Associations Between Opioid Prescribing Patterns and Overdose Among Privately Insured Adolescents

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abstract

OBJECTIVES: Little is known about the risk for overdose after opioid prescription. We assessed associations between the type of opioid, quantity dispensed, daily dose, and risk for overdose among adolescents who were previously opioid naive.

METHODS: Retrospective analysis of 1 146 412 privately insured adolescents ages 11 to 17 years in the United States captured in the Truven MarketScan commercial claims data set from January 2007 to September 2015. Opioid overdose was defined as any emergency department visit, inpatient hospitalization, or outpatient health care visit during which opioid overdose was diagnosed.

RESULTS: Among our cohort, 725 participants (0.06%) experienced an opioid overdose, and the overall rate of overdose events was 28 events per 100 000 observed patient-years. Receiving ≥30 opioid tablets was associated with a 35% increased risk for overdose compared to receiving ≤18 tablets (hazard ratio [HR] = 1.35; 95% confidence interval: 1.05–1.73; $P = .02$). Daily prescribed opioid dose was not independently associated with an increased risk for overdose. Tramadol exposure was associated with a 2.67-fold increased risk for opioid overdose compared to receiving oxycodone (adjusted HR = 2.67; 95% confidence interval: 1.90–3.75; $P < .0001$). Adolescents with preexisting mental health conditions demonstrated increased risk for overdose, with HRs ranging from 1.65 (anxiety) to 3.09 (substance use disorders).

CONCLUSIONS: One of 1600 (0.06%) previously opioid-naive adolescents who received a prescription for opioids experienced an opioid overdose a median of 1.75 years later that resulted in medical care. Preexisting mental health conditions, use of tramadol, and higher number of dispensed tablets (>30 vs <18) were associated with an increased risk of opioid overdose.

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WHAT'S KNOWN ON THIS SUBJECT: Outpatient opioid prescriptions to adolescents may be associated with complications, including the risk for overdose. Whether certain patterns of opioid prescribing are associated with an increased risk of opioid overdose is unknown.

WHAT THIS STUDY ADDS: Opioid overdose occurred in 1 of 1600 (0.06%) adolescents after an initial opioid prescription. Preexisting mental health conditions, use of tramadol, and higher number of dispensed tablets (>30 vs <18) were associated with an increased risk of opioid overdose.

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Rates of opioid overdose deaths among adolescents tripled between 1999 (0.8 of 100 000) and 2015 (2.4 of 100 000).[1] Although death is the most serious result of opioid overdose, the Centers for Disease Control and Prevention (CDC) estimates that there were ~120 emergency department (ED) visits and 30 substance abuse treatment admissions for each opioid death among adolescents in the United States in 2011.[2,3] Among adults, leftover opioids from previous prescriptions are a common source of opioid abuse and overdose.[4,5] Adult opioid prescribing practices have been linked to opioid overdose events, with those receiving opioids for >7 days and receiving higher morphine daily equivalents demonstrating an increased risk for overdose.[4] These findings have contributed to an intense and ongoing public health response, including the recent introduction of guidelines aimed at reducing opioid prescribing to adults in the United States and Canada.[6,7]Among adolescents, in contrast to adults, limited data are available to guide specific efforts to modify opioid prescribing patterns, and extrapolating data from the adult population may result in ill-informed policies. These gaps in knowledge impede public health efforts to reduce the impact of the opioid epidemic on adolescents.

Opioids are relatively overprescribed in adolescents, and leftover opioids are important sources for problematic opioid use.[8] Little is known, however, about possible links between initial patterns of opioid prescribing and subsequent risk for opioid overdose. The aim of this study, therefore, was to determine if a relationship exists between opioid prescribing patterns and opioid overdose among adolescents (11–17 years of age) who were previously opioid naive in the United States. Specifically, our first objective was to estimate the rate of opioid overdose among opioid-naive adolescents who received an initial opioid prescription during 2007–2015. We then evaluated whether specific patterns of opioid prescribing were related to risk of opioid overdose. We a priori hypothesized that increased quantity of opioid tablets prescribed, as well as increased daily dose of opioid prescribed, would both be associated with an increased probability of opioid overdose, even after adjustment for known risk factors such as a history of mental health disorders and substance use disorders.

