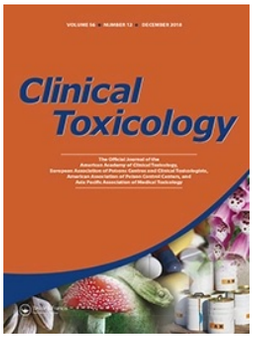


Clinical Toxicology

ISSN: 1556-3650 (Print) 1556-9519 (Online) Journal homepage: https://www.tandfonline.com/loi/ictx20

# Child and adolescent benzodiazepine exposure and overdose in the United States: 16 years of poison center data

Joseph M. Friedrich, Christie Sun, Xue Geng, Diane P. Calello, Michael Gillam, Kaelen L. Medeiros, Mark Smith, Bruce Ruck & Maryann Mazer-Amirshahi

**To cite this article:** Joseph M. Friedrich, Christie Sun, Xue Geng, Diane P. Calello, Michael Gillam, Kaelen L. Medeiros, Mark Smith, Bruce Ruck & Maryann Mazer-Amirshahi (2019): Child and adolescent benzodiazepine exposure and overdose in the United States: 16 years of poison center data, Clinical Toxicology, DOI: 10.1080/15563650.2019.1674321

**To link to this article:** https://doi.org/10.1080/15563650.2019.1674321

Published online: 15 Oct 2019.

CLINICAL TOXICOLOGY
https://doi.org/10.1080/15563650.2019.1674321

Taylor & Francis
Taylor & Francis Group

POISON CENTRE RESEARCH



# Child and adolescent benzodiazepine exposure and overdose in the United States: 16 years of poison center data

Joseph M. Friedrich[a,b], Christie Sun[c], Xue Geng[b], Diane P. Calello[d], Michael Gillam[e], Kaelen L. Medeiros[e], Mark Smith[e], Bruce Ruck[d] and Maryann Mazer-Amirshahi[b,f]

[a]Harbor-UCLA Medical Center, Torrance, CA, USA; [b]Georgetown University School of Medicine, Washington, DC, USA; [c]Kaiser Permanente South Bay Medical Center, Harbor City, CA, USA; [d]New Jersey Poison Information and Education System, Rutgers New Jersey Medical School, Rutgers, NJ, USA; [e]MedStar Institutes for Innovation, Washington, DC, USA; [f]MedStar Washington Hospital Center, Washington, DC, USA

**ABSTRACT**

**Background:** Recently, there has been an increase in prescription drug abuse and related fatalities. Although opioid analgesics are commonly implicated, there have been significant increases in the prevalence of benzodiazepine exposures and overdoses.

**Objective:** To describe national trends in pediatric benzodiazepine exposures from 2000 to 2015.

**Methods:** A retrospective database analysis was conducted. Data regarding benzodiazepine exposures in children ages 0 to <18 years reported to participating United States poison centers from January 2000 through December 2015 were obtained from the National Poison Data System. Population data were obtained from the US Census Bureau to determine annual population estimates. Data were analyzed using chi-square tests.

**Results:** A total of 296,838 pediatric benzodiazepine exposures were identified during the study period. The rate of pediatric benzodiazepine exposure increased 54% between 2000 and 2015. The severity of medical outcomes also increased, as did the prevalence of co-ingestion of multiple drugs, especially in children ages 12 to <18 years. Nearly half of all reported exposures in 2015 were documented as intentional abuse, misuse, or attempted suicide, reflecting a change from prior years. The most commonly identified pediatric benzodiazepines of exposures were alprazolam, clonazepam, and lorazepam.

**Conclusions:** The rate and severity of reported pediatric benzodiazepine exposure is increasing over time. Adolescent exposures are of specific concern, as co-ingestion and intentional abuse were found to be more common in this group. Medical providers and caretakers should be cognizant of this growing epidemic to avoid preventable harm to adolescents, young children, and infants.

**Abbreviations:** US: United States; ED: Emergency Department; NPDS: National Poison Data System; SPIs: Specialists in Poison Information; BZD: Benzodiazepine

**ARTICLE HISTORY**
Received 11 June 2019
Revised 25 August 2019
Accepted 15 September 2019
Published online 10 October 2019

**KEYWORDS**
Benzodiazepine; overdose; pediatric; adolescent; child; toxicology; opioid epidemic

## Introduction

Non-therapeutic ingestion of medication is a major pediatric public health issue. Approximately 70,000 children receive care in an Emergency Department (ED) annually due to non-therapeutic pharmaceutical poisoning, and nearly 12% of these visits result in inpatient hospitalization [1–3]. Despite the introduction of child-resistant packaging in the 1970s and the Overdose and Treatment Exposures Task force of 2008, poisonings from prescription medications continue to be a major cause of pediatric morbidity [2–4].

