BJA

British Journal of Anaesthesia, 126 (6): 1217–1225 (2021)

doi: 10.1016/j.bja.2020.12.046
Advance Access Publication Date: 3 March 2021
Pain

Association between sex and perioperative opioid prescribing for total joint arthroplasty: a retrospective population-based study

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Abstract

Background: Scarce data exist on differential opioid prescribing between men and women in the pre-, peri-, and postoperative phases of care among patients undergoing total hip/knee arthroplasty (THA/TKA).
Methods: In this retrospective population-based study, Truven Health MarketScan claims data were used to establish differences between men and women in (1) opioid prescribing in the year before THA/TKA surgery, (2) the amount of opioids prescribed at discharge, and (3) chronic opioid prescribing (3–12 months after surgery). Multivariable regression models measured odds ratios (OR) with 95% confidence intervals (95% CI).
Results: Among 29 038 THAs (42% men) and 48 523 TKAs (52% men) men (compared with women) were less likely to receive an opioid prescription in the year before surgery (54% *vs* 60%, and 54% *vs* 60% for THA and TKA, respectively); $P<0.001$. However, in multivariable analyses male sex was associated with higher total opioid dosages prescribed at discharge after THA (OR=1.04; 95% CI 1.03, 1.06) and TKA (OR=1.05; 95% CI 1.04, 1.06); both $P<0.001$. Chronic opioid prescribing was found in 10% of the cohort (THA: $n=2333$; TKA: $n=5365$). Here, men demonstrated lower odds of persistent opioid prescribing specifically after THA (OR=0.90; 95% CI 0.82, 0.99) but not TKA (OR=0.96; 95% CI 0.90, 1.02); $P=0.026$ and $P=0.207$, respectively.
Conclusions: We found sex-based differences in opioid prescribing across all phases of care for THA/TKA. The results highlight temporal opportunities for targeted interventions to improve outcomes after total joint arthroplasty, particularly for women, and to decrease chronic opioid prescribing.

Keywords: opioids; opioid prescribing; sex differences; total hip arthroplasty; total joint arthroplasty; total knee arthroplasty

Editor's key points

- It has been recognised that surgery may contribute to persistent opioid use, but further work is needed to understand risk factors in order to develop targeted interventions.
- In a large population dataset, covering a wider geographical area, data from patients undergoing total

Accepted: 28 December 2020

hip (THA) or knee arthroplasty (TKA) were studied for 12 months before and after surgery.
- Clear sex differences were demonstrated, with women more likely to be prescribed opioids preoperatively after total joint arthroplasty (TJA), and be on persistent opioids after THA. Men were likely to be prescribed a higher dose of opioid at hospital discharge.
- The reasons for these differences are not clear, and may include prescriber bias, and a range of biopsychosocial factors, which require further study in order to improve outcomes.

Opioid-related deaths increased sharply among women in the USA between 1999 and 2017.[1,2] Although men suffered more opioid-related deaths over this interval, the rate of increase in deaths was much higher in women overall (503% in women *vs* 404% in men), and highest among women aged 55–64 yr. Despite these trends, sex differences have not been a priority in research seeking to identify causes and consequences of chronic opioid prescribing, use, and misuse.[2,3]

These trends have a parallel in orthopaedic surgery, where the majority of patients undergoing total hip (THA) and knee arthroplasty (TKA) are women.[4] Although multiple risk factors for chronic opioid use after total joint arthroplasty (TJA) have been identified, the influence of sex on opioid prescribing, use, and related outcomes is unclear.[5–11] Most studies associated female sex with higher risk for long-term use after TJA,[5,6,8,9] but others found no difference[7,10] or higher risk for male patients.[11] To date, these associations have not been well defined at the population level. Most of the available data are derived from institutional registries[5,6,8] or a prescription drug monitoring system,[9] which may lack generalisability. Other limited sources of information on the topic come from a small retrospective study[11] or a prospective study with incomplete follow-up.[7] Furthermore, preoperative opioid use was accounted for in some[7–9,12] – but not all – investigations,[5,6] and none accounted for the quantity of opioid prescribed at discharge.

Given these conflicting data, the current study was performed to assess population-based sex differences in opioid prescribing in the year before THA or TKA, the amount of opioid prescribed at discharge from the hospital, and the incidence of persistent prescribing (up to 12 months after surgery). We additionally assessed predictors of chronic opioid prescribing, including preoperative opioid status (naïve *vs* tolerant), use of non-opioid analgesic agents, peripheral nerve blocks, and length of stay. We hypothesised that compared with men, (1) more women would be opioid tolerant at the time of surgery; (2) women would be prescribed more opioids (defined as a higher total dose, in oral morphine equivalents [OME]) at the time of discharge; and (3) women would be more likely to be prescribed opioids at 3–12 months after surgery. Understanding these patterns is important because each of these phases of care may represent temporal opportunities for targeted interventions to prevent persistent opioid use and improve outcomes for women after total joint arthroplasty.

