiveness tier*, n (%)			0.059			−0.050
1	2 (2.6)	22 (3.9)		8 (5.5)	16 (3.2)	
2	26 (33.3)	191 (33.6)		52 (35.6)	165 (32.9)	
3	42 (53.8)	309 (54.3)		69 (47.3)	282 (56.3)	
4	8 (10.3)	47 (8.3)		17 (11.6)	38 (7.6)	
Preoperative opioid use, n (%)	36 (46.2)	204 (35.9)	0.211	82 (56.2)	158 (31.5)	0.512
History of anxiety, n (%)	–	–	–	50 (34.2)	28 (5.6)	0.769
Anxiolytic use, n (%)	50 (64.1)	96 (16.9)	1.098	–	–	–
History of depression, n (%)	44 (56.4)	63 (11.1)	1.093	41 (28.1)	66 (13.2)	0.375
Antidepressant use, n (%)	50 (64.1)	145 (25.5)	0.843	72 (49.3)	123 (24.6)	0.531

	History of depression		Standardized difference	Antidepressant use		Standardized difference
	Yes (n=107)	No (n=540)		Yes (n=195)	No (n=452)	
Age (years), mean ± SD	72.9 ± 5.5	73.7 ± 6.0	−0.138	72.6 ± 5.3	73.9 ± 6.1	−0.233
BMI (kg/m2), mean ± SD	30.5 ± 6.3	28.7 ± 5.2	0.304	29.6 ± 6.0	28.8 ± 5.2	0.141
Women, n (%)	68 (63.6)	264 (48.9)	0.299	125 (64.1)	207 (45.8)	0.374
ASA, n (%)			0.215			0.164
2	29 (27.1)	200 (37.0)		59 (30.3)	170 (37.6)	
3	76 (71.0)	333 (61.7)		132 (67.7)	277 (61.3)	
4	2 (1.9)	7 (1.3)		4 (2.1)	5 (1.1)	
Reoperation, n (%)	9 (8.4)	30 (5.6)	0.112	13 (6.7)	26 (5.8)	0.038
Surgical invasiveness tier*, n (%)			−0.131			−0.008
1	4 (3.7)	20 (3.7)		9 (4.6)	15 (3.3)	
2	42 (39.3)	175 (32.4)		66 (33.8)	151 (33.4)	
3	53 (49.5)	298 (55.2)		100 (51.3)	251 (55.5)	
4	8 (7.5)	47 (8.7)		20 (10.3)	35 (7.7)	
Preoperative opioid use, n (%)	56 (52.3)	184 (34.1)	0.375	90 (46.2)	150 (33.2)	0.267
History of anxiety, n (%)	44 (41.1)	34 (6.3)	0.898	50 (25.6)	28 (6.2)	0.551
Anxiolytic use, n (%)	41 (38.3)	105 (19.4)	0.426	72 (36.9)	74 (16.4)	0.478
History of depression, n (%)	–	–	–	83 (42.6)	24 (5.3)	0.970
Antidepressant use, n (%)	83 (77.6)	112 (20.7)	1.382	–	–	–

Notes: *Tier 1: microdiscectomy, tier 2: lumbar laminectomy, anterior cervical procedures, or minimally invasive fusions, tier 3: lumbar fusion, trauma, or posterior cervical fusion procedures, and tier 4: tumor, infection, deformity, or combined anterior and posterior cervical procedures. Standardized difference with absolute value greater than or equal to 0.1 were taken to indicate a greater difference between groups than would be expected by chance.

detected between the preoperative history of depression and postoperative opioid consumption at 24–48 or 48–72 hours post-surgery, or with the highest or average pain severity at any postoperative time point (Supplementary Tables 2–4). No interactions were detected between sex and preoperative history of depression with respect to opioid consumption, highest pain severity, or average pain severity at any postoperative time point (Tables 2–4).