METHODS

Participants and Procedure

We performed a cross-sectional analysis of data captured in the Truven Health MarketScan Commercial Claims and Encounters database for the years 2007–2015 (Truven Health Analytics, Ann Arbor, MI).[9] MarketScan includes private insurance claims from employees, their spouses, and their dependents. MarketScan includes deidentified inpatient, outpatient, and filled-prescription pharmaceutical claims. Filled-prescription claims include the drug name, date dispensed, National Drug Code, quantity dispensed, and dose dispensed. Approximately 50% of the US population is commercially insured, and the 2007–2015 MarketScan data set contains data on ~24 million unique adolescents. The University of Washington's Institutional Review Board has determined that this study did not constitute human subjects research because MarketScan contains no protected health information.

Study Cohort

Our cohort included adolescents 11 to 17 years of age with at least 12 months of opioid prescription-free continuous insurance enrollment (including pharmaceutical coverage) before a first opioid prescription. We identified 1 146 412 individuals who fit these criteria. Individuals were observed from the first day of their initial opioid prescription until 1 of 3 end points: (1) any unenrollment from MarketScan, (2) the end date of September 30, 2015, or (3) an opioid overdose event, whichever came first. The median period of observation was 1.75 years (interquartile range 0.7–6.7 years). The last 3 months of 2015 were not considered in this study because of the national transition from *International Classification of Diseases, Ninth Revision* (ICD-9), to *International Classification of Diseases, 10th Revision*, diagnosis coding.

Opioid Use Variables

We included all opioids dispensed from outpatient pharmacies; we did not examine opioids received during hospitalization. We included both isolated opioid products (eg, oxycodone), as well as opioid-combination products (eg, acetaminophen-oxycodone). Opioids were categorized as oxycodone, codeine, hydrocodone, tramadol, and other opioids (primarily morphine and hydromorphone). We excluded prescriptions for buprenorphine and methadone both because of their extreme rarity as initial opioids for opioid-naive patients and because of their common use as substance use disorder treatments. We also extracted data on the number of opioid tablets prescribed, dosages in morphine milligram equivalents per day, and the total number of opioid prescriptions each enrollee received during the study period. Morphine equivalent dosing per day was estimated by converting the total opioid dose prescribed (pill dose × number of tablets) to their morphine equivalent dosing by using established guidelines from the CDC and then dividing by the number of days prescribed to determine the average morphine equivalents

prescribed per day.[10] MarketScan does not contain data on individuals' weight, necessitating that we impute individual weights using medians from age- and sex-specific CDC growth charts.[11] Morphine equivalent daily dose per kilogram per day was converted to a categorical variable with the values of <0.5, 0.5 to 0.9, and >0.9 mg/kg per day. Because several states have passed regulations limiting the number of pills dispensed to adolescents for acute painful conditions (18 tablets or 3 days maximum), the number of tablets prescribed were categorized as 0 to 18 tablets, 19 to 30 tablets, and >30 tablets.[12] We used an "as prescribed" approach to opioid use, which means that the assumption made is that patients took them in the dose and frequency as prescribed. We excluded opioid prescriptions with >90 days' supply and quantities of >1000 tablets to reduce the impact of probable data errors on our analysis.

Opioid Overdose Events

Our primary outcome of interest was prescription opioid overdose, which we defined using ICD-9 codes published for surveillance by the CDC (ICD-9 codes 965.00, 965.02, 965.09, E850.1, and E850.2).[13–15] We did not include overdose due to illicit opioids such as heroin and fentanyl. We searched all ED visits, outpatient ambulatory visits, and hospitalizations for these ICD-9 codes.

Other Variables

Data on age, sex, region of the United States (North Central, Northeast, South, West, unknown), and residing in an urban versus rural location (metropolitan statistical area versus nonmetropolitan statistical area) were collected for each participant.

