Root Causes, Clinical Effects, and Outcomes of Unintentional Exposures to Buprenorphine by Young Children

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Objective To characterize the rates, root causes, and clinical effects of unintentional exposures to buprenorphine sublingual formulations among young children and to determine whether exposure characteristics differ between formulations.

Study design Unintentional exposures to buprenorphine-containing products among children 28 days to less than 6 years old were collected from the Researched Abuse, Diversion, and Addiction-Related Surveillance System Poison Center Program and Reckitt Benckiser Pharmaceuticals' pharmacovigilance system from October 2009-March 2012. After adjustment for drug availability, negative binomial regression was used to estimate average exposure rates. Root cause assessment was conducted, and an expert clinician panel adjudicated causality and severity of moderate to severe adverse events (AEs).

Results A total of 2380 cases were reviewed, including 4 deaths. Exposures to buprenorphine-naloxone combination film were significantly less frequent than exposures to buprenorphine tablets (rate ratio 3.5 [95% CI, 2.7-4.5]) and buprenorphine-naloxone combination tablets (rate ratio 8.8 [7.2-10.6]). The most commonly identified root causes were medication stored in sight, accessed from a bag or purse, and not stored in the original packaging. Among 536 panel review cases, the most common AEs reported for all formulations were lethargy, respiratory depression, miosis, and vomiting. The highest level AE severity did not differ significantly by formulation.

Conclusions Unintentional exposure to buprenorphine can cause central nervous system depression, respiratory depression, and death in young children. Exposure rates to film formulations are significantly less than to tablet formulations. Package and storage deficiencies contribute to unintentional exposures in young children. *(J Pediatr 2013;163:1377-83)*.

Unintentional poisonings among children are an important public health problem.[1-3] One out of 180 two-year-olds visits an emergency department for a medication poisoning each year.[4] Several opioids, including buprenorphine, have been recognized for their potential to cause death in children with a single dose.[5,6] During 2010-2011, an average of 1499 children aged less than 6 years were evaluated in emergency departments in the US each year for unintentional exposure to buprenorphine.[7]

Buprenorphine, a potent partial agonist of the mu-opioid receptor, was introduced in the US in 2002 to treat opioid addiction in adults.[8,9] Buprenorphine ingestion by young children can cause central nervous system depression, respiratory depression, and death.[10] Little is known about the root causes of unintentional exposure to opioids in young children, including whether formulation and child-resistant packaging affect the risk of poisoning.[2,6,11,12]

In the US, 3 sublingual formulations of buprenorphine are available: single-ingredient tablets containing buprenorphine, buprenorphine-naloxone combination tablets, and buprenorphine-naloxone combination film. The opioid antagonist naloxone, which is poorly absorbed orally, is included in the combination formulations to deter abuse by nasal insufflation ("snorting") or injection. The tablet formulations are typically dispensed in medication bottles

AE	Adverse event
MedDRA	Medical Dictionary for Regulatory Activities
RADARS	Researched Abuse, Diversion, and Addiction-Related Surveillance
REMS	Risk evaluation and mitigation strategies
URDD	Unique recipients of a dispensed drug

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with child-resistant caps, and the film formulation, which was released in October 2010, is dispensed in child-resistant single dose foil packaging.

The purpose of this study is to characterize the rates, root causes, and clinical effects of unintentional exposure to buprenorphine sublingual formulations among young children and to determine whether these exposures and patient outcomes differ between formulations.

Methods

This is a retrospective cross-sectional study. Cases of unintentional exposure to any of 3 buprenorphine sublingual formulations involving children aged 28 days to less than 6 years were obtained from 2 sources. The date range for all events was October 1, 2009-March 31, 2012. The Researched Abuse, Diversion, and Addiction-Related Surveillance (RADARS) System Poison Center Program collects information from participating poison centers in the US; in the first quarter of 2012, 49 of 57 US poison centers covering more than 90% of the US population provided data. Methods for the RADARS System have been described previously.[6,13] In brief, certified specialists in poison information enter clinical information as part of patient management. After care is completed, standardized data fields and de-identified narrative notes are transmitted to the RADARS System, where a quality control process verifies products involved, exposure characteristics, and medical outcome. During the second and third quarters of 2011, this quality control process resulted in revised coding of approximately 37% of buprenorphine/naloxone tablet and oral film exposures reported by regional poison centers to the RADARS System Poison Center Program.[14] To capture reported exposures from more than 1 source, the Reckitt Benckiser Pharmaceuticals postmarketing pharmacovigilance database was also searched for eligible cases, using 4 search terms from the Medical Dictionary for Regulatory Activities (MedDRA; v 15.0, Northrop Grumman, Falls Church, Virginia), the standard taxonomy used by the Food and Drug Administration Adverse Event Reporting System: "accidental drug intake by child," "accidental exposure," "accidental overdose," and "accidental poisoning." Duplicate cases from the Poison Center Program and pharmacovigilance databases were identified and combined for analysis.