Table 2 Assessment of Whether the Association of Preoperative Anxiety or Depression Indicators with Opioid Consumption 0–24, 24–48, and 48–72 Hours After Elective Spine Surgery Differs by Sex

Postoperative Time (Hours)	Sex	n	Opioid Consumption (MME), Mean ± SD	n	Opioid Consumption (MME), Mean ± SD	Adjusted Difference in Means (99.6% CI)	Adjusted Difference Between Sexes in Difference in Means (99.6% CI)	P value for Interaction
			Preoperative history of anxiety					
			Yes		**No**			
0–24	Women	64	31.2 ± 24.3	268	26.3 ± 17.6	2.9 (−3.1, 8.9)	−16.6 (−29.2, −4.0)	<0.001
	Men	14	45.5 ± 39.9	301	22.8 ± 18.0	19.5 (8.1, 31.0)		
24–48	Women	55	14.6 ± 12.1	245	11.8 ± 12.0	−0.1 (−6.3, 6.2)	−11.8 (−24.6, 1.0)	0.008
	Men	14	24.4 ± 34.1	250	10.9 ± 12.4	11.7 (0.3, 23.2)		
48–72	Women	46	12.8 ± 15.7	183	9.5 ± 9.9	2.0 (−4.7, 8.6)	−12.4 (−26.5, 1.7)	0.012
	Men	10	29.2 ± 35.7	169	9.1 ± 11.1	14.4 (1.6, 27.1)		
			Preoperative anxiolytic use					
			Yes		**No**			
0–24	Women	93	28.6 ± 20.7	239	26.8 ± 18.6	−1.4 (−6.6, 3.9)	−5.4 (−13.5, 2.6)	0.053
	Men	53	30.6 ± 25.4	262	22.4 ± 18.4	4.1 (−2.3, 10.4)		
24–48	Women	76	12.8 ± 10.6	224	12.1 ± 12.5	−3.7 (−9.2, 1.8)	−5.8 (−14.2, 2.7)	0.049
	Men	48	16.0 ± 23.2	216	10.6 ± 11.7	2.1 (−4.6, 8.7)		
48–72	Women	57	11.5 ± 10.2	172	9.8 ± 11.7	0 (−6.0, 6.0)	−1.7 (−11.2, 7.7)	0.598
	Men	33	16.3 ± 22.3	146	8.8 ± 11.3	1.8 (−5.7, 9.2)		
			Preoperative history of depression					
			Yes		**No**			
0–24	Women	68	32.4 ± 24.8	264	26 ± 17.2	3.4 (−2.7, 9.4)	−3.7 (−12.9, 5.5)	0.248
	Men	39	33.0 ± 24.2	276	22.5 ± 18.9	7.1 (−0.1, 14.3)		
24–48	Women	58	13.4 ± 12.2	242	12 ± 12	−2.7 (−9.0, 3.6)	−3.0 (−12.7, 6.7)	0.381
	Men	33	14.6 ± 17.2	231	11.1 ± 14.2	0.3 (−7.4, 7.9)		
48–72	Women	48	13.0 ± 17.4	181	9.4 ± 9.1	0.4 (−6.3, 7.1)	−2.9 (−13.6, 7.8)	0.441
	Men	23	16.9 ± 19.6	156	9.2 ± 13	3.3 (−5.3, 11.9)		
			Preoperative antidepressant use					
			Yes		**No**			
0–24	Women	125	30.2 ± 22.2	207	25.5 ± 16.9	1.8 (−3.0, 6.6)	−5.6 (−12.9, 1.7)	0.028
	Men	70	30.6 ± 27.6	245	21.8 ± 16.7	7.4 (1.8, 13.1)		
24–48	Women	109	14.8 ± 14.4	191	10.8 ± 10.2	0.1 (−4.9, 5.0)	−3.7 (−11.4, 3.9)	0.163
	Men	62	15.3 ± 22.8	202	10.4 ± 10.7	3.8 (−2.2, 9.7)		
48–72	Women	88	12.4 ± 14.7	141	8.8 ± 8.5	0.2 (−5.1, 5.6)	−2.0 (−10.5, 6.5)	0.503
	Men	42	14.6 ± 23.1	137	8.9 ± 9.7	2.2 (−4.5, 9.0)		

