Buprenorphine Exposures Among Children and Adolescents Reported to US Poison Control Centers

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abstract

OBJECTIVE: To investigate buprenorphine exposures among children and adolescents ≤19 years old in the United States.

METHODS: Data were analyzed from calls to US poison control centers for 2007–2016 from the National Poison Data System.

RESULTS: From 2007 to 2016, there were 11 275 children and adolescents ≤19 years old exposed to buprenorphine reported to US poison control centers. Most exposures were among children <6 years old (86.1%), unintentional (89.2%), and to a single substance (97.3%). For single-substance exposures, children <6 years old had greater odds of hospital admission and of serious medical outcome than adolescents 13 to 19 years old. Adolescents accounted for 11.1% of exposures; 77.1% were intentional (including 12.0% suspected suicide), and 27.7% involved multiple substances. Among adolescents, the odds of hospital admission and a serious medical outcome were higher for multiple-substance exposures than single-substance exposures.

CONCLUSIONS: Buprenorphine is important for the treatment of opioid use disorder, but pediatric exposure can result in serious adverse outcomes. Manufacturers should use unit-dose packaging for all buprenorphine products to help prevent unintentional exposure among young children. Health providers should inform caregivers of young children about the dangers of buprenorphine exposure and provide instructions on proper medication storage and disposal. Adolescents should receive information regarding the risks of substance abuse and misuse. Suspected suicide accounted for 12% of adolescent exposures, highlighting the need for access to mental health services for this age group.

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WHAT'S KNOWN ON THIS SUBJECT: Buprenorphine-containing products are increasingly prescribed in the United States and, in recent years, have become a commonly ingested medication by children. Children <6 years old account for the majority of pediatric buprenorphine exposures, which can have serious medical outcomes.

WHAT THIS STUDY ADDS: Among children <6 years old, 48.1% of buprenorphine exposures resulted in hospital admission and 21.4% in a serious medical outcome. Among adolescents 13 to 19 years old, 21.5% of exposures resulted in hospital admission and 22.0% in a serious medical outcome.

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There is an opioid crisis in the United States. In 2016, an estimated 2.1 million people had an opioid use disorder, and 11.5 million people misused prescription opioids.[1] Buprenorphine is a prescription opioid which, relative to others, has a lower maximum effect and reported lower risk of abuse or misuse.[2] In 2002, the US Food and Drug Administration (FDA) approved buprenorphine, either alone or in combination with naloxone, for the treatment of opioid dependence.[2] From 2005 to 2010, the annual number of individual patients who received a buprenorphine prescription increased from 100 000 to >800 000.[2]

US children have been affected by the opioid crisis. Ninety percent of buprenorphine exposures reported to US poison control centers (PCCs) from 2000 to 2015 occurred among children <6 years old, and, from 2010 to 2011, the combination of buprenorphine and naloxone was the most common medication ingestion resulting in hospitalization among young children.[3,4] In 2016, the American Academy of Pediatrics recommended expanding access to buprenorphine for the treatment of severe opioid use disorder in adolescents; therefore, buprenorphine access is anticipated to increase in the pediatric population.[5]

Authors of previous studies on pediatric buprenorphine exposures have investigated buprenorphine toxicity and clinical outcomes among children, but the majority of studies were case studies, emergency department visits and/or hospital admissions only, or those in which authors focused solely on young children.[4,6–10] With the current study, we use the National Poison Data System (NPDS) database from 2007 to 2016 to investigate the epidemiology of buprenorphine exposures among US children 19 years of age and younger.

METHODS

Data Sources

Data regarding buprenorphine exposures among US children were obtained from the NPDS, a database owned and maintained by the American Association of Poison Control Centers (AAPCC). The NPDS includes data from regional PCCs throughout the United States regarding telephone calls they receive in which a poison exposure is reported.[11] US Census Bureau July 1 intercensal and postcensal population estimates from 2007 to 2016 were used to calculate population-based exposure rates.[12]

Case Selection Criteria

By using the AAPCC's proprietary product codes for buprenorphine-containing products, the NPDS was queried for all buprenorphine exposures involving children 19 years and younger that occurred from January 1, 2007, through December 31, 2016. Exposures to multiple substances were included only if the first-ranked substance (the substance most likely to have contributed to the clinical effect[s] observed) was a buprenorphine-containing product. Cases were excluded if (1) the medical outcome was a "confirmed non-exposure" or "unrelated effect, the exposure was probably not responsible for the effect(s)" or (2) it was a multiple-substance exposure and buprenorphine was not the first-ranked substance.

Study Variables

Child age was grouped as <6 years, 6 to 12 years, and adolescents (13–19 years). The AAPCC's proprietary product codes were used to segregate buprenorphine-containing products into formulation categories (tablet, film, injection or patch, and unknown). Reasons for exposure were categorized as unintentional (exposure resulted from an unforeseen or unplanned event), intentional (exposure resulted from a purposeful action), other (including adverse reaction and other known reasons), and unknown. Unintentional reasons were subcategorized into general (includes exposure associated with child exploratory behavior), therapeutic error, and other and/or unknown reasons. Intentional reasons were subcategorized into misuse and/or abuse, suspected suicide, and unknown. Exposure site was grouped into residence (own or other), other, and unknown.

The level of care received at a health care facility (HCF) was categorized as no HCF care received, treated and released from an HCF, admitted to an HCF (including to a critical care unit [CCU], non-CCU, or psychiatric facility), and other (patient refused referral, did not arrive at the HCF, was lost to follow-up, or left against medical advice). Medical outcomes were grouped into serious outcome (including death, major effect, and moderate effect), minor effect, no effect, not followed (at most minimal clinical effect expected), and unable to follow (potentially toxic). As defined by the NPDS, major effects are life-threatening or result in significant residual disability or disfigurement. Moderate effects are more pronounced, prolonged, or systemic relative to minor effects and involve some form of indicated treatment. Minor effects are minimally bothersome and usually resolve rapidly.[13] Other variables included the year of exposure, number of products involved, related clinical effects and their duration, and therapies performed.

Statistical Analysis and Ethical Concerns

IBM SPSS Statistics version 24 (IBM SPSS Statistics, IBM Corporation, Armonk, NY) and SAS Enterprise Guide 7.11 HF3 (SAS Institute, Inc, Cary, NC) statistical software were used to analyze NPDS data.

