OPIOIDS & SUBSTANCE USE DISORDERS SECTION

Opioid Prescribing and Polypharmacy in Children with Chronic Musculoskeletal Pain

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Abstract

Objective. Thirty percent of adults with fibromyalgia receive an opioid, but the prevalence of opioid prescribing in pediatric chronic musculoskeletal pain is unknown. The aims of this study were to determine the prevalence of and factors associated with opioid exposure and polypharmacy among children with chronic musculoskeletal pain. **Methods.** In this retrospective cohort study using health care claims data from 2000 to 2013, the index date was the first ICD-9 code 729.1. Included subjects were ≥ 2 and < 18 years old at the index date with two or more codes within 12 months and 18 months of continuous enrollment. Subjects with burns, sickle cell disease, or malignancy were excluded. Opioid exposure was defined as one or more prescriptions within six months before or any time after the index date. Polypharmacy was considered minor (2–4 medications) or major (≥ 5 medications). **Results.** Of 25,321 included subjects, 20% received an opioid and 26% experienced minor polypharmacy. Opioid exposure was associated with female sex (odds ratio [OR] = 1.27, $P < 0.01$), Caucasian race (OR = 1.27, $P < 0.01$), hospitalization (OR = 1.20, $P < 0.01$), and visit with anesthesiology (OR = 1.97, $P < 0.01$) or orthopedics (OR = 1.09, $P < 0.05$). Mental health codes were associated with decreased odds of opioid exposure (all $P < 0.05$). Children seen by a chiropractor or physiatrist had a reduced odds of receipt of an opioid (OR = 0.42 and 0.84, respectively, both $P < 0.01$). **Conclusions.** Twenty percent of children with chronic musculoskeletal pain received an opioid. Twenty-six percent experienced polypharmacy, with the majority receiving 2–4 medications. Increased availability of psychological and nonpharmacologic services are potential strategies to reduce opioid exposure.

Key Words: Fibromyalgia, Chronic Pain, Opioids, Pediatric

Introduction

Pediatric chronic pain, defined as pain for at least three months [1], is a major public health issue with a high prevalence [2] and socioeconomic burden [3,4]. Juvenile fibromyalgia syndrome (JFMS) is the most common pediatric idiopathic musculoskeletal pain syndrome, affecting 2–6% of all children [5]. Children with chronic pain have increased health care utilization [6–8], more mental health

and social problems [9,10], and greater school absenteeism, while parents suffer financial, social, and psychological consequences [4,11]. Children with chronic pain have a greater likelihood of chronic pain in adulthood, which is one of the most costly medical conditions in Western society [4,12,13]. Further investigation into the optimal treatment regimens for pediatric chronic pain is needed to reduce its overall psychological and socioeconomic burden.

The diagnosis and management of chronic musculoskeletal pain remains challenging because of a lack of pediatric-focused evidence [3]. Pharmacologic management of chronic musculoskeletal pain with opioids is not recommended by rheumatologists because of limited data on their efficacy and safety in children [14,15]. Opioids are ineffective for adults with fibromyalgia syndrome [16] and have potentially detrimental side effects, including new-onset depression [17]. Despite this, approximately 30% of adults with fibromyalgia syndrome are prescribed opioids [18]. The American Pain Society 2005 treatment guidelines state that opioid use for the management of fibromyalgia pain should be used only “after all other pharmacologic and nonpharmacologic therapies have been exhausted” [19]. In 2016, the Centers for Disease Control and Prevention released a “Guideline for Prescribing Opioids for Chronic Pain,” stating that opioids are not firstline or standard therapy for chronic pain, favoring nonpharmacologic and nonopioid pharmacologic interventions [20]. In addition, nonopioid analgesics, antidepressants, anticonvulsants, muscle relaxants, and benzodiazepines are commonly prescribed for children with chronic musculoskeletal pain [21]. The use of multiple medications, or polypharmacy, is a potential risk among children with chronic musculoskeletal pain and can lead to adverse drug reactions. The prevalence of and factors associated with opioid prescribing and polypharmacy in the treatment of pediatric chronic musculoskeletal pain have not been established.