Notes: Adjusted differences in mean opioid consumption with corresponding confidence intervals and P values were calculated for the comparison of patients with and without each preoperative anxiety or depression indicator (within and between sexes, stratified by postoperative day) using linear mixed-effects models each containing parameters for preoperative history of anxiety (except when testing anxiolytic use), anxiolytic use (except when testing history of anxiety), history of depression (except when testing antidepressant use), antidepressant use (except when testing history of depression), age, BMI, ASA physical status, surgical invasiveness tier, reoperation, preoperative opioid use, postoperative timepoint, all two-way interactions between sex / anxiety or depression indicator / postoperative timepoint as well a three-way interaction term for sex by anxiety or depression indicator by postoperative timepoint. Each comparison was evaluated at a Bonferroni-corrected two-sided alpha-level of 0.05/12=0.004.

Preoperative Antidepressant Use

Preoperative antidepressant use was associated with an adjusted mean (99.6% CI) 4.3 (0.6, 8.0) MME greater opioid consumption in men and women combined 0–24 hours post-surgery (Supplementary Table 2). No associations were detected between preoperative antidepressant use and postoperative opioid consumption at 24–48 or 48–72 hours post-
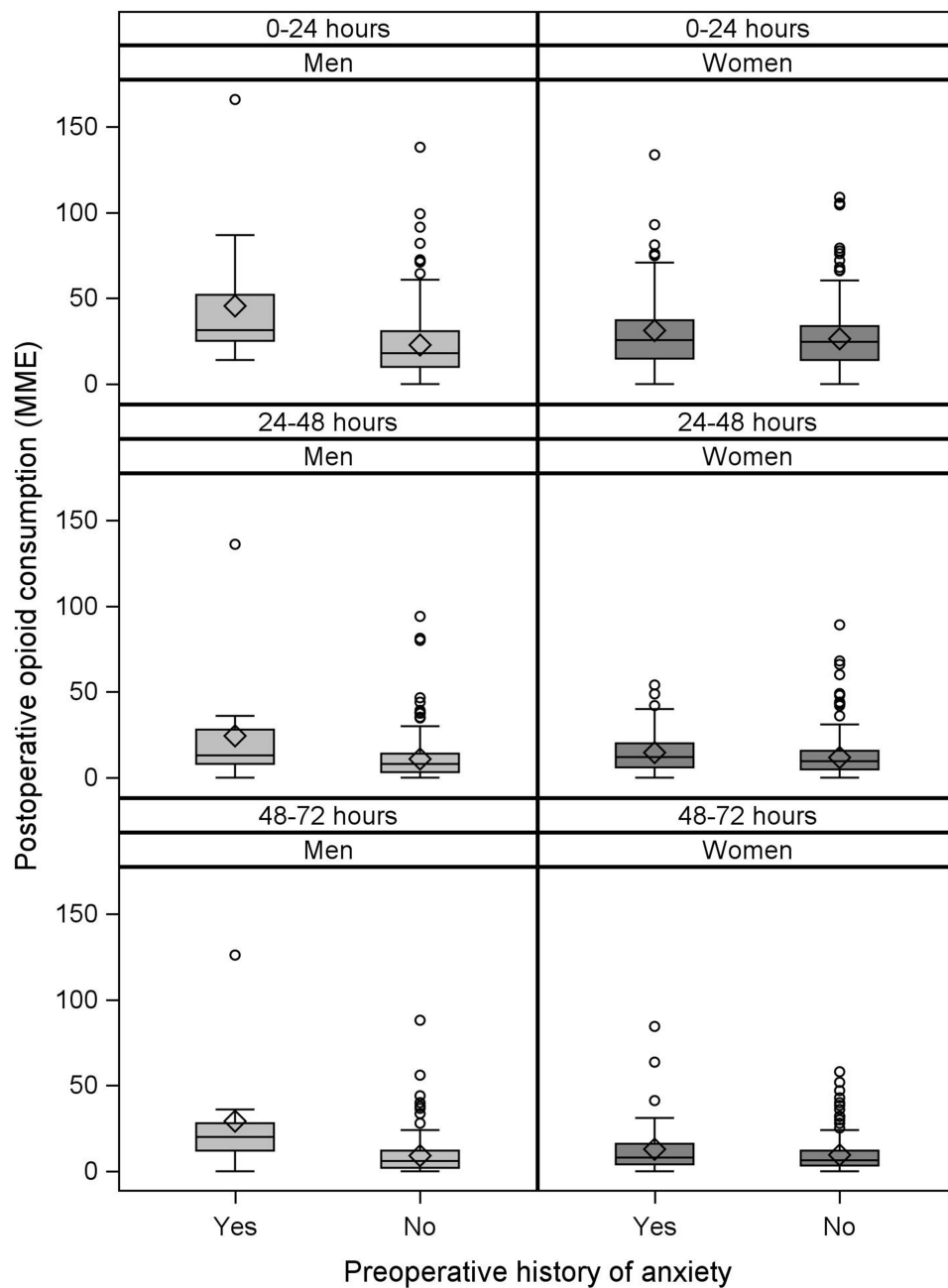
Figure 2 Boxplots of postoperative opioid consumption at 0–24, 24–48, and 48–72 hours post elective spine surgery stratified by preoperative history of anxiety and sex. Diamonds represent mean values. Boxes consist of the first quartile, median, and third quartiles. The whiskers extend to the most extreme observations within 1.5 times the interquartile range below and above the first and third quartiles, respectively. Small circles represent outliers.