Benzodiazepines, a class of medications which contain, sedative, anxiolytic, and hypnotic properties, are commonly prescribed medications in the United States (US), and the number of benzodiazepines prescribed in the US continues to increase on an annual basis [5–7]. Medical prescriptions represent the primary source of supply for individuals who abuse benzodiazepines and rates of visits to EDs and overdose deaths involving benzodiazepines are increasing [5,7]. The increased availability of opioid analgesics is often implicated as a cause of both adult and pediatric pharmaceutical poisonings [3,8,9], and a significant rise in the availability of benzodiazepines has been implicated as an additional driver of morbidity and mortality in prescription medication poisonings [5,6,10–12]. Adult prescription medications are the source of the offending drug in the majority of pediatric pharmaceutical poisonings. Increases in the prevalence of adult prescription medications are associated with poisoning in children, particularly those ages 0 to <6 years, usually as a result of unsupervised or accidental ingestion [1,3,4]. However, it is unknown if the rise in benzodiazepine prescribing specifically has impacted the pediatric population. Furthermore, if such an impact exists, it is unclear how its effects are spread between infants and young children (ages

CONTACT Joseph M. Friedrich jfriedrich@dhs.lacounty.gov Department of Emergency Medicine, Los Angeles County Harbor-UCLA Medical Center, 1000 W Carson Street, Building D9, Torrance, CA 90502, USA

0 to <6 years), older children (ages 6 to <12 years), and adolescents (ages 12 to <18 years).

This study analyzes data extracted from the National Poison Data System (NPDS) in order to describe the characteristics of and trends in pediatric benzodiazepine exposures reported to US poison control centers. Furthermore, this study will: (1) describe the severity of medical outcome associated with pediatric benzodiazepine exposure, (2) determine which individual benzodiazepines are involved in pediatric exposure, and (3) determine trends in child and adolescent benzodiazepine exposures based on age and the reason for exposure.

## Methods

A retrospective analysis of the NPDS was conducted. The NPDS contains records of all poisoning cases reported to US poison control centers. These poison control centers are staffed by specialists in poison information (SPIs) and an electronic record is created for each call received [1,3]. Data pertaining to benzodiazepine exposures in children ages 0 to <18 years reported to all participating US poison centers from 1 January 2000 through 31 December 2015 were obtained from the NPDS. Exposure data were documented by SPIs using standardized data fields and definitions. Inclusion criteria included any case where a benzodiazepine was identified as an ingested product. This included cases where a benzodiazepine was the only substance ingested as well as cases where a benzodiazepines was one of multiple ingested products. Given the pediatric focus of this study, patients 18 years and older were excluded (36,318 records). Additional exclusions included confirmed non-exposure to benzodiazepines (2793 records) and records where the precise age of the patient in years or months was not documented (1792 records).

Data analyzed in this study included the following: age of patient, the drug ingested including any co-ingestants (if applicable), the reason for the ingestion, and the severity of outcome. Ages were stratified into the following categories: 0 years to <2 year, 2 to <6 years, 6 to <12 years, and 12 to <18 years. Severity of health outcome was stratified into five groups: (1) death, (2) major effect or moderate effect, (3) potentially toxic exposures, (4) minor effect, no effect, or not followed, and (5) unrelated effect. The reported reason for benzodiazepine exposure was also stratified into five groups: intentional, unintentional, adverse reaction, other, and unknown reason.

In order to generate the rate of benzodiazepine exposures per 100,000 US children, population data was obtained from the US Census Bureau's 2000 and 2010 July 1st population estimates for calendar years 2000 to 2015 [23–25]. Data were analyzed using Chi-square tests in order to determine if annual changes in the distribution of severity of exposure, presence of co-ingestions, sub-group analyses, reason for exposure, and benzodiazepine of exposure were statistically significant. A $p$ value of less than .05 was considered significant. Statistical analysis was performed using R on the Jupyter Notebook platform. Data tables which reflect multiple chi-square analyses done across the entire 16-year study period are presented in an appendix. Additionally, Tables 1, 2a, 2b, 4, and 5 display select data from four individual years of the study (2000, 2005, 2010, and 2015) in order to illustrate qualitative trends that were observed in the data across the study period. All graphs and tables were prepared using Microsoft Excel version 16.10. Complete tables on an annualized basis are available as an appendix. This study was approved by the institutional review board at the Georgetown University School of Medicine.