We conducted a retrospective cohort study to analyze a large US administrative health care claims database to 1) determine the prevalence of and factors associated with opioid prescribing and 2) determine the extent and predictors of polypharmacy in children with chronic musculoskeletal pain.

Methods

Data Source

Clinformatics DataMart (OptumInsight, Eden Prairie, MN, USA) is a large, contemporary US database of managed care claims. Member coverage is geographically diverse, with coverage across all US Census regions. The database consists of aggregated enrollment data for more than 45 million unique managed care members. The medical claims include *International Classification of Disease, Ninth Revision, Clinical Modification* (ICD-9-CM) diagnosis and procedure codes. Outpatient pharmacy claims include National Drug Code (NDC) numbers for medications, including fill date, quantity dispensed, dose, and number of days' supply. Key information extracted from the database included demographics (age, sex, and index year), outpatient pharmacy claims to determine medications received, clinically relevant comorbidities (ICD-9-CM diagnoses codes, Current Procedure Terminology codes), and dates of service.

Subjects

We included subjects with claims data available between May 1, 2000, and June 30, 2013, who were two to less than 18 years of age. ICD-9-CM code 729.1 (myalgia and myositis, unspecified) was appended twice in a 12-month period. Included subjects had continuous enrollment six months before and 12 months after the index date. The index date was defined as date of the subject's first ICD-9-CM code 729.1. Subjects with burns, sickle cell disease, or malignancy were excluded. These inclusion/exclusion criteria were employed to identify a cohort of children receiving medical care for chronic musculoskeletal pain as we would not be able to definitively determine whether subjects in this health care claims database met the American College of Rheumatology criteria for fibromyalgia syndrome. The Institutional Review Board (IRB) of the Children's Hospital of Philadelphia determined that the study did not meet the definition of human subjects research; therefore, ongoing IRB oversight was not required, and ethics approval was waived.

Outcomes

The primary outcome, opioid exposure, was binary and was defined as one or more prescriptions within six months before or any time after the index date, with data censored at 18 years of age. We included the six months before the index date because it is known that there is significant delay in diagnosis for children with chronic musculoskeletal pain [22,23]; therefore, we suspected that for six months before the first ICD-9 code, subjects could potentially be treated with opioids for chronic pain. Opioids were categorized into strong opioids (e.g., morphine, oxycodone, etc.) and weak opioids (codeine, hydrocodone, propoxyphene, and tramadol) [18]. The secondary outcome, polypharmacy, was defined as an ordinal variable (0 = no polypharmacy; 1 = minor polypharmacy [2–4 medications]; 2 = major polypharmacy [≥ 5 medications]) [24]. This definition of polypharmacy was employed to be consistent with commonly used definitions of polypharmacy according to a published meta-analysis so that our findings could be interpreted in the context of previously reported research [25]. We identified drug prescriptions for nonopioid analgesics, glucocorticoids, antidepressants, muscle relaxants, stimulants, anxiolytics, anticonvulsants, antipsychotics, opioid antagonists, biologics, and disease-modifying antirheumatic drugs (DMARDs). We limited polypharmacy to that which occurred within six months before or any time after the index date, and we evaluated for polypharmacy based on the number of filled prescriptions on a single encounter date. Lastly, we assessed for opioid overdose (binary variable) at any time during the study interval employing previously implemented opioid medication poisoning codes (965.00, 965.02, 965.09, E.850.1, E.850.2) [26].