surgery, or with the highest or average pain severity at any postoperative time point (Supplementary Tables 2–4). No interactions were detected between sex and preoperative antidepressant use with respect to opioid consumption, highest pain severity, or average pain severity at any postoperative time point (Tables 2–4).

Discussion

The aim of this secondary analysis of a retrospective cohort study was to assess whether any observed association of anxiety or depression indicators with opioid consumption in the first 72 hours after elective spine surgery varies by sex in

Table 3 Assessment of Whether the Association of Preoperative Anxiety and Depression Indicators with Highest Pain Severity 0–24, 24–48, and 48–72 Hours After Elective Spine Surgery Differs by Sex

Postoperative Time (Hours)	Sex	n	Highest NRS Pain Score, Mean ± SD	n	Highest NRS Pain Score, Mean ± SD	Adjusted Difference in Means (99.6% CI)	Adjusted Difference Between Sexes in Difference in Means (99.6% CI)	P value for Interaction
			Preoperative history of anxiety					
			Yes		**No**			
0–24	Women	64	8.1 ± 2.0	266	7.7 ± 2.0	0.2 (−0.8, 1.1)	−1.0 (−2.9, 0.9)	0.138
	Men	14	8.3 ± 1.4	292	6.8 ± 2.4	1.2 (−0.6, 2.9)		
24–48	Women	55	7.7 ± 2.3	238	6.9 ± 1.9	0.4 (−0.5, 1.4)	0 (−1.9, 2.0)	0.952
	Men	14	6.7 ± 1.7	241	6.2 ± 2.5	0.4 (−1.4, 2.2)		
48–72	Women	44	7.6 ± 1.7	174	6.7 ± 2.2	0.7 (−0.4, 1.7)	0 (−2.2, 2.2)	0.996
	Men	10	6.4 ± 2.6	155	5.9 ± 2.5	0.7 (−1.3, 2.6)		
			Preoperative anxiolytic use					
			Yes		**No**			
0–24	Women	92	7.9 ± 1.9	238	7.8 ± 2.1	0 (−0.8, 0.8)	−0.2 (−1.4, 1.1)	0.693
	Men	52	7.3 ± 2.3	254	6.7 ± 2.4	0.2 (−0.8, 1.1)		
24–48	Women	75	7.4 ± 1.9	218	7.0 ± 2.1	0.1 (−0.7, 0.9)	0.3 (−1.0, 1.6)	0.533
	Men	44	6.3 ± 2.4	211	6.2 ± 2.4	−0.2 (−1.2, 0.9)		
48–72	Women	55	7.2 ± 1.8	163	6.7 ± 2.3	0.4 (−0.5, 1.4)	0.1 (−1.4, 1.6)	0.807
	Men	30	6.5 ± 1.8	135	5.8 ± 2.6	0.3 (−0.9, 1.5)		
			Preoperative history of depression					
			Yes		**No**			
0–24	Women	68	8.1 ± 2.1	262	7.7 ± 2.0	0 (−0.9, 1.0)	−0.6 (−2.0, 0.8)	0.199
	Men	38	7.7 ± 1.9	268	6.7 ± 2.5	0.7 (−0.4, 1.8)		
24–48	Women	59	7.6 ± 2.1	234	6.9 ± 2.0	0.4 (−0.6, 1.3)	0.3 (−1.2, 1.8)	0.548
	Men	32	6.5 ± 2.2	223	6.2 ± 2.5	0.1 (−1.1, 1.2)		
