Trends in Dispensed Opioid Analgesic Prescriptions to Children in South Carolina: 2010–2017

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abstract

BACKGROUND AND OBJECTIVES: Despite published declines in opioid prescribing and dispensing to children in the past decade, in few studies have researchers evaluated all children in 1 state or examined changes in mean daily opioid dispensed. In this study, we evaluated changes in the rate of dispensed opioid analgesics and the mean daily opioid dispensed to persons 0 to 18 years old in 1 state over an 8-year period.

METHODS: We identified opioid analgesics dispensed to children 0 to 18 years old between 2010 and 2017 using South Carolina prescription drug monitoring program data. We used generalized linear regression analyses to examine changes over time in the following: (1) rate of dispensed opioid prescriptions and (2) mean daily morphine milligram equivalents (MMEs) per prescription.

RESULTS: From the first quarter of 2010 to the end of the fourth quarter of 2017, the quarterly rate of opioids dispensed decreased from 18.68 prescriptions per 1000 state residents to 12.03 per 1000 residents (P < .0001). The largest declines were among the oldest individuals, such as the 41.2% decline among 18-year-olds. From 2010 through 2017, the mean daily MME dispensed declined by 7.6%, from 40.7 MMEs per day in 2010 to 37.6 MMEs per day in 2017 (P < .0001), but the decrease was limited to children 0 to 9 years old.

CONCLUSIONS: The rate of opioid analgesic prescriptions dispensed to children 0 to 18 years old in South Carolina declined by 35.6% over the years 2010–2017; however, the MME dispensed per day declined minimally, suggesting that more can be done to improve opioid prescribing and dispensing.

WHAT’S KNOWN ON THIS SUBJECT: Studies have revealed decreases in opioid dispensing, but no researchers have looked at opioid analgesic dispensing for all children in 1 state using prescription drug monitoring program data, and few have evaluated changes in mean daily opioid dispensed.

WHAT THIS STUDY ADDS: In these data, dispensed opioid analgesic prescriptions declined by 35.6% between 2010 and 2017, but the mean daily opioid dispensed, measured in morphine milligram equivalents, declined by only 7.6% for all children and only among those 0 to 9 years old.


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Drs Ball, Basco, and Mauldin conceptualized and designed the study, interpreted analyses, and wrote, reviewed, and revised the manuscript; Drs McCauley and Simpson provided input on the design of the study, interpreted analyses, and reviewed and revised the manuscript; Ms Zhang and Mr Marsden conducted data verification steps and data analyses, assisted with interpretation of analyses, produced tables and figures, and reviewed and revised the manuscript; Mr Heidari provided content expertise on the databases used and reviewed and assisted with revision of the manuscript; and all authors approved the final manuscript as submitted.

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Children are a less explored group compared with adults in regard to the effects of the opioid epidemic, but children experience harm as a result of the opioid epidemic as well.\textsuperscript{1-3} Studies have revealed increases in births affected by neonatal opioid withdrawal syndrome, the number of young children accidentally ingesting opioids prescribed to other household members, and pediatric hospital admissions due to opioid poisonings and a striking increase in PICU admissions due to opioid exposures, both intentional and accidental.\textsuperscript{4-6} Childhood deaths due to prescribed and illicit opioid use continue to increase.\textsuperscript{3,7,8} Proper opioid stewardship involves navigating the ethical balance between treating patients and not inducing harm.\textsuperscript{9}

Focusing on the rate opioids are dispensed to children is important because even indicated opioid prescribing and use among children and adolescents confers risks, including adverse drug events and the possibility of potentially predisposing opioid-exposed children to opioid misuse in young adulthood.\textsuperscript{10-13} Although recent reports reveal downward trends in opioid prescriptions for children overall, the studies have been completed in single settings, such as emergency departments (EDs), have evaluated one payer source (eg, Medicaid), or have excluded younger children, such as those 0 to 2 years old.\textsuperscript{11,14,15} National estimates of codeine prescribing after an ED visit by children aged 3 to 17 revealed a decline from 3.7% to 2.9% of visits associated with a codeine prescription from 2001 to 2010, and National Hospital Ambulatory Medical Care Survey data from 2005 to 2015 revealed decreased opioid prescriptions for patients 13 to 22 years old.\textsuperscript{11,15} Single-state Medicaid data for children 2 to 17 years old revealed a decline from 17 opioid analgesic prescriptions per 1000 population to 10 opioid analgesic prescriptions per 1000 population between 1999 and 2014.\textsuperscript{14} All these studies excluded children 0 to 2 years old.