## Results

A total of 296,838 pediatric benzodiazepine exposures that met inclusion criteria were identified during the study period. Instances where the precise age of the child could not be identified were excluded (1792 records). The rate of pediatric benzodiazepine exposure reported to US poison centers has increased 54% over the study period, from 17.7 exposures per 100,000 children in 2000, to 27.30 exposures per 100,000 children in 2015. Using a Chi-square analysis, the change in distribution of benzodiazepine exposure per 100,000 children by calendar year was found to be significant. (Figure 1, $p < .001$). Furthermore, a qualitative review of the data suggests that the severity of medical outcome increased across the study period (Table 1). Statistical analysis revealed a significant change in distribution of severity of outcome across calendar years throughout the study period (Table A1, $p < .001$).

In addition to increasing severity of outcome, the majority of pediatric benzodiazepine exposures involved co-ingestion of one or more additional substances (Table A2a, $p < .001$), and a qualitative analysis of the data suggests that the prevalence of co-ingestion increased throughout the study period (Table 2a). This trend of increasing polysubstance abuse or exposure was most pronounced in adolescents ages 12 to <18 (Table 2b, Table A2b). Additionally, co-ingestion of one or more substances was found to have a significant effect on severity outcome (Table 3, $p < .001$). A qualitative analysis of the data suggests that children who engaged in co-ingestion were more likely to experience a moderate effect, a major effect, or death.

Furthermore, the documented reason of pediatric benzodiazepine exposure changed significantly throughout the study period. A qualitative review of the data suggests that intentional benzodiazepine exposures steadily increased throughout the study period. By the conclusion of the study period nearly half (48%) of all pediatric benzodiazepine exposures were intentional in nature, representing abuse, intentional misuse, or attempted suicide (Table 4). The change in distribution of reason for exposure by calendar year was found to change significantly between calendar years (Table A3, $p < .001$).

Analysis also revealed that the distribution of benzodiazepine exposure by age group changed significantly by calendar year throughout the study period (Table A4, $p < .001$). A qualitative review of the data demonstrates that while reported benzodiazepine exposures decreased in children

**Table 1.** Changes in severity of NPDS outcome for benzodiazepine exposure, select years.

| NPDS outcome | 2000 | 2005 | 2010 | 2015 |
|---|---|---|---|---|
| Death | 5 (0.0%) | 10 (0.1%) | 27 (0.1%) | 23 (0.1%) |
| Major effect or moderate effect | 1728 (13.5%) | 2612 (14.6%) | 3730 (17.4%) | 4780 (23.8%) |
| Potentially toxic exposure | 1075 (8.4%) | 1447 (8.1%) | 1529 (7.1%) | 1046 (5.2%) |
| Minor effect, no effect, or not followed | 9838 (76.7%) | 13,616 (76.4%) | 15,872 (74.2%) | 14,019 (69.7%) |
| Unrelated effect | 181 (1.4%) | 145 (0.8%) | 231 (1.1%) | 238 (1.2%) |

NPDS Outcome Definitions [22].
Death: The patient expired as a result of the exposure.
Major effect: The exposure caused life threating symptoms that may result in permanent sequalae.
Moderate effect: The patient experience significant symptoms, which may be systemic but do not typically result in permanent disability or disfigurement.
Potentially toxic exposure: The patient was lost to follow-up; however, the exposure was significant and may have resulted in a moderate effect, major effect, or death.
Minor effect: Minimal symptoms that resolve quickly.
No effect: No clinical effect was observed as a result of the exposure.
Not followed: The exposure was judged as a non-toxic exposures and was not followed.
Unrelated effect: The exposure was likely not responsibly for the patient's symptoms.