Methods

This retrospective population-based cohort study was approved by the Hospital for Special Surgery Institutional Review Board (New York, NY, USA; IRB 2017–0169).

Patients who underwent inpatient THA or TKA between 2012 and 2016 were identified from the Truven Health MarketScan database (Truven Health Analytics Inc., Greenwood Village, CO, USA), a claims database consisting of the largest convenience sample of patients throughout the United States with employer-sponsored health insurance. The MarketScan database contains detailed longitudinal data from more than 300 employers and 25 contributing health plans, including information from both in- and outpatient visits in addition to pharmaceutical claims.[13]

Study variables

The main outcomes of interest were (1) sex differences in opioid use in the year before THA or TKA, (2) the amount of opioids prescribed at discharge from the hospital (in OME), and (3) the incidence of persistent opioid prescribing, defined as 10 or more opioid prescriptions or prescriptions for at least 120 pills within the period from 90 days to 1 yr after discharge.[14]

The main predictor of interest was patient sex. Opioid/pain management-related covariates included prescriptions for opioids in the year before surgery (opioid naïve – yes/no), discharge prescriptions for non-opioid analgesics, anxiolytics, or antidepressants (yes/no; specific medications detailed in Supplementary Appendix), peripheral nerve block use, and the specific opioid prescribed upon discharge (fentanyl, hydrocodone, hydromorphone, meperidine, morphine, oxycodone, oxymorphone, tramadol, a combination of two opioids, or exclusively non-opioid analgesics). Additional covariates of interest included type of procedure (THA/TKA), patient age, Charlson–Deyo comorbidity index (categorised as 0, 1, 2, 3+), obesity, obstructive sleep apnoea, year of procedure, whether or not the procedure was bilateral, length of stay, region of patient residence (Northeast, North Central, South, West), discharge status (home, home health service, transfer to other facility, or other), median household income (<$45 000, $45 000–60 000, or >$60 000), and insurance plan type (Comprehensive, Exclusive Provider Organisations [EPO], Health Maintenance Organisations [HMO], Preferred Provider Organisations [PPO], Consumer-driven Health Plans/High Deductible Health Plans [CDHP/HDHP], Point of Service [POS], or POS with capitation).

Statistical analysis

Descriptive summaries of all outcomes and covariates of interest were reported, stratified by procedure type and patient sex. Categorical variables were reported as frequencies (%) and analysed via χ^2 tests whereas continuous variables (age, length of stay, and OME prescribed upon discharge) were reported as median (inter-quartile range [IQR]) and analysed via Kruskal–Wallis tests.

Multivariable regression analyses were conducted separately for THA and TKA cohorts. To evaluate the association between patient sex and total OME prescribed upon adjusting for all other covariates, we utilised generalised linear models with a gamma distribution and log-link to account for its skewed distribution. Results are reported as exponentiated coefficients (e^{β}) and their corresponding 95% confidence intervals (95% CI), representing the ratio of total OME prescribed relative to the reference group. These models did not adjust for the type of opioid prescribed as this information is captured within the outcome. Multivariable logistic regression models were utilised to evaluate the association between patient sex

and persistent postoperative opioid use. These models adjusted for all covariates of interest including total OME prescribed upon discharge. Odds ratios (OR) and 95% CI or percentages were reported. Results with a P value <0.05 were considered statistically significant. All analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC, USA).

Results

Among 77 561 included patients a total of 13 888 women and 15 150 men underwent THA (total n=29 038) and 27 966 women and 20 557 men underwent TKA (total n=48 523) (Table 1). Women more commonly received a prescription for an opioid medication in the year before surgery (THA: 60% [n=8315] of women *vs* 54% [n=8138] of men; TKA: 60% [n=16 627] of women *vs* 54% [n=10 999] of men). Among the 83% of the cohort that received an opioid prescription at discharge after surgery (THA, n=24 068; TKA, n=39 929), men were prescribed more total opioids at discharge after both THA and TKA compared with women: 80 OME (IQR 52.5, 100) *vs* 75 OME (IQR 46.2, 100) (P<0.001) and 85.7 OME (IQR 58.3, 114.4) *vs* 83.3 OME (IQR 53.3, 110) (P<0.001), respectively. Oxycodone was the most frequently prescribed opioid at discharge among both men and women.

Overall, 10% of the cohort received a prescription for an opioid between 3 and 12 months after total joint arthroplasty (THA, n=2333; TKA, n=5365). However, women were more likely than men to be prescribed opioids on a persistent basis after discharge following both THA (9% of women [n=1222] *vs* 7% of men [n=1111]; P<0.001) and TKA (12% [n=3275] of women *vs* 10% [n=2090] of men; P<0.001).