Descriptive statistics and odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. Although we included both single-substance and first-ranked multiple-substance exposures in this study, only single-substance exposures were included in analyses of the clinical effects and clinical effect duration associated with buprenorphine. This eliminated the possibility of misattribution of effects and drug interactions associated with the multiple-substance exposures. For the same reasons, only single-substance exposures were included when comparing HCF admission and serious medical outcome between age groups and between tablet and film exposures (excluding injection or patch and unknown formulations) among children <6 years old. The institutional review board at the authors' institution judged this study as exempt.

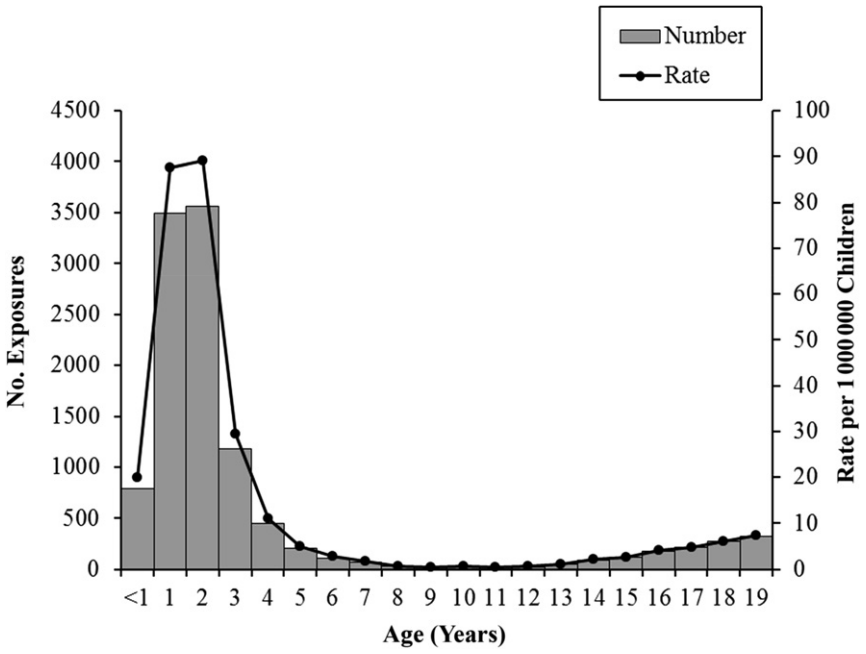

FIGURE 1
Number and rate of buprenorphine exposures by child age, NPDS 2007–2016.

RESULTS

General Characteristics and Trends

A total of 11 275 children ≤19 years old exposed to buprenorphine were reported to PCCs during 2007–2016. The mean age of children exposed to buprenorphine was 3.8 years (SD = 4.9; median = 2.0; interquartile range = 1.5–3.0). Children <6 years old accounted for 86.1% of exposures with exposure frequency peaking among 1- and 2-year-olds (Fig 1). The overall exposure rate per 1 000 000 children increased by 215.6% from 6.4 in 2007 to 20.2 in 2010, followed by a 42.6% decline from 2010 to 11.6 in 2013 before increasing by 8.6% to 12.6 in 2016. The overall trends were driven by trends among children <6 years old (Fig 2). Most of the exposures involved a single buprenorphine product (93.7%), occurred at a residence (96.0%), and occurred by ingestion (97.8%). Male patients accounted for the majority of all exposures (53.1%) and within each age group (Table 1). "Unintentional" was the most common (89.2%) reason for exposures, but the reason varied by age group. Tablets (65.8%) and film (20.8%) were the most common buprenorphine formulations involved, and these proportions persisted within each age group. Many exposures (44.6%) resulted in an HCF admission (including 21.9% admitted to a CCU), 29.9% were treated and released from an HCF, and 21.2% resulted in a serious medical outcome (including 11 fatalities) (Table 1). Multiple-substance exposures resulted in a higher percentage of an HCF admission (50.8% vs 44.2%) and serious medical outcome (34.3% vs 20.3%) than single-substance exposures.

Clinical Effects and Therapies Among Single-Substance Exposures

Among the 10 570 children exposed to a single buprenorphine product, 59.0% (n = 5456) experienced at least 1 related symptom. The most common symptoms were drowsiness and/or lethargy (46.8%), vomiting (17.0%), and miosis (12.6%) (Table 2). Serious clinical effects included respiratory depression (n = 891), bradycardia (n = 98), coma (n = 65), cyanosis (n = 36), respiratory arrest (n = 23), seizure (n = 10), and cardiac arrest (n = 6). Among children who experienced at least 1 related symptom, 6.8% of symptoms lasted ≤2 hours, 31.6% lasted ≤8 hours, and 77.7% lasted ≤24 hours (Table 2). Of the 4905 (46.4%) children who received at least 1 therapy, naloxone (19.2%; n = 2027), intravenous fluids (16.8%; n = 1773), and single-dose or multiple-dose charcoal (8.0%; n = 850) were among the most common therapies given. Most (96.3%) of the children who received naloxone were <6 years old. In addition, 52 children (0.5%) received endotracheal intubation.

Children <6 Years Old

Most (96.4%) buprenorphine exposures among children <6 years old were single-substance exposures, and the reason for exposure for 98.3% was "unintentional-general" (Table 1). The exposure rate per 1 000 000 children <6 years old increased 229.9% from 18.4 in 2007

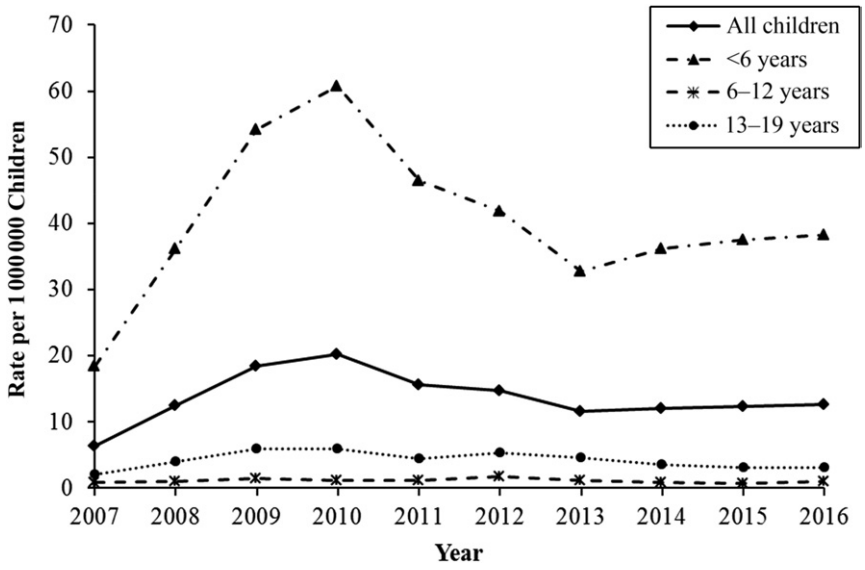

FIGURE 2
Annual rate of buprenorphine exposures among children 19 years old and younger by age group, NPDS 2007–2016.