Preexisting health conditions were defined in 2 ways. First, chronic complex conditions were defined as medical conditions that can be reasonably expected to last at least 12 months and involve either several different organ systems or 1 organ system severely enough to require specialty pediatric care and probably hospitalization in a tertiary care center. We identified whether individuals were diagnosed with chronic complex conditions (eg, scoliosis, inflammatory bowel disease, genetic or congenital disorders) during the 12 months before first receipt of the index opioid using the complex chronic condition classification system.[16,17] Second, we determined whether individuals were diagnosed with anxiety disorders, mood disorders, alcohol-related disorders, and substance-related disorders in the 12 months before opioid receipt using Clinical Classifications Software as specified by the Agency for Healthcare Research and Quality.[18]

Statistical Analysis

Data were analyzed by using R version 3.2.2 (R Foundation for Statistical Computing, Vienna, Austria) and Stata version 14.2 (Stata Corp, College Station, TX). Rates of opioid overdose events associated with each sociodemographic, health condition, and opioid use variable were determined and compared by using the log-rank test of equality. Rates are presented as the number of overdose events per 100 000 observed person-years for consistency with previous publications on this topic.[4,19]

We developed multivariable Cox proportional hazards models to examine the relationship of opioid use measures and risk of opioid overdose adjusting for sociodemographic data, chronic complex health conditions, mental health conditions, and year of MarketScan enrollment. In our Cox proportional hazard models, characteristics of each person's first opioid prescription was the independent variable. The dependent variable was opioid overdose events. All individuals were included in our multivariable modeling. We prespecified a P value of .05 as statistically significant.

RESULTS

Our cohort included 1 146 412 individuals who filled 1 955 715 opioid prescriptions between 2007 and 2015. Most (66.6%) filled 1 opioid prescription, with 19.4% filling 2 prescriptions and 14.3% filling ≥3 prescriptions. Table 1 presents demographic characteristics of our sample. The sample contained a slight preponderance of girls (50.6%), and 40.2% were from the southern region of the United States. Hydrocodone was the most commonly prescribed opioid (62.9%).

During the study period, 725 individuals (~0.06% or ~1 of 1600) had an opioid overdose event. The cumulative incidence rate of opioid overdose for the total sample was 28 overdose events (95% confidence interval [CI]: 26–31) per 100 000 observed person-years (Table 2). The estimated unadjusted cumulative incidence rates of overdose events according to sample characteristics are presented in Table 2. Rates of overdose increased with age but were similar between boys and girls. There was no difference in rates for individuals living in a metropolitan statistical area compared with those in more rural areas. Rates of opioid overdose were slightly higher in western states compared to other regions. Adolescents with complex chronic conditions were not at increased risk for overdose compared with adolescents without such conditions.

Preexisting mental health conditions, including anxiety, mood, substance-related, and alcohol-related disorders, were strongly associated with an increased risk of overdose. For

TABLE 1 Characteristics of Adolescents at the Time of First Opioid Prescriptions

Characteristic	%
Sociodemographic variables	
Age, y	
11	3.0
12	7.3
13	9.8
14	13.5
15	18.3
16	23.0
17	25.2
Sex	
Female	50.6
Male	49.4
MSA	
MSA	84.9
Non-MSA	15.1
Region of the United States	
North Central	25.0
Northeast	13.2
South	40.2
West	19.5
Unknown	2.0
Preexisting health conditions	
Complex chronic condition	14.7
Anxiety disorder	7.2
Mood disorder	7.9
Substance-related disorders	1.2
Alcohol-related disorders	0.6
Opioid prescribing variables	
Type of opioid prescribed	
Oxycodone	15.4
Codeine	17.9
Hydrocodone	62.9
Tramadol	3.6
Other (hydromorphone and morphine)	0.2
Morphine equivalent daily dose prescribed, mg/kg per d	
<0.5	29.9
0.5–0.9	45.7
>0.9	24.4
Quantity of opioid tablets prescribed	
0–18	32.6
19–30	55.0
>30	12.4
No. opioid prescriptions during study period	
1	66.3
2	19.4
≥3	14.3

MSA, metropolitan statistical area.

example, the overdose rate among adolescents with substance use disorder was 243 events per 100 000 person-years compared to 26 events per 100 000 person-years among those without substance use disorder ($P < .0001$).