Covariates

Medical encounter history was assessed by provider type and place of service and was defined as one or more

Table 1. Demographics and comorbidities by opioid exposure

	Total (N = 25,321)	Opioid-Exposed (N = 4,903)	Opioid-Unexposed (N = 20,418)
Demographics			
Female, No. (%)	13,808 (54.5)	2,963 (60.4)	10,845 (53.1)
Caucasian,* No. (%)	19,592 (79.5)	3,900 (81.5)	15,692 (79.0)
Non-Hispanic,* No. (%)	22,938 (93.0)	4,493 (93.9)	18,445 (92.8)
Age at index date, median (IQR), y	14 (11–16)	14 (12–16)	14 (10–16)
Psychological comorbidities, No. (%)			
Any psychological comorbidity	7,709 (30.5)	2,094 (42.7)	5,448 (26.7)
Adjustment disorder	2,666 (10.5)	725 (14.8)	1,941 (9.5)
Anxiety	3,963 (15.7)	1,168 (23.8)	2,795 (13.7)
Conversion disorder	476 (1.9)	198 (4.0)	278 (1.4)
Eating disorder	178 (0.7)	52 (1.1)	126 (0.6)
Depression	4,177 (16.5)	1,271 (25.9)	2,906 (14.2)
Alcohol misuse/abuse	538 (2.1)	177 (3.6)	361 (1.8)
Other substance abuse	1,077 (4.3)	416 (8.5)	661 (3.2)
Opioid misuse	118 (0.5)	77 (1.6)	41 (0.2)
Psychosis	220 (0.9)	64 (1.3)	156 (0.8)
Medical comorbidities, No. (%)			
Inflammatory arthritis	1,713 (6.8)	572 (11.7)	1,141 (5.6)
SLE	83 (0.3)	37 (0.8)	46 (0.2)
Sjögren syndrome	24 (0.1)	12 (0.2)	12 (0.1)
CRPS	82 (0.3)	45 (0.9)	37 (0.2)
Hypermobility	199 (0.8)	73 (1.5)	126 (0.6)
IBD	147 (0.6)	49 (1.0)	98 (0.5)
Any CCC	3,699 (14.6)	901 (18.4)	2,798 (13.7)

CCC = complex chronic condition; CRPS = complex regional pain syndrome; IBD = inflammatory bowel disease; IQR = interquartile range; SLE = systemic lupus erythematosus.

*Race and ethnicity was missing for 663 subjects. Any psychological comorbidity was defined as an encounter with at least one ICD-9 code indicating one of the following conditions: adjustment disorder, anxiety, conversion disorder, eating disorder, depression, alcohol misuse/abuse, other substance abuse, opioid misuse, or psychosis.

encounters for each assessed provider type and place of service before or at the time of first opioid prescription. Places of service assessed included the emergency department, urgent care center, mental health facility, and inpatient visit. Psychological and medical comorbidities were identified by ICD-9-CM codes. Complex chronic conditions were assessed utilizing the algorithm developed by Feudtner et al. [27], including the following categories: neurologic and neuromuscular, cardiovascular, respiratory, renal and urologic, gastrointestinal, hematologic or immunologic, metabolic, other congenital or genetic defect, premature and neonatal, transplant, and technology dependent (malignancy was excluded).

Data Analysis

We characterized subjects with chronic musculoskeletal pain by demographic variables (age, sex, race, US Census region), medications prescribed, and presence of psychological and medical comorbidities. Demographics were summarized by standard descriptive statistics including frequencies and percentages for categorical variables (e.g., sex, race), and by range, median, and interquartile range (IQR) for continuous or count variables. Two medians were compared by Wilcoxon rank-sum test, and two proportions were compared by the chi-square test or Fisher exact test, as appropriate. The trend in the number of absolute opioid prescriptions prescribed for subjects with chronic musculoskeletal pain per calendar year was

tested by the “nptrend” command implemented in Stata. Univariate logistic regression modeling was performed to estimate the unadjusted odds ratio (OR) of opioid exposure with each of the independent variables. Multivariate logistic regression modeling with forward selection procedure ($P < 0.1$ for entering the model) was used to identify factors associated with opioid exposure, adjusting for demographics, comorbidities, and medical encounter history (places of service and provider types). Multicollinearity was assessed between the continuous covariates before the multivariate logistic regression analyses, and goodness of fit was assessed using the Hosmer–Lemeshow (H–L) test. A sensitivity analysis was performed in which opioid exposure was defined as at least 2 opioid prescribing events on separate encounter dates. For the secondary outcome of polypharmacy (coded as no, minor, and major polypharmacy), ordinal logistic regression was used, and the proportional odds assumption was tested with the Brant test. The Fisher exact test was used to assess for differences based on opioid overdose. All data analyses were performed using STATA 14 (STATA Corp, College Station, TX, USA).