to 60.7 in 2010, decreased 46.1% from 2010 to 32.7 in 2013, and then increased by 17.1% to 38.3 in 2016 (Fig 2). Exposure trends during 2007–2010 were driven by exposures to buprenorphine tablets, which accounted for 96.3% of exposures during this period. From 2007 to 2010, buprenorphine tablet exposures increased by 236.2%, followed by an 82.1% decrease from 2010 to 2014 and a gradual decrease of 7.8% from 2014 to 2016 (Fig 3). The increase in exposures during 2013–2016 was related to increases in exposure to buprenorphine film (29.9%) and unknown forms of buprenorphine (138.9%) (Fig 3). This followed a 35.7% decrease in the number of exposures to buprenorphine film during 2011–2013.

Almost half (48.1%) of children <6 years old were admitted to an HCF (including 23.6% to a CCU), and 21.4% experienced serious medical outcomes (including 2.0% with major effects and 7 deaths) (Table 1). Compared with single-substance exposures, a greater percentage of multiple-substance exposures were admitted to an HCF and had a serious medical outcome (Table 3). Among the 7 deaths, all were single-substance exposures, 6 were children 1 and 2 years old, and 6 involved tablet (n = 4) or film (n = 2) formulations.

For single-substance exposures, children <6 years old had greater odds of an HCF admission (OR: 2.13; 95% CI: 1.66–2.73) and a serious medical outcome (OR: 2.00; 95% CI: 1.41–2.84) than the 6- to 12-year-old age group. Children <6 years old also had greater odds of an HCF admission (OR: 5.84; 95% CI: 4.81–7.10) and a serious medical outcome (OR: 1.35; 95% CI: 1.13–1.63) than adolescents 13 to 19 years of age. In addition, children <6 years old exposed to buprenorphine film had similar odds of experiencing a serious medical outcome compared with those exposed to tablets (OR: 1.03; 95% CI: 0.91–1.17) (Table 3).

Children 6 to 12 Years Old

Children 6 to 12 years old accounted for 2.8% (n = 315) of exposures. Although 6- to 12-year-old children represent a behavioral transition group between children <6 years old and adolescents, similar to younger children, most of their exposures were unintentional (83.2%), specifically, unintentional-general (57.5%) and unintentional-therapeutic errors (17.8%) (Table 1). HCF admission occurred for 29.8% of exposures, and 11.7% of children experienced serious medical outcomes but no fatalities.

Adolescents 13 to 19 Years Old

Adolescents accounted for 11.1% of exposures. In contrast to young children, 77.1% of buprenorphine exposures among adolescents were intentional, and 27.7% involved >1 substance. The exposure rate per 1 000 000 adolescents increased by 195.0% from 2.0 in 2007 to 5.9 in 2010, followed by a 47.5% decline from 2010 to 3.1 in 2016 (Fig 2). More than one-fifth (21.5%) of adolescent exposures resulted in an HCF admission (including 11.5% admitted to a CCU), and 22.0% experienced a serious medical outcome (including 2.6% with a major effect and 4 deaths). All 4 deaths were multiple-substance exposures; 2 involved buprenorphine with benzodiazepines, ethanol, and other substances; 1 involved buprenorphine with benzodiazepines and marijuana; and 1 involved buprenorphine with ethanol. The odds of an HCF admission (OR: 4.74; 95% CI: 3.56–6.31) and serious medical outcome (OR: 2.97; 95% CI: 2.24–3.93) were higher for adolescents exposed to multiple substances than those exposed to buprenorphine alone.

Of the 150 (12.0%) adolescents suspected of a suicide attempt, 58.7% were multiple-substance exposures, 65.3% were admitted (including 32.0% to a CCU), and 42.7% experienced a serious medical outcome (including 12 with major effects and 1 death; Table 4). Female patients accounted for 58.7% of suspected suicides.

Of the 759 (60.7%) adolescents with intentional abuse and/or misuse exposures, 17.9% were admitted (including 9.9% to a CCU), and

TABLE 1 Characteristics of Buprenorphine Exposures Among Children 19 Years Old and Younger by Age Group, NPDS 2007–2016