Several specific opioid prescribing patterns were associated with an increased risk of opioid overdose. Adolescents who received tramadol had rates of overdose almost 3 times higher compared with those who received oxycodone, codeine, and hydrocodone (Table 2). This association held in our multivariable model: tramadol was associated with a 2.67-fold increase in risk for overdose compared to oxycodone after controlling for sociodemographic variables, preexisting health conditions, pill quantity, and dose of opioid (hazard ratio [HR] = 2.67; 95% CI: 1.90–3.75) (Table 3). Adolescents who received ≥30 tablets were at increased risk compared with those who received fewer tablets (HR = 1.35; 95% CI: 1.05–1.73). As expected, adolescents who received >1 opioid prescription during the study period were at increased risk for overdose. We did not find an association between opioid dose (mg/kg per day) and risk for overdose (HR = 0.82; 95% CI: 0.65–1.04).

DISCUSSION

A prescription opioid overdose was observed in 1 of 1600 (0.06%) privately insured previously opioid naive adolescents who received a first prescription for an opioid during 2007–2015. Consistent with our hypothesis, opioid prescribing patterns were associated with an increased risk of opioid overdose. Adolescents receiving ≥30 opioid tablets had a 35% increased risk for overdose compared with adolescents receiving ≤18 tablets. Surprisingly, adolescents receiving tramadol had a 2.67-fold increased risk for overdose compared with adolescents receiving oxycodone. Furthermore, the risk for opioid overdose was significantly higher among adolescents with co-occurring mental health conditions and those receiving multiple opioid prescriptions during the study period.

Each year, between 5% and 15% of adolescents receive an opioid prescription in the United States (depending on the population studied),[20,21] and by the age of 18, almost 45% of adolescents have received at least 1 opioid prescription.[22] Furthermore, prescription opioids are among the most common medications implicated in pharmaceutical poisonings presenting to EDs in the United States. Despite the frequency with

TABLE 2 Unadjusted Rates of Opioid Overdose by Participant Characteristics

Characteristic	No. Overdose Events	Person-Years Observed	Rate of Overdose per 100 000 Person-Years (95% CI)	*P*
Total sample	725	2 554 413	28 (26–31)	
Sociodemographic variables				
Age, y				.0012
11	17	75 003	23 (14–36)	
12	29	190 734	15 (11–22)	
13	55	255 595	22 (17–28)	
14	101	347 299	29 (24–35)	
15	142	471 725	30 (26–35)	
16	193	586 357	33 (29–38)	
17	188	627 701	30 (26–35)	
Sex				.09
Female	388	1 286 397	30 (27–33)	
Male	337	1 268 016	27 (24–30)	
MSA				.6
MSA	101	371 400	27 (22–33)	
Non-MSA	624	2 183 014	29 (26–31)	
Region				<.0001
North Central	180	650 665	28 (24–32)	
Northeast	87	341 130	26 (21–31)	
South	257	1 022 073	25 (22–28)	
West	187	502 329	37 (32–43)	
Unknown	14	38 216	37 (22–62)	
Health conditions				
Complex chronic condition				.33
No	615	2 202 761	28 (22–62)	
Yes	110	351 652	31 (26–38)	
Anxiety				<.0001
No	591	2 400 919	25 (23–27)	
Yes	134	153 494	87 (74–103)	
Mood				<.0001
No	534	2 373 316	23 (21–24)	
Yes	191	181 098	105 (92–122)	
Substance				<.0001
No	659	2 527 276	26 (24–28)	
Yes	66	27 137	243 (191–310)	
Alcohol				<.0001
No	688	2 540 378	27 (25–29)	
Yes	37	14 035	264 (191–364)	
Opioid prescribing variables				
Type of opioid prescribed				<.0001
Oxycodone	94	388 308	24 (20–30)	
Codeine	108	481 449	22 (19–27)	
Hydrocodone	450	1 598 702	28 (26–31)	
Tramadol	70	81 927	85 (68–108)	
Other	3	4027	75 (24–231)	
Morphine equivalent daily dose, mg/kg per d				.017
<0.5	248	753 589	33 (29–37)	
0.5–0.9	323	1 189 651	27 (24–30)	
>0.9	154	611 173	25 (22–30)	
Quantity of opioid tablets supplied				.01
0–18	218	835 340	26 (23–30)	
19–30	399	1 423 794	28 (25–31)	
>30	108	295 279	37 (30–44)	
No. opioid prescriptions during study period				<.0001
1	337	1 387 794	24 (22–27)	

which these drugs are prescribed and dispensed, factors that underlie these risks among adolescents remain poorly described.[23] Our study adds to this research area by estimating the risk of opioid overdose associated with different patterns of opioid prescribing to adolescents receiving their first opioid prescription.

