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Opioid Prescribing and Potential Overdose Errors Among Children 0 to 36 Months Old

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Abstract

Objective—To estimate the frequency of potential overdoses among outpatient opioid-containing prescriptions.

Method—Using 11 years of outpatient Medicaid prescription data, we compared opioid dose dispensed (observed) versus expected dose to estimate overdose error frequencies. A potential overdose was defined as any preparation dispensed that was >110% of expected based on imputed, 97th percentile weights.

Results—There were 59 536 study drug prescriptions to children 0 to 36 months old. Overall, 2.7% of the prescriptions contained potential overdose quantities, and the average excess amount dispensed was 48% above expected. Younger ages were associated with higher frequencies of potential overdose. For example, 8.9% of opioid prescriptions among infants 0 to 2 months contained potential overdose quantities, compared with 5.7% among infants 3 to 5 months old, 3.6% among infants 6 to 11 months old, and 2.3% among children >12 months ($P < .0001$).

Conclusions—Opioid prescriptions for infants and children routinely contained potential overdose quantities.

Keywords

child; children; medication errors; overdose; patient safety

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Author Contributions

WTB, TCH, and KS conceived of the project, obtained the data, devised the analyses plan, supervised analyses, and wrote and reviewed manuscript. SSG assisted with analyses plan, interpreted outcomes with WTB, and assisted with preparation and review of manuscript. ME managed the data set, worked under the supervision of WTB to perform data management and analyses, and assisted with manuscript preparation and review.

Declaration of Conflicting Interests

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Introduction

Errors in medication dosing are among the most common medication error types in children.^{1–5} However, relatively few studies on dosing errors have been completed in outpatient pediatric, nonemergency department settings, evaluating general pediatric populations.^{5–8} Two studies that reviewed large numbers of pediatric prescriptions (not from claims data) found dosing errors in the 8% to 15% range. An evaluation of 1933 child ambulatory visit records where a prescription was given demonstrated dosing errors in 15% of the prescriptions, with approximately 50% of the errors being overdoses.⁷ Similarly, an evaluation of 2259 prescriptions at 6 outpatient sites found dosing errors in 8.9% of prescriptions.⁸ Dosing errors also comprise more than 40% of the medication errors that lead to patient death based on reports to the US Food and Drug Administration (FDA).⁹

Opioid-containing preparations are frequently cited as the drug class most commonly involved in adverse drug events and deaths.^{10–13} The American Academy of Pediatrics advocates limiting use of opioids in children based on safety concerns.¹⁴ In addition, recent evidence has shown that opioids offer limited efficacy for treating pain (compared with nonsteroidal anti-inflammatory agents) and cough in children.^{15–17} Young children have a narrower margin of safety when using weight-based dosage calculations and may be a particular risk for dosing error. Among 821 reported cardiovascular drug errors in children, approximately 50% were in children younger than 1 year,¹⁸ and children 0 to 4 years old account for 43% of adverse drug event visits.¹⁰

Given the greater risk of adverse drug events posed by opioid medications and the greater risk of adverse drug events in young children, focusing on outpatient opioid prescriptions to children 0 to 36 months old represents a potentially high-yield opportunity to improve patient safety. In this study, we sought to estimate the frequency of potential overdoses among outpatient opioid-containing prescriptions and to determine if the frequency of potential overdose was inversely associated with age.

Method

Data Source

The study was a retrospective evaluation of 2000–2010 South Carolina paid Medicaid administrative pharmacy claims data for subjects 0 to 36 months old. The study was approved by the institutional review board at the Medical University of South Carolina and the South Carolina Office of Research and Statistics. Each prescription in the dataset was linked to an enrollee file using encrypted identifiers. The enrollee files contained limited demographic data but included age in months, gender, race/ethnicity, and county of residence. Hispanic ethnicity is treated as a racial category in the South Carolina Medicaid database and is used as such in these analyses. We included county of residence and year of prescription as control variables.

