

Prescription Opioid Exposures Among Children and Adolescents in the United States: 2000–2015

Jakob D. Allen,^a Marcel J. Casavant, MD,^{a,b,c} Henry A. Spiller, MS, D.ABAT,^{b,c} Thiphalak Chounthirath, MS,^a Nichole L. Hodges, PhD,^a Gary A. Smith, MD, DrPH^{a,c}

abstract

OBJECTIVES: This study analyzes and compares exposures to prescription opioids among children and adolescents younger than 20 years old in the United States.

METHODS: Data from the National Poison Data System for 2000 through 2015 were analyzed.

RESULTS: Poison control centers received reports of 188 468 prescription opioid exposures among children aged <20 years old from 2000 through 2015. The annual number and rate of exposures increased early in the study period, but declined after 2009, except for buprenorphine exposures, which increased during the last 3 study years. Hydrocodone accounted for the largest proportion of exposures (28.7%), and 47.1% of children exposed to buprenorphine were admitted to a health care facility (HCF). The odds of being admitted to an HCF were higher for teenagers than for children aged 0 to 5 years (odds ratio [OR]: 2.86; 95% confidence interval [CI]: 2.78–2.94) or children aged 6 to 12 years (OR: 6.62; 95% CI: 6.06–7.02). Teenagers also had greater odds of serious medical outcomes than did children aged 0 to 5 years (OR: 3.03; 95% CI: 2.92–3.15) or children aged 6 to 12 years (OR: 4.59; 95% CI: 4.21–5.00). The rate of prescription opioid–related suspected suicides among teenagers increased by 52.7% during the study period.

CONCLUSIONS: Prescription opioid–related HCF admissions and serious medical outcomes were higher among teenagers. Contrary to trends for other prescription opioids, exposures to buprenorphine have increased in recent years; children aged 0 to 5 years accounted for almost 90% of buprenorphine exposures. These findings indicate that additional prevention efforts are needed.



^aCenter for Injury Research and Policy of the Research Institute at Nationwide Children's Hospital, Columbus, Ohio; ^bCentral Ohio Poison Center, Columbus, Ohio; and ^cDepartment of Pediatrics, The Ohio State University College of Medicine, Columbus, Ohio

Mr Allen conducted the data analysis and drafted and revised the manuscript; Dr Casavant and Mr Spiller contributed to the conceptualization of the study, assisted in data analysis, and critically reviewed the manuscript; Mr Chounthirath assisted in data analysis and revised the manuscript; Dr Hodges assisted in data interpretation and critically reviewed and revised the manuscript; Dr Smith contributed to the conceptualization of the study, assisted in data analysis, and critically reviewed and revised the manuscript; and all authors approved the final manuscript as submitted.

DOI: 10.1542/peds.2016-3382

Accepted for publication Jan 10, 2017

Address correspondence to Gary A. Smith, MD, DrPH, Director, Center for Injury Research and Policy, The Research Institute at Nationwide Children's Hospital, 700 Children's Dr, Columbus, OH 43205. E-mail: gary.smith@nationwidechildrens.org

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

WHAT'S KNOWN ON THIS SUBJECT: Previous reports have shown that opioids are heavily prescribed to the general population in the United States and have the highest overdose rate among all prescription drugs. Analgesics are the third most commonly implicated substances in poison center pediatric exposures.

WHAT THIS STUDY ADDS: From 2000 through 2015, 188 468 pediatric opioid exposures were reported to US poison control centers. Health care facility admission occurred in 8.7% and 21.5% of exposures among 0- to 5-year-olds and teenagers, respectively. Serious outcomes were more frequent among teenagers.

To cite: 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

Pain is one of the most common reasons individuals in the United States seek health care, and of those, 20% are prescribed opioid analgesics.^{1,2} Eighty percent of opioid prescriptions worldwide are distributed in the United States.³ From 1999 to 2010, opioid sales in the United States quadrupled, and in 2012, an estimated 259 million prescriptions for opioid medications were written.² This rapid increase stemmed from concerns raised in the 1990s that physicians were not adequately treating patient pain.⁴ As a result, pain management guidelines were revised to favor more liberal prescribing of opioid medications. As opioid use became more prevalent, pediatric exposures to these drugs increased. From 2006 to 2012, >22 000 children were treated in US emergency departments for opioid poisoning.⁵ The annual rate of opioid poisoning-related hospitalization increased by 165% from 1997 to 2012.⁶ Opioid exposures at even relatively low doses can result in life-threatening effects in children.⁷ In September 2016, the American Academy of Pediatrics recommended halting codeine use among children because of the risk of breathing complications.⁸

Currently, there is an opioid epidemic in the United States, with the rate of opioid overdose deaths, including deaths from opioid medications and heroin, doubling since 2000.⁹⁻¹² Unintentional poisonings are now the leading cause of injury-related mortality in the United States.¹³ Among teenagers aged 15 to 19 years, there was a 91% increase in fatal poisoning from 2000 to 2009, which was mostly attributable to an increase in prescription drug overdoses.¹⁴ Nearly 1 in 4 high school seniors in the United States has had some lifetime exposure to prescription opioids, either medically or nonmedically.¹⁵ These exposures can lead to future use of illegal substances; almost 80% of new

heroin users have previously used opioid pain medications.¹⁶⁻¹⁸

Although multiple studies have described the epidemiology of opioid overdose^{10-12,19} and misuse^{12,14} in the United States, little research has been published examining opioid poisoning among children, particularly those aged <6 years old. Three studies on opioid poisoning among children included only individuals treated in emergency departments^{5,20} or those who were hospitalized.⁶ Other research has focused on pediatric poisoning fatalities.²¹ The current study analyzes National Poison Data System (NPDS) data to define the epidemiology of opioid exposures among US children aged <20 years old.

METHODS

Data Sources and Study Design

Opioid exposure data were obtained from the NPDS, a poison surveillance database maintained by the American Association of Poison Control Centers (AAPCC). NPDS data are collected by regional poison control centers (PCCs) covering the entire population of the United States and its territories. PCC specialists receive telephone calls reporting poison exposures, provide medical advice on exposure management, and record details about each exposure.²²

Case Selection Criteria

The AAPCC uses generic codes to group broad categories of related substances. Generic codes were used to query the NPDS for all single-substance exposure calls involving opioids among children aged <20 years old from 2000 through 2015. The search identified 195 813 cases, of which 188 468 met study inclusion criteria. Cases were excluded if the exposure reason was “adverse reaction–food,” “adverse reaction–other,” “other–contamination/tampering,” “unintentional–bite/

sting,” “unintentional–environmental,” or “unintentional–food poisoning.” Cases were also excluded if the medical outcome was “confirmed nonexposure” or if the PCC specialist did not believe the exposure was responsible for the observed clinical effect(s).