Characteristics	<6 y, *n* (%[a])	6–12 y, *n* (%[a])	13–19 y, *n* (%[a])	Total, *n* (%[a])
Sex				
Male	5083 (52.4)	181 (57.5)	721 (57.6)	5985 (53.1)
Female	4560 (47.0)	134 (42.5)	527 (42.1)	5221 (46.3)
Unknown	66 (0.7)	0 (0.0)	3 (0.2)	69 (0.6)
Formulation				
Tablet	6374 (65.7)	204 (64.8)	841 (67.2)	7419 (65.8)
Film	1992 (20.5)	60 (19.0)	298 (23.8)	2350 (20.8)
Injection or patch	153 (1.6)	11 (3.5)	11 (0.9)	175 (1.6)
Unknown	1190 (12.3)	40 (12.7)	101 (8.1)	1331 (11.8)
Exposure site				
Residence	9460 (97.4)	296 (94.0)	1070 (85.5)	10 826 (96.0)
Other	148 (1.5)	16 (5.1)	93 (7.4)	257 (2.3)
Unknown	101 (1.0)	3 (1.0)	88 (7.0)	192 (1.7)
Reason for exposure				
Unintentional	9628 (99.2)	262 (83.2)	163 (13.0)	10 053 (89.2)
General	9548 (98.3)	181 (57.5)	53 (4.2)	9782 (86.8)
Therapeutic error	54 (0.6)	56 (17.8)	93 (7.4)	203 (1.8)
Other or unknown	26 (0.3)	25 (7.9)	17 (1.4)	68 (0.6)
Intentional	8 (0.1)	29 (9.2)	964 (77.1)	1001 (8.9)
Misuse and/or abuse	2 (0.0)[b]	16 (5.1)	759 (60.7)	777 (6.9)
Suspected suicide	5 (0.1)[b]	3 (1.0)	150 (12.0)	158 (1.4)
Unknown	1 (0.0)	10 (3.2)	55 (4.4)	66 (0.6)
Other	37 (0.4)	1 (0.3)	98 (7.8)	136 (1.2)
Unknown	36 (0.4)	23 (7.3)	26 (2.1)	85 (0.8)
Management site				
Patient already in (en route to) HCF when PCC called	5096 (52.5)	119 (37.8)	622 (49.7)	5837 (51.8)
Patient was referred by PCC to an HCF	3724 (38.4)	120 (38.1)	346 (27.7)	4190 (37.2)
Managed on site (not at an HCF)	795 (8.2)	69 (21.9)	246 (19.7)	1110 (9.8)
Other	40 (0.4)	2 (0.6)	11 (0.9)	53 (0.5)
Unknown	54 (0.6)	5 (1.6)	26 (2.1)	85 (0.8)
Level of HCF care received				
No HCF treatment received	889 (9.2)	76 (24.1)	283 (22.6)	1248 (11.1)
Treated or evaluated and released	2877 (29.6)	82 (26.0)	410 (32.8)	3369 (29.9)
Admitted	4669 (48.1)	94 (29.8)	269 (21.5)	5032 (44.6)
Admitted to CCU	2287 (23.6)	41 (13.0)	144 (11.5)	2472 (21.9)
Admitted to non-CCU	2380 (24.5)	52 (16.5)	79 (6.3)	2511 (22.3)
Admitted to psychiatric facility	2 (0.0)[b]	1 (0.3)	46 (3.7)	49 (0.4)
Other	1274 (13.1)	63 (20.0)	289 (23.1)	1626 (14.4)
Medical outcome				
No effect	2299 (23.7)	76 (24.1)	105 (8.4)	2480 (22.0)
Minor effect	3558 (36.6)	102 (32.4)	404 (32.3)	4064 (36.0)
Serious outcome	2079 (21.4)	37 (11.7)	275 (22.0)	2391 (21.2)
Moderate effect	1882 (19.4)	34 (10.8)	239 (19.1)	2155 (19.1)
Major effect	190 (2.0)	3 (1.0)	32 (2.6)	225 (2.0)
Death	7 (0.1)	0 (0.0)	4 (0.3)	11 (0.1)
Not followed (at most minimal clinical effects possible)	520 (5.4)	44 (14.0)	228 (18.2)	792 (7.0)
Unable to follow (potentially toxic exposure)	1253 (12.9)	56 (17.8)	239 (19.1)	1548 (13.7)
Total, row %[c]	9709 (86.1)	315 (2.8)	1251 (11.1)	11 275 (100.0)

[a] Column percentages may not sum to 100.0% because of rounding error.
[b] Potentially miscoded cases given children's young age.
[c] Row percentages may not sum to 100.0% because of rounding error.

20.6% experienced a serious medical outcome (including 13 with major effects and 2 deaths; Table 4). Male patients accounted for 62.7% of abuse and/or misuse exposures. Among the 193 (25.4%) intentional abuse and/or misuse exposures involving multiple substances, buprenorphine was commonly used with benzodiazepines (31.1%; *n* = 60), ethanol (18.7%; *n* = 36), and marijuana (13.5%; *n* = 26).

DISCUSSION

During the 10-year study period, >11 000 buprenorphine exposures among individuals ≤19 years old were reported to US PCCs. Most were among children <6 years old (86.1%) and adolescents 13 to 19 years old (11.1%); therefore, we will focus on these age groups in our discussion. Approximately 45% of children exposed to buprenorphine were admitted to an HCF, and more than one-fifth had a serious

TABLE 2 Selected Related Clinical Effects and Duration of Clinical Effects Observed Among Children 19 Years Old and Younger Exposed to a Single Buprenorphine Product by Age Group, NPDS 2007–2016

Characteristics	<6 y, *n* (%)	6–12 y, *n* (%)	13–19 y, *n* (%)	Total, *n* (%)
Total single-substance exposures	9358	307	905	10570
Selected related clinical effects[a]				
Neurologic				
Drowsiness and/or lethargy	4568 (48.8)	103 (33.6)	277 (30.6)	4948 (46.8)
Agitated and/or irritable	346 (3.7)	2 (0.7)	21 (2.3)	369 (3.5)
Ataxia	330 (3.5)	5 (1.6)	16 (1.8)	351 (3.3)
Dizziness and/or vertigo	66 (0.7)	30 (9.8)	72 (8.0)	168 (1.6)
Confusion	51 (0.5)	5 (1.6)	22 (2.4)	78 (0.7)
Coma	51 (0.5)	0 (0.0)	14 (1.5)	65 (0.6)
Slurred speech	39 (0.4)	3 (1.0)	18 (2.0)	60 (0.6)
Seizure (single or multiple)	6 (0.1)	1 (0.3)	3 (0.3)	10 (0.1)
Hallucinations and/or delusions	3 (0.0)	1 (0.3)	4 (0.4)	8 (0.1)
Syncope	5 (0.1)	0 (0.0)	6 (0.7)	11 (0.1)
Gastrointestinal				
Vomiting	1463 (15.6)	63 (20.5)	273 (30.2)	1799 (17.0)
Nausea	184 (2.0)	42 (13.7)	161 (17.8)	387 (3.7)
Ocular				
Miosis	1279 (13.7)	26 (8.5)	32 (3.5)	1337 (12.6)
Pupil(s) nonreactive	11 (0.1)	0 (0.0)	0 (0.0)	11 (0.1)
Respiratory				
Respiratory depression	852 (9.1)	15 (4.9)	24 (2.7)	891 (8.4)
Cyanosis	35 (0.4)	0 (0.0)	1 (0.1)	36 (0.3)
Dyspnea	27 (0.3)	0 (0.0)	7 (0.8)	34 (0.3)
Respiratory arrest	22 (0.2)	0 (0.0)	1 (0.1)	23 (0.2)
Cardiovascular				
Tachycardia	149 (1.6)	4 (1.3)	44 (4.9)	197 (1.9)
Hypotension	99 (1.1)	0 (0.0)	6 (0.7)	105 (1.0)
Bradycardia	82 (0.9)	3 (1.0)	13 (1.4)	98 (0.9)
Hypertension	19 (0.2)	0 (0.0)	12 (1.3)	31 (0.3)
Cardiac arrest	5 (0.1)	0 (0.0)	1 (0.1)	6 (0.1)
Conduction disturbance	3 (0.0)	0 (0.0)	1 (0.1)	4 (0.0)
Clinical effects duration[b]				
≤2 h	375 (6.9)	15 (9.3)	35 (5.6)	425 (6.8)
>2, ≤8 h	1363 (25.0)	34 (21.0)	151 (24.2)	1548 (24.8)
>8, ≤24 h	2649 (48.6)	70 (43.2)	156 (25.0)	2875 (46.1)
>24 h, ≤3 d	504 (9.2)	11 (6.8)	31 (5.0)	546 (8.7)
>3 d	43 (0.8)	1 (0.6)	5 (0.8)	49 (0.8)
Unknown or missing	522 (9.6)	31 (19.2)	245 (39.4)	798 (12.7)
Subtotal	5456	162	623	6241

[a] Percentages for selected related clinical effects were calculated by using the study's total number of single-substance exposures as the denominator and may sum to >100.0% because some exposures may result in >1 related clinical effect.