Dispensed prescription rates provide only 1 measure of opioid prescribing and dispensing. Another measure of interest is the daily amount of opioid dispensed, measured in morphine milligram equivalents (MMEs) to standardize the potency of the different opioids. In Tennessee Medicaid claims data for children 2 to 17 years old, daily MME dispensed correlated with the risk of adverse events such as ED visit, hospital admission, or death.\textsuperscript{14} Among privately insured subjects 12 to 21 years old, the daily MME correlated with the risk of overdose.\textsuperscript{13} Less is known about changes in daily MME on a population level over time.

Although a single-institution study of postoperative opioid prescribing to children 0 to 18 years old revealed concurrent declines in opioid prescription numbers, days’ supply, and daily dose between 2013 and 2017, there are concerns that state-specific regulatory limitations on days’ supply of opioids that can be prescribed may lead prescribers to prescribe higher MME per day, as has been seen in adult data.\textsuperscript{16}

We conducted this study to address two gaps in the pediatric opioid pharmacoepidemiology literature using South Carolina prescription drug monitoring program (PDMP) data from 2010 to 2017. One advantage of PDMP data is that all controlled substance prescriptions dispensed in a state are captured, regardless of patient funding source, thereby giving a more complete population-based estimate of ambulatory child opioid dispensing. We sought first to answer the question of whether the downward trends in opioid prescribing seen in studies using data from EDs or using claims data from subsets of children on the basis of insurance type hold for all children in a state regardless of location of care, age, or payer. The second gap we sought to address was whether changes in the rate of dispensed opioid prescriptions was accompanied by a change in daily MME.

**METHODS**

**Subjects**

The subjects were aged 0 to 18 years at the time they appeared in the South Carolina PDMP data between 2010 and 2017 as a result of receiving one of the opioids on the study list, described later.

**Data**

The South Carolina Reporting & Identification Tracking System (SCRIPTS), South Carolina's PDMP registry, went into effect in 2008 under the maintenance of the Bureau of Drug Control at the South Carolina Department of Health and Environmental Control (DHEC). SCRIPTS collects data through daily downloads on Schedule II–Schedule IV controlled substances dispensed in South Carolina or by mail-order pharmacies for South Carolina residents. In 2016, researchers at our institution commenced a partnership with the South Carolina DHEC to evaluate South Carolina PDMP data. On receipt of eight 12-month de-identified SCRIPTS data sets, we completed data quality activities. Using initial data quality checks, we identified minor gaps in SCRIPTS data for correction.

Demographic data available in the PDMP included age at the time of dispensing. We used age as a continuous variable in 1-year increments (eg, 0–1 year old = infant) up to age 18 (age 18 years, plus 364 days). Variables in PDMP data that require pharmacists' input at the time of dispensing include medication prescribed, quantity prescribed, and days' supply. PDMP data do not include the indications for prescriptions.
Drugs Included

We built a product file on the basis of the National Drug Code (NDC) of all drug products dispensed 2010–2017 that fall under SCRIPTS reporting using both Centers for Disease Control and Prevention (CDC) Opioid Overdose Indicator Support Toolkit and Red Book sources to add data fields needed for analysis.17,18 The study list excluded opioid analgesics not typically used by outpatient children, such as hospital-administered opioids, buprenorphine, and cough and cold preparations as recommended by the CDC.17 Propoxyphene was excluded from all analyses because it was withdrawn from the market in 2010. Tramadol was excluded because it was not consistently reported to the South Carolina PDMP until it was reclassified as a Schedule IV controlled substance in August 2014. Conducting analyses for both outcomes with and without Tramadol revealed no clinically meaningful differences. After identification of opioid products of interest using NDCs, we used data from the CDC and Red Book sources to identify the following for each drug product: generic name, strength per unit, unit of measure, MME conversion factor, opioid (yes or no), opioid classification, and US Drug Enforcement Administration Class.17–19 NDCs formed a many-into-one grouping with each unique product name in SCRIPTS. A single NDC from each grouping was selected to cross-reference selected fields in the online Red Book file and the 2017 CDC MME conversion file to ensure accuracy of the product name and newly added fields. The CDC MME conversion file was the primary source to obtain the strength per unit, unit of measure, and MME conversion factor for each opioid product.19 The use of these data was approved by the South Carolina DHEC, and the institutional review board at our institution deemed this not human research.

