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Research article

# Opioid prescription patterns among adults with cerebral palsy and spina bifida

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ABSTRACT

*Background:* Pain is the most common symptom of cerebral palsy and spina bifida (CP/SB). The objective of this study was to compare the opioid prescription patterns for differing pain types and overlapping pain among adults living with and without CP/SB.

*Methods:* Privately-insured beneficiaries were included if they had CP/SB (n = 22,647). Adults without CP/SB were also included as controls (n = 931,528). Oral morphine equivalents (OMEs) were calculated. A multivariable logistic regression was used to analyze the association between CP/SB and OMEs, across the three pain categories: (1) no pain, (2) isolated pain, and (3) pain multimorbidity.

*Results:* Adults living with CP/SB had a higher OME prescription pattern per year than adults without CP or SB (8,981.0 ± 5,183.0 vs. 4,549.1 ± 2,988.0), and for no pain (4,010.8 ± 828.1 vs. 1,623.53 ± 47.5), isolated pain (7,179.9 ± 378.8 vs. 3,531.0 ± 131.0), and pain multimorbidity (15,752.4 ± 1,395.5 vs. 8,492.9 ± 398.0) (all $p < 0.001$), and differences were to a clinically meaningful extent. Adjusted odds ratios (OR) for prescribed OMEs were higher for adults with CP/SB vs. control and (1) no pain (OR: 1.51; 95%CI: 1.46, 1.56), (2) isolated pain (OR: 1.48; 95%CI: 1.44, 1.52), and (3) pain multimorbidity (OR: 1.79; 95%CI: 1.72, 1.86).

*Conclusions:* Adults with CP/SB obtain significantly higher prescription of OMEs than adults without CP/SB.

## 1. Introduction

Pain-related opioid prescription and associated overdoses are significant public health issues, and premature deaths from opioid overdoses represents an immense burden in the US [1]. Moreover, the prescription opioids and related analgesics in the U.S. differs according to race and ethnicity-a disparity that is not based on empirical evidence or specific to pain management strategies [2]. Although opioid use is generally opposed for the treatment of chronic, non–cancer- pain, physicians readily prescribe these drugs as an acceptable therapeutic intervention for severe, acute pain and for chronic overlapping pain among patients with complex medical conditions. Chronic pain conditions are a set of painful chronic conditions characterized by high levels of co-occurrence [3]. Chronic pain is the most common somatic symptom in cerebral palsy and spina bifida (CP/SB), and yet chronic pain is the most inconsistently managed comorbidity of CP/SB [4, 5, 6, 7]. The pain phenotype in adults with CP/SB may arise from nociceptive mechanisms associated with spastic muscle, dysplasia and arthritis, and invasive surgies [8]. Alternatively, we have shown that pain among adults with CP and SB is variable, and may arise through multiple mechanisms including mixed neuropathic and nociplastic subtypes [9, 10]. However, what remains to be examined is the opioid analgesic prescribing patterns among adults living with CP/SB. Given that adults living with CP and SB are known to experience high rates of chronic pain *and* psychiatric disorders [11, 12, 13], as well as the known multidirectional links between chronic pain, opioid addiction and iatrogenic harm to the patient, it is critical to understand the extent to which they are receiving opioid analgesics for treatment of chronic pain. This study aimed to compare the average

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yearly prescribed oral morphine equivalents (OMEs) for adults with and without CP/SB across pain types.

## 2. Methods

### 2.1. Data source

This study was a retrospective cohort design including only with CP or SB, whose CP/SB diagnostic code could come from any health care provider. This investigation incorporated data from privately-insured individuals in the U.S. The Clinformatics DataMart Database (OptumInsight, Eden Prairie, MN) is a de-identified claims dataset of >80 million individuals with insurance on a single, large national private payer with both medical and pharmacy coverage. This study was deemed exempt by the University of Michigan Institutional Review Board.

### 2.2. Sample selection

All individuals ≥18 years of age at the time of their enrollment, which could start from 2009 to 2014 were eligible for this analysis, as previously described [10]. Briefly, this enrollment period was chosen for two reasons, including: (1) in 2015 ICD-10 codes were implemented which significantly changed the diagnoses of pain and the prevalence of pain; and (2) the ICD-9 Coordination and Maintenance Committee expanded pain diagnoses codes in 2006 [14], which took a few years stabilization in the claims. We eliminated adults with <1 year of continuous enrollment, to ensure adequate insurance claims history. All claims except outpatient pharmacy claims were considered to identify prevalence for these pain conditions during their enrollment.