We first sorted all prescriptions in the analysis file by frequency. We then identified opioid-containing preparations using the “drug name” variable in the data set. Opioid-containing compounds were identified by independent review of the frequency-sorted list by 2 authors

(WTB and SSG). In the prescription data, we identified the corresponding National Drug Codes (NDC) for the drug names we identified as study drugs. We included all prescriptions with the same NDC numbers as the preparations in the “drug name” field. Other brand or generic preparations of the drug name were not examined if they did not match the NDC numbers. We limited prescriptions to liquid preparations. In order to identify study drugs with sufficient dispensing events in the data set, we conducted a sample size analysis on the difference in potential overdose frequency in infants (0–11 months old) compared with children 12 to 36 months old. Review of the prescribing data demonstrated that there are approximately 4 children 12 to 36 months old who received an opioid for every 1 child 0 to 11 months old who received an opioid. In order to have a power of 0.80 ($\alpha = 0.05$) to detect a 50% lower frequency of potential overdose among the older children, a drug would have to have 1,245 prescriptions in the data set. Therefore, these analyses contain any opioid preparation with at least 1245 prescriptions.

Dosing Calculations and Definitions of Error

The Medicaid prescription files contain the quantity dispensed (volume, in the case of liquid preparations) and the days-supply (number of days for which the drug was supplied). The days-supply variable is taken from the prescription data and entered into the pharmacy computer system by the pharmacist dispensing the prescription. The daily volume dispensed was determined by the formula: total volume dispensed/number of days supply.

Prescriptions without a volume or days-supply were excluded. We did not have access to whether the drug was prescribed in an “as needed” manner or whether the intent was to prescribe at the low or high end of a recommended dosing range. Therefore, we assumed that the prescription as dispensed represented the most frequent recommended dosing interval and the highest dose recommended (per dose), a conservative approach consistent with that of other investigators.⁷ By knowing the concentration of the preparation, the days-supply, and the volume dispensed, we were able to calculate the daily dose dispensed (the “observed” values).

We used the *Pediatric Dosage Handbook*, 17th edition, to determine the maximum recommended doses and frequencies of the opioid preparations, based on the opioid component.¹⁹ For example, the recommended analgesic dose of codeine is 0.5 to 1.0 mg/kg/dose, given every 4 to 6 hours. Therefore, the maximum recommended daily codeine dose for this study was 1 mg/kg/dose (maximum recommended dose) given every 4 hours (maximum recommended frequency) for a maximum daily dose of 6 mg/kg/d, corresponding to the “expected” daily dose per kilogram for codeine-containing preparations. The highest recommended hydrocodone dose was 0.2 mg/kg/dose every 3 hours for a total of 1.6 mg/kg/d.¹⁹

We used the Centers for Disease Control and Prevention Growth Chart data to impute the estimated weight of each child as the 97th percentile weight based on age (in months) and gender. We chose the 97th as a conservative weight estimate, approximating 2 standard deviations above the mean. For each subject, we then calculated the maximum expected daily dose of the opioid based on the 97th percentile weight. Using the 97th percentile weight, maximum expected daily dose, the drug concentrations per volume, and the volume

dispensed, we could calculate the dose dispensed, allowing the calculation of the observed/expected ratio for each preparation. We considered a child to have been dispensed a potential overdose quantity if the observed daily dose dispensed was >10% above the maximum expected daily dose based on the 97th percentile weight (observed/expected >1.10), consistent with how other pediatric medication error studies have defined overdose using outpatient prescription data.^{2,7} We also calculated the average percentage potential overdose per drug and by age group.

Analyses

All analyses were completed using the prescription as the unit of analyses, not accounting for multiple prescriptions to any individual. After determining drug frequencies and the demographics of the prescription recipients, we completed bivariate comparisons (χ^2) for association between the following variables and receiving a potential overdose: age (grouped 0–2, 3–5, 6–11, and 12–36 months), gender, race/ethnicity, year, and preparation. Age was classified by oldest completed month, such that a child who was 2 months 21 days old at the time of a prescription was classified as “2 months” old for assigning weights. Because of limitations in the data, Hispanic ethnicity was treated as a race category, along with black, white, and other. We completed a multivariable logistic regression model predicting receipt of potential overdose, using age category as the criterion variable, controlling for race/ethnicity, gender, county of residence (to account for potential regional variation in prescribing), and year of prescription (to account for preparations entering and exiting approved use in the United States and other temporal prescribing trends).

Results

Of the 442 217 children 0 to 36 months old in the Medicaid data set from the study years, 41 706 (9.4%) received one of the study opioid preparations. There were 59 536 prescriptions for the opioid-containing preparations amounting to ~1.6 opioid prescriptions per patient among those who received an opioid. Mean age of prescription recipients was 20.5 months. Table 1 presents the 10 drug preparations, the number of prescriptions for each preparation, and prescription rank by frequency. The number of prescriptions per preparation varied from 1297 to 30 183.