**Table 2a.** Prevalence of co-ingestant(s), select years, ages 0–17.

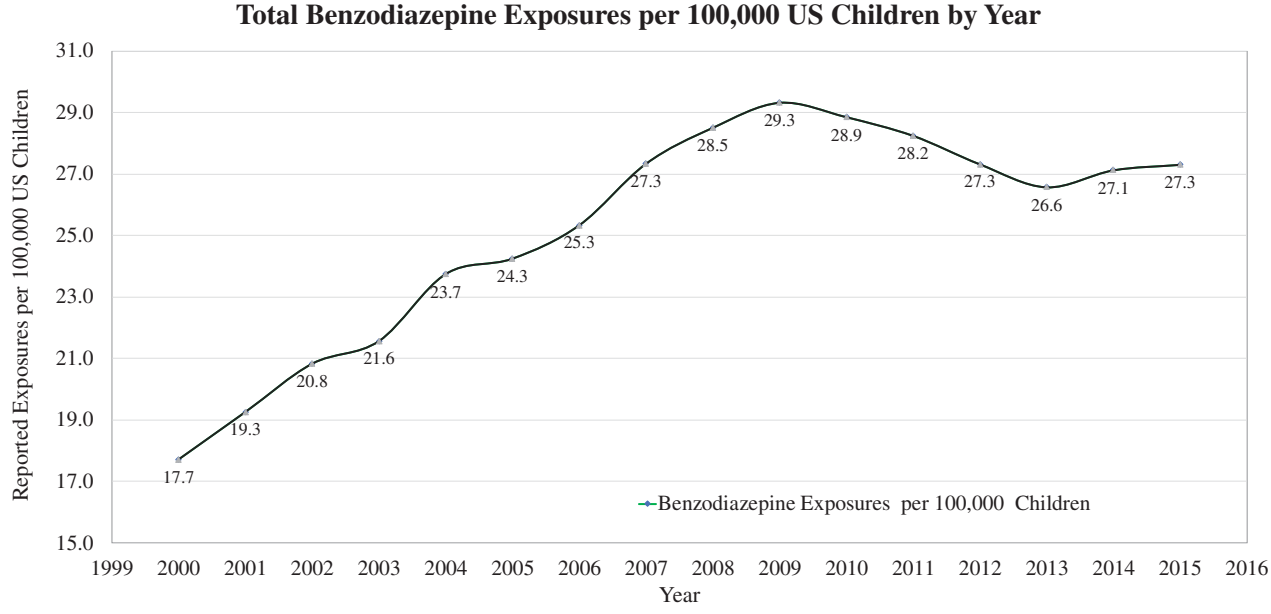
| Co-ingestant(s) | 2000 | 2005 | 2010 | 2015 |
|---|---|---|---|---|
| BZD exposure only | 5982 (46.6%) | 8059 (45.2%) | 9523 (44.5%) | 7690 (38.2%) |
| BZD exposure AND one or more co-ingestants | 6845 (53.4%) | 9771 (54.8%) | 11,866 (55.5%) | 12,416 (61.8%) |

BZD: Benzodiazepine.

**Table 2b.** Prevalence of co-ingestant(s), select years, children ages 12–17 Only.

| Co-ingestant(s) | 2000 | 2005 | 2010 | 2015 |
|---|---|---|---|---|
| BZD exposure only | 1511 (27.9%) | 1903 (25.3%) | 2065 (24.1%) | 2182 (20.9%) |
| BZD exposure AND one or more co-ingestants | 3911 (72.1%) | 5608 (74.7%) | 6490 (75.9%) | 8261 (79.1%) |

BZD: Benzodiazepine.




| Year | 2000 | 2001 | 2002 | 2003 | 2004 | 2005 | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 | 2015 | $p < 0.001$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Benzodiazepine Exposures per 100,000 Children | 17.7 | 19.3 | 20.8 | 21.6 | 23.7 | 24.3 | 25.3 | 27.3 | 28.5 | 29.3 | 28.9 | 28.2 | 27.3 | 26.6 | 27.1 | 27.3 | |

**Figure 1.** Total Reported Benzodiazepine Exposures per 100,000 United States Children, by year, from 2000 to 2015.

aged 0 to <6 years (50% in 2000 vs. 42% in 2015), reported exposures for adolescents aged 12 to <18 years were noted to have increased (42% in 2000 vs. 52% in 2015) (Table 5). Table 6 details the distribution of ages across all benzodiazepine exposures reported throughout the study period.