Variables

Opioid medications were categorized as hydrocodone, codeine, oxycodone, propoxyphene, tramadol, morphine, methadone, buprenorphine, meperidine, hydromorphone, fentanyl, oxymorphone, and as “other” (see Supplemental Information). The level of care received was used to describe whether individuals were admitted to a health care facility (HCF; critical care unit, non-critical care unit, or psychiatric care unit) or not admitted (treated/evaluated and released, no HCF treatment received, lost to follow-up or left against medical advice, or refused referral/did not arrive at HCF). Medical outcomes were grouped into serious outcome (death, major effect, or moderate effect), minor effect, no effect, and not followed/unable to follow. The NPDS defines major effects as symptoms that are life-threatening or result in significant disability or disfigurement.²³ Moderate effects are more pronounced, prolonged, or systemic than minor symptoms and typically require treatment.²³ Patients displaying minor effects have minimal symptoms that resolve quickly.²³

Reason for exposure was categorized as unintentional-general (including exploratory behaviors), unintentional–therapeutic error, intentional (abuse, misuse, suspected suicide, unknown), other (adverse reaction, malicious intent, withdrawal, occupational exposure, unintentional misuse), and unknown. Substance formulations were grouped into solid (tablets/capsules/caplets), liquid, other

(aerosol/mist/spray/gas, cream/lotion/gel, patch, powder/granules, or other), and unknown. Exposure site was classified as residence (own or other), other (HCF, public area, restaurant/food service, school, workplace, or other), or unknown. Children were divided into 3 age groups: 0 to 5 years, 6 to 12 years, and teenagers (13–19 years). Other analyzed variables included the following: sex, chronicity of exposure, exposure management site, type of therapeutic error, route of exposure, and scenario of access to medication.

Statistical Analysis and Ethical Concerns

NPDS data were analyzed by using SPSS 21.0 for Windows (IBM Corporation) and SAS Enterprise Guide 7.11 HF3 (SAS Institute, Cary, NC) software. Exposure rates were calculated by using US Census Bureau July 1st intercensal and postcensal population estimates for children aged <20 years old from 2000 through 2015.^{24,25} Piecewise linear regression was used to analyze exposure trends with the use of 2009 as a breakpoint. The estimated slope from the regression model (m) is reported along with the associated P value. Logistic regression was used to analyze serious medical outcomes and HCF admissions by type of opioid exposure and age group. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. Statistical significance was determined at $\alpha = 0.05$. NPDS data did not include patient identifiers. This study was judged exempt by the institutional review board at the Research Institute at Nationwide Children's Hospital.

RESULTS

General Characteristics

From 2000 through 2015, PCCs reported 188 468 opioid exposures among children aged <20 years old, averaging 11 779 exposures annually or 14.34 exposures per 100 000

children. Most opioid exposures occurred at a residence (95.8%; Table 1) and resulted from ingestion (98.4%). Exposures were most common among children aged 0 to 5 years (59.7%), followed by teenagers (29.9%). Examining the data by single years of age, opioid exposure frequency and rate increased sharply at 1 and 2 years and then declined before increasing modestly among teenagers (Fig 1). The mean and median ages of exposure were 7.1 (SD: 6.6) years and 3 (interquartile range: 2–14) years, respectively. Boys accounted for 50.9% of exposures to opioids overall, 53.2% of exposures among children aged 0 to 5 years, and 57.9% of exposures among children aged 6 to 12 years of age (Table 1). Among teenagers, more exposures occurred among girls (55.7%). The opioid medications most commonly implicated in exposure were hydrocodone (28.7%), oxycodone (17.6%), and codeine (16.5%).

Unintentional-general was the most common reason for opioid exposure overall (56.1%), but there were variations by age (Table 1). Among children aged 6 to 12 years, more than one-half of all exposures (54.5%) were therapeutic errors. Among teenagers, 71.5% of exposures were intentional, including the following: suspected suicide (34.2%), abuse (20.8%), and misuse (11.2%). Overall, 93.8% of exposures were acute. Therapeutic errors accounted for 18.1% of all exposures; of these, inadvertently took/given someone else's medication (25.3%), wrong medication taken/given (24.7%), and other incorrect dose (13.7%) were the most common types of errors (Table 2). Scenarios of access to the medication were recorded for 6286 exposures (3.3%), and 94.6% of these were for children aged 0 to 5 years. Among this age group, product stored within sight of the child (34.8%), product stored inappropriately (13.6%), and child accessed medication from purse

(13.3%) were the most commonly documented scenarios.

Trends

From 2000 to 2009, the overall annual number of opioid exposures increased significantly by 86.0% ($m = 745.8$, $P < .001$) and the rate per 100 000 children increased significantly by 79.9% ($m = 0.86$, $P < .001$), followed by a significant decline in the number (–31.4%; $m = -712.5$, $P < .001$) and rate (–30.5%; $m = -0.82$, $P < .001$) from 2009 through 2015 (Fig 2). The annual rate of opioid exposures per 100 000 children aged 0 to 5 years old increased significantly by 93.2% ($m = 2.02$, $P < .001$) from 2000 to 2009, followed by a 29.4% ($m = -1.47$, $P < .001$) decrease from 2009 through 2015 (Fig 2). Similarly, the rate increased significantly among children aged 6 to 12 years old (53.4%; $m = 0.14$, $P < .001$) and teenagers (56.8%; $m = 0.53$, $P < .001$) during 2000–2009, before declining by 31.7% ($m = -0.25$, $P < .001$) and 30.9% ($m = -0.79$, $P < .001$), respectively, from 2009 through 2015 (Fig 2). Notable exceptions to these trends are buprenorphine exposures, which declined from 2011 to 2013 before increasing in 2014–2015, and tramadol exposures, which decreased from 2000 to 2003 and then increased steadily before plateauing after 2012. In addition, propoxyphene exposures declined slowly from 2005 to 2009 and more sharply from 2010 through 2015. Another exception to the overall trend was the rate of suspected suicide among teenagers, which increased by 52.7% ($m = 0.10$, $P < .001$) from 2000 through 2015.