Overall, 1582 (2.7%) of the 59 536 prescriptions contained a potential overdose quantity dispensed, and the average excess amount dispensed was 48% among the potential overdose prescriptions (average observed/expected = 1.48). In bivariate analyses (χ^2), prescriptions dispensed for infants, especially those 0 to 2 months old, were more likely to contain a potential overdose quantity than prescriptions dispensed for children 12 months (Table 2). For example, 8.9% of opioid prescriptions dispensed for infants 0 to 2 months old contained a potential overdose quantity, compared with 5.7% of opioid prescriptions dispensed for infants 3 to 5 months old, 3.6% of opioid prescriptions dispensed for infants 6 to 11 months old, and 2.3% of opioid prescriptions dispensed for children older than 12 months (χ^2 , $P < .0001$).

The adjusted analyses (logistic regression) demonstrated that the overall pattern of potential overdose was similar to that found in bivariate analyses—the association of potential

overdose frequency with younger ages remained significant, with each successively younger group less than 12 months old experiencing greater odds of potential overdose relative to older subjects (Table 3). Children classified as “black” in the data set were more likely to experience a potential overdose.

Discussion

These data show that opioid prescriptions dispensed to infants and young children often contain potential overdose quantities, with the excess amount dispensed equaling almost 50% greater than expected using a generous estimate of child weight. Our primary goal for this study was to define the magnitude of the problem of potential overdose in opioids, a high risk drug class, and the frequencies of potential overdose appear concerning. These data suggest that the period of infancy is particularly high risk for improper opioid dosing, with 9% of the opioid prescriptions dispensed for infants containing an excess quantity. These are some of the few data to evaluate age-related risk of dosing errors, but other pediatric studies have also shown that younger children or infants are at higher risk of experiencing a medication error or adverse drug event.^{10,18,20} While the nature of these data do not allow us to determine if these potential errors represent errors at the prescribing or dispensing stages, other outpatient studies have demonstrated that ordering errors occur approximately 15 times more commonly than dispensing errors.²¹ Therefore, we believe that most of these potential errors originated at the prescribing stage. While Black race was associated with increased odds of potential overdose, the range of overdose frequency among the races/ethnicities was in the 2.0% to 2.9% range, and there was not a significant difference in percentage overdose. This finding may represent a novel association, but the extent of the demographic data in the data set are limited making further inference about the meaning of the association difficult.

Overall, the frequency of dosing error among the prescriptions in this study, at 2.7%, is qualitatively in the range of dosing errors found in other outpatient pediatric studies. The studies by McPhillips et al⁷ and Kaushal et al⁸ found overdose error frequencies of 7% to 9%, but those studies did not focus specifically on any drug class. It should also be noted that the aforementioned studies reviewed written prescriptions (meaning, after the provider produced the prescription but before dispensing), allowing the investigators to identify prescription errors created by the providers. The data used for this study represent dispensed prescriptions and therefore likely represent an underestimate of the error rate at the point of writing the prescriptions. We have been unable to identify published frequencies of how well pharmacists identify pediatric prescription errors in outpatient settings. However, inpatient data show that pharmacists in pediatric hospital settings identify up to 78% of prescription errors before dispensing.²² Applying the inpatient error correction rate to the potential error frequencies identified in this study suggests that the frequency of potential overdose as written by the providers in these data may be as high as 15%.

More concerning, the frequency of potential overdose error among infants was much higher, especially for those 0 to 2 months old. Our findings suggest that younger infants in particular should have careful review of opioid prescriptions for appropriate dosing. In addition to the frequency of potential overdosing, the degree of potential overdosing is

concerning. One might argue that an overall potential error frequency of 2.7% correlates almost exactly with the fact that we assigned each subject the 97th percentile weight. However, we feel that these represent true overdoses because the average excess amount dispensed was 48%. In addition, our assumptions were biased toward underestimation of overdose in that we identified the highest recommended dose at the most frequently recommended intervals to determine the expected doses. If even a portion of the prescriptions were meant to be taken on an as-needed basis, then the excess amount dispensed is even greater than reported, again suggesting that these events represent true errors.