[b] Percentages were calculated by using only cases with at least 1 related clinical effect and may not sum to 100.0% because of rounding error.

medical outcome. The proportion of exposures resulting in an HCF admission for buprenorphine was higher than that reported for other prescription opioids during 2000–2015, as was the proportion of exposures resulting in serious medical outcomes, with the exceptions of methadone and fentanyl.[3]

Children <6 Years Old

Because children <6 years old accounted for 86% of all buprenorphine exposures, trends in this age group were the major influence on overall exposure trends. From 2007 to 2010, exposure rates increased >200%, which is likely attributable to the increasing number of buprenorphine prescriptions dispensed since the FDA approved its use as a treatment of opioid dependence in 2002.[14–16] Despite the number of dispensed buprenorphine and naloxone prescriptions almost tripling from 2008 to 2016,[4] there was a transient decrease in buprenorphine exposures during 2010–2013, which may have been influenced by several factors. One factor may be a shift in buprenorphine prescriptions to a population less likely to have young children in the home. From 2003 to 2013, office visits for buprenorphine treatment among individuals 20 to 39 years old decreased by 20.2% with a concomitant 22.3% increase among individuals 40 to 59 years old.[17] In addition, the Prevention of Overdose and Treatment Errors in Children Taskforce initiative used to reduce medication exposures among young children and the Up and

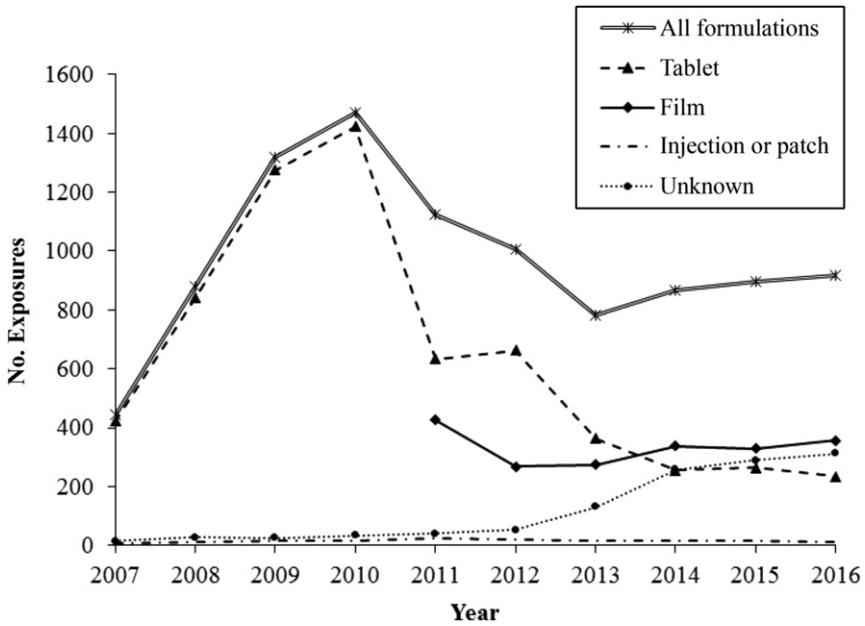

FIGURE 3
Annual number of buprenorphine exposures among children younger than 6 years old by product formulation, NPDS 2007–2016.

Away and Out of Sight medication safety program may have influenced exposure trends.[18]

In addition, the observed decrease in buprenorphine exposures was likely associated with concurrent changes in buprenorphine packaging, which also have the potential to reduce the severity of exposures that do occur. Similar to previous study findings,[8,19] tablets accounted for almost all exposures in this study from 2007 to 2010. This is because almost all of the buprenorphine and naloxone prescriptions dispensed from 2008 to 2010 were tablets.[4] The decline in the exposure rate in this study coincided with the August 2010 FDA approval of a buprenorphine film[17] that was sold only in unit-dose child-resistant packaging.[4] The observed decrease in the exposure rate from 2010 to 2013 was associated with a decrease in both tablet and film exposures. The decline in tablet exposures was driven, in part, by a 19% decrease in sales of the leading brand-name tablets as the manufacturer transitioned to a film formulation.[20] Then, in 2013, the leading brand-name tablets were voluntarily withdrawn from the US market because of potential risk of unintentional pediatric exposures,[21] which likely contributed to a further decrease in tablet exposures. It is unknown why the number of exposures to buprenorphine film decreased by 35.7% from 2011 to 2013, despite a doubling in sales to >$764 million from 2011 to 2012.[20] The unit-dose packaging of buprenorphine film may make it less accessible to young children.

From 2013 to 2016, there was a 30% increase in the frequency of exposures to buprenorphine film, which may be attributable to the continued increase in the number of prescriptions for this formulation. During the same period, there was a 139% increase in exposures to buprenorphine of unknown formulation. If these unknown formulation exposures were dominated by 1 type of formulation, such as tablets, this would alter the trends of tablets versus film observed during 2013–2016 in this study.

In this study, the type of formulation (tablet versus film) did not affect the odds of a serious medical outcome among young children. Therefore, regardless of formulation, buprenorphine is dangerous to young children, and primary prevention of access is key. Unit-dose packaging is a proven strategy for limiting access to medications by young children[22] and is the preferred type of packaging for buprenorphine products. Proper storage out of sight and reach of young children, preferably in a locked location (which limits access to adolescents as well), is important. In May 2016, the FDA approved the first buprenorphine subcutaneous implant for the treatment of opioid use disorder, which may also help limit child access.[23]

Among single-substance exposures, children <6 years of age had greater odds of an HCF admission and of experiencing a serious medical outcome than adolescents. Therapeutic doses of buprenorphine-naloxone for pediatric patients are 2 to 6 μg/kg, so ingestion of a single 2 mg sublingual tablet in a 10 kg child can result in more than a 30-fold overdose.[6] This is particularly dangerous, because children exposed to buprenorphine do not display the "ceiling effect" reported in adults, in which escalating doses do not lead to additional increases in respiratory depression.[24] In addition, young children may be admitted to an HCF more often because physicians may exercise more caution in this age group. In this study, almost half of exposed children <6 years old were admitted to an HCF, but only 21.4% experienced serious medical outcomes. Young children also often experience a delay in the onset of symptoms after buprenorphine exposure; the median time from exposure to respiratory depression was 4.4 hours in 1 study.[25] This known delay in symptom onset likely contributes to the higher admission rate for young children.