Results

A total of 25,321 subjects met study inclusion and exclusion criteria and were identified as children with chronic musculoskeletal pain. Table 1 lists subject characteristics.

Figure 1. Number of absolute opioid prescriptions for children labeled with chronic musculoskeletal pain per year. Over the course of the study interval, there was an increasing trend in the number of absolute opioid prescriptions prescribed for subjects with chronic musculoskeletal pain per calendar year ($P < 0.01$). We excluded the years 2000 and 2013 because data were not available for the entire calendar year. Weak opioid prescriptions included codeine ($N = 4,844$), tramadol ($N = 2,364$), hydrocodone ($N = 576$), and propoxyphene ($N = 16$).

The majority were female (54.5%), and subjects were predominantly Caucasian (79.5%). The median age at time of first code 729.1 was 14 (IQR: 11–16) years. The median duration of continuous subject enrollment was 5.4 (IQR: 3.7–7.7) years.

Subjects had a number of comorbid psychological and medical diagnoses (Table 1). Nearly one-third (30.5%) of subjects had at least one type of documented psychological diagnosis at any time during the study interval. Depression was documented in 16.5% of subjects ($N = 4,177$), and an anxiety disorder was documented in 15.7% ($N = 3,963$). At least one rheumatologic comorbidity occurred in 8.3% of subjects ($N = 2,111$). Inflammatory arthritis ($N = 1,713$), hypermobility syndrome ($N = 199$), and inflammatory bowel disease ($N = 147$) were the most common. Approximately 15% ($N = 3,669$) of the entire cohort had at least one complex chronic condition (excluding malignancy). The most commonly represented complex chronic conditions included congenital or genetic defects ($N = 1,402$), metabolic ($N = 1,022$), cardiovascular ($N = 637$), gastrointestinal ($N = 424$), and neurologic and neuromuscular ($N = 354$).

Opioids

Nearly one in five (19.4%) received at least one prescription for an opioid medication within six months before or any time after the index date; 18.7% had their first prescription within six months before the index date, and 81.3% after the index date. The median age at time of first opioid prescription was 16 (IQR: 13–17) years. The most common opioid medications included codeine (70.4%), tramadol (20.0%), oxycodone (13.5%), and hydrocodone (6.9%). Figure 1 demonstrates the number

of unique opioid prescriptions prescribed by calendar year. Between 2000 and 2012, there was an increasing trend in the prescribing of opioids for children with chronic musculoskeletal pain (“nptrend” $P < 0.01$), and this was true for both weak and strong opioids (both $P < 0.01$). Of the subjects exposed to opioids, the majority (68.3%) had only one opioid exposure, whereas 31.7% of subjects ($N = 1,556$) had two or more opioid exposures, and 5.3% ($N = 260$) had more than four opioid exposures.

In multivariate logistic regression (Table 2), opioid exposure was associated with female sex (OR = 1.27, 95% confidence interval [CI] = 1.18–1.35), older age (OR = 1.05, 95% CI = 1.04–1.06), white race (OR = 1.27, 95% CI = 1.17–1.38), residence in the Western United States compared with the Northeast (OR = 1.16, 95% CI = 1.02–1.31), any complex chronic condition (OR = 1.22, 95% CI = 1.11–1.33), and history of hospitalization (OR = 1.20, 1.09–1.31). Children with a mental health disorder, including anxiety (OR = 0.86, 95% CI = 0.78–0.95), alcohol misuse/abuse (OR = 0.75, 95% CI = 0.57–0.98), and psychosis (OR = 0.62, 95% CI = 0.40–0.95), were less likely to be opioid exposed. An encounter with a primary care physician was associated with a decreased odds of opioid exposure (OR = 0.59, 95% CI = 0.51–0.70), as was a visit with a physiatrist (OR = 0.84, 95% CI = 0.75–0.94) or a psychologist (OR = 0.67, 95% CI = 0.46–0.99). Children seen by anesthesiologists (OR = 1.97, 95% CI = 1.83–2.13) or orthopedic surgeons (OR = 1.09, 95% CI = 1.02–1.17) had an increased odds of opioid exposure. A sensitivity analysis redefining opioid-exposed patients as those with at least two opioid exposures confirmed the above associations, with the exception of alcohol misuse/abuse, which