#### 2.2.1. Cohort identification

Adults with a diagnostic code for CP or SB were identified using *International Classification of Diseases, Ninth revision, Clinical Modification* (ICD-9-CM) (Supplementary File 1). A control cohort of adults without CP or SB were also identified using the same inclusion criteria. Further exclusion criteria for the control patients were to remove any patients with neurological or neuromuscular disorders (e.g., spinal cord injuries, etc.). Among these remaining controls, we obtained a 20% random sample using a fixed randomization seed. We examined that no unintentional bias was introduced by performing a post-hoc effect size (ES) analysis between the larger control cohort and the 20% sample on factors such as sociodemographic information and prevalent pain conditions.

#### 2.2.2. Pain morbidities

Clinician diagnosed pain conditions were defined based on encounters per year that included relevant ICD-9 pain codes (see Supplemental File 2 for list). The pain conditions were categorized as: (1) no pain, (2) isolated pain (i.e., one source of pain), and (3) pain multimorbidity (i.e., the presence of at least two diagnosed pain conditions from different pain outcome groups).

#### 2.2.3. Opioid prescriptions

Optum prescription data are based on pharmacy fills. Patients were considered to be taking an opioid if they were prescribed medication(s) containing oxycodone, hydrocodone, codeine, tramadol, morphine, hydromorphone, transdermal fentanyl, buprenorphine, or propoxyphene. Only oral medications were studied, apart from transdermal fentanyl. Opioids prescribed for each patient was converted to an oral morphine equivalent (OME), thus standardizing each drug into an equianalgesic dosage. This strategy allowed us to compare different medications using morphine as a reference. Initial discharge OMEs were determined by multiplying the tablet number by the tablet dose prescribed, and/or liquid volume and dosage, and then multiplying by the morphine equivalent conversion.

### 2.3. Statistical analysis

The analyses were conducted out to compare the average yearly OMEs for adults with CP/SB and without CP/SB, as well as for the different categories of pain. Cohen's h effect size (ES) calculations were used to determine the standardized mean differences (SMD) in conjunction with formal p-values to better understand clinically meaningful differences [15]. We used a multivariable logistic regression to analyze the association between CP/SB (reference: controls) and proportion of OME prescription, across the three pain categories: (1) no pain, (2) isolated pain, and (3) pain multimorbidity. A repeated measures analysis was used with generalized estimating equations (GEE) since patients could be enrolled across multiple calendar years. Models were used to calculate the adjusted odds ratios for the OME patterns across pain categories, comparing individuals with CP/SB as the main exposure variable, versus those without CP/SB. Covariates for the fully-adjusted

**Table 1.** Descriptive characteristics, OMEs, and pain conditions among adults with (Case) and without (Control) CP/SB.