Adolescents 13 to 19 Years Old

More than three-fourths of buprenorphine exposures among

TABLE 3 Characteristics of Buprenorphine Exposures Among Children Younger Than 6 Years Old by Type of Exposure and Selected Product Formulation, NPDS 2007–2016

Characteristics	Single-Substance Exposures			Multiple-Substance Exposures		
	Subtotal[a], *n* (%[b])	Tablet, *n* (%[b])	Film, *n* (%[b])	Subtotal[a], *n* (%[b])	Tablet, *n* (%[b])	Film, *n* (%[b])
Management site						
Patient already in (en route to) HCF when PCC called	4846 (51.8)	3083 (50.2)	1143 (59.1)	250 (71.2)	155 (67.7)	45 (77.6)
Patient was referred by PCC to an HCF	3636 (38.9)	2502 (40.7)	652 (33.7)	88 (25.1)	66 (28.8)	13 (22.4)
Managed on site (not at an HCF)	784 (8.4)	503 (8.2)	114 (5.9)	11 (3.1)	6 (2.6)	0 (0.0)
Other	39 (0.4)	23 (0.4)	9 (0.5)	1 (0.3)	1 (0.4)	0 (0.0)
Unknown	53 (0.6)	34 (0.6)	16 (0.8)	1 (0.3)	1 (0.4)	0 (0.0)
Level of HCF care received						
No HCF treatment received	876 (9.4)	560 (9.1)	139 (7.2)	13 (3.7)	8 (3.5)	0 (0.0)
Treated or evaluated and released	2771 (29.6)	1876 (30.5)	563 (29.1)	106 (30.2)	80 (34.9)	14 (24.1)
Admitted	4460 (47.7)	2851 (46.4)	1012 (52.3)	209 (59.5)	125 (54.6)	40 (69.0)
Admitted to CCU	2166 (23.1)	1370 (22.3)	505 (26.1)	121 (34.5)	80 (34.9)	17 (29.3)
Admitted to non-CCU	2292 (24.5)	1479 (24.1)	507 (26.2)	88 (25.1)	45 (19.7)	23 (39.7)
Admitted to psychiatric facility[c]	2 (0.0)	2 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	1251 (13.4)	858 (14.0)	220 (11.4)	23 (6.6)	16 (7.0)	4 (6.9)
Medical outcome						
No effect	2223 (23.8)	1367 (22.2)	504 (26.1)	76 (21.7)	51 (22.3)	11 (19.0)
Minor effect	3429 (36.6)	2275 (37.0)	718 (37.1)	129 (36.8)	88 (38.4)	22 (37.9)
Serious outcome	1965 (21.0)	1291 (21.0)	416 (21.5)	114 (32.5)	66 (28.8)	21 (36.2)
Moderate effect	1783 (19.1)	1166 (19.0)	386 (20.0)	99 (28.2)	58 (25.3)	19 (32.8)
Major effect	175 (1.9)	121 (2.0)	28 (1.4)	15 (4.3)	8 (3.5)	2 (3.4)
Death	7 (0.1)	4 (0.1)	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Not followed (at most minimal clinical effects possible)	507 (5.4)	340 (5.5)	84 (4.3)	13 (3.7)	10 (4.4)	1 (1.7)
Unable to follow (potentially toxic exposure)	1234 (13.2)	872 (14.2)	212 (11.0)	19 (5.4)	14 (6.1)	3 (5.2)
Total	9358 (100.0)	6145 (100.0)	1934 (100.0)	351 (100.0)	229 (100.0)	58 (100.0)

[a] Subtotal includes patch, injection, and unknown formulation.
[b] Percentages may not sum to 100.0% because of rounding error.
[c] Potentially miscoded cases given children's young age.

adolescents were intentional. Although buprenorphine abuse has been reported, it is regarded as 1 of the least-abused opioids.[1,26] However, in non-opioid dependent individuals, buprenorphine produces the euphoric effects and positive reinforcement properties associated with other opioids.[26] As medical prescribing of opioids (including buprenorphine) increased, so did abuse and diversion of these medications.[27] Friends and relatives are a major source for young adult nonmedical opioid users, who state that the main motivations for illicit buprenorphine use are self-medication of withdrawal symptoms and getting high.[28]

More than one-fourth of exposures among adolescents involved >1 substance; specifically, benzodiazepines were used concurrently with buprenorphine in 60 of the intentional abuse and/or misuse exposures. Benzodiazepine use has previously been reported to increase the high of other drugs and lessen withdrawal symptoms, both of which coincide with the main motivations identified for buprenorphine use.[29] The combination of benzodiazepines with buprenorphine is known to enhance central nervous system and respiratory depression.[30] Three of the 4 deaths of 13- to 19-year-old individuals involved this combination of medications.

Suspected suicide accounted for 12% of exposures among adolescents. Female patients accounted for almost 60% of suspected suicides, whereas male patients accounted for >60% of abuse and/or misuse exposures. Female patients tend to use less violent methods to commit suicide, such as ingestion of medications.[3,31] Our findings corroborate previous reports of higher rates of illicit buprenorphine use by male patients.[28]

TABLE 4 Outcomes Associated With Buprenorphine Exposures Among Adolescents 13–19 Years Old by Selected Reason for Exposure and Type of Exposure, NPDS 2007–2016