Table 2. Univariate and multivariate logistic regression models for primary outcome of opioid exposure

Variable	Univariate Model			Multivariate Model		
	OR	95% CI	P Value	Adjusted OR	95% CI	P Value
Female	1.35	1.27–1.44	<0.01	1.27	1.18–1.35	<0.01
Age at index, y	1.05	1.04–1.06	<0.01	1.05	1.04–1.06	<0.01
White race	1.17	1.08–1.27	<0.01	1.27	1.17–1.38	<0.01
Non-Hispanic	1.18	1.04–1.35	<0.05	—	—	—
Region						
Northeast	1.00	—	—	1.00	—	—
Midwest	1.01	0.91–1.13	0.85	1.02	0.91–1.15	0.71
South	1.09	0.98–1.21	0.11	1.04	0.93–1.16	0.55
West	1.03	0.91–1.16	0.67	1.16	1.02–1.31	<0.05
Previous comorbidities						
Adjustment disorder	0.98	0.88–1.09	0.69	0.91	0.81–1.02	0.09
Anxiety disorder	0.99	0.91–1.09	0.88	0.86	0.78–0.95	<0.01
Conversion disorder	1.29	1.01–1.65	0.04	—	—	—
Eating disorder	1.06	0.72–1.56	0.78	—	—	—
Depression	1.11	1.02–1.21	<0.05	—	—	—
Alcohol misuse/abuse	0.85	0.66–1.10	0.21	0.75	0.57–0.98	<0.05
Other substance abuse	1.20	1.02–1.41	<0.05	—	—	—
Psychosis	0.72	0.48–1.08	0.12	0.62	0.40–0.95	<0.05
Inflammatory arthritis	1.44	1.28–1.62	<0.01	—	—	—
SLE	1.81	1.07–3.07	<0.05	—	—	—
Sjögren syndrome	2.08	0.78–5.55	0.14	—	—	—
CRPS	2.48	1.46–4.21	<0.01	—	—	—
Hypermobility	1.16	0.80–1.69	0.44	—	—	—
IBD	1.28	0.85–1.92	0.24	—	—	—
Any CCC	1.42	1.31–1.54	<0.01	1.22	1.11–1.33	<0.01
Previous place of service encounters						
Urgent care	0.99	0.84–1.18	0.95	—	—	—
Emergency department	0.70	0.66–0.75	<0.01	0.90	0.84–0.97	<0.01
Inpatient	1.53	1.41–1.66	<0.01	1.20	1.09–1.31	<0.01
Mental health facility	1.02	0.66–1.58	0.93	—	—	—
Previous provider type encounters						
Primary care	0.63	0.55–0.73	<0.01	0.59	0.51–0.70	<0.01
Rheumatology	1.54	1.33–1.78	<0.01	0.87	0.75–1.02	0.09
Anesthesiology	2.09	1.95–2.24	<0.01	1.97	1.83–2.13	<0.01
Neurology	1.26	1.14–1.38	<0.01	—	—	—
Acupuncturist	0.96	0.87–1.07	0.47	0.90	0.81–1.02	0.06
Chiropractor	0.41	0.38–0.44	<0.01	0.42	0.39–0.45	<0.01
Orthopedist	1.23	1.15–1.31	<0.01	1.09	1.02–1.17	<0.05
Physiatrist	1.06	0.95–1.19	0.28	0.84	0.75–0.94	<0.01
Psychology	0.66	0.45–0.97	0.03	0.67	0.45–0.99	<0.05
Psychiatry	1.00	0.92–1.10	0.96	—	—	—

CCC = complex chronic condition; CI = confidence interval; CRPS = complex regional pain syndrome; IBD = inflammatory bowel disease; OR = odds ratio; SLE = systemic lupus erythematosus.

was no longer statistically significantly associated with opioid exposure (OR = 1.13, 95% CI = 0.79–1.63).