A trained researcher independently reviewed each report to identify study eligibility, buprenorphine formulation, root causes for exposure (ie, accessibility/storage, packaging, caregiver, intended recipient for the medication, and other risk factors), and adverse events (AEs). Because mandatory patient and provider education are incorporated in the buprenorphine risk evaluation and mitigation strategies (REMS) program, data about the relationship between education and the exposure were also extracted.[15] Data were passively collected by specialists in poison information for the purposes of patient care; when no information about a specific root cause was found in the record, it was impossible to determine whether the root cause was absent or not asked. Therefore, data about identified root causes were presented as the number of cases in which the root cause was mentioned.

A focused review to collect and classify AEs systematically was performed on a subset of cases with more serious outcomes. There was no attempt to differentiate between known and unexpected side effects, as this medication is not intended to be administered therapeutically to young children. Cases from the Poison Center Program were reviewed if the medical outcome was classified by the specialist in poison information as moderate effect, major effect, or death, using standard definitions established by the American Association of Poison Control Centers' National Poison Data System.[16] Cases classified by the specialist in poison information using the medial outcome codes for "not followed, judged as nontoxic exposure (clinical effects not expected)" and "not followed, minimal clinical effects possible" were excluded. Cases with a medical outcome of "unable to follow, judged as a potentially toxic exposure" were included if the level of health care facility care code or other clinical documentation indicated that the patient was admitted to the hospital. Cases from the manufacturer's pharmacovigilance database were reviewed by the panel if they met the age and date criteria and the clinical effects met the Food and Drug Administration definition of a serious AE.[17] The review panel consisted of 3 experienced clinicians: a pediatric intensivist/medical toxicologist, a pediatrician/pharmacoepidemiologist, and an emergency physician/medical toxicologist. Panel members reviewed each case to identify all documented AEs. The severity of each AE was classified by panel members using Common Terminology Criteria for AEs nomenclature.[18] The causal relationship between each AE and each drug exposure was determined using standard criteria[19,20](**Table I**; available at www.jpeds.com). Disagreements were resolved by consensus. Trained researchers then coded each AE using MedDRA taxonomy.

Exposures, root causes, and AEs were analyzed using descriptive statistics. Because the number of children potentially at risk of exposure to buprenorphine could not be estimated, we used buprenorphine prescription fulfillment data as a surrogate measure of drug availability. Prescription data were obtained from IMS Health Solutions (Parsippany, New Jersey), and the number of patients filling prescriptions for each of the 3 buprenorphine formulations in a geographic area contributing data to the RADARS System Poison Center Program during the year-quarter of the exposure (unique recipients of a dispensed drug [URDD]) was used as the denominator for rate calculations.[21] A negative binomial regression model was used to test for difference in average rates across the 3 drug groups, where URDD was an offset variable. Average rates were calculated for the year/quarters during the study period for which each formulation was available. Unintentional exposure rates, 95% CIs, and tests of significance were calculated. Two-sided tests were used for all statistical comparisons. AEs were summarized by MedDRA System Organ Class and Preferred Terms.

The operation of the RADARS System Poison Center Program is approved by the Colorado Multiple Institutional

Table II. Characteristics of children aged 28 days to <6 years with unintentional exposures to buprenorphine