Characteristics	Misuse and/or Abuse			Suspected Suicide		
	Single-Substance, *n* (%[a])	Multiple-Substance, *n* (%[a])	Subtotal, *n* (%[a])	Single-Substance, *n* (%[a])	Multiple-Substance, *n* (%[a])	Subtotal, *n* (%[a])
Sex						
Male	350 (61.8)	126 (65.3)	476 (62.7)	23 (37.1)	38 (43.2)	61 (40.7)
Female	214 (37.8)	67 (34.7)	281 (37.0)	38 (61.3)	50 (56.8)	88 (58.7)
Unknown	2 (0.4)	0 (0.0)	2 (0.3)	1 (1.6)	0 (0.0)	1 (0.7)
Management site						
Patient already in (en route to) HCF when PCC called	259 (45.8)	125 (64.8)	384 (50.6)	48 (77.4)	81 (92.0)	129 (86.0)
Patient was referred by PCC to an HCF	179 (31.6)	33 (17.1)	212 (27.9)	14 (22.6)	6 (6.8)	20 (13.3)
Managed on site (non-HCF)	110 (19.4)	30 (15.5)	140 (18.4)	0 (0.0)	0 (0.0)	0 (0.0)
Unknown	11 (1.9)	3 (1.6)	14 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)
Other	7 (1.2)	2 (1.0)	9 (1.2)	0 (0.0)	1 (1.1)	1 (0.7)
Level of HCF care received						
No HCF treatment received	128 (22.6)	35 (18.1)	163 (21.5)	0 (0.0)	1 (1.1)	1 (0.7)
Treated or evaluated and released	216 (38.2)	66 (34.2)	282 (37.2)	20 (32.3)	14 (15.9)	34 (22.7)
Admitted	73 (12.9)	63 (32.6)	136 (17.9)	33 (53.2)	65 (73.9)	98 (65.3)
Admitted to CCU	29 (5.1)	46 (23.8)	75 (9.9)	13 (21.0)	35 (39.8)	48 (32.0)
Admitted to non-CCU	30 (5.3)	11 (5.7)	41 (5.4)	12 (19.4)	14 (15.9)	26 (17.3)
Admitted to psychiatric facility	14 (2.5)	6 (3.1)	20 (2.6)	8 (12.9)	16 (18.2)	24 (16.0)
Other	149 (26.3)	29 (15.0)	178 (23.5)	9 (14.5)	8 (9.1)	17 (11.3)
Medical outcome						
No effect	42 (7.4)	15 (7.8)	57 (7.5)	13 (21.0)	8 (9.1)	21 (14.0)
Minor effect	213 (37.6)	57 (29.5)	270 (35.6)	21 (33.9)	20 (22.7)	41 (27.3)
Serious outcome	92 (16.3)	64 (33.2)	156 (20.6)	17 (27.4)	47 (53.4)	64 (42.7)
Moderate effect	87 (15.4)	54 (28.0)	141 (18.6)	15 (24.2)	36 (40.9)	51 (34.0)
Major effect	5 (0.9)	8 (4.1)	13 (1.7)	2 (3.2)	10 (11.4)	12 (8.0)
Death	0 (0.0)	2 (1.0)	2 (0.3)	0 (0.0)	1 (1.1)	1 (0.7)
Not followed (at most minimal clinical effects possible)	100 (17.7)	28 (14.5)	128 (16.9)	3 (4.8)	3 (3.4)	6 (4.0)
Unable to follow (potentially toxic exposure)	119 (21.0)	29 (15.0)	148 (19.5)	8 (12.9)	10 (11.4)	18 (12.0)
Total	566 (100.0)	193 (100.0)	759 (100.0)	62 (100.0)	88 (100.0)	150 (100.0)

[a] Percentages may not sum to 100.0% because of rounding.

In 2016, the American Academy of Pediatrics issued a statement advocating for increased access to buprenorphine for opioid-addicted adolescents in primary care settings.[5] This recommendation is warranted because of the high and increasing prevalence of opioid dependence among adolescents. However, caution should be used, because increased prescriptions among adolescents could lead to increased diversion and abuse and increased access to younger children in the home. Therefore, patient education for adolescents should include information about the dangers of misusing and/or abusing prescription drugs and the proper storage of medications.

Study Limitations

Because not all pediatric buprenorphine exposures are reported to PCCs, the true number of buprenorphine exposures is underestimated, and the results of our study may not be representative of those exposures not reported to PCCs. Reported exposures do not necessarily represent a poisoning or overdose. The NPDS does not collect patient identifiers, so repeat exposures cannot be identified. Newer generic forms of buprenorphine do not have specific product codes in the NPDS, which limited some of our analyses. Although authors of 1 small study suggested less-common clinical effects and treatments may be undercoded in NPDS,[32] other analyses have revealed the accuracy of PCC data to be as good as, or better than, other hospital or emergency department databases.[33–35] The NPDS relies on self-reports, which cannot fully be verified by the PCCs or AAPCC. However, highly qualified poison experts enter NPDS data using strict quality controls and case follow-up methods. Despite its limitations, the NPDS is an appropriate and informative data source for research on buprenorphine exposures among US children. Although population-based rates were calculated, these rates were not adjusted for increasing buprenorphine prescriptions or sales during the study period; we did not have access to these data.

CONCLUSIONS

Buprenorphine is important for the treatment of opioid use disorder, but pediatric exposure can result in serious adverse outcomes. Prevention efforts should be tailored according to children's age group. Manufacturers should use unit-dose packaging for all buprenorphine products to help prevent unintentional exposure among young children. Health care providers should inform caregivers of young children about the dangers of buprenorphine exposure and provide instructions on proper storage and disposal of medications. Adolescents should receive information regarding the risks of substance abuse and misuse. In addition, suspected suicide was the second most common reason for exposure among adolescents, highlighting the need for access to mental health services for this age group.

ABBREVIATIONS

AAPCC: American Association of Poison Control Centers
CCU: critical care unit
CI: confidence interval
FDA: Food and Drug Administration
HCF: health care facility
NPDS: National Poison Data System
OR: odds ratio
PCC: poison control center

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REFERENCES

1. Substance Abuse and Mental Health Services Administration. *Key Substance Use and Mental Health Indicators in the United States: Results From the 2016 National Survey on Drug Use and Health*. Rockville, MD: Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration; 2017. Available at: https://www.samhsa.gov/data/sites/default/files/NSDUH-FFR1-2016/NSDUH-FFR1-2016.htm. Accessed January 24, 2018
2. Crane EH. *Emergency Department Visits Involving Buprenorphine. The CBHSQ Report*. Rockville, MD: Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration; 2013. Available at: https://www.ncbi.nlm.nih.