Management Site, Level of Health Care Received, and Medical Outcome

Overall, more than half of exposed children were either referred to an HCF by a PCC (28.1%) or already in (or en route to) an HCF when the PCC was called (27.5%; Table 2). Twenty-eight percent of exposed

TABLE 1 Characteristics of Prescription Opioid Exposures Among Children <20 Years of Age by Age Group, NPDS 2000–2015

Characteristics	Age Group, <i>n</i> (%)			
	0–5 Years	6–12 Years	13–19 Years	Total
Sex				
Male	59 770 (53.2)	11 412 (57.9)	24 804 (44.1)	95 986 (50.9)
Female	52 193 (46.4)	8267 (41.9)	31 354 (55.7)	91 814 (48.7)
Unknown	502 (0.5)	44 (0.2)	122 (0.2)	668 (0.4)
Reason				
Unintentional-general	96 134 (85.5)	5905 (29.9)	3759 (6.7)	105 798 (56.1)
Intentional	201 (0.2)	1988 (10.1)	40 255 (71.5)	42 444 (22.5)
Intentional–suspected suicide	46 (0.0)	360 (1.8)	19 239 (34.2)	19 645 (10.4)
Intentional-abuse	40 (0.0)	447 (2.3)	11 721 (20.8)	12 208 (6.5)
Intentional-misuse	86 (0.1)	670 (3.4)	6297 (11.2)	7053 (3.7)
Intentional-unknown	29 (0.0)	511 (2.6)	2998 (5.3)	3538 (1.9)
Unintentional–therapeutic error	15 124 (13.4)	10 749 (54.5)	8292 (14.7)	34 165 (18.1)
Other	643 (0.6)	560 (2.8)	2633 (4.7)	3836 (2.0)
Unknown	363 (0.3)	521 (2.6)	1341 (2.4)	2225 (1.2)
Exposure site				
Residence ^a	110 511 (98.3)	19 022 (96.4)	50 958 (90.5)	180 491 (95.8)
Other ^b	1445 (1.3)	541 (2.7)	3004 (5.3)	4990 (2.6)
Unknown	509 (0.5)	160 (0.8)	2318 (4.1)	2987 (1.6)
Type of opioid				
Hydrocodone	29 088 (25.9)	5447 (27.6)	19 491 (34.6)	54 026 (28.7)
Oxycodone	20 011 (17.8)	3205 (16.3)	9968 (17.7)	33 184 (17.6)
Codeine	19 151 (17.0)	5025 (25.5)	6938 (12.3)	31 114 (16.5)
Tramadol	12 403 (11.0)	1778 (9.0)	7115 (12.6)	21 296 (11.3)
Propoxyphene	5799 (5.2)	748 (3.8)	3363 (6.0)	9910 (5.3)
Morphine	3781 (3.4)	576 (2.9)	1928 (3.4)	6285 (3.3)
Methadone	3466 (3.1)	533 (2.7)	2218 (3.9)	6217 (3.3)
Buprenorphine	5078 (4.5)	174 (0.9)	509 (0.9)	5761 (3.1)
Meperidine	422 (0.4)	147 (0.7)	236 (0.4)	805 (0.4)
Hydromorphone	330 (0.3)	75 (0.4)	129 (0.2)	534 (0.3)
Fentanyl	222 (0.2)	28 (0.1)	163 (0.3)	413 (0.2)
Oxymorphone	183 (0.2)	22 (0.1)	132 (0.2)	337 (0.2)
Other	12 531 (11.1)	1965 (10.0)	4090 (7.3)	18 586 (9.9)
Chronicity				
Acute	109 954 (97.8)	18 424 (93.4)	48 483 (86.1)	176 861 (93.8)
Acute-on-chronic	1795 (1.6)	978 (5.0)	4066 (7.2)	6839 (3.6)
Chronic	478 (0.4)	223 (1.1)	1454 (2.6)	2155 (1.1)
Unknown	238 (0.2)	98 (0.5)	2277 (4.0)	2613 (1.4)
Formulation				
Solid	78 495 (69.8)	11 204 (56.8)	45 797 (81.4)	135 496 (71.9)
Liquid	20 623 (18.3)	6052 (30.7)	3215 (5.7)	29 890 (15.9)
Other	2297 (2.0)	245 (1.2)	1122 (2.0)	3664 (1.9)
Unknown	11 050 (9.8)	2222 (11.3)	6146 (10.9)	19 418 (10.3)
Total (row percentage)	112 465 (59.7)	19 723 (10.5)	56 280 (29.9)	188 468 (100.0)

Column and row percentages may not sum to 100.0% due to rounding errors.

^a Residence includes own residence and other residence.

^b Other includes HCF, public area, restaurant/food service, school, unknown, and workplace.

children were treated/evaluated and released and 12.0% were admitted for care. Overall, 6.6% of exposed children experienced serious medical outcomes, including 175 fatalities (0.1%). Of the children who died, 54.9% were teenagers, 71.4% were boys, 49.1% had intentional exposures, and most were exposed to either methadone (40.0%) or oxycodone (22.9%). Children intentionally exposed to prescription

opioids had 4.56 (95% CI: 4.43–4.70) times higher odds of being admitted than children exposed to prescription opioids for other reasons. The odds of being admitted to an HCF were higher for teenagers than for children aged 0 to 5 years (OR: 2.86; 95% CI: 2.78–2.94) or children aged 6 to 12 years (OR: 6.52; 95% CI: 6.06–7.02) (Table 3). Teenagers also had greater odds of experiencing serious medical outcomes than children aged 0 to 5

years (OR: 3.03; 95% CI: 2.92–3.15) or children aged 6 to 12 years (OR: 4.59; 95% CI: 4.21–5.00). Compared with children aged 6 to 12 years, children aged 0 to 5 years old had greater odds of being admitted to an HCF (OR: 2.28; 95% CI: 2.12–2.47) or experiencing serious medical outcomes (OR: 1.51; 95% CI: 1.39–1.65).

Children exposed to buprenorphine had greater odds of HCF admission

(OR: 7.26, 95% CI: 6.88–7.66), whereas children exposed to fentanyl had greater odds of serious medical outcomes (OR: 5.94; 95% CI: 4.80–7.35) compared with those exposed to other prescription opioids (Table 3). Among children younger than 13 years, buprenorphine and methadone exposures were most likely to result in HCF admission and serious medical outcomes. Children aged 0 to 5 years accounted for 88.1% of buprenorphine exposures, and of these, 51.0% were admitted to an HCF (Table 3). Among teenagers, the proportion of exposures resulting in HCF admission was highest among those exposed to fentanyl (35.0%), oxycodone (33.3%), methadone (32.3%), and tramadol (31.5%).

Clinical Effects and Therapies

More than one-fourth of children (28.6%) experienced at least 1 exposure-related symptom. Drowsiness/lethargy (17.6%) and vomiting (6.0%) were most frequent overall and also within each age group. Duration of clinical effects was reported for 21.7% of exposures; the majority (91.6%) lasted ≤ 24 hours. Although relatively uncommon, serious clinical effects were observed, including respiratory depression (1.8%; $n = 3386$), coma (0.8%; $n = 1479$), hypotension (0.4%; $n = 757$), respiratory arrest (0.2%; $n = 463$), and cardiac arrest/asystole (0.1%; $n = 195$). One or more therapies were performed for 37.7% of exposures; the most common therapies were dilute/irrigate/wash (15.1%) and charcoal–single dose (9.6%). Naloxone was administered to 8751 children (4.6%).