Our study may be compared to findings by Chung et al[21] who described opioid risk in a Medicaid population in Tennessee. They found that 1 of every 2611 opioid prescriptions for children were followed by an opioid-related adverse event. Significant differences between our study and Chung et al's[21] deserve mention: we used guidelines from the CDC to define an opioid overdose event, whereas Chung et al[21] used a wider group of ICD-9 codes to identify a broader range of opioid-related adverse events. Furthermore, Chung et al[21] examined opioid-related adverse events for 14 days after an opioid prescription, whereas we examined long-term opioid overdose risk. We specifically designed our study to follow patients over the longer term because of an increasing understanding of the long-term risks associated with access to opioids; in addition to events during the therapeutic window, exposure to opioids and leftover opioids from a prescription may predispose adolescents to problematic opioid use behaviors many years into the future, including heroin use and overdose.[24–26] Finally, our study was focused on a privately insured population, whereas Chung et al[21] used a publicly insured population. Differences in opioid risk between publicly and privately insured patients are generally posited to exist, but we can make no comment on them here because of the nature of our data set.

Our findings are timely because opioid overdose is an ongoing public

TABLE 2 Continued

Characteristic	No. Overdose Events	Person-Years Observed	Rate of Overdose per 100 000 Person-Years (95% CI)	*P*
2	153	597 754	26 (22–30)	
≥3	235	568 865	41 (36–47)	

MSA, metropolitan statistical area.

health crisis affecting adolescents in the United States. Using data from the Kids' Inpatient Database, Gaither et al[13] estimated that the annual incidence rate of hospitalizations due to prescription opioid overdose increased from ∼3.69 to 10.17 per 100 000 adolescents between 1997 and 2012. Allen et al[27] estimated that the national rate of prescription opioid poisonings was ∼10 per 100 000 for adolescents based on calls to poison control centers, most of whom required referral to a health care facility.

The ongoing and increasing epidemic of opioid overdose among adolescents indicates an urgent need for evidence to guide clinicians and policy makers on how to alter prescribing practices as they seek to protect patients from harm. Our analysis, although observational in nature, represents an attempt to illuminate a poorly understood problem. Our finding that an initial tramadol prescription was associated with an increased risk of overdose compared to other opioids was surprising to us and should be carefully placed in context. The CDC recently found that adults who received tramadol were more than twice as likely to have persistent use at both 1 and 3 years after an initial prescription compared with those receiving oxycodone and hydrocodone.[28] Furthermore, tramadol is now the second most common opioid prescribed to adults in the United States, and ED visits related to tramadol misuse increased by 250% between 2005 and 2011.[29,30] Multiple reasons for this increase in tramadol prescriptions can be hypothesized: tramadol's weaker affinity for the μ-opioid receptor might be translated by clinicians into a belief that it is "safer" than traditional opioids, or perhaps even more probably, tramadol's status as a Schedule 3 opioid makes it functionally easier to prescribe. In our study, only 3.6% of all opioid prescriptions were for tramadol. Thus, our finding that an initial tramadol prescription was associated with an increased risk of opioid overdose could be explained by differences in the practices of physicians who frequently prescribe tramadol, clinical features of patients who receive tramadol, or characteristics of the drug itself: our data set does not contain the necessary data to explore which of these potential causal mechanisms (or others) underlies this increased risk. Consequently, we caution readers not to interpret our findings as a warning against tramadol use. We interpret our findings as a signal that deserves further study, and we plan to explore clinical features of tramadol prescription and use by adolescents in further studies to better understand this initial result.

Our finding that increased number of tablets prescribed was associated with risk for overdose should be considered in the context of other risk factors as well as recent opioid guidelines that are focused on adolescents. Indeed, many health agencies now recommend severely limiting the amount of opioid prescribed to adolescents; for example, the Washington State Health Care Authority recommends an opioid supply of 3 days or less.[12] Our findings do not, in our opinion, provide robust support for limiting tablet number alone as a powerful intervention to decrease overdose risk; it would perhaps be more prudent to individualize opioid prescribing on the basis of each adolescent's underlying mental health conditions and projected clinical course. Indeed, preexisting mental health conditions were much stronger risk factors for opioid overdose than quantity of opioids prescribed. Regardless, there exists a clear need for prospective studies used to examine which factors place adolescents at increased risk for adverse events after an opioid prescription.