| | Case | Control |
|---|---|---|
| **Overall, n (% cohort)** | 22,647 (100%) | 931,528 (100%) |
| **Full Enrollment Length** | | |
| Mean (SD) | 7.8 (3.3) | 7.6 (3.3) |
| Median (Q1-Q3) | 7.0 (5.1–9.7) | 6.7 (5.0–9.3) |
| **Age, Group, n (%)** | | |
| 18-30 | 5,060 (22.3%) | 142,861 (15.3%) |
| 31-54 | 10,182 (45.0%) | 397,909 (42.7%) |
| 55-64 | 3,239 (14.3%) | 149,841 (16.1%) |
| 65 or Older | 4,167 (18.4%) | 241,012 (25.9%) |
| **Gender, n (% cohort)** | | |
| Female | 12,948 (57.2%) | 488,160 (52.4%) |
| **Race, n (% cohort)** | | |
| White | 15,473 (68.3%) | 627,918 (67.4%) |
| Black | 2,511 (11.1%) | 84,431 (9.1%) |
| Hispanic | 2,059 (9.1%) | 94,709 (10.2%) |
| Asian | 506 (2.2%) | 40,233 (4.3%) |
| Unknown | 2,099 (9.3%) | 84,332 (9.1%) |
| **Pain Category, n (% cohort)** | | |
| No Pain | 9,987 (44.1%)* | 603,473 (64.8%) |
| Isolated Pain | 7,892 (34.9%)* | 249,770 (26.8%) |
| Pain Multimorbidity | 4,769 (21.1%)* | 78,380 (8.4%) |
| **Opioid Prescriptions, n (% cohort)** | | |
| Oxycodone Hydrochloride | 877 (3.9%)* | 9,676 (1.0%) |
| Oxycodone Hydrochloride + Acetaminophen | 2,252 (9.9%)* | 46,386 (5.0%) |
| Hydrocodone + Acetaminophen | 5,409 (23.9%)* | 137,479 (14.8%) |
| Tramadol Hydrochloride | 1,747 (7.7%)* | 32,545 (3.5%) |
| Tramadol Hydrochloride + Acetaminophen | 187 (0.8%)* | 4,071 (0.4%) |
| Codeine + Acetaminophen | 793 (3.5%)* | 18,839 (2.0%) |
| Morphine Sulfate | 460 (2.0%)* | 3,371 (0.4%) |
| Fentanyl | 307 (1.4%)* | 2,432 (0.3%) |
| Propoxyphene + Acetaminophen | 638 (2.8%)* | 16,788 (1.8%) |
| Methadone Hydrochloride | 152 (0.7%)* | 1,309 (0.1%) |
| Hydromorphone Hydrochloride | 315 (1.4%)* | 2,908 (0.3%) |
| Buprenorphine Hydrochloride + Naloxone | 43 (0.2%) | 801 (0.1%) |
| **Total Average Yearly OMEs (SD)** | 8,981.0 (5,183.0)* | 4,549.1 (2,988.0) |
| **Pain Category, OMEs (SD)** | | |
| No Pain | 4,010.8 (828.1)* | 1,623.5 (47.5) |
| Isolated Pain | 7,179.9 (378.8)* | 3,531.0 (131.0) |
| Pain Multimorbidity | 15,752.4 (1,395.5)* | 8,492.9 (398.0) |

*P < .01 and standard mean difference (SMD) ≥0.2.

models included sex, race, age, household net worth, and educational attainment. Secondary analyses were performed to examine interactions by age categories and gender. Covariance structures were tested and the models that minimized the Akaike Information Criterion (AIC) was used as the most appropriate model fit. All analyses were conducted using SAS 9.4 (SAS Institute, Cary, NC). All models were fit using PROC GENMOD with binomial distribution and log link with repeated measures on patient. Statistical testing was two-tailed with a significance level of 0.01 and effect sizes used a 0.2 SMD as a meaningful difference cutoff.

## 3. Results

The average length of enrollment for eligible individuals was 7.8 ± 3.3 and 7.6 ± 3.3 years for patients with CP/SB and controls respectively, with a range of one (i.e., "inclusion criterion") to eleven years (Table 1).

Adults with CP/SB had a higher average OME prescription pattern per year than adults without CP/SB (8,981.0 ± 5,183.0 vs. 4,549.1 ± 2,988.0) (Table 1), over the 5 years. Adults with CP/SB also had a higher OMEs prescription pattern over the 5 years for no pain (4,010.8 ± 828.1 vs. 1,623.5 ± 47.5), isolated pain (7,179.9 ± 378.8 vs. 3,531.0 ± 131.0), and pain multimorbidity (15,752.4 ± 1,395.5 vs. 8,492.9 ± 398.0) (all $p < 0.001$) (Figure 1), and differences were to a clinically meaningful extent.

Adjusted odds ratios (OR) for the proportion of patients prescribed OMEs were higher for adults with CP/SB vs. control *and* (1) no pain (OR: 1.51; 95%CI: 1.46, 1.56), (2) isolated pain (OR: 1.48; 95%CI: 1.44, 1.52), and (3) pain multimorbidity (OR: 1.79; 95%CI: 1.72, 1.86).

There was a differential risk across age group for adults with and without CP/SB. Specifically, as compared to young adults with CP/SB (18–30 years), we found an increased odds of OME prescription for adults with CP/SB aged 31–54 years (OR: 1.28; 95%CI: 1.21–1.36), 55–64 years (OR: 1.46; 95%CI: 1.35–1.57), and ≥65 years (OR: 1.36; 95%CI: 1.27–1.46) (all $p < 0.001$). Similarly, as compared to young adults *without* CP/SB (18–30 years), we found an increased odds of OME prescription for adults aged 31–54 years (OR: 1.16; 95%CI: 1.15–1.17), 55–64 years (OR: 1.36; 95%CI: 1.35–1.38), and ≥65 years (OR: 1.24; 95%CI: 1.23–1.25) (all $p < 0.001$). However, there was also a CP/SB exposure effect that systematically affected all age groups. For example, young adults with CP/SB (18–30 years) were at higher risk for opioid prescription (OR: 1.46; 95%CI: 1.39–1.53) than young adults without CP/SB (Table 2).