Finally, of the 296,838 exposures analyzed, the three most commonly identified benzodiazepines were alprazolam, clonazepam, and lorazepam, with 58,404 (19.7%), 53,836 (18.1%), and 28,164 (9.4%) exposures recorded, respectively. Benzodiazepine of exposure was found to significantly impact the distribution of medical outcomes ($p < .001$), however qualitative review of this data suggests that there is little meaningful difference in exposure outcomes between these three benzodiazepines (Table 7). Two hundred fifty-three deaths occurred during the study period, and exposures that included alprazolam had the highest rate of death,

with 34 pediatric deaths recorded. Of the 34 deaths attributed to exposures involving alprazolam, 22 were characterized as "intentional," which included the subcategories of "abuse," "misuse," or "suspected suicide." In contrast, exposures which included clonazepam had the highest rate of moderate or severe outcome (13%), (Table 7). More than 15 unique benzodiazepines of exposure were identified throughout the study period.

## Discussion

This study found that the population adjusted rates of pediatric benzodiazepine exposures in the US increased 54% between 2000 to 2015. It is unclear to the authors what may have caused the decrease in reported benzodiazepine exposures between 2009 and 2013, and further analyses should address the root causes underlying these trends. However, the overall increasing rate of reported benzodiazepine exposure found throughout this study period appears to reflect the increasing rates of benzodiazepine prescription that have been reported across the US over the past decade [7,13–15]. Although prior studies have reported on the impact of benzodiazepine and opioid co-ingestions in the adolescent population in an emergency department setting [7], prior to this study, there appears to be a lack of data with regard to how benzodiazepine availability affects the pediatric population across all ages.

Previous studies have demonstrated that pediatric trends in medication overdose and poisonings mirror prescribing patterns in the adult population. For example, Burghardt et al. demonstrated that increases in adult prescriptions were associated with an increased risk of exposure and poisoning in children, particularly those children aged 0 to <6 years [3]. In this age group, accidental exposure or ingestion was found to be the most common form of poisoning. In contrast to prior pediatric literature, this study suggests that the rising availability of benzodiazepines most directly affects the adolescent population rather than the youngest of children, as the percentage of exposures involving adolescents increased throughout the study period (42.3% in 2000 to 51.9% in 2015), and the percentages of exposures involving children ages <6 years and younger decreased (See Table 5 and Table A4). However, as the NPDS database does not delineate the source of the exposure substance, it is not possible to analyze the proportion of adolescent exposures that result from misuse of an adult prescription medication. In cases of adolescent benzodiazepine exposure, it is possible that the benzodiazepine used was initially prescribed to or intended to be used by an adolescent.

Furthermore, the findings of this study are particularly alarming, as they demonstrate that the outcomes of

**Table 3.** Impact of co-ingestant(s) on NPDS outcome between 2000–2015 ($p < .001$).

| NPDS outcome | BZD alone | BZD with co-ingestant(s) |
|---|---|---|
| Death | 2 (0.0%) | 251 (0.2%) |
| Major or Moderate effect | 8721 (6.4%) | 43,574 (26.1%) |
| Potentially toxic exposure | 11,249 (8.7%) | 10,228 (6.1%) |
| Minor effect, no effect, or not followed | 108,377 (83.8%) | 110,887 (66.4%) |
| Unrelated effect | 1448 (1.1%) | 2101 (1.3%) |

BZD: Benzodiazepine.
See Table 1 for NPDS outcome definitions.

**Table 5.** Distribution of benzodiazepine exposure by age group, select years.

| Age Group (years) | 2000 | 2005 | 2010 | 2015 |
|---|---|---|---|---|
| Age 0 to <2 | 2244 (17.5%) | 3082 (17.3%) | 3930 (18.4%) | 3056 (15.2%) |
| Age 2 to < 6 | 4193 (32.7%) | 6154 (34.5%) | 7785 (36.4%) | 5495 (27.3%) |
| Age 6 to <12 | 968 (7.5%) | 1083 (6.1%) | 1119 (5.2%) | 1112 (5.5%) |
| Age 12 to <18 | 5422 (42.3%) | 7511 (42.1%) | 8555 (40.0%) | 10,443 (51.9%) |

**Table 6.** Distribution of benzodiazepine exposure by age group across all study years ($p < .001$).

| Age group (years) | Total exposures | Percent |
|---|---|---|
| Age 0 to <2 | 50,399 | 17% |
| Age 2 to < 6 | 98,552 | 33% |
| Age 6 to <12 | 17,900 | 6% |
| Age 12 to <18 | 129,987 | 44% |
| Total: | 296,838 | 100% |