DISCUSSION

General

During the 16-year study period, there were 188 468 opioid exposures among children aged <20 years reported to PCCs in the United States. The majority of exposures occurred

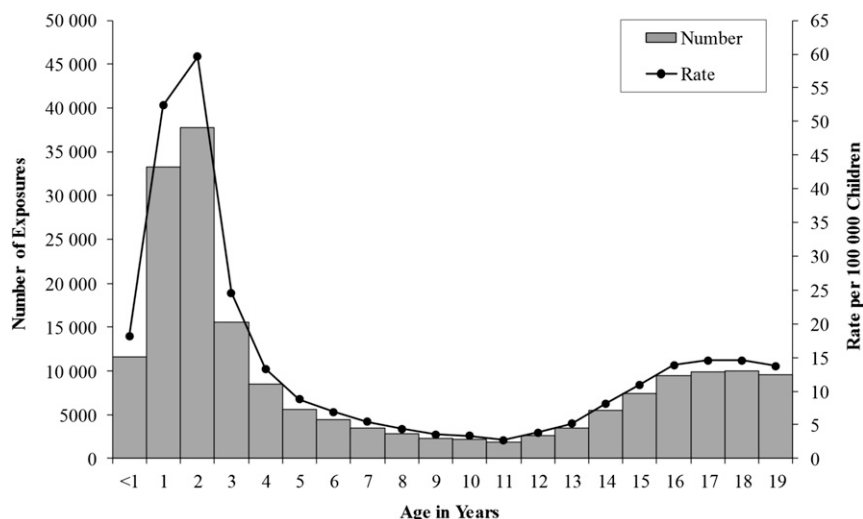


FIGURE 1
Number and rate of prescription opioid exposures by child age, NPDS 2000–2015.

among children aged 0 to 5 years and were managed on site without serious medical outcomes. There was a steady increase in the frequency and rate of opioid exposures from 2000 until 2009, after which both decreased. The observed increase in exposures was likely driven by increased opioid prescribing in the United States, with the number of opioid prescriptions dispensed by US retail pharmacies increasing from 126 million in 2000 to 219 million in 2011 before declining to 207 million in 2013.¹⁹ It is unclear why the decline in exposures began 2 years before the decline in the number of prescriptions. Possible factors contributing to the observed decline in exposures after 2009 include the 9.2% reduction in the number of US patients filling opioid prescriptions from 2009 to 2013, the Centers for Disease Control and Prevention (CDC) implementation of the PROTECT initiative, and the US Drug Enforcement Administration's 2014 decision to designate hydrocodone combination products as schedule II drugs.^{26–29}

Overall, male and female exposure trends were similar. Consistent with previous studies, reasons for exposure varied by age, with children aged 0 to 5 years experiencing

unintentional exposures attributable to exploratory behaviors and teenagers exhibiting risk-taking behaviors by using opioids intentionally.^{18,30–33} Combined, children aged 0 to 5 years old and teenagers accounted for nearly 90% of all prescription opioid exposures. Hydrocodone was the most common medication implicated in exposures. Methadone and buprenorphine were associated with a large percentage of HCF admissions and serious medical outcomes, including fatalities, despite having fewer exposures overall. HCF admission was likely more common for these medications because of concerns about prolonged or delayed respiratory depression seen with their long half-lives.³⁴

Exposures Among Children 0 to 5 Years of Age

Children aged 0 to 5 years old experienced the largest number of exposures. Most were unintentional-general (nontherapeutic) exposures (85.5%) attributable to exploratory behaviors common among young children.^{30,35} The toxicity of an opioid exposure can be greater for children than adults due to their smaller body mass. Nearly 90% of buprenorphine exposures in this study were among children aged 0 to

TABLE 2 Characteristics of Prescription Opioid Exposures Among Children <20 Years of Age by Age Group, NPDS 2000–2015

Characteristics	Age Group, <i>n</i> (%)			
	0–5 Years	6–12 Years	13–19 Years	Total
Management site				
Managed on site (non-HCF)	51 658 (45.9)	12 731 (64.5)	15 820 (28.1)	80 209 (42.6)
Patient was referred by PCC to an HCF	32 283 (28.7)	4 104 (20.8)	16 600 (29.5)	52 987 (28.1)
Patient already in (en route to) HCF when PCC called	26 920 (23.9)	2 413 (12.2)	22 458 (39.9)	51 791 (27.5)
Other	721 (0.6)	198 (1.0)	611 (1.1)	1 530 (0.8)
Unknown	883 (0.8)	277 (1.4)	791 (1.4)	1 951 (1.0)
Subtotal (row percentage)	112 465 (59.7)	19 723 (10.5)	56 280 (29.9)	188 468 (100.0)
Level of care received				
Admitted	9 824 (8.7)	794 (4.0)	12 091 (21.5)	22 709 (12.0)
Admitted to critical care unit	4 835 (4.3)	325 (1.6)	4 014 (7.1)	9 174 (4.9)
Admitted to non-critical care unit	4 975 (4.4)	377 (1.9)	3 091 (5.5)	8 443 (4.5)
Admitted to psychiatric care unit	14 (0.0)	92 (0.5)	4 986 (8.9)	5 092 (2.7)
Treated/evaluated and released	35 736 (31.8)	2 810 (14.2)	13 992 (24.9)	52 538 (27.9)
Patient lost to follow-up/left AMA	7 898 (7.0)	1 672 (8.5)	8 224 (14.6)	17 794 (9.4)
Patient refused referral/did not arrive at HCF	5 746 (5.1)	1 241 (6.3)	4 751 (8.4)	11 738 (6.2)
No HCF treatment received	53 261 (47.4)	13 206 (67.0)	17 222 (30.6)	83 689 (44.4)
Subtotal (row percentage)	112 465 (59.7)	19 723 (10.5)	56 280 (29.9)	188 468 (100.0)
Medical outcome				
Serious	4 932 (4.4)	580 (2.9)	6 869 (12.2)	12 381 (6.6)
Moderate effect	4 092 (3.6)	506 (2.6)	5 628 (10.0)	10 226 (5.4)
Major effect	772 (0.7)	63 (0.3)	1 145 (2.0)	1 980 (1.1)
Death	68 (0.1)	11 (0.1)	96 (0.2)	175 (0.1)
Minor effect	13 957 (12.4)	2 917 (14.8)	14 712 (26.1)	31 586 (16.8)
No effect	52 145 (46.4)	5 020 (25.5)	9 649 (17.1)	66 814 (35.5)
Not followed/unable to follow	41 431 (36.8)	11 206 (56.8)	25 050 (44.5)	77 687 (41.2)
Subtotal (row percentage)	112 465 (59.7)	19 723 (10.5)	56 280 (29.9)	188 468 (100.0)
Type of therapeutic error^a				
Inadvertently took/given someone else's medication	4 216 (27.9)	3 293 (30.6)	1 132 (13.7)	8 641 (25.3)
Wrong medication taken/given	3 625 (24.0)	2 933 (27.3)	1 888 (22.8)	8 446 (24.7)
Other incorrect dose	2 180 (14.4)	1 280 (11.9)	1 214 (14.6)	4 674 (13.7)
Inadvertently took/given medication twice	1 203 (8.0)	786 (7.3)	974 (11.7)	2 963 (8.7)
Confused units of measure	916 (6.1)	579 (5.4)	429 (5.2)	1 924 (5.6)
Medication doses given/taken too close together	545 (3.6)	366 (3.4)	811 (9.8)	1 722 (5.1)
Incorrect formulation or concentration given	795 (5.3)	429 (4.0)	168 (2.0)	1 392 (4.1)
Dispensing-cup error	535 (3.5)	366 (3.4)	218 (2.6)	1 119 (3.3)
Health professional/iatrogenic error: nurse/physician	386 (2.6)	254 (2.4)	123 (1.5)	763 (2.2)
Incorrect formulation or concentration dispensed	155 (1.0)	113 (1.1)	54 (0.7)	322 (0.9)
Exposure through breast milk	160 (1.1)	0 (0.0)	0 (0.0)	160 (0.5)
Tenfold dosing error	112 (0.7)	28 (0.3)	16 (0.2)	156 (0.5)
More than 1 product containing same ingredient	50 (0.3)	37 (0.3)	48 (0.6)	135 (0.4)
Incorrect dosing route	35 (0.2)	15 (0.1)	21 (0.3)	71 (0.2)
Drug interaction	11 (0.1)	5 (0.0)	11 (0.1)	27 (0.1)
Other/unknown therapeutic error	779 (5.2)	505 (4.7)	589 (7.1)	1 873 (5.5)
Subtotal (row percentage)	15 124 (44.3)	10 749 (31.5)	8 292 (24.3)	34 165 (100.0)