These patterns persisted in multivariable analyses: male sex was associated with higher total opioids prescribed at discharge after both THA (OR=1.04; 95% CI 1.03, 1.06; P<0.001) and TKA (OR=1.05; 95% CI 1.04, 1.06; P<0.001). Preoperative opioid naïve status was associated with lower OME prescribed at discharge in both cohorts (THA: OR=0.91; 95% CI 0.90, 0.92; P<0.001; TKA: OR=0.92; 95% CI 0.92, 0.93; P<0.001). Length of hospital stay was associated with lower OME prescribed at discharge after TKA (OR=0.99; 95% CI 0.99, 0.99; P<0.001; Table 2).

In THA patients, male sex (OR=0.90; 95% CI 0.82, 0.99; P<0.05) and preoperative opioid-naïve status (OR=0.04; 95% CI 0.03, 0.05; P<0.001) were associated with a lower odds of chronic opioid prescribing, whereas higher odds were associated with longer length of stay (OR=1.05; 95% CI 1.03–1.08; P<0.001) (Table 3). There was no significant association between sex and chronic opioid prescribing after TKA (OR=0.96; 95% CI 0.90, 1.02; P>0.05). Opioid-naïve status (OR=0.06; 95% CI 0.05, 0.06; P<0.001), and use of non-opioid analgesia (OR=0.91; 95% CI 0.85, 0.97; P<0.005) were associated with lower odds of persistent opioid prescribing. Conversely, longer length of stay (OR=1.04; 95% CI 1.02, 1.05; P<0.001) was associated with higher odds of persistent opioid prescribing (Table 3). Chronic opioid prescribing was not significantly associated with use of a peripheral nerve block for THA (OR=1.04; 95% CI 0.87, 1.25; P>0.005) or TKA (OR=0.98; 95% CI 0.91, 1.04; P>0.05).

Discussion

In this analysis of population-based data, we found that compared with men, more women were exposed to opioids within 1 yr before TJA surgery. However, women were prescribed less opioid than men at discharge after TJA surgery and had disproportionately higher odds of receiving longer term opioid prescriptions than men.

Attention is increasingly being paid to both general strategies to prevent opioid use disorder[15] and specific strategies to minimise opioid requirements for patients undergoing TJA.[16] However, sex differences in opioid-related prescribing and outcomes have been neglected in research and policy planning efforts.[3] Given the increasing incidence of opioid-related deaths among women, it is imperative to understand sex-related differences in prescription opioid use which might burgeon into opioid misuse, abuse, addiction, and even overdose.[2] There are surprisingly little data which address these associations. Reasons for the discrepancies found here must remain speculative but may include patient and prescriber related factors. Although this information is not available from our data source, we aimed to delineate the role of sex differences between pre-TJA opioid prescribing, the amount of opioid prescribed at discharge, and the odds of persistent prescribing.

Preoperative opioid status

Preoperative opioid tolerance has been identified as a major risk factor for worse outcomes and more complications after TKA, including revision surgery, fractures, readmission, and 30 day opioid overdose,[17–19] and for persistent opioid use after both THA and TKA.[7,8,20] In contrast, there is a paucity of evidence exploring interactions between sex and preoperative opioid use and tolerance. We found 57% of the cohort had received prescriptions for opioid medications within 1 yr before TJA, and the majority of these (almost 60%) were women. Interactions among sex, other biopsychosocial characteristics, comorbidities, and the expression of pain are complex and likely to contribute to both preoperative opioid use and recovery after TJA.[21] For example, prior research highlights depression as a comorbidity affecting more women than men; this, in turn, is also an independent risk factor for new persistent opioid use after THA.[22] Although our study was not designed to address these questions, the results presented here suggest that efforts to understand the determinants of pre-TJA opioid use among women are warranted.

Discharge opioid prescribing

The effect(s) of discharge opioid prescribing on persistent opioid use is an emerging focus of research. Recent data show that the amount of opioid prescribed is an important factor determining long-term opioid consumption, in which higher amounts of prescribed opioid are associated with higher ongoing patient-reported consumption, an effect not explained by severity of pain.[23] We found that men were prescribed more total opioid than women at discharge after both THA and TKA. Sex-based differences in pain management have been described as a paradox, in which women tend to report more pain and yet receive less and less effective analgesia compared with men.[24] A potential interpretation of our findings is that women's pain is undertreated compared with men after TJA. Although possible, this explanation seems less likely considering that oxycodone was the most frequently prescribed opioid among both men and women after TJA, usually with the same quantity of pills. An alternative interpretation is that sex-based differences in discharge prescribing may be related to higher perceived risk of associated adverse events and contraindications among female

Table 1 Summary of patient characteristics and opioid use patterns stratified by type of procedure (total hip vs knee arthroplasty) and patient sex.