**Table 7.** Impact of benzodiazepine of exposure on NPDS outcome between 2000–2015 ($p < .001$).

| NPDS Outcome | Alprazolam | Clonazepam | Lorazepam |
|---|---|---|---|
| Death | 34 (0.1%) | 13 (0.0%) | 8 (0.0%) |
| Major effect or moderate effect | 6402 (11.0%) | 6777 (12.6%) | 3400 (12.1%) |
| Potentially toxic exposure | 5575 (9.5%) | 4149 (7.7%) | 2041 (7.2%) |
| Minor effect, no effect, or not followed | 45,797 (78.4%) | 42,240 (78.5%) | 22,347 (79.3%) |
| Unrelated effect | 596 (1.0%) | 657 (1.2%) | 368 (1.3%) |
| TOTAL | 58,404 (100%) | 53,836 (100%) | 28,164 (100%) |

See Table 1 for NPDS outcome definitions.

**Table 4.** Reported reason for benzodiazepine exposure, select years.

| Reason | 2000 | 2005 | 2010 | 2015 |
|---|---|---|---|---|
| Intentional (e.g., overdose, abuse suicide) | 4752 (37.0%) | 6676 (37.4%) | 7795 (36.4%) | 9590 (47.7%) |
| Unintentional (e.g., accidental ingestion, incorrect dose) | 7787 (60.7%) | 10,762 (60.4%) | 13,109 (61.3%) | 10,008 (49.8%) |
| Adverse reaction | 103 (0.8%) | 154 (0.9%) | 146 (0.7%) | 184 (0.9%) |
| Other | 72 (0.6%) | 80 (0.4%) | 79 (0.4%) | 86 (0.4%) |
| Unknown reason | 113 (0.9%) | 158 (0.9%) | 260 (1.2%) | 238 (1.2%) |

Category combination rules.
Intentional – Includes: Intentional Abuse, Intentional Misuse, Intentional Suspected Suicide, and Intentional Unknown.
Unintentional – Includes: Unintentional Therapeutic Error, Unintentional Misuse, Unintentional Bite/Sting, Unintentional Environmental, Unintentional Food Poisoning, Unintentional General, Unintentional Occupational, and Unintentional Unknown.
Adverse reaction – Includes: Adverse Reaction Drug, Adverse Reaction Food, and Adverse Reaction Other.
Other – Includes: Other Contamination / tampering, Other Malicious, and Other Withdrawal.
Unknown Reason – Includes: Unknown reason.

benzodiazepine exposures appear to be increasing in severity (Table 1). This is due to the fact that the proportion of benzodiazepine exposures that involve one or more co-ingested substances also appears to be increasing (Table 2). The literature reports that benzodiazepines overdose is typically not life-threatening in isolation [5], and our findings reflect the concept that co-ingestion of one or more substances increases the severity of exposure outcome (Table 3) [8,15]. While this study did not seek to identify the specific co-ingestants involved in these exposures, the nature these of co-ingestants are driving the increased severity of outcome seen across all pediatric benzodiazepine exposures. For example, the prevalence of benzodiazepine and opioid co-ingestion is a well-established phenomenon [6,8], and it has previously been reported that concomitant ingestion of opioids and benzodiazepines may play a role in rising rate adverse outcomes and overdose deaths seen across the US [7,16]. The phenomenon of multiple drug co-ingestions is particularly prevalent in the adolescent population (ages 12 to <18) [17], and our results demonstrate that the majority of adolescent benzodiazepine exposures involve ingestion of a benzodiazepine with one or more substances.

Further education regarding the prevalence of benzodiazepine exposure will be necessary for medical providers to limit unnecessary prescribing. Additionally, those in primary or emergency care settings will be on the front lines of screening and caring for these patients. Lastly, parents and caretakers must be educated as well, and caregivers must be counseled regarding proper use, storage, and disposal of these high-risk medications.

There are limitations to this study. First, NPDS is a voluntary database, as healthcare providers and the general public have no obligation to report to poison control centers. Second, it is possible that there is an underestimation of pediatric exposure to benzodiazepines by medical professionals, which may lead to underdiagnoses and underreporting. Third, in many medical settings, the determination of benzodiazepine exposure is made by rapid drug testing, which may exclude various types of benzodiazepines and typically does not include confirmatory testing. This may generate both false negative and false positive results [18–21]. All of these factors further obscure and likely underestimate the true prevalence of benzodiazepine overdose and exposure in the pediatric population. Finally, the identity of specific co-ingestants was not analyzed in this study. It is unclear what role specific co-ingestants played affecting the results seen throughout this study.