Variable	Value	Total buprenorphine* n = 2380	Buprenorphine tablets n = 154	Buprenorphine/naloxone tablets n = 2107	Buprenorphine/naloxone film n = 118
Sex	Male	1229 (51.6%)	74 (48.1%)	1106 (52.5%)	49 (41.5%)
	Female	1127 (47.4%)	79 (51.3%)	983 (46.7%)	64 (54.2%)
	Not reported	24 (1.0%)	1 (0.6%)	18 (0.9%)	5 (4.2%)
Age group	28-364 d	148 (6.2%)	15 (9.7%)	123 (5.8%)	10 (8.5%)
	1 y-<2 y	885 (37.2%)	58 (37.7%)	788 (37.4%)	39 (33.1%)
	2 y-<3 y	888 (37.3%)	61 (39.6%)	787 (37.4%)	40 (33.9%)
	3 y-<4 y	320 (13.4%)	18 (11.7%)	279 (13.2%)	22 (18.6%)
	4 y-<5 y	100 (4.2%)	2 (1.3%)	94 (4.5%)	4 (3.4%)
	5 y-<6 y	36 (1.5%)	0 (0.0%)	35 (1.7%)	1 (0.8%)
	Exact age not reported	3 (0.1%)	0 (0.0%)	1 (0.0%)	2 (1.7%)
Number of other products involved in exposure	0	2271 (95.4%)	142 (92.2%)	2016 (95.7%)	112 (94.9%)
	1	72 (3.0%)	7 (4.5%)	61 (2.9%)	4 (3.4%)
	2	23 (1.0%)	5 (3.2%)	16 (0.8%)	2 (1.7%)
	3 or more	14 (0.6%)	0 (0.0%)	14 (0.7%)	0 (0.0%)
Exposure site	Own residence	2195 (93.8%)	146 (95.4%)	1942 (93.7%)	107 (93.0%)
	Other residence	103 (4.4%)	6 (3.9%)	90 (4.3%)	7 (6.1%)
	Unknown	14 (0.6%)	0 (0.0%)	14 (0.7%)	0 (0.0%)
	Public area	13 (0.6%)	1 (0.7%)	12 (0.6%)	0 (0.0%)
	Health care facility	3 (0.1%)	0 (0.0%)	3 (0.1%)	0 (0.0%)
	Other	12 (0.5%)	0 (0.0%)	11 (0.5%)	1 (0.9%)

*Includes data for buprenorphine formulation unspecified (n = 1).

Review Board and by the institutional review boards of each participating center. The authors had full control of all aspects of study design, data collection, data analysis and management, manuscript writing, and the decision to publish. Reckitt Benckiser Pharmaceuticals was able to review the manuscript only for proprietary information.

Results

A total of 2380 unique eligible cases were identified (Figure 1; available at www.jpeds.com). Of these, 154 cases (6.5%) involved exposure to buprenorphine tablets, 2107 cases (88.5%) involved exposure to buprenorphine-naloxone tablets, and 118 cases (5.0%) involved exposure to buprenorphine-naloxone film (Table II). In 1 additional case, the record clearly demonstrated a tablet exposure but did not contain information about whether buprenorphine or buprenorphine-naloxone tablets were involved. In 109 cases (4.6%), ingestion of at least 1 additional substance was suspected. The median patient age was 2 years, with no sex predominance. Although most exposures occurred in the child's residence, 145 cases (6.1%) occurred in other locations.

The mean exposure rates were 2.51 cases per 10 000 URDD (95% CI, 2.13-2.95 cases per 10 000 URDD) for buprenorphine tablets, 6.25 (5.92-6.61) cases per 10 000 URDD for buprenorphine-naloxone tablets, and 0.71 (0.59-0.86) cases per 10 000 URDD for buprenorphine-naloxone film. The mean exposure rates for both tablet formulations were significantly greater than the rate for the film formulation (rate ratio 8.76 (7.21-10.64) for combination tablets and 3.51 (2.75-4.50) for single ingredient tablets, $P < .001$ for both). These relationships were stable over the 30-month study period (Figure 2).

At least 1 root cause was identified in 1361 (57.2%) of the 2380 cases reviewed. The most commonly identified root causes for unintentional pediatric exposure involved medication storage, including medication stored in sight (415 cases; 30.5% of cases with a root cause identified and 17.4% of all cases), medication accessed from a bag or purse (110 cases; 8.1% and 4.6%), and medication stored in a package other than the original packaging (75 cases; 5.5% and 3.2%) (Table III). Ingestion of dropped or inappropriately stored medications was a common identified root cause and included buprenorphine found in wallets, purses, couches, automobiles, parents' pockets, floors, hotel rooms, cups, cigarette packages, eyeglass cases, cellophane, tissue paper, breath mint containers, and trash cans. Case notes showed that buprenorphine was intended for somebody other than the parent in 374 cases (36.1% and 15.7%), and in 117 cases

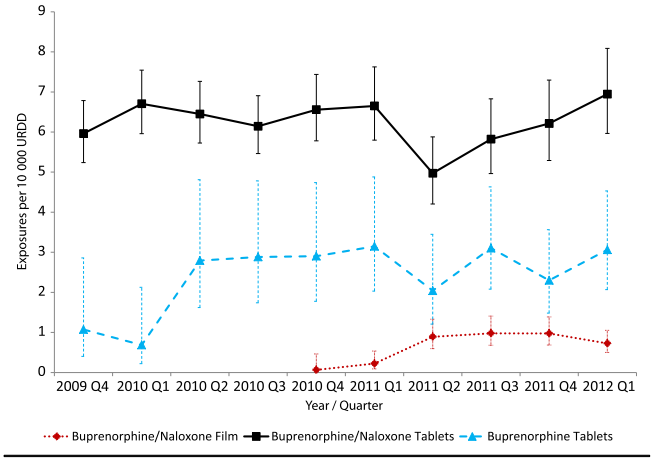

Figure 2. Rates of unintentional exposure to buprenorphine among children aged 28 days to less than 6 years, adjusted for drug availability.