48–72	Women	45	7.3 ± 2.0	173	6.8 ± 2.2	0.2 (−0.8, 1.3)	0.2 (−1.5, 1.9)	0.766
	Men	21	6.1 ± 2.6	144	5.9 ± 2.4	0.1 (−1.3, 1.4)		
			Preoperative antidepressant use					
			Yes		**No**			
0–24	Women	124	8.0 ± 2.1	206	7.7 ± 2.0	−0.1 (−0.8, 0.7)	−0.2 (−1.3, 0.9)	0.566
	Men	68	7.1 ± 2.6	238	6.8 ± 2.4	0.2 (−0.7, 1.0)		
24–48	Women	107	7.4 ± 2.1	186	6.9 ± 2.0	0.2 (−0.5, 1.0)	0.5 (−0.7, 1.7)	0.197
	Men	59	6.1 ± 2.5	196	6.3 ± 2.4	−0.3 (−1.2, 0.6)		
48–72	Women	84	7.3 ± 1.9	134	6.6 ± 2.3	0.4 (−0.4, 1.2)	0.3 (−1.0, 1.6)	0.510
	Men	38	6.2 ± 2.3	127	5.8 ± 2.5	0.1 (−1.0, 1.2)		

Notes: Adjusted differences in mean highest pain severity with corresponding confidence intervals and P values were calculated for the comparison of patients with and without each preoperative anxiety or depression indicator (within and between sexes, stratified by postoperative day) using linear mixed-effects models each containing parameters for preoperative history of anxiety (except when testing anxiolytic use), anxiolytic use (except when testing history of anxiety), history of depression (except when testing antidepressant use), antidepressant use (except when testing history of depression), age, BMI, ASA physical status, surgical invasiveness tier, reoperation, preoperative opioid use, postoperative timepoint, all two-way interactions between sex / anxiety or depression indicator / postoperative timepoint as well a three-way interaction term for sex by anxiety or depression indicator by postoperative timepoint. Each comparison was evaluated at a Bonferroni-corrected two-sided alpha-level of 0.05/12=0.004.

adults 65 years and older. We found that preoperative history of anxiety was associated with greater opioid consumption 0–24 hours post-surgery in men and women combined, and that this increase was much greater in men than in women. These results are consistent with research conducted by Nandi et al,[16] where the association between negative affect and

Table 4 Assessment of Whether the Association of Preoperative Anxiety or Depression Indicators with Average Pain Severity 0–24, 24–48, and 48–72 Hours After Elective Spine Surgery Differs by Sex