Outcomes

The rate outcome corresponds to an indicator defined by the CDC in the context of their Prescription Drug Overdose Prevention for States surveillance program, and the definitions, drugs used in calculation, and population denominators chosen are intended to allow comparison of the indicators across counties within a state and among states.17 The CDC-defined indicators apply to all ages. The first outcome of interest was the prescription opioid-dispensing frequency, calculated quarterly as the number of observed dispensing events divided by the age-referenced US census population estimates for the state, producing a rate of opioid analgesic prescriptions per 1000 state residents per quarter.17 For evaluating changes over time by age group, we calculated dispensed prescription rates per year, first for all children aged 0 to 18, then by 1-year age strata across the 8 calendar years of data available. The denominator for this calculation was the mid-year census estimate of the South Carolina child population for the respective calendar year.

The second outcome of interest was the mean daily MME per dispensed prescription, calculated by using the following formula: daily MME = strength per unit × quantity × MME conversion factor / days’ supply. Analyses describe the sample, the annual rate of dispensed opioid analgesic prescriptions for all children aged 0 to 18 years, then for each 1-year age stratum, per year. Because of evident differences in the trajectory of the rate outcome based on age, we also conducted post hoc analyses by age grouped 0 to 8 years old and 9 to 18 years old. For the daily MME outcome, we prespecified age groupings of 0 to 4, 5 to 9, 10 to 14, and 15 to 18 years. We used univariate generalized linear regression (accounting for autocorrelation) to determine if the rate of opioid analgesic dispensing had declined significantly from 2010 to 2017 and if the mean daily MME dispensed changed over the same years.

RESULTS

From the first quarter of 2010 to the end of the fourth quarter of 2017, there were 630,004 prescriptions for opioid analgesics dispensed to children 0 to 18 years old. This corresponded to a quarterly rate of 18.68 prescriptions per 1000 residents 0 to 18 years old in quarter 1 of 2010, declining to 12.03 in quarter 4 of 2017, a 35.6% decline over the 8 calendar years (P < .001; Fig 1, Supplemental Table 2). When looking at differences by age, dispensed opioid prescription rate for infants aged 0 to 12 months increased during the years studied from 10 per 1000 population to 14 per 1000 (P < .01), with similar statistically significant increases among children up to age 8 years (all P values < .05, Table 1). Post hoc assessment of the drugs dispensed revealed that, beginning in 2014, there was a marked increase in the appearance of acetaminophen-hydrocodone combination products in the data. From the period of 2010–2013 to 2014–2017, acetaminophen-hydrocodone combination products-dispensing events (not rate) increased by >700% for children 0 to 4 years old and >350% for children 5 to 9 years old. Acetaminophen-hydrocodone combination products also increased as a share of opioids dispensed from 24.6% of the opioids dispensed to children 0 to 4 years old in 2010–2013 to 70.6% of the opioids dispensed to children 0 to 4 years old in 2010–2013, accompanied by a large percentage increase among 5- to 9-year-old children (Supplemental Table 3). For ages 9 to 18, however, there was an annual decline in dispensed opioid prescriptions, with each 1-year group reaching its lowest level in 2017. The largest declines were among those aged 12 to 18 years, who experienced declines of 32% to 41% over the 8 years studied (all P values < .05; Table 1). Age
was positively associated with rate, regardless of calendar year (Table 1).

From 2010 to 2017, the mean daily MME dispensed per prescription declined by 7.6% among children 0 to 18 years old, from 40.7 daily MMEs in 2010 to 37.6 daily MMEs in 2017 (generalized linear regression, $P < .001$). Figure 2 displays the mean daily MME of dispensed prescriptions by calendar year and by age group.