Table III. Identified root causes of unintentional exposure to buprenorphine among children aged 28 days to less than 6 years*

Type	Detail	Total buprenorphine† n = 2380	Buprenorphine tablets n = 154	Buprenorphine naloxone tablets n = 2107	Buprenorphine naloxone film n = 118
Access/storage	Stored in sight, not secure, left out	415(17.4%)	27 (17.5%)	371 (17.6%)	16 (13.6%)
	Accessed from bag (purse, diaper bag, luggage, etc)	110 (4.6%)	5 (3.2%)	101 (4.8%)	4 (3.4%)
	Drug stored in package other than original packaging (tissue, plastic wrap, foil, cup, etc)	75 (3.2%)	4 (2.6%)	66 (3.1%)	5 (4.2%)
	Patient opened bottle	30 (1.3%)	1 (0.6%)	27 (1.3%)	2 (1.7%)
	Mixed medications stored in a bag/bottle	6 (0.3%)	0 (0.0%)	6 (0.3%)	0 (0.0%)
	Child resistant cap closure issue	4 (0.2%)	0 (0.0%)	4 (0.2%)	0 (0.0%)
	Child resistant cap left open by adult	2 (0.1%)	0 (0.0%)	2 (0.1%)	0 (0.0%)
Behavioral disorders	Behavioral disorders	2 (0.1%)	0 (0.0%)	2 (0.1%)	0 (0.0%)
Cutting medication	Tablet found in pill cutter or found broken	5 (0.2%)	0 (0.0%)	5 (0.2%)	0 (0.0%)
Developmentally delayed	Developmentally delayed (autism, etc)	4 (0.2%)	1 (0.6%)	3 (0.1%)	0 (0.0%)
Diversion	Purchased on the street	10 (0.4%)	0 (0.0%)	10 (0.5%)	0 (0.0%)
	Obtained from unknown location	4 (0.2%)	1 (0.6%)	3 (0.1%)	0 (0.0%)
	Obtained from a friend	3 (0.1%)	0 (0.0%)	3 (0.1%)	0 (0.0%)
	Obtained from relative	1 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)
Intended recipient	Parent's medication	663 (27.9%)	44 (28.6%)	582 (27.6%)	37 (31.4%)
	Others' medication (uncle, friend of parent, house guest, boyfriend, etc)	298 (12.5%)	17 (11.0%)	274 (13.0%)	7 (5.9%)
	Grandparent's medication	68 (2.9%)	6 (3.9%)	61 (2.9%)	1 (0.8%)
	Sibling's medication	8 (0.3%)	0 (0.0%)	8 (0.4%)	0 (0.0%)
Mistaken for candy	Child thought medication was candy	9 (0.4%)	1 (0.6%)	8 (0.4%)	0 (0.0%)
Other children present	Other child present	44 (1.8%)	5 (3.2%)	36 (1.7%)	3 (2.5%)
	Sibling administered medication	6 (0.3%)	0 (0.0%)	5 (0.2%)	1 (0.8%)
	Other child administered medication	2 (0.1%)	0 (0.0%)	2 (0.1%)	0 (0.0%)
Other risk factors	Child protective services/police involved	167 (7.0%)	12 (7.8%)	145 (6.9%)	9 (7.6%)
	Evidence or history of child abuse/neglect	18 (0.8%)	0 (0.0%)	17 (0.8%)	0 (0.0%)
	Previous accidental unsupervised ingestions in home	13 (0.5%)	2 (1.3%)	11 (0.5%)	0 (0.0%)
	Evidence or history of parental drug usage/possession	9 (0.4%)	1 (0.6%)	7 (0.3%)	1 (0.8%)
	Parental criminal history/ suspicious behavior	6 (0.3%)	1 (0.6%)	5 (0.2%)	0 (0.0%)
	Child left unsupervised	5 (0.2%)	2 (1.3%)	3 (0.1%)	0 (0.0%)
	Exposure to medication in utero	5 (0.2%)	1 (0.6%)	4 (0.2%)	0 (0.0%)
	Lives with other relative (grandparent, aunt/uncle, etc)	4 (0.2%)	0 (0.0%)	4 (0.2%)	0 (0.0%)
	Parent intoxicated	4 (0.2%)	0 (0.0%)	4 (0.2%)	0 (0.0%)
	Medication removed from/fell out of intended recipient's mouth	3 (0.1%)	1 (0.6%)	2 (0.1%)	0 (0.0%)
	Other risk factors- other (parental custody issues, absence of adequate health care)	2 (0.1%)	2 (1.3%)	0 (0.0%)	0 (0.0%)
	Unsafe surroundings at home	2 (0.1%)	0 (0.0%)	2 (0.1%)	0 (0.0%)
	Child accessed medication after pet exposure	1 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)
	Evidence or history of family violence	1 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)
	Ingestion of other hazardous items	1 (0.0%)	1 (0.6%)	0 (0.0%)	0 (0.0%)
	Old prescription kept in home	1 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)
Special needs child	Special needs child	3 (0.1%)	0 (0.0%)	3 (0.1%)	0 (0.0%)
Supervised by alternate caregiver	Grandparent	62 (2.6%)	4 (2.6%)	55 (2.6%)	3 (2.5%)
	Family member (other than grandparent)	23 (1.0%)	0 (0.0%)	23 (1.1%)	0 (0.0%)
	Babysitter	21 (0.9%)	1 (0.6%)	17 (0.8%)	3 (2.5%)
	Friend of parent	8 (0.3%)	1 (0.6%)	6 (0.3%)	1 (0.8%)
	Supervised by mom's boyfriend/fiancé	3 (0.1%)	0 (0.0%)	2 (0.1%)	1 (0.8%)
Visiting another home/away from home/outside of home/homeless	Visiting a friend/neighbor/mother's boyfriend/house sitting	18 (0.8%)	0 (0.0%)	16 (0.8%)	2 (1.7%)
	Visiting a relative	9 (0.4%)	0 (0.0%)	9 (0.4%)	0 (0.0%)
	Away from home-other (staying in a hotel, on vacation, at church camp/retreat)	5 (0.2%)	0 (0.0%)	5 (0.2%)	0 (0.0%)
	Exposed while outdoors	3 (0.1%)	0 (0.0%)	3 (0.1%)	0 (0.0%)
	Living in homeless shelter/recovery home	3 (0.1%)	0 (0.0%)	2 (0.1%)	1 (0.8%)