Postoperative Time (Hours)	Sex	n	Average NRS Pain Score, Mean ± SD	n	Average NRS Pain Score, Mean ± SD	Adjusted Difference in Means (99.6% CI)	Adjusted Difference Between Sexes in Difference in Means (99.6% CI)	P value for Interaction
Preoperative history of anxiety								
			Yes		**No**			
0–24	Women	64	5.5 ± 1.7	265	5.0 ± 1.7	0.3 (−0.5, 1.0)	−0.7 (−2.3, 0.8)	0.176
	Men	14	5.5 ± 1.4	292	4.2 ± 1.9	1.0 (−0.4, 2.4)		
24–48	Women	55	5.2 ± 2.0	237	4.3 ± 1.7	0.7 (−0.1, 1.5)	−0.1 (−1.7, 1.5)	0.834
	Men	14	4.8 ± 1.8	241	3.8 ± 1.8	0.8 (−0.6, 2.2)		
48–72	Women	44	5.1 ± 2.1	174	4.3 ± 1.9	0.6 (−0.2, 1.4)	−0.3 (−2.1, 1.4)	0.608
	Men	10	4.8 ± 2.0	155	3.5 ± 1.9	0.9 (−0.7, 2.5)		
Preoperative anxiolytic use								
			Yes		**No**			
0–24	Women	91	5.4 ± 1.7	238	4.9 ± 1.8	0.2 (−0.5, 0.8)	−0.2 (−1.2, 0.8)	0.592
	Men	52	4.9 ± 1.9	254	4.1 ± 1.9	0.3 (−0.4, 1.1)		
24–48	Women	74	5.0 ± 1.7	218	4.3 ± 1.8	0.3 (−0.3, 1.0)	0.1 (−1.0, 1.1)	0.809
	Men	44	4.3 ± 1.9	211	3.8 ± 1.8	0.3 (−0.6, 1.1)		
48–72	Women	55	4.8 ± 2.0	163	4.4 ± 2.0	0.2 (−0.6, 0.9)	−0.4 (−1.6, 0.8)	0.370
	Men	30	4.5 ± 1.4	135	3.4 ± 2.0	0.6 (−0.4, 1.5)		
Preoperative history of depression								
			Yes		**No**			
0–24	Women	67	5.4 ± 1.8	262	5.0 ± 1.7	0.1 (−0.6, 0.9)	−0.4 (−1.6, 0.7)	0.261
	Men	38	5.0 ± 1.9	268	4.1 ± 1.9	0.6 (−0.3, 1.4)		
24–48	Women	58	4.9 ± 1.9	234	4.3 ± 1.7	0.2 (−0.6, 1.0)	0 (−1.2, 1.2)	0.911
	Men	32	4.2 ± 1.9	223	3.8 ± 1.8	0.1 (−0.8, 1.1)		
48–72	Women	45	4.9 ± 2.2	173	4.3 ± 1.9	0.1 (−0.7, 1.0)	0 (−1.4, 1.3)	0.919
	Men	21	4.0 ± 1.9	144	3.6 ± 1.9	0.2 (−0.9, 1.3)		
Preoperative antidepressant use								
			Yes		**No**			
0–24	Women	123	5.4 ± 1.8	206	4.9 ± 1.7	0.2 (−0.4, 0.7)	−0.2 (−1.1, 0.7)	0.542
	Men	68	4.6 ± 2.1	238	4.1 ± 1.9	0.3 (−0.4, 1.1)		
24–48	Women	106	4.7 ± 1.9	186	4.3 ± 1.7	0.1 (−0.5, 0.7)	0 (−0.9, 1.0)	0.909
	Men	59	4.0 ± 2.0	196	3.8 ± 1.8	0.1 (−0.7, 0.8)		
48–72	Women	84	5.0 ± 2.0	134	4.2 ± 1.9	0.4 (−0.3, 1.1)	0.1 (−1, 1.2)	0.741
	Men	38	4.1 ± 2.0	127	3.5 ± 1.9	0.3 (−0.6, 1.1)		