	Hip					Knee				
	Female (N=13 888)	%	Male (N=15 150)	%	P-value	Female (N=27 966)	%	Male (N=20 557)	%	P-value
Age, median (IQR)*	57 (52, 61)		56 (51, 60)		<0.001	58 (54, 61)		58 (54, 61)		<0.001
Oral morphine equivalent, median (IQR)*	75 (46.2, 100)		80 (52.5, 100)		<0.001	83.3 (53.3, 110)		85.7 (58.3, 114.4)		<0.001
Opioid prescriptions year before surgery	8315	59.9	8138	53.7	<0.001	16 627	59.5	10 999	53.5	<0.001
Persistent opioid use	1222	8.8	1111	7.33	<0.001	3275	11.71	2090	10.17	<0.001
Non-opioid analgesic	5151	37.1	5718	37.8	0.252	9537	34.1	7085	34.5	0.403
Discharge prescription										
Fentanyl	8	0.06	5	0.03	<0.001	15	0.05	10	0.05	<0.001
Hydrocodone	4130	29.74	4393	29		7440	26.6	5373	26.14	
Hydromorphone	465	3.35	391	2.58		1191	4.26	611	2.97	
Meperidine	15	0.11	8	0.05		118	0.42	25	0.12	
Morphine	37	0.27	39	0.26		99	0.35	47	0.23	
Oxycodone	6163	44.38	7336	48.42		13 375	47.83	10 483	50.99	
Oxymorphone	3	0.02	6	0.04		6	0.02	3	0.01	
Tramadol	634	4.57	435	2.87		783	2.8	350	1.7	
Combo 2 opioids	1916	13.8	2061	13.6		4136	14.79	3188	15.51	
Non-opioid	517	3.72	476	3.14		803	2.87	467	2.27	
Discharge antidepressant	130	0.94	68	0.45	<0.001	279	1	122	0.59	<0.001
Discharge anxiolytic	343	2.47	306	2.02	0.01	794	2.84	539	2.62	0.148
Charlson–Deyo index										
0	7686	55.34	8657	57.14	<0.001	12 991	46.45	10 471	50.94	<0.001
1	3140	22.61	3181	21		7670	27.43	5006	24.35	
2	1692	12.18	1732	11.43		3753	13.42	2504	12.18	
3	1370	9.86	1580	10.43		3552	12.7	2576	12.53	
Obesity	2608	18.78	2421	15.98	<0.001	7957	28.45	4194	20.4	<0.001
Obstructive sleep apnoea	1170	8.42	2443	16.13	<0.001	4155	14.86	4686	22.8	<0.001
Bilateral surgery	896	6.45	1015	6.7	0.394	2201	7.87	1702	8.28	0.102
Peripheral nerve block	882	6.35	932	6.15	0.484	11 000	39.33	8293	40.34	0.025
Year of procedure										
2012	3047	21.94	3220	21.25	0.116	6318	22.59	4666	22.7	0.052
2013	3034	21.85	3326	21.95		6095	21.76	4678	22.76	
2014	2574	18.53	2977	19.65		5470	19.56	4036	19.63	
2015	2780	20.02	2951	19.48		5361	19.17	3811	18.54	
2016	2453	17.66	2676	17.66		4722	16.88	3366	16.37	
Length of stay, median (IQR)*	2 (2, 3)		2 (1, 3)		<0.001	2 (2, 3)		2 (2, 3)		<0.001
Region										
Northeast	2417	17.4	2992	19.75	<0.001	3524	12.6	2792	13.58	<0.001
North Central	3643	26.23	4156	27.43		8232	29.4	6159	29.96	
South	5388	38.8	5530	36.5		12 132	43.4	8476	41.23	
West	2271	16.35	2343	15.47		3789	13.6	2932	14.26	
Unknown	169	1.22	129	0.85		289	1.03	198	0.96	
Discharge status										
Home	7171	51.63	8252	54.47	<0.001	14 041	50.21	10 741	52.25	<0.001
Home health service	5849	42.12	5996	39.58		11 892	42.52	8401	40.87	
Transfer to other facility	123	0.89	65	0.43		332	1.19	176	0.86	
Other/unknown	745	5.36	837	5.52		1701	6.08	1239	6.03	
Median household income										
<$45 000	1057	7.61	1112	7.37	0.555	2497	8.93	1770	8.61	0.113
$45 000–60 000	5876	42.31	6414	42.34		12 686	45.36	9232	44.91	
>$60 000	1516	10.92	1598	10.55		2309	8.26	1787	8.69	
Unknown	5439	39.16	6026	39.78		10 474	37.45	7768	37.79	
Insurance plan type										
Comprehensive	654	4.71	660	4.36	0.256	1664	5.95	1083	5.27	<0.001
Exclusive provider organisations	108	0.78	130	0.86		190	0.68	164	0.8	
Health maintenance organisations	1472	10.6	1632	10.77		2900	10.37	2034	9.89	
Point of service	1012	7.29	1082	7.14		2232	7.98	1504	7.32	
Preferred provider organisations	8341	60.06	9096	60.04		16 633	59.48	12 539	61	
Point of service with capitation	65	0.47	56	0.37		99	0.35	71	0.35	
Consumer driven/high deductible health plans	2103	15.14	2377	15.69		3989	14.26	2982	14.51	
Unknown	133	0.96	117	0.77		259	0.93	180	0.88	