Our finding that adolescents with preexisting mental health conditions demonstrated an increased risk of opioid overdose is consistent with previous research revealing that mental health conditions are associated with greater risk of long-term opioid use in adolescents.[31] We believe our data add credence to the importance of universal screening for mental health conditions before prescribing opioids. Providers should carefully monitor the clinical course of adolescent patients with mental health conditions who are prescribed opioids and make referrals for mental health treatment of patients with identified psychiatric conditions. For example, it is prudent that physicians query prescription drug–monitoring programs and ensure that adolescents (and parents) understand the risks associated with opioids. Parents should be counseled on safe storage behaviors (eg, secure locked containers for opioid storage) and should dispose of leftover opioids using established guidelines.[32,33] However, we also want to highlight that our study does not suggest that adolescents with a history of substance use and/or mental health problems should be denied opioids for pain relief. There is a strong

TABLE 3 Cox Proportional Hazard Models of Risk of Opioid Overdose by Participant Characteristics

Characteristic	HR	95% CI	*P*
Sociodemographic variables			
Age	1.02	0.97–1.07	.42
Sex			
Female	1.0	—	—
Male	0.95	0.82–1.10	.51
MSA			
MSA	1.0	—	—
Non-MSA	1.02	0.82–1.26	.88
Region			
North central	1.0	—	—
Northeast	0.98	0.75–1.26	.85
South	0.99	0.81–1.20	.88
West	1.39	1.13–1.71	.002
Unknown	1.29	0.75–2.24	.35
Health conditions			
Complex chronic condition			
None	1.0	—	—
Yes	0.94	0.77–1.16	.57
Anxiety			
None	1.0	—	—
Yes	1.65	1.33–2.06	<.0001
Mood disorders			
No	1.0	—	—
Yes	2.77	2.26–3.34	<.0001
Substance-related disorders			
No	—	—	—
Yes	3.09	2.27–3.39	<.0001
Alcohol-related disorders			
No	1.0	—	—
Yes	2.45	1.66–3.60	<.0001
Opioid prescribing variables			
Type of opioid prescribed			
Oxycodone	1.0	—	—
Codeine	0.94	0.70–1.27	.71
Hydrocodone	1.13	0.90–1.44	.28
Tramadol	2.67	1.90–3.75	<.0001
Other opioids	2.55	0.81–8.08	.11
Morphine equivalent daily dose, mg/kg per d			
<0.5	1.0	—	—
0.5–0.9	0.89	0.75–1.06	.20
>0.9	0.82	0.65–1.04	.10
Quantity of opioid tablets supplied			
0–18	1.0	—	—
19–30	1.09	0.91–1.30	.32
>30	1.35	1.05–1.73	.02
No. opioid prescriptions during study period			
1	1.0	—	—
2	1.05	0.86–1.27	063
≥3	1.54	1.29–1.82	<.0001

Model adjusted for age, sex, region, MSA, health conditions, opioid prescribing variables, and year of MarketScan enrollment. MSA, metropolitan statistical area; —, not applicable.

possibility that these adolescents with a substance abuse history may overdose on opioids available in the community regardless of whether they received an opioid prescription themselves. As suggested in previous work, denial of medications to these individuals would likely have little effect on their risk for overdose while leaving them in uncontrolled pain.