gov/books/NBK384655/pdf/Bookshelf_NBK384655.pdf. Accessed October 2, 2017

3. Allen JD, Casavant MJ, Spiller HA, Chounthirath T, Hodges NL, Smith GA. Prescription opioid exposures among children and adolescents in the United States: 2000-2015. *Pediatrics*. 2017;139(4):e20163382
4. Budnitz DS, Lovegrove MC, Sapiano MR, et al. Notes from the field: pediatric emergency department visits for buprenorphine/naloxone ingestion - United States, 2008-2015. *MMWR Morb Mortal Wkly Rep*. 2016;65(41):1148–1149
5. Committee on Substance Use and Prevention. Medication-assisted treatment of adolescents with opioid use disorders. *Pediatrics*. 2016;138(3):e20161893
6. Boyer EW, McCance-Katz EF, Marcus S. Methadone and buprenorphine toxicity in children. *Am J Addict*. 2010;19(1):89–95
7. Hayes BD, Klein-Schwartz W, Doyon S. Toxicity of buprenorphine overdoses in children. *Pediatrics*. 2008;121(4). Available at: www.pediatrics.org/cgi/content/full/121/4/e782
8. Lavonas EJ, Banner W, Bradt P, et al. Root causes, clinical effects, and outcomes of unintentional exposures to buprenorphine by young children. *J Pediatr*. 2013;163(5):1377–1383.e1–e3
9. Martin TC, Rocque MA. Accidental and non-accidental ingestion of methadone and buprenorphine in childhood: a single center experience, 1999-2009. *Curr Drug Saf*. 2011;6(1):12–16
10. Geib AJ, Babu K, Ewald MB, Boyer EW. Adverse effects in children after unintentional buprenorphine exposure. *Pediatrics*. 2006;118(4):1746–1751
11. Mowry JB, Spyker DA, Brooks DE, Zimmerman A, Schauben JL. 2015 annual report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 33rd annual report. *Clin Toxicol (Phila)*. 2016;54(10):924–1109
12. United States Census Bureau. Population and housing unit estimates datasets. Available at: https://www.census.gov/programs-surveys/popest/data/data-sets.All.html. Accessed October 2, 2017
13. American Association of Poison Control Centers. National Poison Data System (NPDS): NPDS coding users' manual© version 3.1. 2014. Available at: https://aapcc.s3.amazonaws.com/pdfs/member-resources/NPDS_Coding_Users_Manual_v3.1_07May2014.pdf. Accessed October 2, 2017
14. Burghardt LC, Ayers JW, Brownstein JS, Bronstein AC, Ewald MB, Bourgeois FT. Adult prescription drug use and pediatric medication exposures and poisonings. *Pediatrics*. 2013;132(1):18–27
15. Atluri S, Sudarshan G, Manchikanti L. Assessment of the trends in medical use and misuse of opioid analgesics from 2004 to 2011. *Pain Physician*. 2014;17(2):E119–E128
16. IMS Institute for Healthcare Informatics. *Use of Opioid Recovery Medications: Recent Evidence on State Level Buprenorphine Use and Payment Types*. Parsippany, NJ: IMS Institute for Healthcare Informatics; 2016. Available at: https://www.iqvia.com/-/media/iqvia/pdfs/institute-reports/use-of-opioid-recovery-medications.pdf?la=en&hash=3394B7ED845A486E07C1282A68CF5A04E69EF05C. Accessed October 2, 2017
17. Turner L, Kruszewski SP, Alexander GC. Trends in the use of buprenorphine by office-based physicians in the United States, 2003-2013. *Am J Addict*. 2015;24(1):24–29
18. Centers for Disease Control and Prevention. PROTECT initiative. Advancing children's medication safety. Available at: https://www.cdc.gov/medicationsafety/protect/protect_initiative.html. Accessed October 2, 2017
19. Centers for Disease Control and Prevention (CDC). Buprenorphine prescribing practices and exposures reported to a poison center–Utah, 2002-2011. *MMWR Morb Mortal Wkly Rep*. 2012;61(49):997–1001
20. Silverman E. Reckitt's suboxone strategy is really about patients or profits? *Forbes*. 2012. Available at: https://www.forbes.com/sites/edsilverman/2012/10/12/reckitts-suboxone-strategy-is-really-about-patients-or-profits/2/#26c3ea893d8b. Accessed February 21, 2018
21. Knopf A. Reckitt pulls suboxone tablets, citing pediatric exposures. *Alcoholism & Drug Abuse Weekly*. 2012. Available at: www.alcoholismdrugabuseweekly.com/article-detail/reckitt-pulls-suboxone-tablets-citing-pediatric-exposures.aspx. Accessed October 2, 2017
22. 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
23. U.S. Food and Drug Administration. FDA approves first buprenorphine implant for treatment of opioid dependence. 2016. Available at: https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm503719.htm. Accessed October 2, 2017
24. Boyer EW. Management of opioid analgesic overdose. *N Engl J Med*. 2012;367(2):146–155
25. Toce MS, Burns MM, O'Donnell KA. Clinical effects of unintentional pediatric buprenorphine exposures: experience at a single tertiary care center. *Clin Toxicol (Phila)*. 2017;55(1):12–17
26. Yokell MA, Zaller ND, Green TC, Rich JD. Buprenorphine and buprenorphine/naloxone diversion, misuse, and illicit use: an international review. *Curr Drug Abuse Rev*. 2011;4(1):28–41
27. Compton WM, Volkow ND. Major increases in opioid analgesic abuse in the United States: concerns and strategies. *Drug Alcohol Depend*. 2006;81(2):103–107
28. Daniulaityte R, Falck R, Carlson RG. Illicit use of buprenorphine in a community sample of young adult non-medical users of pharmaceutical opioids. *Drug Alcohol Depend*. 2012;122(3):201–207
29. Mateu-Gelabert P, Jessell L, Goodbody E, et al. High enhancer, downer, withdrawal helper: multifunctional nonmedical benzodiazepine use among young adult opioid users in New York City. *Int J Drug Policy*. 2017;46:17–27
30. Jann M, Kennedy WK, Lopez G. Benzodiazepines: a major component in unintentional prescription drug

overdoses with opioid analgesics. *J Pharm Pract*. 2014;27(1):5–16

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. Jaramillo JE, Marchbanks B, Willis B, Forrester MB. Evaluation of completeness of selected poison control center data fields. *J Med Syst*. 2010;34(4):499–507
33. Coben JH, Steiner CA, Barrett M, Merrill CT, Adamson D. Completeness of cause of injury coding in healthcare administrative databases in the United States, 2001. *Inj Prev*. 2006;12(3):199–201
34. Lorence DP, Ibrahim IA. Benchmarking variation in coding accuracy across the United States. *J Health Care Finance*. 2003;29(4):29–42
35. Simone KE, Spiller HA. Poison center surveillance data: the good, the bad and … the flu. *Clin Toxicol (Phila)*. 2010;48(5):415–417

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