* Analysed using Kruskal–Wallis tests; all other P-values derived from χ^2 tests. IQR, inter-quartile range.

Table 2 Results from generalised linear model predicting total oral morphine equivalents prescribed upon discharge. Data are presented as median (inter-quartile range).

	Hip		Knee	
	Total discharge Morphine equivalent		Total discharge Morphine equivalent	
	e^{β}	P-value	e^{β}	P-value
Age	0.99 (0.99, 0.99)	<0.001	0.99 (0.99, 0.99)	<0.001
Sex				
Male	1.04 (1.03, 1.06)	<0.001	1.05 (1.04, 1.06)	<0.001
Female	Reference		Reference	
Opioid naïve	0.91 (0.90, 0.92)	<0.001	0.93 (0.92, 0.93)	<0.001
Non-opioid analgesic	1.03 (1.01, 1.04)	<0.001	1.04 (1.03, 1.05)	<0.001
Discharge antidepressant	1.12 (1.04, 1.20)	0.002	1.08 (1.02, 1.13)	0.006
Discharge anxiolytic	1.18 (1.13, 1.23)	<0.001	1.17 (1.14, 1.21)	<0.001
Bilateral	0.97 (0.95, 0.99)	0.015	1.00 (0.98, 1.01)	0.688
Peripheral nerve block	1.01 (0.98, 1.03)	0.615	1.04 (1.03, 1.05)	<0.001
Year of procedure				
2012	Reference	0.006	Reference	<0.001
2013	1.00 (0.98, 1.02)		1.01 (1.00, 1.03)	
2014	1.02 (1.00, 1.04)		1.02 (1.01, 1.04)	
2015	1.02 (1.00, 1.04)		1.05 (1.03, 1.06)	
2016	1.03 (1.01, 1.05)		1.06 (1.04, 1.08)	
Length of stay	0.99 (0.99, 1.00)	0.001	0.99 (0.99, 0.99)	<0.001
Deyo index				
0	Reference	0.136	Reference	0.23
1	0.99 (0.97, 1.01)		1.00 (0.99, 1.01)	
2	0.98 (0.96, 1.00)		1.02 (1.00, 1.03)	
3	1.00 (0.98, 1.02)		1.00 (0.98, 1.02)	
Obesity	1.00 (0.99, 1.02)	0.571	0.99 (0.98, 1.00)	0.096
Sleep apnoea	1.02 (1.01, 1.04)	0.011	1.02 (1.01, 1.04)	<0.001
Region				
Northeast	Reference	<0.001	Reference	<0.001
North Central	1.09 (1.07, 1.11)		1.03 (1.02, 1.05)	
South	1.04 (1.02, 1.06)		0.99 (0.98, 1.01)	
West	1.24 (1.21, 1.27)		1.25 (1.22, 1.27)	
Unknown	1.11 (1.04, 1.17)		1.11 (1.05, 1.16)	
Discharge status				
Home	Reference	<0.001	Reference	<0.001
Home health service	1.02 (1.01, 1.03)		1.02 (1.01, 1.03)	
Transfer to other facility	1.13 (1.05, 1.22)		1.05 (1.00, 1.10)	
Other/unknown	0.99 (0.96, 1.01)		0.98 (0.96, 1.00)	
Median household income				
<$45 000	Reference	<0.001	Reference	<0.001
$45 000–60 000	1.06 (1.03, 1.08)		1.07 (1.05, 1.09)	
>$60 000	1.09 (1.06, 1.13)		1.10 (1.07, 1.12)	
Unknown	1.02 (1.00, 1.05)		1.01 (0.99, 1.03)	
Insurance plan type				
Comprehensive	Reference	<0.001	Reference	<0.001
Exclusive provider organisations	1.04 (0.96, 1.11)		1.00 (0.95, 1.06)	
Health maintenance organisations	0.97 (0.94, 1.00)		0.97 (0.95, 1.00)	
Point of service	1.04 (1.00, 1.07)		1.05 (1.02, 1.08)	
Preferred provider organisations	1.01 (0.98, 1.04)		1.04 (1.02, 1.06)	
Point of service with capitation	0.78 (0.70, 0.86)		0.83 (0.76, 0.91)	
Consumer driven/high deductible health plans	0.99 (0.96, 1.02)		1.02 (1.00, 1.04)	
Unknown	1.11 (1.02, 1.19)		0.96 (0.90, 1.01)	

patients. Finally, differences in patient preference between women and men may account, at least in part, for differences observed in discharge opioid prescribing.