Column and row percentages may not sum to 100.0% due to rounding errors. AMA, against medical advice.

^a Column percentages may sum to >100.0% because each exposure can involve >1 type of therapeutic error.

5 years old. Ingesting even a partial buprenorphine tablet (0.07–0.40 mg/kg body weight) can harm a child.³⁶ Although the high rate of HCF admission for buprenorphine exposure may reflect clinical decisions to monitor patients or allow for investigation into the home environment, the frequency of these exposures has remained elevated, whereas most other opioid medication exposures in this age

group have declined. Buprenorphine is almost exclusively prescribed for adults, so exposures among children represent a failure to safeguard the medication.³⁶

Opioids can cause severe central nervous system impairment and respiratory depression; therefore, preventing exposures among young children is imperative. Unit-dose packaging is 1 strategy that has

been shown to prevent unintentional medication exposure deaths.^{37,38} Alternate drug formulations and delivery systems, such as subcutaneous implants, also should be considered as a means of reducing pediatric exposures. In 2008, the CDC established the PROTECT initiative to prevent unintentional pediatric medication exposures by bringing together key stakeholders to develop prevention

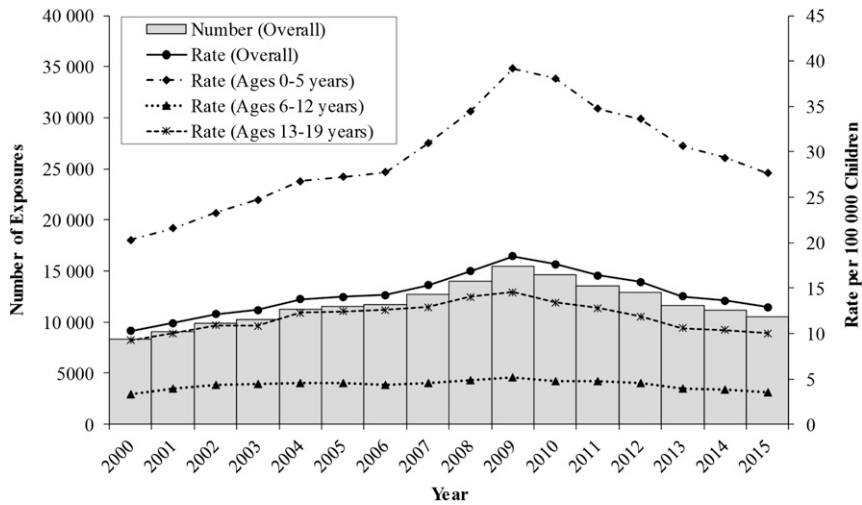


FIGURE 2 Annual number and rate of prescription opioid exposures among children by age group, NPDS 2000–2015.

strategies.²⁹ For example, the “Up and Away and Out of Sight” campaign educates parents on how to safely store medications.³⁹ Patient-provider agreements are another recommended intervention strategy. It should be noted, however, that not all opioid users obtain their drugs legally. Buprenorphine, for example, is frequently purchased illegally by individuals with opioid addiction, who are seeking to self-medicate or cope with withdrawal.⁴⁰ Addressing this and other examples of opioid diversion requires additional prevention strategies.

Exposures Among Teenagers

Teenagers represented the age group with the second highest number of opioid exposures and more than two-thirds were intentional exposures. This finding agrees with previous research indicating that this is the only age group in which intentional poisonings are more common than unintentional ones.²² Also consistent with previous research, boys accounted for a larger proportion of intentional opioid exposures than girls.⁴¹ The majority of teenage fatalities resulting from intentional

opioid exposures were among boys, but girls comprised a greater proportion of suspected suicide exposures. Previous studies indicate that girls tend to use less violent suicide methods, such as medication ingestion, than males.^{31,32}

It is especially concerning that the rate of opioid exposure attributable to suspected suicide increased by 52.7% among teenagers during the study period. This finding is consistent with results from another study that showed that the rate of opioid-related hospitalization among adolescents aged 15 to 19 years attributed to suicide or self-inflicted injury increased by 140% from 1997 to 2012.⁶ Teenagers had greater odds of being admitted to an HCF and experiencing serious outcomes than the younger age groups in this study. The higher rate of HCF admission may partially reflect the need to thoroughly evaluate incidents of suspected self-harm. Intentional opioid exposures among teenagers may also result from risk-taking behaviors or attempts to self-medicate psychological problems.^{33,41} In addition, prescription opioid misuse may increase the likelihood of an individual using heroin or other illicit drugs in the future.^{16,17}