There are several limitations of our study that should be considered when interpreting the findings. As a cross-sectional analysis, we have reported associations without the ability to delineate causal relationships. For example, it is possible that adolescents in our cohort who experienced opioid overdose could have used either leftover opioids from their own prescription[8] or diverted opioids from someone else's prescription[23]: both mechanisms would appear identical in the MarketScan data set. Second, the administrative nature of the MarketScan database creates a lack of clinical details: for example, explanatory ICD-9 codes that precipitated the opioid prescription were missing for ∼50% of our sample. Some potential reasons for the absence of an associated ICD-9 code could include dental visits (which are not captured in MarketScan) or opioids prescribed without a health care visit (such as phoned-in prescriptions for Schedule 3 opioids). Because of this weakness, we elected not to include the diagnoses associated with the initial opioid prescription in our main analysis, although sensitivity analyses revealed that inclusion versus exclusion of these variables did not affect the magnitude nor direction of associations in our Cox models. Third, although we control for preexisting health conditions in our analysis, it is possible that there are other unmeasured clinical risk factors that increase risk for opioid overdose. Fourth, our study is limited to privately insured individuals who may have different rates of overdose compared with those who are publicly insured. Despite these limitations, our study permits us to characterize opioid prescribing patterns and related overdose risks over consecutive years in a well-defined privately insured adolescent population in the United States. In the absence of more granular data, our findings can help guide future research and inform the development of clinical guidelines on opioid prescribing for adolescents.

CONCLUSIONS

We have identified several factors that are associated with increased risk of overdose among adolescents who are opioid naive and believe these data should stimulate the development of further prospective studies to better characterize these risks. Furthermore, considering that the opioid epidemic continues to progress unabated in the United States and is partially driven by prescription opioid use, this study contributes to a better understanding of opioid prescribing patterns in adolescents in an effort to guide effective efforts to prevent patient harm.

ABBREVIATIONS

CDC: Centers for Disease Control and Prevention
CI: confidence interval
ED: emergency department
HR: hazard ratio
ICD-9: International Classification of Diseases: Ninth Revision

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REFERENCES

1. Curtin SC, Tejada-Vera B, Warmer M. Drug overdose deaths among adolescents aged 15-19 in the United States: 1999-2015. *NCHS Data Brief*. 2017;(282):1–8
2. Banerjee S, Roland CL, Willke R, Mardekian J, Garrison LP Jr.. Prevalence of and comorbid health conditions associated with pediatric prescription opioid use in the US. *J Pain Palliat Care Pharmacother*. 2017; 31(3–4):218–227
3. Groenewald CB, Law EF, Fisher E, Beals-Erickson SE, Palermo TM. Associations between adolescent chronic pain and prescription opioid misuse in adulthood. *J Pain*. 2019;20(1):28–37
4. Bohnert AS, Valenstein M, Bair MJ, et al. Association between opioid prescribing patterns and opioid overdose-related deaths. *JAMA*. 2011;305(13):1315–1321
5. Han B, Compton WM, Blanco C, et al. Prescription opioid use, misuse, and use disorders in U.S. adults: 2015 national survey on drug use and health. *Ann Intern Med*. 2017;167(5):293–301
6. Dowell D, Haegerich TM, Chou R. CDC guideline for prescribing opioids for chronic pain–United States, 2016. *JAMA*. 2016;315(15):1624–1645
7. Busse JW, Craigie S, Juurlink DN, et al. Guideline for opioid therapy and chronic noncancer pain. *CMAJ*. 2017; 189(18):E659–E666
8. Voepel-Lewis T, Wagner D, Tait AR. Leftover prescription opioids after minor procedures: an unwitting source for accidental overdose in children. *JAMA Pediatr*. 2015;169(5):497–498
9. Hansen L. *The MarketScan Databases for Life Sciences Researchers*. Ann Arbor, MI: Truven Health Analytics; 2016
10. Centers for Disease Control and Prevention. Calculating total daily dose of opioids for safer dosage. Available at: https://www.cdc.gov/drugoverdose/pdf/calculating_total_daily_dose-a.pdf. Accessed March 21, 2019
11. Centers for Disease Control and Prevention, National Center for Health Statistics. Clinical growth charts. Available at: https://www.cdc.gov/growthcharts/clinical_charts.htm. Accessed March 14, 2019
12. Washington State Health Care Authority. Opioids. 2017. Available at: https://www.hca.wa.gov/billers-providers-partners/programs-and-services/opioids. Accessed December 13, 2018
13. Gaither JR, Leventhal JM, Ryan SA, Camenga DR. National trends in hospitalizations for opioid poisonings among children and adolescents, 1997 to 2012. *JAMA Pediatr*. 2016;170(12): 1195–1201
14. Slavova S, Bunn TL, Talbert J. Drug overdose surveillance using hospital discharge data. *Public Health Rep*. 2014; 129(5):437–445
15. Centers for Disease Control and Prevention. Prescription drug overdose data & statistics. Guide to ICD-9-CM and ICD-10 codes related to poisoning and pain. 2013. Available at: https://www.cdc.gov/drugoverdose/pdf/pdo_guide_to_icd-9-cm_and_icd-10_codes-a.pdf. Accessed February 7, 2019
16. Feudtner C, Christakis DA, Connell FA. Pediatric deaths attributable to complex chronic conditions: a population-based study of Washington State, 1980-1997. *Pediatrics*. 2000;106(1 pt 2):205–209