*An individual case may have multiple root causes.
†Includes data for buprenorphine formulation unspecified (n = 1).

(8.6% and 4.9%), a grandparent, babysitter, or other alternate caregiver was noted to be supervising the child at the time of ingestion. Child protective services involvement was documented in 167 cases (12.3% and 7.0%); case notes rarely specified whether this involvement preceded or followed the exposure. No pattern emerged that differentiated a root cause by formulation. Clinical notes rarely (2 cases, 0.1%) contained any data about the effect of patient and provider

Table V. Maximum AE severity in cases undergoing focused review

Maximum AE severity	All formulations* n = 536	Buprenorphine tablets n = 38	Buprenorphine/naloxone tablets n = 471	Buprenorphine/naloxone film n = 26
Not applicable or panel excluded	17 (3.2%)	0 (0.0%)	16 (3.4%)	1 (3.8%)
Unable to determine	4 (0.7%)	0 (0.0%)	4 (0.8%)	0 (0.0%)
Grade 1, mild	99 (18.5%)	8 (21.1%)	85 (18.0%)	6 (23.1%)
Grade 2, moderate	180 (33.6%)	9 (23.7%)	161 (34.2%)	10 (38.5%)
Grade 3, severe	190 (35.4%)	14 (36.8%)	167 (35.5%)	9 (34.6%)
Grade 4, life-threatening	42 (7.8%)	6 (15.8%)	36 (7.6%)	0 (0.0%)
Grade 5, death	4 (0.7%)	1 (2.6%)	2 (0.4%)	0 (0.0%)

*Includes data for buprenorphine formulation unspecified (n = 1).

education required by the buprenorphine REMS, and no analysis of patient or provider education could be performed.

Focused review by the expert clinical panel was performed in 536 cases (22.5%), including those of 4 (0.2%) children who died. Overall, 95.5% of documented AEs were determined by the panel to be at least potentially related to buprenorphine exposure. The most common AEs reported were lethargy (438 cases), respiratory depression (231), miosis (197), and vomiting (150), and similar AEs were observed following exposure to all three formulations (**Table IV**; available at www.jpeds.com) Although no cases of life-threatening toxicity or death were observed in children who ingested the film, no significant association between formulation and highest level of AE severity in each case was found (χ^2 $P = .46$; **Table V**).