Restricting access to opioids by teenagers is an important prevention

TABLE 3 HCF Admissions and Serious Medical Outcomes Associated With Exposure to Each Type of Prescription Opioid by Age Group, NPDS 2000–2015

Type of Opioid	Admission to an HCF, n (%)				Serious Medical Outcome, n (%)			
	0–5 Years ^a	6–12 Years ^a	13–19 Years ^a	Total ^b	0–5 Years ^a	6–12 Years ^a	13–19 Years ^a	Total ^b
Buprenorphine	2589 (51.0)	57 (32.8)	70 (13.8)	2716 (47.1)	1127 (22.2)	24 (13.8)	102 (20.0)	1253 (21.7)
Methadone	1269 (36.6)	124 (23.3)	716 (32.3)	2109 (33.9)	761 (22.0)	73 (13.7)	712 (32.1)	1546 (24.9)
Oxymorphone	50 (27.3)	4 (18.2)	44 (33.3)	98 (29.1)	21 (11.5)	1 (4.5)	48 (36.4)	70 (20.8)
Fentanyl	38 (17.1)	1 (3.6)	57 (35.0)	96 (23.2)	29 (13.1)	2 (7.1)	90 (55.2)	121 (29.3)
Morphine	817 (21.6)	75 (13.0)	365 (18.9)	1257 (20.0)	361 (9.5)	50 (8.7)	316 (16.4)	727 (11.6)
Hydromorphone	60 (18.2)	6 (8.0)	32 (24.8)	98 (18.4)	30 (9.1)	3 (4.0)	16 (12.4)	49 (9.2)
Tramadol	555 (4.5)	90 (5.1)	2244 (31.5)	2889 (13.6)	227 (1.8)	66 (3.7)	1795 (25.2)	2088 (9.8)
Propoxyphene	122 (2.1)	22 (2.9)	919 (27.3)	1063 (10.7)	28 (0.5)	14 (1.9)	328 (9.8)	370 (3.7)
Oxycodone	1342 (6.7)	139 (4.3)	1568 (15.7)	3049 (9.2)	746 (3.7)	104 (3.2)	957 (9.6)	1807 (5.4)
Meperidine	37 (8.8)	9 (6.1)	28 (11.9)	74 (9.2)	18 (4.3)	8 (5.4)	23 (9.7)	49 (6.1)
Hydrocodone	424 (1.5)	99 (1.8)	3760 (19.3)	4283 (7.9)	223 (0.8)	74 (1.4)	1291 (6.6)	1588 (2.9)
Codeine	269 (1.4)	80 (1.6)	1395 (20.1)	1744 (5.6)	164 (0.9)	108 (2.1)	502 (7.2)	774 (2.5)
Other	2252 (18.0)	88 (4.5)	893 (21.8)	3233 (17.4)	1197 (9.6)	53 (2.7)	689 (16.8)	1939 (10.4)
Total	9824 (8.7)	794 (4.0)	12 091 (21.5)	22 709 (12.0)	4932 (4.4)	580 (2.9)	6869 (12.2)	12 381 (6.6)

^a Percentages were calculated by using the total number of exposures for each type of prescription opioid within each age group.

^b Percentages were calculated by using the total number of exposures for each type of prescription opioid.

strategy. Seventy percent of teenagers who use prescription medications without a physician's order obtain the drugs from friends or relatives.⁴² Physicians can help reduce the availability of opioids by using correct dosing (not prescribing a higher dose or greater supply than necessary), reminding parents to safeguard prescription medications (including from teenagers), and encouraging prompt and proper disposal of unused medications. The National Institute on Drug Abuse offers online training to teach physicians techniques for managing patients prescribed opioids.⁴³ The CDC encourages states to use prescription drug-monitoring programs and supports insurance policies and legal strategies to reduce abuse, diversion, and overdose.⁴⁴ The provision of naloxone kits to laypersons who might witness a prescription opioid overdose is another promising intervention.⁴⁵ An estimated 22% of teenagers in the United States have mental health disorders that result in severe impairment or distress.⁴⁶ Increasing access to mental health screening and treatment of adolescents may reduce the abuse of opioids for self-medication and self-harm. The National Institute on Drug Abuse recommends several research-based programs to prevent adolescent

drug abuse, including the Life Skills Training Program and the Strengthening Families Program.⁴⁷ For teenagers with opioid use disorders, the American Academy of Pediatrics recommends medication-assisted treatment.⁴⁸ This method requires precautions to avoid increased exposure among young children.

Limitations

This study has some limitations. The number of pediatric exposures to prescription opioids is underestimated because not all exposures are reported to PCCs. The NPDS does not collect patient identifiers and therefore cannot determine repeat exposures to individuals. The NPDS relies on self-reports, which cannot be completely verified by PCCs or the AAPCC. Reported exposures do not necessarily represent a poisoning or overdose. In addition, some reporting fields are optional, such as the scenario associated with opioid exposure, which may limit interpretation. Despite these limitations, data in the NPDS national database are entered by highly qualified poison experts who use strict quality controls and case follow-up methods. The NPDS offers the most inclusive and comprehensive database available

for research on prescription opioid exposures among US children.

Conclusions

Children are frequently overlooked in efforts to prevent prescription opioid exposures; however, these exposures can be life-threatening. Particular attention should be paid to buprenorphine exposures among young children, which frequently result in HCF admission and are not declining in frequency such as exposures to most other opioids. Teenagers are more likely to be intentionally exposed to opioids as a result of risk-taking or self-harm and have greater odds of HCF admission or serious medical outcomes than younger children. Greater efforts are needed to prevent opioid exposure to children of all ages.

ABBREVIATIONS

AAPCC: American Association of Poison Control Centers
 CDC: Centers for Disease Control and Prevention
 CI: confidence interval
 HCF: health care facility
 m: estimated slope from the regression model
 NPDS: National Poison Data System
 OR: odds ratio
 PCC: poison control center

Copyright © 2017 by the American Academy of Pediatrics

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: Mr Allen received a research stipend from the National Student Injury Research Training Program at Nationwide Children's Hospital, funded by the Centers for Disease Control and Prevention (grant R49CE002106), while he worked on this study. The interpretations and conclusions in this article do not necessarily represent those of the funding organization.

POTENTIAL CONFLICT OF INTEREST: Dr Casavant has been retained to review and comment on a legal case involving buprenorphine; the other authors have indicated they have no potential conflicts of interest to disclose.