Polypharmacy

Minor polypharmacy occurred in 26.4% of subjects (N = 669), and major polypharmacy in 0.23% (N = 58). Subjects were most commonly exposed to nonopioid analgesics (35.9%) and glucocorticoids (33.8%), though antidepressants (18.5%), muscle relaxants (13.6%), and stimulant medications (10.9%) were also commonly prescribed. Less common were anxiolytics (8.3%), anticonvulsants (5.2%), antipsychotics (3.7%), DMARDs (1.0%), opioid antagonists (0.2%), and biologics (0.1%).

Children exposed to opioids had a greater likelihood of any polypharmacy than those who were not opioid exposed (87.4% vs 12.1%, $P < 0.001$) (Table 3). In multivariate ordinal logistic regression modeling (Table 4), female sex (OR = 1.13, 95% CI = 1.07–1.20), Caucasian race (OR = 1.34, 95% CI = 1.24–1.45), and older age at index date (OR = 1.08, 95% CI = 1.07–1.09) were all associated with an increased odds of polypharmacy. The same was true for a prior diagnosis of anxiety (OR = 1.42, 95% CI = 1.30–1.55), depression (OR = 1.77, 95% CI = 1.62–1.93), or a complex chronic condition (OR = 1.37, 95% CI = 1.27–1.49). At least one previous encounter in a mental health facility (OR = 2.05, 95% CI = 1.33–3.17) or hospitalization (OR = 1.19, 95% CI = 1.09–1.30) was

Table 3. Demographics and opioid use by polypharmacy exposure

	Total (N = 25,321)	No Polypharmacy (N = 18,568)	Minor Polypharmacy (N = 6,695)	Major Polypharmacy (N = 58)
Demographics				
Female, No. (%)	13,808 (54.5)	9,772 (52.6)	3,996 (59.7)	40 (69.0)
Caucasian,* No. (%)	19,592 (79.5)	14,198 (78.6)	5,351 (81.9)	43 (76.8)
Non-Hispanic,* No. (%)	22,938 (93.0)	16,758 (92.7)	6,127 (93.8)	53 (94.6)
Age at index date, median (IQR), y	14 (11–16)	14 (10–16)	15.0 (12–16)	15 (13–16)
Opioid exposure, No. (%)	4,903 (19.4)	619 (3.3)	4,243 (63.4)	41 (70.7)
Age at first opioid exposure, median (IQR), y	16 (13–17)	16 (14–18)	16 (13–17)	16 (14–18)

IQR = interquartile range.

*Race and ethnicity missing for 663 subjects.

Table 4. Multivariate ordinal logistic regression modeling for polypharmacy exposure

Variable	Adjusted OR	95% CI	P Value
Demographics			
Female	1.13	1.07–1.20	<0.01
Age at index, y	1.08	1.07–1.09	<0.01
White	1.34	1.24–1.45	<0.01
Region			
Northeast (reference)	1.00	—	—
Midwest	1.09	0.98–1.21	0.12
South	1.23	1.11–1.36	<0.01
West	1.06	0.94–1.20	0.32
Previous comorbidities			
Anxiety	1.42	1.30–1.55	<0.01
Depression	1.77	1.62–1.93	<0.01
Any CCC	1.37	1.27–1.49	<0.01
Previous place of service encounters			
Emergency department	0.87	0.81–0.93	<0.01
Inpatient	1.19	1.09–1.30	<0.01
Mental health facility	2.05	1.33–3.17	<0.01
Previous provider type encounters			
Primary care	0.55	0.48–0.63	<0.01
Anesthesiologist	1.44	1.34–1.56	<0.01
Neurologist	1.29	1.17–1.41	<0.01
Chiropractor	0.36	0.34–0.39	<0.01
Orthopedist	0.92	0.87–0.98	<0.05

CCC = complex chronic condition; CI = confidence interval; OR = odds ratio.

associated with an increased odds of polypharmacy. Encounters with an anesthesiologist (OR = 1.44, 95% CI = 1.34–1.56) or neurologist (OR = 1.29, 95% CI = 1.17–1.41) were also associated with polypharmacy.