17. Colorado University Data Science to Patient Value. Pediatric complex chronic conditions: an R package. Available at: https://github.com/CUD2V/pccc. Accessed February 7, 2019

18. The Healthcare Cost and Utilization Project. Clinical Classifications Software (CCS) for ICD-9-CM. Rockville, MD: Agency for Healthcare Research and Quality; 2017. Available at: https://www.hcup-us.ahrq.gov/toolssoftware/ccs/ccs.jsp. Accessed December 13, 2018

19. Dunn KM, Saunders KW, Rutter CM, et al. Opioid prescriptions for chronic pain and overdose: a cohort study. *Ann Intern Med*. 2010;152(2):85–92

20. Groenewald CB, Rabbitts JA, Gebert JT, Palermo TM. Trends in opioid prescriptions among children and adolescents in the United States: a nationally representative study from 1996 to 2012. *Pain*. 2016;157(5):1021–1027

21. Chung CP, Callahan ST, Cooper WO, et al. Outpatient opioid prescriptions for children and opioid-related adverse events. *Pediatrics*. 2018;142(2):e20172156

22. McCabe SE, Boyd CJ, Young A. Medical and nonmedical use of prescription drugs among secondary school students. *J Adolesc Health*. 2007;40(1):76–83

23. Burghardt LC, Ayers JW, Brownstein JS, et al. Adult prescription drug use and pediatric medication exposures and poisonings. *Pediatrics*. 2013;132(1):18–27

24. Miech R, Johnston L, O'Malley PM, Keyes KM, Heard K. Prescription opioids in adolescence and future opioid misuse. *Pediatrics*. 2015;136(5). Available at: www.pediatrics.org/cgi/content/full/136/5/e1169

25. Lankenau SE, Teti M, Silva K, et al. Initiation into prescription opioid misuse amongst young injection drug users. *Int J Drug Policy*. 2012;23(1):37–44

26. McCabe SE, West BT, Boyd CJ. Leftover prescription opioids and nonmedical use among high school seniors: a multi-cohort national study. *J Adolesc Health*. 2013;52(4):480–485

27. Allen JD, Casavant MJ, Spiller HA, et al. Prescription opioid exposures among children and adolescents in the United States: 2000-2015. *Pediatrics*. 2017;139(4):e20163382

28. Shah A, Hayes CJ, Martin BC. Characteristics of initial prescription episodes and likelihood of long-term opioid use - United States, 2006-2015. *MMWR Morb Mortal Wkly Rep*. 2017;66(10):265–269

29. Bush DM. *Emergency Department Visits for Drug Misuse or Abuse Involving the Pain Medication Tramadol. The CBHSQ Report*. Rockville, MD: Substance Abuse and Mental Health Services Administration (US); 2013:1–8

30. Fuentes AV, Pineda MD, Venkata KCN. Comprehension of top 200 prescribed drugs in the US as a resource for pharmacy teaching, training and practice. *Pharmacy (Basel)*. 2018;6(2):E43

31. Quinn PD, Hur K, Chang Z, et al. Association of mental health conditions and treatments with long-term opioid analgesic receipt among adolescents. *JAMA Pediatr*. 2018;172(5):423–430

32. Garbutt JM, Kulka K, Dodd S, Sterkel R, Plax K. Opioids in adolescents' homes: prevalence, caregiver attitudes, and risk reduction opportunities. *Acad Pediatr*. 2019;19(1):103–108

33. McDonald EM, Kennedy-Hendricks A, McGinty EE, et al. Safe storage of opioid pain relievers among adults living in households with children. *Pediatrics*. 2017;139(3):e20162161