**Table 2.** Generalized estimating equations models were completed to examine the effects of the exposure variable (CP/SB) as compared to the reference (beneficiaries without CP/SB), within age groups, as well as within cases and controls between age groups. Results are presented as odds ratios (OR) and 95% confidence intervals (CI).

| Parameters | Estimate | SE | OR | 95%CI |
|---|---|---|---|---|
| **Adults without CP/SB (Reference)** | | | | |
| 18–30 years | 0.38 | 0.02 | 1.46 | 1.39–1.53 |
| Age 31–54 years | 0.48 | 0.02 | 1.61 | 1.56–1.67 |
| Age 55–64 years | 0.44 | 0.03 | 1.55 | 1.47–1.65 |
| ≥65 years | 0.47 | 0.03 | 1.60 | 1.52–1.68 |
| **Adults with CP/SB** | | | | |
| 18-30 (Reference) | | | | |
| Age 31–54 years | 0.25 | 0.03 | 1.28 | 1.21–1.36 |
| Age 55–64 years | 0.38 | 0.04 | 1.46 | 1.35–1.57 |
| ≥65 years | 0.31 | 0.04 | 1.36 | 1.27–1.46 |
| **Adults without CP/SB** | | | | |
| 18-30 (Reference) | | | | |
| Age 31–54 years | 0.15 | 0.01 | 1.16 | 1.15–1.17 |
| Age 55–64 years | 0.31 | 0.01 | 1.36 | 1.35–1.38 |
| ≥65 years | 0.22 | 0.01 | 1.24 | 1.23–1.25 |

There was also an effect for gender, within cases and controls. Specifically, among adults with CP/SB, men had a lower odds of OME prescription than women with CP/SB (OR: 0.79; 95%CI: 0.75–0.83). Similarly, men *without* CP/SB had a lower odds of OME prescription than women without CP/SB (OR: 0.86; 95%: 0.86–0.87). However, there was also a CP/SB exposure, such that both men (OR: 1.49; 95%CI: 1.43–1.54) and women (OR: 1.62; 95%CI: 1.57–1.68) with CP/SB had a greater odds of OME prescription than men and women without CP/SB.

## 4. Discussion

The primary finding of this investigation was that adults with CP/SB had a significantly higher OME prescription pattern as compared to adults without CP/SB. This is the first study and largest to date to investigate the prescription patterns of opioids among adults living with CP/SB. We have previously found that adults with CP and those with co-occurring neurodevelopmental disabilities have an elevated prevalence