Recently, discussion has intensified as to whether opioid prescribing for children of any age is appropriate based on concerns about both the efficacy and the safety of opioids, particularly codeine.^{23–25} Two randomized trials in children with pain demonstrated that ibuprofen performed as well as or better than opioids for pain.^{15,16} The American Academy of Pediatrics has long held that opioids are not appropriate for cough in children, and reviews of published studies show that efficacy of opioids for cough is limited.¹⁷ Increasing awareness of genetic variability in metabolism of codeine and potentially fatal outcomes in those with altered codeine metabolism have also heightened safety concerns.²³ In fact, the US FDA has determined to add a “black box warning” to codeine’s FDA label, stating that codeine should not be used posttonsillectomy in children.²⁶ Nevertheless, primary care practitioners appear to be common prescribers of opioid medications, and future research into why office-based practitioners prescribe opioids would be an important aspect of making the use of these medications safer for children.²⁷

Options to reduce dosing error at the provider point of producing the prescription are multiple. To begin, electronic prescribing and other health information technology functions have significant potential to reduce opioid-associated dosing errors.²⁸ If electronic medication ordering, whether inpatient or outpatient, were to complete dose calculations automatically, it would reduce the opportunity for human error.²⁹ At a minimum, electronic prescribing programs could print a patient’s weight on a prescription to allow pharmacy dose checking. Even without electronic prescribing, requiring providers to record a weight on any opioid-containing prescription, especially for infants and younger children, would allow dose checking by pharmacists. Pharmacy work site interventions, including adjusting lighting, limits on pharmacist dispensing volume per hour, and efforts to reduce distractions can play an important role in reducing pharmacist dispensing errors.^{30–33} These error-reduction strategies have not been tested specifically regarding pediatric opioid prescribing or dispensing.

The need to reduce dosing error at both the provider and pharmacy dispensing points of the drug delivery process is heightened by documented difficulties that parents have in administering proper medication doses to children. Parents have difficulty properly measuring liquid preparations.³⁴ In an older but very illuminating study of reports to poison control centers, the investigators identified that measuring cups appeared to raise the risk of 2- and 3-fold dosing errors, in part arising from parents’ assumption that the whole cupful was the intended dose.³⁵ Parents have difficulty with or knowledge deficits of measurement concepts, such as “teaspoon,” and marked syringes allow parents to provide more accurate

dosing compared with cups, both marked and un-marked, and un-marked syringes.³⁶ Concrete, visually reinforced instructions for dosing and frequency of administration have been effective in reducing parental administration error.^{2,34,37}

There are several limitations of this study. The most significant limitation is that we did not know the actual weights of the subjects, so we are reporting estimations of overdose frequency. We did, however, use a very generous weight estimate (97th percentile for gender and age in months), so we believe that our estimates of overdose are biased toward underestimation. The frequency of potential overdose would have been higher had we used any lower percentile weight as the estimate for each patient. Although we do not know how many of the subjects experienced a true overdose, the percentage overdose also suggests real errors. With an average overdose amount of 48%, we would have had to underestimate weight by an average of 33% for the “error” dispensed amounts to be appropriate for the subjects. We do not know if the drugs were administered as scheduled or “prn” (*pro re nata* meaning as needed). Given that many of these drugs are likely prescribed “prn,” the majority of the subjects who received an excess quantity likely did not experience adverse events. However, intending these drugs to be used “prn” but dispensing amounts that would be excessive even if taken on a standing schedule raises even greater potential problems given concerns of opioid diversion, ingestions by children, and inadvertent administration of opioid drugs.^{11,38,39} We also do not know the origin of the error—the excess amounts dispensed could have occurred at the prescribing stage or at the dispensing stage. Other studies have demonstrated that many more errors are made in the prescribing (in ambulatory settings) or ordering steps (in inpatient settings) than are made in the dispensing step, suggesting that providers are major contributors to dosing error.⁸ Another limitation is that we evaluated only 1 drug class, so it is unclear if similar error frequencies would be found with a sampling of other drug classes. We note, however, that the frequency of potential overdose error found in these data is similar to that in other pediatric ambulatory studies. These data are from lower income children (Medicaid), and it is unclear whether either privately insured or uninsured children would experience different error frequencies. The data are now 4 years old, but recent national pediatric data suggest that the frequency of opioid prescribing has not appreciably changed despite multiple publications since 2010 in the medical press addressing the potential adverse effects of opioids in children.⁴⁰ Finally, the data are from only 1 state, and data suggest state-by-state variation in opioid prescribing for adults.⁴¹

Conclusions

Prescriptions dispensed for infants and young children often contained potential overdose quantities, with infants receiving potential overdose quantities the most often. When viewed in the light of other studies, these data suggest that greater safeguards are needed to improve the safety of opioid prescribing to children younger than 3 years.