Opioid overdose occurred in 30 subjects (0.12%). Anxiety (56.7% vs 15.6%) and depression (86.7% vs 16.4%) were both more common in those who overdosed ($P < 0.001$). Any polypharmacy (minor or major) was more likely in those exposed to opioids (0.37% vs 0.03%, $P < 0.001$), although the total number of events was small. We were unable to evaluate deaths related to opioid overdose because the data source did not include mortality data.

Discussion

In this study of more than 25,000 children with chronic musculoskeletal pain from across the United States, we

found that nearly 20% were exposed to opioids and nearly 25% experienced any polypharmacy (minor or major). Encounters with an anesthesiologist or in the inpatient setting were associated with opioid exposure, whereas access to mental health resources and nonpharmacologic treatment options were associated with a decreased odds of opioid exposure. These findings provide possible targets for educational interventions as well as evidence to support the need for improved access to mental health care and nonpharmacological treatment options in the management of pediatric chronic musculoskeletal pain. In the era of an opioid epidemic, more judicious use of opioids and minimization of unnecessary polypharmacy among children is paramount. Opioid prescribing among the pediatric population doubled between 1990 and 2010 [14]. Between the years 1976 and 2015, one-quarter of high school seniors self-reported medical or nonmedical use of prescription opioids [28]. This alarming trend has been associated with a number of adverse consequences such as accidental opioid poisonings in young children [29–31]. Emphasis on the limitation of the use of opioids for children, especially among those with chronic musculoskeletal pain, may serve as a potential avenue for curbing the opioid epidemic.

The majority of opioid exposures in this study included weak opioids; however, their risks are similar to those of strong opioids [32]. For example, a report by the Substance Abuse and Mental Health Services Administration determined that emergency department visits associated with tramadol-related adverse events increased by 145% during 2005–2011 [33]. Furthermore, when combined with anti-anxiety medications or other opioids, the sedative effects of tramadol can be enhanced [33], underscoring how polypharmacy modifies the potentially dangerous side effects of even a weak opioid. In a study among commercially insured, opioid-naïve, cancer-free adults, it was found that after strong opioids, tramadol was the medication with the next highest probability of long-term use, suggesting its potential for dependence and abuse [34]. Although there is evidence to support the use of tramadol in the treatment of adult fibromyalgia syndrome [35–37], there are no controlled pediatric data to support its use in pediatric chronic

musculoskeletal pain [38]. Moreover, the use of tramadol and oxycodone among the pediatric population has fallen out of favor in recent years [39]. Future studies looking at more recent trends in prescribing patterns of weak opioids for children with chronic musculoskeletal pain are needed.

Although the majority of opioid-exposed subjects in our study received only one opioid prescription, one-third had two or more prescriptions. Because our data are limited to filled prescriptions, subjects might not have filled subsequent opioid prescriptions due to their inefficacy in treating their pain. Nonetheless, research in adults demonstrates that even a single opioid prescription can be associated with an increased risk of long-term opioid use. In a study of a cohort of commercially insured, opioid-naïve adults, a one-day opioid prescription carried a 6% risk of use at one year later and a 2.9% risk of use three years later [34].

Regarding factors associated with opioid prescribing, we found that the presence of a mental health disorder and an encounter with a psychologist were associated with a decreased odds of receipt of an opioid prescription but increased odds of polypharmacy. These findings suggest that improved mental health care for children with chronic musculoskeletal pain might serve as a barrier against prescribing of opioids in this patient population. Prior visits with a physiatrist or chiropractor were also associated with decreased odds of opioid exposure. These findings suggest that increased availability and accessibility of nonpharmacologic interventions might reduce the prescribing of opioids among children with chronic musculoskeletal pain [40].