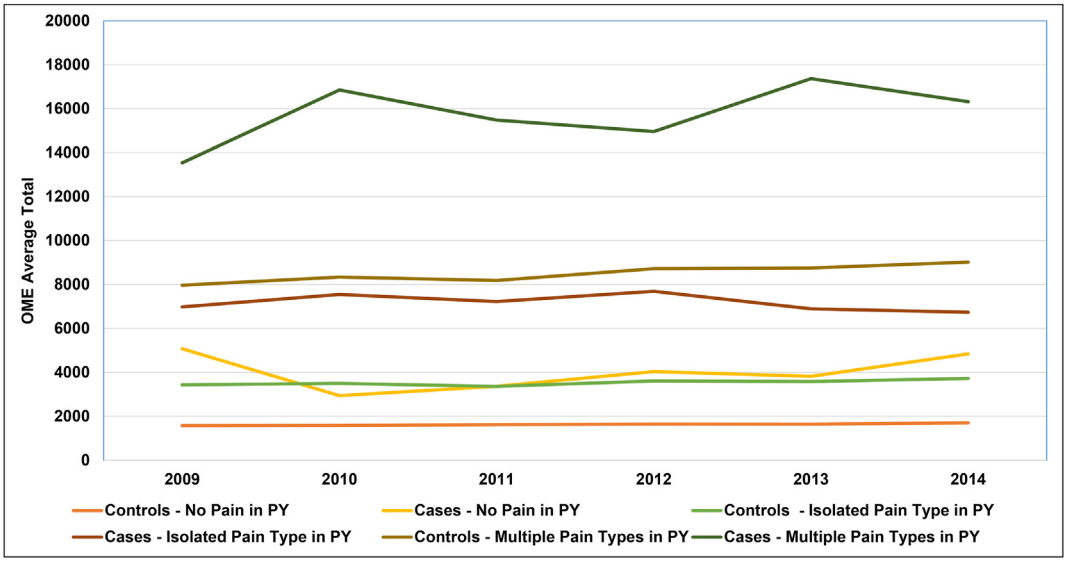


**Figure 1.** OME Average Total for each year: Cerebral Palsy or Spina Bifida (Cases) and General Population (Controls)-Stratified by No Pain, Isolated Pain, and Pain Multimorbidity for Patient Calendar Years (PY) 2009–2014.

of polypharmacy compared with adults without CP, even after accounting for multimorbidity [16]. In combination with these findings, future research and public health efforts are needed to better understand the healthcare burden associated with pain and opioid prescription in these populations, as well as to understand the disparities to access appropriate pain management options across insurance types (i.e., private versus Medicare/Medicaid) for individuals living with these and other disabilities.

Our findings for adults with CP/SB who have pain multimorbidity are of great concern, given the known links between persistent opioid use patterns and behavioral and pain disorders, as well as with overdose mortality [17, 18, 19]. Many individuals with CP/SB undergo frequent orthopedic surgeries over the lifespan. Optimized multimodal perioperative analgesia (which may include combinations of anesthesia [including peripheral nerve blocks, local infiltration analgesia and/or single-shot or continuous central neuraxial], opioid analgesics, and non-opioid systemic analgesics [acetaminophen, and nonsteroidal anti-inflammatories]) could reduce post-operative and chronic pain, and thus may be an effective means of decreasing long-term opioid abuse in these populations. Further, while substance abuse, in general, is prevalent among adults with chronic disabilities, many adults with disabilities develop problems related to prescription narcotic drugs. In 2014, Morden et al. [20] showed that more than 40% of all Medicaid beneficiaries with a disability took opioids, and more than 20% were chronic opioid users. These estimates are alarming for a variety of reasons. Most importantly, chronic use of opioids represents a heightened risk of addiction; however, study findings have begun to raise questions about whether the long-term use of opioids is an appropriate option in the treatment of non-cancer chronic pain. For example, opioid prescription may synergistically contribute to the pathology of spinal cord injury (SCI) by increasing the development of neuropathic pain, decreasing locomotor recovery, and leaving individuals at increased infection risk [21, 22, 23]. Future research is required to better understand the effectiveness of non-opioid analgesics and complementary and alternative pain management strategies (e.g., cognitive behavior therapy, psychosocial therapy/counseling, and physical therapy, tetrahydrocannabinol, etc.) for adults living with CP/SB.

### 4.1. Limitations

The cohort of patients with CP/SB may not be representative of the entire U.S. population of adults with CP/SB, and particularly those who are insured through Medicare or Medicaid. Moreover, we could not determine the severity of disability for the adults CP/SB through the use of data from administrative claims. Thus, our sample may reflect a healthier and higher-functioning segment of the population of adults with CP/SB.

## 5. Conclusion

Adults with CP/SB receive greater opioid prescriptions as compared to the privately insured beneficiaries without CP/SB. Moreover, adults with chronic pain have a higher opioid prescription pattern with increasing age-a problem that is destined to lead to worse physical and mental health outcomes and addiction, regardless of disability status. Increasing public health awareness of the pain taxonomy, improving clinical pain screening strategies, and developing better referral options for pain management in these populations may help reduce the burden of opioid addiction and overdose.

## Declarations

### Author contribution statement

Mark D. Peterson: Conceived and designed the experiments; Analyzed and interpreted the data; Wrote the paper.

Neil Kamdar, Chad Brummett, Edward A. Hurvitz: Analyzed and interpreted the data; Wrote the paper.

Heidi J. Haapala: Conceived and designed the experiments; Wrote the paper.

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### Data availability statement

The data that has been used is confidential.

### Declaration of interests statement

The authors declare no conflict of interest.

### Additional information

Supplementary content related to this article has been published online at https://doi.org/10.1016/j.heliyon.2022.e09918.

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