Discussion

In this large retrospective study, we found that unintentional exposure to buprenorphine is frequently associated with severe AEs in young children, and that exposure rates to tablet formulations, which are typically dispensed in bottles containing a 30-day supply, were 3.5 and 8.8 times the exposure rates to the film formulation, which is dispensed in single dose, child-resistant foil packets. Because of its observational design, this study cannot determine whether the difference in exposure rates is due to the formulation, packaging, or other factors. This important poisoning prevention question requires urgent study. Although buprenorphine is a partial agonist at the mu-opioid receptor, in this group of opioid-naïve children the effects were similar to those of a pure agonist, and included central nervous system depression, respiratory depression, and death.

Our study population is similar to a recent Centers for Disease Control and Prevention report, which found 59.5% of unintentional buprenorphine exposures occurred in boys, 76.8% involved children aged 1-2 years, and 95.8% involved a buprenorphine/naloxone combination product.[7] Similar to our results, a study conducted among US children reported that ingestion of prescription opioids typically occurred in the home, at a median age of 2 years, and occurred at higher rates in regions with greater numbers of opioid prescriptions filled.[6]

These results are congruent with the observations of Hayes et al, who reported that lethargy, vomiting, miosis, and respiratory depression were the most common pediatric AEs observed following unintentional buprenorphine exposures.[10] Severe (grade 3 or higher) clinical effects were reported in 6/86 (7.0%) patients in that series and in approximately 236/2380 (9.9%) patients in our report; the slight difference is likely due to differences in the study population and analytic approach.

Our results are also analogous to a recent publication using data from the Utah Poison Control Center (2002-2011) that found 94% of 179 exposures to buprenorphine sublingual formulations among children aged ≤ 5 years involved tablet rather than the film formulations.[22] Similar to our results, drowsiness (58.6%), vomiting (26.2%), respiratory depression (19.0%), miosis (15.1%), agitation (10.1%), and tachycardia (8.4%) were the most common reported AEs in buprenorphine-exposed young children.

We were unable to measure whether the compulsory patient education, provider education, and medication guide components of the buprenorphine REMS helped to reduce pediatric exposures. The education materials, which are similar across formulations, include specific instructions to keep buprenorphine products secure and away from children.[9,15] Nonetheless, improper storage of medication was a common root cause of buprenorphine exposure. We believe that an engineered solution, such as providing all potent opioids and other "one pill can kill" medications in single dose, child resistant packaging, such as a blister pack or foil pouch, by default, is more likely to be effective than additional efforts at education. Failure to engage a child-proof cap and/or failure of the cap to function, though uncommon in our data, is particularly dangerous because this scenario allows a child to ingest a large number of pills quickly. Although the Poison Prevention Packaging Act allows medication to be dispensed in packaging that is not child resistant, the observation that at least 15.7% of ingestions involved a medication prescribed for somebody other than the parent suggests that effective child resistant packaging is important for many patients who are secondary caregivers for children.[23] Whenever young children are visiting or supervised by grandparents or other adults who have dangerous medications, additional steps should be taken to reduce the risk of unintentional exposure.

In contrast to previously published analyses, we were able to measure and compare pediatric unintentional exposure event ratios (rates) based on a measure of drug availability in the community, URDD. Other denominators, such as the total number of prescriptions, the total amount of

buprenorphine (in kg) distributed, the total number of patient-days of therapy, or the number of extended dosing units (ie, tablets or film presentations), can be used to represent supply.[24]

Our results are subject to several additional limitations. Poison center consultations and most manufacturer pharmacovigilance database reports are passive data collection systems. As a result, information such as root cause was not present in the source data for each exposure. Reliance on spontaneous reporting undercounts the number of cases, particularly exposures in which clinical effects are not severe.[25] For this reason, the exposure rates we report do not include all unintentional buprenorphine pediatric exposures. As in all retrospective studies, a clinical effect or exposure may have been present but not documented, and our observations regarding these proportions must be considered lower bound estimates. Because AEs related to generic single-ingredient buprenorphine formulations are unlikely to appear in the Reckitt Benckiser Pharmaceuticals pharmacovigilance database, the estimated rate of exposures to single-ingredient buprenorphine tablets may be artificially low. Fewer than 2% of cases in this series came from the pharmacovigilance database, so this effect is likely minimal.

Most symptomatic children in this series were treated with naloxone and supportive care, including advanced airway management in many cases. The spectrum of severity we observed is less than would have occurred without timely medical intervention. Because of the comparatively small number of film formulation exposures, this study was unable to detect a difference between formulations in severity outcomes. The panel determined that 0/26 (0%) of film formulation cases and 38/471 (8.1%) of combination tablet cases led to life-threatening AEs or death. The question about whether film formulations are associated with lesser AE severity should be revisited when more quarterly data are available.