Anaesthetic type and regional analgesia may influence pain and opioid-related outcomes after TJA, and we considered whether these factors contributed to the results described here. Although we were unable to assess the influence of anaesthetic type on outcomes, a prior study of neuraxial anaesthesia use concluded no significant differences based on sex.[25] In addition, we adjusted for use of peripheral nerve blocks in both multivariable models and found no sex-based differences in outcomes of interest.

Long-term opioid prescribing

Several risk factors for long-term opioid use after TJA have been identified, including high BMI, depression, greater overall body pain, more pain at the affected joint, and greater

Table 3 Results from multivariable logistic regression model predicting persistent opioid use.

	Hip		Knee	
	Chronic opioid use (*n*=2333)		Chronic opioid use (*n*=5365)	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Age	0.99 (0.98, 0.99)	<0.001	0.97 (0.97, 0.98)	<0.001
Opioid naïve	0.04 (0.03, 0.05)	<0.001	0.06 (0.05, 0.06)	<0.001
Sex				
Male	0.91 (0.83, 0.99)	0.036	0.96 (0.91, 1.03)	0.257
Female	Reference		Reference	
Discharge prescription oral Morphine equivalent	1.01 (1.00, 1.01)	<0.001	1.00 (1.00, 1.00)	<0.001
Discharge prescription				
Fentanyl	6.67 (1.89, 23.59)	<0.001	3.81 (1.49, 9.79)	<0.001
Hydrocodone	0.77 (0.68, 0.86)		0.76 (0.70, 0.82)	
Hydromorphone	1.08 (0.85, 1.38)		1.00 (0.85, 1.17)	
Meperidine	0.76 (0.17, 3.39)		1.10 (0.64, 1.91)	
Morphine	2.18 (1.22, 3.88)		2.21 (1.48, 3.31)	
Oxycodone	Reference		Reference	
Oxymorphone	1.68 (0.25, 11.24)		2.11 (0.22, 19.75)	
Tramadol	0.68 (0.47, 0.98)		0.67 (0.51, 0.89)	
Combo 2 opioids	0.88 (0.77, 1.01)		0.97 (0.89, 1.06)	
Non-opioid	2.24 (1.77, 2.84)		1.88 (1.57, 2.26)	
Non-opioid analgesic	0.94 (0.85, 1.04)	0.22	0.90 (0.84, 0.97)	0.003
Discharge antidepressant	1.49 (0.99, 2.25)	0.055	1.67 (1.28, 2.17)	<0.001
Discharge anxiolytic	1.50 (1.18, 1.90)	0.001	1.50 (1.28, 1.75)	<0.001
Bilateral	1.20 (1.01, 1.43)	0.041	1.00 (0.89, 1.12)	0.98
Peripheral nerve block	1.04 (0.86, 1.25)	0.691	0.98 (0.91, 1.04)	0.484
Year of procedure				
2012	Reference	0.044	Reference	<0.001
2013	0.95 (0.83, 1.08)		0.94 (0.89, 1.06)	
2014	0.90 (0.79, 1.04)		0.75 (0.68, 0.82)	
2015	0.85 (0.74, 0.98)		0.76 (0.69, 0.83)	
2016	0.81 (0.70, 0.94)		0.74 (0.66, 0.82)	
Length of stay	1.05 (1.03, 1.08)	<0.001	1.04 (1.02, 1.05)	<0.001
Deyo index				
0	Reference	<0.001	Reference	<0.001
1	1.53 (1.37, 1.71)		1.27 (1.18, 1.37)	
2	1.51 (1.31, 1.73)		1.51 (1.38, 1.65)	
3	2.06 (1.80, 2.35)		1.81 (1.65, 1.98)	
Obesity	1.05 (0.94, 1.18)	0.42	0.98 (0.91, 1.05)	0.504
Sleep apnoea	1.10 (0.97, 1.25)	0.147	0.98 (0.91, 1.06)	0.628
Region				
Northeast	Reference	<0.001	Reference	<0.001
North Central	1.44 (1.23, 1.70)		1.17 (1.05, 1.32)	
South	1.59 (1.36, 1.85)		1.28 (1.14, 1.42)	
West	1.55 (1.30, 1.84)		1.29 (1.14, 1.47)	
Unknown	1.75 (1.15, 2.66)		1.10 (0.81, 1.50)	
Discharge status				
Home	Reference	0.016	Reference	0.014
Home health service	1.09 (0.99, 1.20)		1.05 (0.98, 1.11)	
Transfer to other facility	1.84 (1.20, 2.83)		1.48 (1.15, 1.90)	
Other/unknown	1.00 (0.81, 1.22)		1.07 (0.94, 1.21)	
Median household income				
<$45 000	Reference	0.008	Reference	0.008
$45 000–60 000	0.78 (0.66, 0.91)		0.85 (0.76, 0.94)	
>$60 000	0.71 (0.57, 0.88)		0.80 (0.70, 0.94)	
Unknown	0.79 (0.67, 0.94)		0.88 (0.79, 0.99)	
Insurance plan type				
Comprehensive	Reference	0.01	Reference	<0.001
Exclusive provider organisations	0.99 (0.60, 1.63)		0.70 (0.47, 1.03)	
Health maintenance organisations	0.93 (0.73, 1.19)		0.81 (0.70, 0.94)	
Point of service	0.93 (0.72, 1.20)		0.72 (0.61, 0.85)	
Preferred provider organisations	0.89 (0.73, 1.10)		0.72 (0.63, 0.81)	
Point of service with capitation	1.18 (0.59, 2.35)		0.56 (0.30, 1.06)	
Consumer driven/high deductible health plans	0.70 (0.56, 0.89)		0.57 (0.49, 0.66)	
Unknown	1.28 (0.80, 2.04)		0.91 (0.66, 1.26)	
c-Statistic	0.797		0.781	