| TABLE 1 Annual Rates of Opioid Analgesics Dispensed per 1000 State Residents by 1-Year Age Strata, 0–18 Years Old, South Carolina PDMP Data, 2010–2017 |
|---|---|---|---|---|---|---|---|---|---|
| 0–12 mo | 10 | 9 | 9 | 9 | 12 | 10 | 14 | 14 | Increasing | .02 |
| 13–24 mo | 3 | 3 | 2 | 3 | 9 | 7 | 9 | 10 | Increasing | <.01 |
| 25–36 mo | 2 | 2 | 2 | 2 | 8 | 7 | 7 | 6 | Increasing | <.01 |
| 3 y | 2 | 1 | 2 | 2 | 9 | 7 | 8 | 7 | Increasing | .02 |
| 4 y | 3 | 2 | 2 | 3 | 10 | 9 | 10 | 8 | Increasing | .01 |
| 5 y | 3 | 2 | 3 | 2 | 11 | 10 | 11 | 10 | Increasing | <.01 |
| 6 y | 4 | 3 | 3 | 5 | 12 | 12 | 14 | 12 | Increasing | <.01 |
| 7 y | 7 | 5 | 6 | 5 | 14 | 14 | 14 | 14 | Increasing | .01 |
| 8 y | 10 | 9 | 9 | 9 | 17 | 16 | 16 | 14 | Increasing | .03 |
| 9 y | 20 | 17 | 15 | 15 | 22 | 18 | 20 | 17 | No change | .68 |
| 10 y | 28 | 32 | 25 | 23 | 30 | 28 | 25 | 22 | No change | .18 |
| 11 y | 43 | 41 | 42 | 37 | 40 | 36 | 34 | 28 | Decreasing | <.01 |
| 12 y | 65 | 65 | 60 | 59 | 57 | 50 | 49 | 39 | Decreasing | <.001 |
| 13 y | 89 | 87 | 87 | 80 | 82 | 69 | 63 | 53 | Decreasing | <.001 |
| 14 y | 122 | 127 | 119 | 115 | 104 | 97 | 86 | 72 | Decreasing | <.001 |
| 15 y | 176 | 177 | 173 | 156 | 155 | 132 | 127 | 112 | Decreasing | <.001 |
| 16 y | 228 | 237 | 227 | 217 | 207 | 184 | 169 | 155 | Decreasing | <.001 |
| 17 y | 302 | 299 | 294 | 278 | 267 | 228 | 219 | 186 | Decreasing | <.001 |
| 18 y | 325 | 333 | 318 | 298 | 278 | 248 | 215 | 191 | Decreasing | <.001 |
| All children | 78 | 78 | 75 | 70 | 71 | 63 | 60 | 52 | Decreasing | <.001 |

Rates are expressed as the number of prescriptions dispensed to children in the age group of interest per year per 1000 mid-year US Census Bureau population of children in the referenced age group.

DISCUSSION

The number of ambulatory opioid analgesic prescriptions dispensed to children 0 to 18 years old in South Carolina declined significantly between the first quarter of 2010 and the last quarter of 2017, with the largest declines among teenagers. Consistent with previous research, the rate of dispensed opioid prescriptions was positively correlated with patient age. Although a decrease in overall rate of opioid prescriptions dispensed to children is encouraging, that observation is coupled with only a minimal decline in the mean daily MME dispensed, and the majority of the decline in MME per day was seen among those 0 to 9 years old.

There are many factors that likely contribute to the decline in the rate of dispensed opioid prescriptions during the study period. Although our study was not designed as a time-series analysis, there were increasing reports about the adverse effects of opioids on children throughout the 2000s, and states instituted increasingly robust PDMPs during the same years. In 2012 and 2013, specific warnings against using codeine for pain control included a US Food and Drug Administration (FDA)–issued black box warning.

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against the use of codeine post-tonsillectomy because of the heightened risk of respiratory depression among children who rapidly metabolize the prodrug (codeine) to the active molecule (morphine).\textsuperscript{25,26} Robust PDMP programs are associated with decreased opioid prescribing.\textsuperscript{27} Specific to South Carolina, in 2016, some private insurers began requiring that providers check the PDMP database before prescribing opioids and other controlled substances for durations of $\geq$ 5 days and at 3-month intervals for any patient who received long-term controlled substances, quickly followed by similar requirements mandated by the South Carolina Department of Health and Human Services for all Schedule II–Schedule IV controlled substance prescriptions. We found that the mean daily MME dispensed decreased by only 7.6\% during the study years, and the decline in mean daily MME occurred primarily in children $<$ 10 years old, with little change among those 12 to 18 years old (Fig 2). Without diagnostic data, it is not possible to know whether the mean daily MME dispensed was appropriate or why it changed less for the children older than 9 years, but the mean values in these dispensed prescriptions were near the CDC-suggested threshold of 50 MME per day, a point above which patients may experience increased risk of adverse events.\textsuperscript{28} Data from 2009 to 2017 obtained by using a large administrative database revealed that children receiving 30 to 59 daily MME experienced an adjusted odds of overdose of 1.18 (95\% confidence interval: 1.05–1.31) compared with subjects receiving $<$ 30 daily MME.\textsuperscript{13} There are also building data that nonsteroidal anti-inflammatory agents can be as effective as opioids postprocedure.\textsuperscript{29–33} Therefore, even if opioids are prescribed for appropriate indications such as posttrauma or postoperative pain, providers should focus on appropriate daily MME dosing for children to reduce adverse events and reduce the amount of unused opioid doses in homes and communities.

![FIGURE 2](mean_daily_mme_of_opioid_analgesics dispensed per prescription, by age group, South Carolina PDMP, 2010-2017. Data source: South Carolina DHEC; received: July 18, 2018.)