Although the wide variation in exposure rates to different buprenorphine formulations is a robust and consistent observation, unmeasured factors may have led to differential prescribing. Such differences in the underlying patient populations may impact the interpretation of risk as it relates to formulation. In particular, the comparatively low cost of generic single-ingredient buprenorphine tablets compared with the combination formulations may have affected prescribing patterns, pediatric exposure rates, and outcomes. However, as the majority of pediatric exposures were to combination formulations (brand-only during the study period) and the exposure rate to single-ingredient tablets was intermediate between the exposure rates to the combination tablets and combination film, it is unlikely that cost significantly influenced our results.

Finally, because standard opioid screening tests do not detect buprenorphine and definitive testing was rarely performed, the diagnosis of buprenorphine exposure was made based on exposure history and clinical effects and may not have been accurate in all cases. Most reports were missing ingested dose, and those with dose estimates were often found to be imprecise or likely to be inaccurate. Some asymptomatic children may not have ingested buprenorphine at all, and in other cases clinical effects attributed to buprenorphine may have been due to another ingestion or medical condition. ■

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Table I. Standard definitions used to determine AE severity and causal relationship to buprenorphine exposure in cases undergoing focused review

Causal relationship definitions[20]	Severity grade definitions[19]
Related • History of ingestion consistent with exposure • Drug levels (if available) consistent with exposure • Clinical course consistent with exposure • No other cause of event evident	Grade 1: mild • Symptoms: asymptomatic or mild • Therapy: clinical observation or diagnostic studies only; intervention not indicated
At least potentially related • History of ingestion consistent with exposure • Drug levels (if available) consistent with exposure • Clinical course consistent with exposure • Other cause of event unlikely • Drug may have been secondary cause of event	Grade 2: moderate • Symptoms: minimal; limiting more complex and newly-acquired age-appropriate instrumental activities of daily living • Therapy: local or noninvasive intervention indicated for this event
Unlikely related • No clear history of ingestion • Drug levels (if available) inconsistent with exposure • Clinical course inconsistent with exposure • Other cause of event possible	Grade 3: severe • Symptoms: severe or medically significant but not immediately life-threatening; disabling; limiting simple, basic, and long-mastered activities of daily living • Therapy: hospitalization or prolongation of hospitalization
Unable to determine • Not enough case detail to evaluate the relationship of drug exposure to the event	Grade 4: life-threatening • Symptoms: life-threatening • Therapy: urgent intervention indicated Grade 5: death • Death related to exposure Unable to determine • Not enough case detail to evaluate the severity of the event