OR, odds ratio; CI, confidence interval.

functional impairment.[5–8] Preoperative opioid tolerance has been linked to elevated risk of chronic opioid use after THA and TKA, although chronic use has also been described in opioid naïve cohorts.[5–9,11,12] Previous studies associating sex with chronic opioid use after TJA have yielded contradictory results. Several large retrospective series link female sex with higher risk for long-term use after TJA.[5,6,8,9] However, other prospective[7] and population-based[10] analyses found no difference in opioid use between men and women after TJA. More recently, a retrospective cohort study found that male sex predicted ongoing opioid use after TKA.[11]

Given that more women received a prescription for opioids in the year before TJA, we expected more women to also be taking opioids for an extended duration after surgery. However, we found that *disproportionately* more women received an ongoing opioid prescription compared with men on univariate analysis, and after THA on adjusted analyses. We note that this latter procedure-specific difference could represent a source of bias in the current study. Alternatively, these results suggest that preoperative opioid tolerance alone may be less important for women undergoing TJA than for men, and that additional factors may influence the development of persistent opioid use and misuse in women. For example, there is increasing awareness that sex influences both pain and the development of substance use disorders, and women report greater sensitivity to pain and the emotional aspects of pain than men.[26] Furthermore, women may develop substance use disorders more rapidly than men after exposure to an addictive agent.[27] The biological mechanisms by which women may be more sensitive to these events are not entirely clear, but preclinical and clinical studies link ovarian hormones to opioid receptor expression, hyperalgesia, and the reinforcing effects of opioid self-administration.[28]

We found the overall incidence of chronic opioid prescribing was 10%. This is lower than published accounts of persistent opioid use after TJA, which estimate that 15–24% of patients will continue to use opioids at 6–12 months after surgery.[7,8] Conversely, other research has estimated ongoing use to be as low as 1.4% at 2 and 5 yr after TKA.[6] Differences in methods, definitions used, small sample sizes, incomplete follow-up, and comparison of mixed opioid-tolerant and opioid-naive cohorts may contribute to these differences in findings. Furthermore, these discrepancies may be explained by the different patient age groups and time frames included in the analyses. Data sets capturing more remote trends in opioid prescribing,[10] and prescribing in restricted age groups[19] may not be directly comparable with the current results.

Other factors influencing sex-based differences in medication prescribing

Several factors may influence opioid prescribing for men and women irrespective of phase-of-care or type of surgery. Chief among these is the possibility of (unconscious) prescriber bias. Population-based studies of controlled substance co-prescribing link higher rates of benzodiazepine prescribing to female patients, suggesting that female patients may be more often perceived as anxious rather than in pain, compared with male patients.[29,30] Potential sex-related differences in prescribing patterns and medical decision-making may in turn elevate the risk of opioid-related harm among women. For example, women were three times less likely than men to receive naloxone from emergency medical services during attempted resuscitation for subsequent opioid overdose death. Women are also more likely to be given prescription opioids than men for general medical and surgical conditions, and to be prescribed opioids for chronic pain conditions, such as headache, which do not have data supporting treatment benefit. In order to reduce sex-based disparities in outcomes after TJA, it is important to be aware of the potential for sex biases on the part of prescribers in the assessment and treatment of actual pain.