The finding of temporal increases in dispensed opioids among children aged
0 to 8 years was unexpected and not consistent with other published data on opioid prescribing rates in younger children, although those studies did not use PDMP data and excluded children aged <2 years.\textsuperscript{11,12,14} In post hoc analyses of the specific compounds appearing in the database, the increased dispensed opioid rate among children 0 to 8 years old was driven primarily by increased dispensing of acetaminophen-hydrocodone combination products and, to a lesser extent, oxycodone hydrochloride. Although acetaminophen-codeine combination products declined between 2010–2013 and 2014–2017, as might be expected because of the FDA action, the absolute decline of acetaminophen-codeine combination product dispensing was eclipsed by increases in acetaminophen-hydrocodone combination product dispensing (Supplemental Table 3). There are several possible temporal explanations for this shift. tramadol became a controlled substance in 2014, perhaps leading to substitution of acetaminophen-hydrocodone combination products for tramadol. In addition, the FDA rule changes for codeine-containing products may have also pushed providers to use more acetaminophen-hydrocodone combination products. There were no changes in the availability of liquid hydrocodone preparations or changes in FDA indications for hydrocodone during these years, and its schedule changed from III to II just after the change in tramadol schedule. Nevertheless, it is possible that providers saw acetaminophen-hydrocodone combination products as the most logical alternative, given restrictions on codeine and tramadol prescribing. The fact that acetaminophen-hydrocodone combination products composed >70% of opioids dispensed to children 0 to 4 years old between 2014 and 2017 may also explain the large reduction in variability of mean daily MME after 2014 seen among subjects 0 to 4 years old (Fig 2).

All pediatric providers should focus on opioid stewardship. Human epidemiology studies have revealed a relationship between adolescent opioid exposure and enhanced risk for development of a substance use disorder in adulthood,\textsuperscript{34,35} with previous medical use of opioids noted as a risk factor for progression to opioid misuse and addiction.\textsuperscript{10,36} However, risk for prolonged use, misuse, and abuse is variable among adolescents, so exposure to opioids alone does not appear to be the sole driver of opioid misuse after childhood and adolescence.\textsuperscript{37–41} Therefore, clinical decisions regarding opioid prescribing during childhood and adolescence should be made cautiously, weighing individually conferred risks against potential benefits of use.\textsuperscript{9,42}

One strength of this study is that the findings represent a broad, population-based estimate for a single state, evaluating dispensed opioid analgesic prescriptions regardless of location of care or source of payment, including opioids paid for in cash. Nevertheless, the study has several limitations. The data are from a single southern state, and pediatric opioid-dispensing data reveal regional variability.\textsuperscript{15} The population denominator was the mid-year census population for the respective year and age group. Census data have been revealed to undercount children, particularly young children, a fact that would bias our estimated rates toward being higher than actual rates.\textsuperscript{43} However, the dispensed opioid rates were so much lower among subjects 0 to 8 years old than 9 to 18 years old that underestimating the young child denominator would not substantially alter the rate trend among all children. Because the study excluded opioid-containing cough and cold medications, the rate outcome undercounts total opioid-dispensing events. However, the CDC indicators focus on analgesic preparations. The absence of indication data makes interpretation of the unexpected increase in dispensing among children aged 0 to 8 years difficult to interpret. The days’ supply variable is entered by the pharmacist at dispensing, and pharmacists may have to estimate days’ supply on the basis of frequency noted on a prescription and the number of doses on the prescription if specific days’ supply data are not included by the prescriber. We also do not know how many of the drugs were prescribed to be taken on a scheduled versus as-needed basis, so we do not know if the patients actually were intended to receive the calculated mean daily MME. Provider type and treatment setting, missing from these data, are also important in devising stewardship efforts because other studies have revealed that provider type (eg, “non-pediatrician”) and location (eg, ED versus ambulatory) are associated with different rates of opioid prescribing.\textsuperscript{12,44}

CONCLUSIONS

The rate of opioid analgesic prescriptions dispensed to children 0 to 18 years old in South Carolina declined by 35.6% overall between 2010 and 2017, and the slope of the decline suggests that the rate will continue to decrease. However, the mean daily MME dispensed declined minimally during the same time frame, suggesting that more can be done to improve responsible opioid prescribing and dispensing.

**ABBREVIATIONS**

CDC: Centers for Disease Control and Prevention
DHEC: Department of Health and Environmental Control
ED: emergency department
FDA: US Food and Drug Administration
MME: morphine milligram equivalent
NDC: National Drug Code
PDMP: prescription drug monitoring program
SCRIPTS: South Carolina Reporting & Identification Tracking System
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