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Table 1

Selected Opioid-Containing Preparations Prescribed to Children 0 to 36 Months Old, 2000–2010 South Carolina Medicaid Data.^a

Rank ^b	No. of Prescriptions	Drug Name ^c	Opioid Compound and Concentration ^d
1	30 183	Acetaminophen/codeine elixir	Codeine phosphate: 12 mg/5 mL
2	8359	Hydrocodone w/APAP elixir	Hydrocodone bitartrate: 2.5 mg/5 mL
3	4058	Promethazine-codeine syrup	Codeine phosphate: 10 mg/5 mL
4	4014	<i>Histinex HC</i> syrup	Hydrocodone bitartrate: 2.5 mg/5 mL
5	3082	<i>Atuss HD</i> liquid	Hydrocodone bitartrate: 2.5 mg/5 mL
6	2703	<i>De-Chlor HC</i> liquid	Hydrocodone bitartrate: 2.5 mg/5 mL
7	2005	<i>Histinex PV</i>	Hydrocodone bitartrate: 2.5 mg/5 mL
8	2020	<i>Anaplex HD</i> liquid	Hydrocodone bitartrate: 1.7 mg/5 mL
9	1815	<i>Atuss G</i> syrup	Hydrocodone bitartrate: 2.0 mg/5 mL
10	1297	<i>Tussionex/Pennkinetic</i>	Hydrocodone bitartrate: 10 mg/5 mL

^aCompounds that had at least 1245 prescriptions among the data years examined were included.

^bRepresents rank among the 10 drug preparations studied, based on total number of prescriptions in data set.

^cTrade names are shown in *italic* typeface. Drug name is the exact preparation identified in a frequency list from the Medicaid data.

^dRepresents the concentration of the unique preparation identified by the National Drug Codes studied.

Table 2
Bivariate Comparisons of Frequency of Potential Opioid Overdose, 2000–2010 South Carolina Medicaid Data.^a

Variable	Prescriptions, n (%)	Potential Overdose, b n (%)	P Value	Percent Potential Overdose ^b	P Value
Age in months					
0–2	314 (0.5)	28 (8.9)		45	
3–5	1717 (2.9)	97 (5.7)		57	
6–11	9801 (16.5)	350 (3.6)		38	
12–36	47 704 (80.1)	1107 (2.3)	<.0001 ^d	50	Nonsignificant
Race/ethnicity					
Black	20 919 (35.1)	610 (2.9)		49	
White	32 079 (53.9)	841 (2.6)		46	
Hispanic ^c	3264 (5.5)	64 (2.0)		44	
Other	3274 (5.5)	67 (2.1)	.0009	54	Nonsignificant
Gender					
Male	35 756 (60.1)	926 (2.6)		48	
Female	23 780 (39.9)	656 (2.8)	.2	47	Nonsignificant

^a All P values represent χ^2 analyses.

^b Overdose indicates that the amount dispensed was >110% of the amount expected based on maximum recommended dose, dosing interval, and estimated weight based on 97th percentile weight for age and gender. Percent potential overdose represents the average excess amount dispensed among those prescriptions with a potential overdose quantity.

^c In South Carolina Medicaid data, Hispanic ethnicity is treated as a separate category, equal to race, rather than an ethnicity descriptor of the races.

^d P value comparing 0 to 2 months with >3 months.

Table 3

Multivariable Model for Potential Opioid Overdose, 2000–2010 South Carolina Medicaid Data.

Independent Variable	Model ^a for Potential Overdose ^b		
	Odds Ratio	95% CI	P Value
Age in months			
0–2	4.17	2.815–6.176	<.0001
3–5	2.54	2.050–3.143	<.0001
6–11	1.57	1.390–1.775	<.0001
12–36	—		
Race/ethnicity			
Black	1.16	1.049–1.289	.004
White	—		
Gender			
Male	0.91	0.817–1.002	.055
Female	—		

^a Model controls for calendar year and county of residence. Model $P < .001$.

^b Overdose indicates that the amount dispensed was >110% of the amount expected based on maximum recommended dose, dosing interval, and estimated weight based on 97th percentile weight for age and gender.