The observed association between opioid exposure and prior hospitalization or at least one encounter with an anesthesiologist or orthopedic surgeon could be partially due to the fact that these providers will commonly perform medical procedures such as nerve blocks to treat chronic pain. Alternatively, it is possible that the most severe cases of chronic musculoskeletal pain present to these subspecialists, at which point opioids are trialed after other therapeutic options have failed. Therefore, increased education regarding the use of psychological and other nonopioid strategies would likely be beneficial for all practitioners.

Children with chronic musculoskeletal pain also received a wide variety of nonopioid medications. Although the majority of subjects experienced minor, rather than major, polypharmacy, we argue that two to four medications prescribed concurrently can introduce potential harm and should be carefully evaluated by prescribing providers to ensure that this degree of polypharmacy is warranted. Not surprisingly, the presence of medical or psychological comorbidities was associated with an increased risk of polypharmacy. An encounter with a neurologist was also associated with an increased risk of polypharmacy. This could be due to the fact that patients with chronic musculoskeletal pain, especially

those with juvenile fibromyalgia syndrome, have a multitude of symptoms (e.g., migraines, irritable bowel syndrome, and depression), each of which may benefit from a different pharmacologic agent. We cannot conclude that subjects in this study received irrational (or unnecessary) polypharmacy, but given the degree of polypharmacy prevalent in this cohort, it is prudent that patients with chronic musculoskeletal pain receive a coordinated, multidisciplinary treatment approach to mitigate any risks of irrational polypharmacy.

Limitations

Our study has limitations inherent to the use of retrospective claims data, including incomplete/missing data, lack of generalizability, risk of bias from unmeasured confounders, and selection bias of a commercially insured population. However, claims data afford this study's large sample size and otherwise nationally representative data. Additionally, the ICD-9-CM code 729.1 is nonspecific and has not been validated. However, similar to previously published studies, appending 729.1 twice in a 12-month period likely increased the specificity of the code [41–43]. Additionally, we were less concerned with whether the study subjects truly had a particular medical condition such as juvenile fibromyalgia syndrome, but rather whether they were prescribed opioids for chronic musculoskeletal pain or suspected chronic musculoskeletal pain. We acknowledge that we may be failing to capture all subjects with chronic musculoskeletal pain, given that the condition is often misdiagnosed and underdiagnosed. This, however, likely strengthens our findings as we suspect that opioid exposure among children with chronic musculoskeletal pain is likely more prevalent than observed in our data. Underreporting of mental health disorders may have occurred in this cohort given the social stigma and barriers to pediatric psychological care. However, this would bias our results towards the null and further strengthens our findings. We could not definitively determine whether each medication prescription was prescribed specifically for chronic musculoskeletal pain rather than for acute pain or another symptomatology. It is important to acknowledge that all opioid prescribing is not inappropriate, as there may be times during which a brief course of opioids is warranted (e.g., fractures, surgery, etc.), even for children with a history of chronic musculoskeletal pain. Similarly, glucocorticoids may have been prescribed in this cohort for children with asthma flares or active arthritis; however, we chose to include glucocorticoids in the medication exposures because, in the authors' experience, children with chronic musculoskeletal pain are commonly prescribed a trial of glucocorticoids to determine whether an anti-inflammatory response is present. Because there are no standard pharmacologic treatment regimens for chronic musculoskeletal pain, we erred on the side of inclusivity. Lastly, we cannot know

definitively whether prescriptions filled equated to children taking these medications. However, our aim was to identify children at risk of opioid exposure rather than true consumption of opioids.

Conclusion

In this administrative claims database, nearly 20% of children with chronic musculoskeletal pain were prescribed an opioid, and more than 25% experienced some degree of polypharmacy. Increased physician education regarding a multidisciplinary approach for the management of pediatric chronic musculoskeletal pain is likely needed to reduce prescribing of opioids and ensure rational polypharmacy. Increased availability of mental health resources and nonpharmacologic treatment options might represent effective strategies to reduce opioid exposure for pediatric chronic pain. Further standardization of care is needed to reduce potential harm and provide safe nonpharmacologic treatments for children with chronic musculoskeletal pain.

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