Our results suggest sex-based differences in prescribing are not restricted to opioids. Consistent with earlier studies on this topic, we found that women were more likely to be prescribed either an antidepressant or an anxiolytic after THA and more likely to be prescribed antidepressants after TKA.[21,22] In contrast to opioids, there are multiple indications for psychotropics and anxiolytics, and we were unable to distinguish between patients who were taking these medications for mood disorders or as part of a pain management strategy for TJA. However, after adjusting for these prescriptions in multivariable models, the relationship between patient sex and the outcomes of oral morphine equivalents prescribed upon discharge and chronic opioid use remained unchanged. Interestingly, patients prescribed either of these medications were also prescribed greater quantities of opioids upon discharge and both medications were associated with increased odds of chronic opioid use.

These results also raise the possibility of specialty-specific differences in opioid prescribing behaviour. We found women were more likely than men to be prescribed opioids during the preoperative and post-discharge phases of care; these represent phases of care during which surgical teams are more likely to provide opioid prescriptions. In contrast, men were prescribed more opioids at discharge after TJA – a phase of care during which prescribing is likely to be performed or influenced by the anaesthesiologist. These patterns are provocative and suggest the opportunity for cross-disciplinary education and standardisation of best practices for opioid prescribing.

Limitations and strengths

Our study is subject to several limitations. First among these is that the retrospective design does not permit causal conclusions between sex and opioid prescribing to be drawn. Reasons underlying sex-based differences in opioid prescribing found here are purely speculative and should be viewed as hypothesis-generating. Furthermore, other factors which influence relationships between sex and opioid prescribing may not have been identified or controlled for in the present study. Importantly, we were unable to assess pain intensity or trajectory, and severity of preoperative pain at the surgical site has been identified as a risk factor for increased pain after TJA.[31] Our dataset relied on billing codes for pharmacy dispensing, which raises the possibility of misclassification of prescribed medications. Allied to this, the design does not permit an analysis of how prescribing relates to subsequent opioid use and consumption and does not account for possible drug storage or diversion after a prescription is dispensed. Our dataset encompassed 2012–2016, so our reported trends may not reflect current practice – especially as it relates to preoperative opioid prescribing for chronic non-cancer pain.[32] TJA is commonly performed in older patients, and patients on Medicare were not captured in the current dataset. Finally, the analysis was restricted to patients undergoing surgery in the USA, limiting generalisability. However, recent increasing

trends in prescription opioid use, misuse and mortality in European countries suggest the results may also be relevant outside the USA.[33,34]

Strengths of this study include the large sample size drawn from a geographically diverse population, reflecting broad trends in clinical practice. We also included data on regional analgesia techniques used during the TJA admission, which may help minimise the confounding effect of pain on opioid prescribing.

Conclusions

In conclusion, we found sex-based differences in opioid prescribing in a national cohort of patients who underwent THA or TKA. Women were more likely than men to have received an opioid prescription in the year before TJA. Despite men having been prescribed more opioid at discharge than women, women were nonetheless more likely to receive a prescription for an opioid up to 1 yr after surgery. A key question raised by these results is whether preoperative use of opioids is a risk factor for worse outcomes and ongoing use after TJA or if biopsychosocial differences that lead preoperative use of opioids also explain postoperative risk. Our findings additionally raise the possibility of prescriber bias, but do not suggest the direction of bias or underlying reasons for sex-based differences in the choice of opioid, or the dose and duration provided. These are important topics for future investigation as all represent opportunities to tailor interventions to reduce opioid consumption and improve outcomes for women after TJA.

Authors' contributions

Study concept and design: EMS, SGM
Drafting of the manuscript and critical revision for important intellectual content: EMS, LAW, JL, JP, SGM
Acquisition, analysis, and interpretation of data: LAW, JL, JP, SGM
All authors gave final approval of the version to be published and agreed to be accountable for all aspects of the work.

Funding

There are no funding bodies/sources of funding to report for the current work.

Declarations of interests

SGM is a director on the boards of the American Society of Regional Anesthesia and Pain Medicine (ASRA) and the Society of Anesthesia and Sleep Medicine (SASM). He is a one-time consultant for Sandoz Inc. and Teikoku and is currently on the medical advisory board of HATH. He has a pending US Patent application for a Multicatheter Infusion System, US-2017-0361063. He is the owner of SGM Consulting, LLC and co-owner of FC Monmouth, LLC. All other authors declare no conflicts of interest

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2020.12.046.

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Handling editor: Lesley Colvin