REFERENCES

1. Daubresse M, Chang HY, Yu Y, et al. Ambulatory diagnosis and treatment of nonmalignant pain in the United States, 2000-2010. *Med Care*. 2013;51(10):870-878
2. Dowell D, Haegerich TM, Chou R. CDC guideline for prescribing opioids for chronic pain—United States, 2016. *MMWR Recomm Rep*. 2016;65(1):1-49
3. Manchikanti L, Singh A. Therapeutic opioids: a ten-year perspective on the complexities and complications of the escalating use, abuse, and nonmedical use of opioids. *Pain Physician*. 2008;11(2 suppl):S63-S88
4. Follin SL, Charland SL. Acute pain management: operative or medical procedures and trauma. *Ann Pharmacother*. 1997;31(9):1068-1076

5. Tadros A, Layman SM, Davis SM, Bozeman R, Davidov DM. Emergency department visits by pediatric patients for poisoning by prescription opioids. *Am J Drug Alcohol Abuse*. 2016;42(5):550–555
6. 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
7. Sachdeva DK, Stadnyk JM. Are one or two dangerous? Opioid exposure in toddlers. *J Emerg Med*. 2005;29(1):77–84
8. Tobias JD, Green TP, Coté CJ; Section on Anesthesiology and Pain Medicine; Committee on Drugs. Codeine: time to say “no”. *Pediatrics*. 2016;138(4):e20162396
9. Rudd RA, Aleshire N, Zibbell JE, Gladden RM. Increases in drug and opioid overdose deaths—United States, 2000-2014. *MMWR Morb Mortal Wkly Rep*. 2016;64(50–51):1378–1382
10. Centers for Disease Control and Prevention; National Center for Health Statistics. National Vital Statistics System, Mortality File. Number and age-adjusted rates of drug-poisoning deaths involving opioid analgesics and heroin: United States, 2000–2014. Center for Disease Control and Prevention; 2015. Available at: www.cdc.gov/nchs/data/health_policy/AADR_drug_poisoning_involving_OA_Heroin_US_2000-2014.pdf. Accessed October 3, 2016
11. Centers for Disease Control and Prevention. Vital signs: overdoses of prescription opioid pain relievers—United States, 1999–2008. *MMWR Morb Mortal Wkly Rep*. 2011;60(43):1487–1492
12. Centers for Disease Control and Prevention. Vital signs: overdoses of prescription opioid pain relievers and other drugs among women—United States, 1999–2010. *MMWR Morb Mortal Wkly Rep*. 2013;62(26):537–542
13. Centers for Disease Control and Prevention. 10 Leading causes of injury deaths by age group highlighting unintentional injury deaths, United States–2014. Available at: www.cdc.gov/injury/wisqars/leadingcauses.html. Accessed October 3, 2016
14. Centers for Disease Control and Prevention. Vital signs: unintentional injury deaths among persons aged 0-19 years—United States, 2000–2009. *MMWR Morb Mortal Wkly Rep*. 2012;61:270–276
15. McCabe SE, West BT, Teter CJ, Boyd CJ. Medical and nonmedical use of prescription opioids among high school seniors in the United States. *Arch Pediatr Adolesc Med*. 2012;166(9):797–802
16. Jones CM. Heroin use and heroin use risk behaviors among nonmedical users of prescription opioid pain relievers—United States, 2002-2004 and 2008-2010. *Drug Alcohol Depend*. 2013;132(1–2):95–100
17. Muhuri PK, Gfroerer JC, Davies MC. CBHSQ data review: associations of nonmedical pain reliever use and initiation of heroin use in the United States. Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration; August 2013. Available at: www.samhsa.gov/data/sites/default/files/DR006/DR006/nonmedical-pain-reliever-use-2013.htm. Accessed October 3, 2016
18. Mahic M, Fredheim OM, Borchgrevink PC, Skurtveit S. Use of prescribed opioids by children and adolescents: differences between Denmark, Norway and Sweden. *Eur J Pain*. 2015;19(8):1095–1100
19. Volkow ND. Prescription opioid and heroin abuse. 2014. Available at: <https://www.drugabuse.gov/about-nida/legislative-activities/testimony-to-congress/2015/prescription-opioid-heroin-abuse>. Accessed October 3, 2016
20. Qin A, Layton A. *Unintentional pediatric poisoning injury estimates for 2014*. Bethesda, MD: Consumer Product Safety Commission; 2015. Available at: <https://www.cpsc.gov/s3fs-public/PPPAInjury2014.pdf>. Accessed October 3, 2016
21. Qin A. *Pediatric poisoning fatalities from 1972 through 2013*. Bethesda, MD: US Consumer Product Safety Commission; 2016. Available at: <https://www.cpsc.gov/s3fs-public/PPPAMortality2013.pdf>. Accessed October 3, 2016
22. Mowry JB, Spyker DA, Brooks DE, McMillan N, Schauben JL. 2014 Annual report of the American Association of Poison Control Centers’ National Poison Data System (NPDS): 32nd annual report. *Clin Toxicol (Phila)*. 2015;53(10):962–1147
23. National Poison Data System. NPDS coding users’ manual version 3.1. American Association of Poison Control Centers; 2014. Available at: http://aapcc.s3.amazonaws.com/pdfs/member-resources/NPDS_Coding_Users_Manual_v3.1_07May2014.pdf. Accessed October 3, 2016
24. US Census Bureau. US-EST00INT-ALLDATA: intercensal estimates of the resident population by single year of age, sex, race and hispanic origin for the United States: April 1, 2000 to July 1, 2010. 2012. Available at: www.census.gov/popest/data/intercensal/national/nat2010.html. Accessed October 3, 2016
25. US Census Bureau. PEPYASEXN: annual estimates of the resident population by single year of age and sex for the United States: April 1, 2010 to July 1, 2015. 2016. Available at: http://factfinder.census.gov/faces/tableservices/jsf/pages/productview.xhtml?pid=PEP_2015_PEPYASEXN&prodType=table. Accessed October 3, 2016
26. The Express Scripts Lab. A nation in pain: focusing on U.S. opioid trends for treatment of short-term and longer-term pain. Express Scripts Holding Company; 2014. Available at: <http://lab.express-scripts.com/lab/publications/a-nation-in-pain>. Accessed October 3, 2016
27. Drug Enforcement Administration, Department of Justice. Schedules of controlled substances: rescheduling of hydrocodone combination products from schedule III to schedule II: final rule. *Fed Regist*. 2014;79(163):49661–49682
28. Jones CM, Lurie PG, Throckmorton DC. Effect of US Drug Enforcement Administration’s rescheduling of hydrocodone combination analgesic products on opioid analgesic