Notes: Adjusted differences in mean average pain severity with corresponding confidence intervals and P values were calculated for the comparison of patients with and without each preoperative anxiety or depression indicator (within and between sexes, stratified by postoperative day) using linear mixed-effects models each containing parameters for preoperative history of anxiety (except when testing anxiolytic use), anxiolytic use (except when testing history of anxiety), history of depression (except when testing antidepressant use), antidepressant use (except when testing history of depression), age, BMI, ASA physical status, surgical invasiveness tier, reoperation, preoperative opioid use, postoperative timepoint, all two-way interactions between sex / anxiety or depression indicator / postoperative timepoint as well a three-way interaction term for sex by anxiety or depression indicator by postoperative timepoint. Each comparison was evaluated at a Bonferroni-corrected two-sided alpha-level of 0.05/12=0.004.

worse acute pain after total knee arthroplasty was stronger in men than in women. However, in our study, no other interactions were detected between sex and psychosocial factors with respect to opioid use, highest pain, or average pain 0–72 hours after elective spine surgery.

Among the exposures investigated, a history of anxiety had the strongest association with acute postoperative opioid consumption. This result is consistent with the finding of Armaghani et al that a higher preoperative Modified Somatic Perception Questionnaire (MSPQ) score, a measure of anxiety symptoms, was associated with greater opioid consumption in the post-anesthesia care unit among elective spine surgery patients.[21] Beyond the acute postoperative period, Armaghani et al further found that higher preoperative MSPQ scores were associated with lower odds of opioid independence 12 months after surgery,[21] along with other authors who have found an association between anxiolytics and chronic opioid use.[24] The mixed-effects models analysis indicated that a history of anxiety was a stronger predictor of postoperative opioid use in men than women. This result may be partially attributable to the fact that women have higher rates of anxiolytic prescriptions. That is, assuming anxiolytic medications may help to mitigate the emotional burden of the surgery and reduce the fear of pain, the more common use of anxiolytics among women may be modestly protective. On the other hand, men are less likely to access psychological therapies than women and present different coping mechanism.[25]

Our study found a higher prevalence of documented preoperative history of anxiety and depression in women than men. However, we must note this finding in the context that men tend to underreport mental health issues.[26] That said, we found that history of anxiety was associated with greater opioid consumption in the first 24 postoperative hours in men and women combined. This is consistent with the literature on pain, catastrophizing, and anxiety, where the evidence clearly highlights greater long-term opioid use for individuals with mental health conditions, in particular anxiety and depression.[27,28]

While the association between history of anxiety and opioid use was observed for men and women combined during the first 24 postoperative hours, between 24–48 and 48–72 hours post-operatively the association was statistically significant only for men (Table 2). Furthermore, men with a history of anxiety take on average more than double MME (Table 2) in the first 72 hours post-surgery. In this regard, this highlights the importance of studying the gender differences in opioid use.

Floyd et al showed that anxiety has an impact on the length of stay following lumbar spinal surgery[29] with patients taking anxiolytics staying 1.8 days longer in the hospital. Another recent literature review[30] highlighted how patients with the underlying psychological disease tend to present higher rates of delirium, readmission, longer hospital stays, and higher rates of nonroutine discharge following spine surgery, as well as higher rates of chronic postoperative narcotic use and may experience worse surgical outcomes.

The study by Veal et al with 20,000 elders[31] indicated that the use of anxiolytics and opioids tends to be concurrent (41% of opioid users had taken anxiolytics/hypnotic medications). Regarding our population, Table 1 highlights that 56.2% of the patients declaring anxiolytics use were administered opioids preoperatively. Since we are investigating a cohort of elderly patients, this association needs to be particularly highlighted. It constitutes a combination particularly dangerous that it seems to be associated with an increased risk of falls,[32] which in the older population lead to further complications and negative outcomes.[33,34]

A significant difference in length of stay was also found by Walid et al in patients taking antidepressants compared to the ones who were not taking antidepressants.[35] However, we found that antidepressant use was associated with an increase in opioid use in the first 24 hours after surgery, albeit in minor quantities compared to patients with a history of anxiety, and this association was not confirmed 48 to 72 hours post-surgery. It appears from our study that anxiety is the most affecting issue influencing pain and postoperative consumption. Therefore, it is essential to find another way to successfully manage preoperative anxiety in older populations.