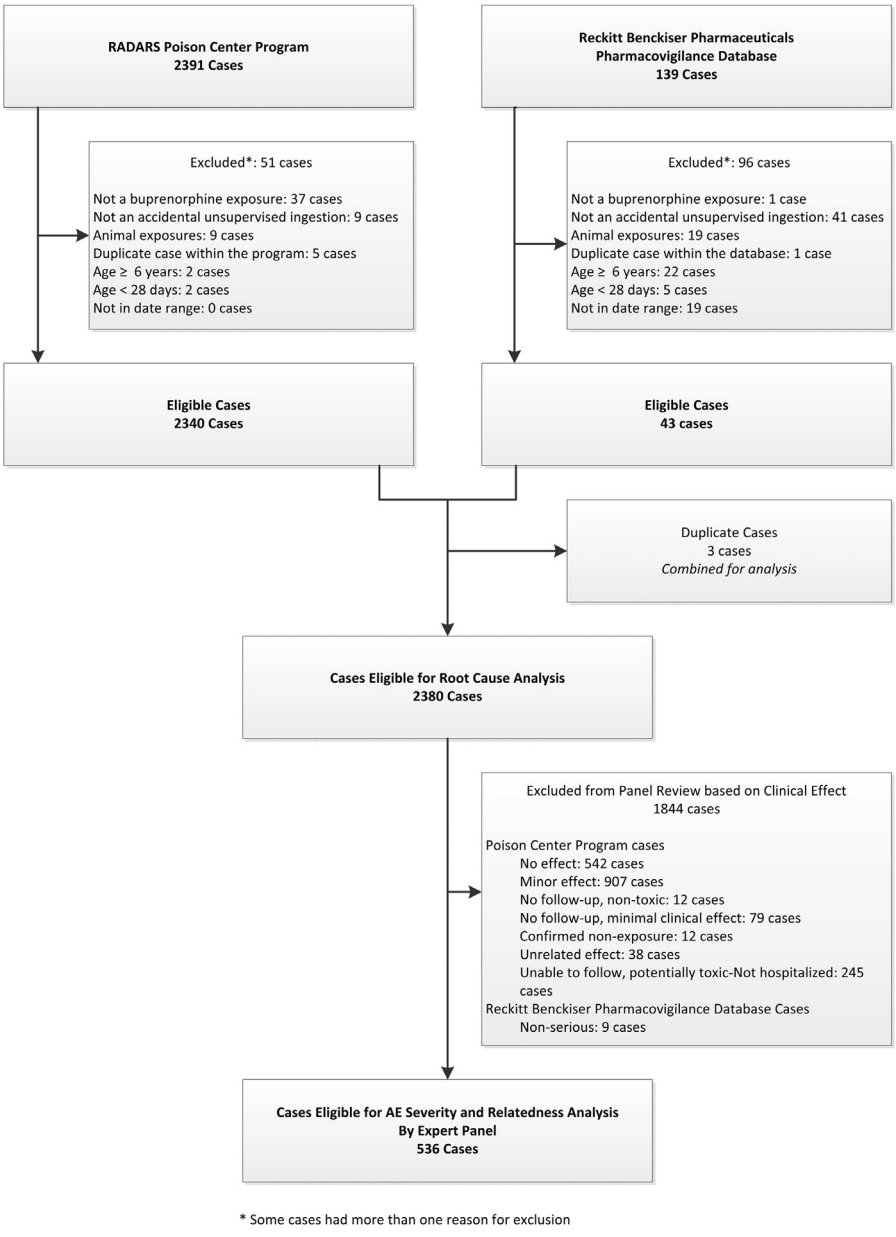

Figure 1. Case processing summary.

Table IV. AEs related or potentially related to buprenorphine exposure in 536 cases under going focused review

	Buprenorphine tablets	Buprenorphine/naloxone tablets	Buprenorphine/naloxone film
System organ class	**Preferred term**		
Cardiac disorders	Tachycardia (9), bradycardia (2), arrhythmia (1), cardiac arrest (1), cyanosis (1), myocardial infarction (1),	Tachycardia (51), bradycardia (42), cyanosis (15), cardiac arrest (2)	Bradycardia (3)
Eye disorders	miosis (10), eyelid ptosis (1), pupil fixed (1)	Miosis (172), eye movement disorder (2), gaze palsy (2), eye edema (1), mydriasis (1)	Miosis (13)
Gastrointestinal disorders	Vomiting (7)	Vomiting (134), nausea (4), gastrointestinal sounds abnormal (3), constipation (2), abdominal pain (1), abdominal pain upper (1), diarrhea (1), dry mouth (1), oral pruritus (1), salivary hypersecretion (1)	Vomiting (4)
General disorders and administration site conditions	Irritability (5), pyrexia (2), death (1), hypothermia (1)	Irritability (33), pyrexia (11), death (1), fatigue (1), feeling cold (1), sluggishness (1)	Gait disturbance (1)
Nervous system disorders	Lethargy (36), ataxia (5), brain edema (1), dizziness (1), nystagmus (1), unresponsive to stimuli (1)	Lethargy (375), ataxia (38), somnolence (28), depressed level of consciousness (6), dizziness (6), dysarthria (5), coma (4), loss of consciousness (3), tremor (3), convulsion (2), syncope (2), tardive dyskinesia (2), tongue paralysis (2), balance disorder (1), brain edema (1), drooling (1), dyskinesia (1), psychomotor hyperactivity (1)	Lethargy (23), ataxia (3), dysarthria (1), psychomotor hyperactivity (1)
Psychiatric disorders	Agitation (6)	Agitation (62), confusional state (8), abnormal behavior (3), hallucination (3), restlessness (2), aggression (1), breath holding (1), staring (1)	Agitation (2), confusional state (1)
Respiratory, thoracic, and mediastinal disorders	Respiratory depression (17), bronchospasm (1), increased bronchial secretion (1), pneumonia aspiration (1), respiratory arrest (1), stridor (1)	Respiratory depression (200), wheezing (6), respiratory arrest (4), stridor (4), dyspnea (3), hypoxia (3), apnea (2), atelectasis (2), cough (2), hypopnea (2), pneumonitis (2), respiratory failure (2), bronchospasm (1), hypoventilation (1), pulmonary edema (1), rhonchi (1), sneezing (1), tachypnea (1)	Respiratory depression (14), bronchospasm (1)
Vascular disorders	Hypotension (6), pallor (2), hemorrhage (1), hypertension (1)	Hypotension (37), hypertension (9), flushing (6), pallor (6)	Hypotension (3), flushing (2), pallor (1)