- prescribing. *JAMA Intern Med.* 2016;176(3):399–402
29. PROTECT Initiative. Advancing children's medication safety. Centers for Disease Control and Prevention; 2010. Available at: www.cdc.gov/medicationsafety/protect/protect_initiative.html. Accessed October 3, 2016
 30. Tolve NS, Suggs JC, McCurdy T, Cohen Hubal EA, Moya J. Frequency of mouthing behavior in young children. *J Expo Anal Environ Epidemiol.* 2002;12(4):259–264
 31. Denning DG, Conwell Y, King D, Cox C. Method choice, intent, and gender in completed suicide. *Suicide Life Threat Behav.* 2000;30(3):282–288
 32. Suicide.org. Suicide statistics. 2005. Available at: www.suicide.org/suicide-statistics.html#death-rates. Accessed October 3, 2016
 33. Steinberg L. Risk taking in adolescence—new perspectives from brain and behavioral science. *Curr Dir Psychol Sci.* 2007;16(2):55–59
 34. Saxon AJ, Hser YI, Woody G, Ling W. Medication-assisted treatment for opioid addiction: methadone and buprenorphine. *J Food Drug Anal.* 2013;21(4):S69–S72
 35. Gibson EJ. Exploratory behavior in the development of perceiving, acting, and the acquiring of knowledge. *Annu Rev Psychol.* 1988;39(1):1–41
 36. Pedapati EV, Bateman ST. Toddlers requiring pediatric intensive care unit admission following at-home exposure to buprenorphine/naloxone. *Pediatr Crit Care Med.* 2011;12(2):e102–e107
 37. Tenenbein M. Unit-dose packaging of iron supplements and reduction of iron poisoning in young children. *Arch Pediatr Adolesc Med.* 2005;159(6):557–560
 38. Institute for Safe Medication Practices. Simple packaging change can reduce Rx drug diversion. 2014. Available at: www.consumermedsafety.org/medication-safety-articles/item/721-simple-packaging-change-can-reduce-rx-drug-diversion. Accessed October 3, 2016
 39. PROTECT Initiative. Up and away and out of sight. 2014. Available at: <http://upandaway.org/>. Accessed October 3, 2016
 40. Sontag D. Addiction treatment with a dark side. *New York Times.* November 17, 2013. Available at: www.nytimes.com/2013/11/17/health/in-demand-in-clinics-and-on-the-street-bupe-can-be-behavior-or-menace.html?_r=0. Accessed October 3, 2016
 41. Back SE, Payne RL, Simpson AN, Brady KT. Gender and prescription opioids: findings from the National Survey on Drug Use and Health. *Addict Behav.* 2010;35(11):1001–1007
 42. Johnston LD, O'Malley PM, Bachman JG, Schulenberg JE. *Marijuana use continues to rise among U.S. teens, while alcohol use hits historic lows* [press release]. Ann Arbor, MI: University of Michigan News Service; 2011. Available at: www.monitoringthefuture.org/pressreleases/11drugpr_complete.pdf. Accessed October 3, 2016
 43. National Institute on Drug Abuse. White House Drug Policy Office and National Institute on Drug Abuse unveil new training materials to combat national prescription drug abuse epidemic. 2012. Available at: <https://www.drugabuse.gov/news-events/news-releases/2012/white-house-drug-policy-office-national-institute-drug-abuse-unveil-new-training-materials-to-combat>. Accessed October 3, 2016
 44. National Center for Injury Prevention and Control. From Epi to policy: prescription drug overdose. Centers for Disease Control and Prevention; 2013. Available at: https://www.cdc.gov/drugoverdose/pdf/pdo_epi_to_policy_meeting-a.pdf. Accessed October 3, 2016
 45. Wheeler E, Jones TS, Gilbert MK, Davidson PJ; Centers for Disease Control and Prevention. Opioid overdose prevention programs providing naloxone to laypersons—United States, 2014. *MMWR Morb Mortal Wkly Rep.* 2015;64(23):631–635
 46. Merikangas KR, He JP, Burstein M, et al. Lifetime prevalence of mental disorders in U.S. adolescents: results from the National Comorbidity Survey Replication—adolescent supplement (NCS-A). *J Am Acad Child Adolesc Psychiatry.* 2010;49(10):980–989
 47. Robertson EB, David SL, Rao SA, National Institute on Drug Abuse. *Preventing Drug Use Among Children and Adolescents: A Research-Based Guide for Parents, Educators, and Community Leaders.* 2nd ed. Bethesda, MD: US Department of Health and Human Services, National Institutes of Health, National Institute on Drug Abuse; 2003
 48. Committee on Substance Use and Prevention. Medication-assisted treatment of adolescents with opioid use disorders. *Pediatrics.* 2016;138(3):e20161893

Prescription Opioid Exposures Among Children and Adolescents in the United States: 2000–2015

Jakob D. Allen, Marcel J. Casavant, Henry A. Spiller, Thiphalak Chounthirath, Nichole L. Hodges and Gary A. Smith

Pediatrics 2017;139;

DOI: 10.1542/peds.2016-3382 originally published online March 20, 2017;

Updated Information & Services

including high resolution figures, can be found at:
<http://pediatrics.aappublications.org/content/139/4/e20163382>

References

This article cites 29 articles, 2 of which you can access for free at:
<http://pediatrics.aappublications.org/content/139/4/e20163382#BIBL>

Subspecialty Collections

This article, along with others on similar topics, appears in the following collection(s):
Injury, Violence & Poison Prevention
http://www.aappublications.org/cgi/collection/injury_violence_-_poison_prevention_sub

Permissions & Licensing

Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:
<http://www.aappublications.org/site/misc/Permissions.xhtml>

Reprints

Information about ordering reprints can be found online:
<http://www.aappublications.org/site/misc/reprints.xhtml>

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN®



PEDIATRICS®

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Prescription Opioid Exposures Among Children and Adolescents in the United States: 2000–2015

Jakob D. Allen, Marcel J. Casavant, Henry A. Spiller, Thiphalak Chounthirath,
Nichole L. Hodges and Gary A. Smith
Pediatrics 2017;139;

DOI: 10.1542/peds.2016-3382 originally published online March 20, 2017;

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://pediatrics.aappublications.org/content/139/4/e20163382>

Data Supplement at:

<http://pediatrics.aappublications.org/content/suppl/2017/03/16/peds.2016-3382.DCSupplemental>

Pediatrics is the official journal of the American Academy of Pediatrics. A monthly publication, it has been published continuously since 1948. Pediatrics is owned, published, and trademarked by the American Academy of Pediatrics, 345 Park Avenue, Itasca, Illinois, 60143. Copyright © 2017 by the American Academy of Pediatrics. All rights reserved. Print ISSN: 1073-0397.

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN®