Perspectives and Significance

Women report on average twice the history of anxiety and take more anxiety medications; on the other hand, men with anxiety seem to be more prone to use opioids in the early postoperative period, leading to think that both genders would benefit from targeted strategies addressing this issue. Given the problems associated with mental health medications in the elderly, it would be key to implement non-pharmacological strategies to manage the psychosocial factors, a solution could be Cognitive Behavioral Therapy (CBT). CBT could provide a toolkit of stress management techniques to individuals experiencing chronic life stress and enhance stress management and coping skills to help patients better

manage pain after surgery and reduce their need for opioid medications. Moreover, more research is needed to uncover potential sex differences in the pain management postoperative journey, to optimize the recovery of both populations.

Limitations

This study has several limitations. This was a retrospective study utilizing data from the electronic medical record, corresponding with non-ideal measurement of exposures, model covariates, and outcomes. Regarding study exposures, preoperative anxiety, and depression would ideally be measured on an ordinal or continuous scale via a validated questionnaire. However, given the retrospective nature of this study, we measured preoperative anxiety and depression as binary yes/no exposures as documented in the pre-admission anesthesia evaluation note. Analyzing anxiety and depression as binary (as opposed to ordinal or continuous) variables decreased our power to detect any existing effect. Further, the reliability of the pre-admission anesthesia evaluation note depends on accurate patient report or documentation in the medical record of mental health diagnoses and associated medications. Any misclassifications of anxiety and depression indicators (with false negatives being much more probable than false positives) would likely bias results toward a null finding. Regarding the measurement of model covariates, we only had a record of a patient who was taking preoperative opioids, not the amount. This dichotomization could have resulted in inadequate regression adjustment for preoperative opioid use. Regarding outcomes, postoperative opioid consumption, and pain scores were only available in the medical record during the inpatient stay, precluding analysis of long-term patient pain and functioning. In addition, patients discharged from the hospital prior to 72 hours led to missing outcomes for the 24–48 and 48–72 postoperative time points. However, mixed-effects models provide valid estimates when the probability of an outcome being missing is dependent only upon observed information (the data are missing at random). We posit that the missing at-random assumption, albeit not verifiable, is reasonable given that in-hospital (observed) opioid consumption and pain intensity as well as covariates like surgical invasiveness tier are associated with hospital length of stay. Furthermore, while we acknowledge that the prescribing practices in many groups have changed since the creation of this dataset, the prescribing practices are surgeon specific. In this specific group of patients, the practices have not changed, and the results are therefore still up to date.

In addition to outcome follow-up limitations, there was likely variability in how patients were queried about their postoperative pain intensity, as well as the unknown reliability of their responses. Further, our detection of an interaction between sex and a history of anxiety with respect to opioid consumption 0–24 hours after elective spine surgery was based on only 14 men with documented anxiety, minimizing the generalizability of this finding. Finally, given our observational study design, we could not draw conclusions about causal relationships between the variables studied.

Conclusion

This secondary analysis of a retrospective cohort study found that preoperative history of anxiety was associated with a greater increase in opioid consumption 0–24 hours after elective spine surgery in men than in women aged 65 and older. However, no other interactions were detected between sex and psychosocial factors with respect to opioid use, highest pain, or average pain 0–72 hours after surgery. While this retrospective study found minimal evidence that the association between psychosocial factors and opioid consumption after elective spine surgery differs by sex in older adults, it is possible that some of the null findings may be at least partly attributable to the limitations of the electronic medical record as the sole data source. Therefore, future prospective studies should utilize more sensitive, granular measurements of anxiety and depression to further explore the potential interaction between sex and psychosocial factors with respect to opioid use and pain after surgery.

Disclosure

Dr Deborah Culley reports grants from NIH, during the conduct of the study; personal fees from American Society of Anesthesiologists, outside the submitted work. The authors have no other competing interests in this work.

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