## Conclusion

The rates of reported pediatric benzodiazepine exposure in the US increased from 2000 to 2015. At the same time, the outcomes of such exposures are increasing in severity. The rise in intentional exposures and exposures involving co-ingestions with benzodiazepines is particularly concerning in the adolescent population, and co-ingestions cause additional harm across all pediatric populations.

Adolescents in particular may be at risk from benzodiazepine exposures both from the standpoint of intentional use as well as the use of co-ingestions. Further investigations should explore the relationship between severity of outcome, increasing prevalence of adolescent ingestion, and the increasing use of co-ingestants. Providers must be cognizant of these trends in order to properly prescribe, screen for abuse, and counsel parents, patients, and caregivers in order to avoid preventable harm to adolescents, young children, and infants.

## Acknowledgements

A limited portion of the data presented in this manuscript was accepted for presentation as a poster at the North American Congress of Clinical Toxicology 2018 annual meeting in Chicago, Illinois.

## Disclosure statement

The authors have indicated they have no potential conflicts of interest to disclose. They also have no financial or interpersonal relationships relevant to this article to disclose.

## ORCID

Joseph M. Friedrich http://orcid.org/0000-0002-5101-6200
Diane P. Calello http://orcid.org/0000-0003-1752-847X

## References

[1] Bond GR, Woodward RW, Ho M. The growing impact of pediatric pharmaceutical poisoning. J Pediatr. 2012;160(5):888–889.
[2] Budnitz DS, Salis S. Preventing medication overdoses in young children: an opportunity for harm elimination. Pediatrics. 2011;127(6):e1597–e1599.
[3] Burghardt LC, Ayers JW, Brownstein JS, et al. Adult prescription drug use and pediatric medication exposures and poisonings. Pediatrics. 2013;132(1):18–27.
[4] Budnitz DS, Lovegrove MC. The last mile: taking the final steps in preventing pediatric pharmaceutical poisonings. J Pediatr. 2012;160(2):265–270.
[5] Longo LP, Johnson B. Addiction: part I. Benzodiazepines-side effects, abuse risk and alternatives. Am Fam Physician. 2000;61(7):2121–2128.
[6] Bachhuber MA, Hennessy S, Cunningham CO, et al. Increasing benzodiazepine prescriptions and overdose mortality in the United States, 1996-2013. Am J Public Health. 2016;106(4):686–688.
[7] Jones CM, McAninch JK. Emergency department visits and overdose deaths from combined use of opioids and benzodiazepines. Am J Prev Med. 2015;49(4):493–501.
[8] Sun EC, Dixit A, Humphreys K, et al. Association between concurrent use of prescription opioids and benzodiazepines and overdose: retrospective analysis. BMJ. 2017;356:j1224.
[9] Centers for Disease Control and Prevention (CDC). Vital signs: overdoses of prescription opioid pain relievers—United States, 1999–2008. Morb Mortal Wkly Rep. 2011;60(43):1487–1492.
[10] Centers for Disease Control and Prevention (CDC). Emergency department visits involving nonmedical use of selected prescription drugs - United States, 2004-2008. Morb Mortal Wkly Rep. 2010;59(23):705–709.
[11] Charlson F, Degenhardt L, McLaren J, et al. A systematic review of research examining benzodiazepine-related mortality. Pharmacoepidem Drug Safe. 2009;18(2):93–103.
[12] 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.

[13] Cai R, Crane E, Poneleit K, et al. Emergency department visits involving nonmedical use of selected prescription drugs in the United States, 2004-2008. J Pain Palliat Care Pharmacother. 2010; 24(3):293–297.
[14] Patorno E, Glynn R, Levin R, et al. Benzodiazepines and risk of all cause mortality in adults: cohort study. BMJ. 2017;358: j2941.
[15] Lembke A, Papac J, Humphreys K. Our other prescription drug problem. N Engl J Med. 2018;378(8):693–695.
[16] Hwang CS, Kang EM, Kornegay CJ, et al. Trends in the concomitant prescribing of opioids and benzodiazepines, 2002-2014. Am J Prev Med. 2016;51(2):151–160.
[17] National Institute on Drug Abuse. Topics in brief. Prescription drug abuse – May 2011. [cited 2018 Oct 14]. Available from: https://www.drugabuse.gov/sites/default/files/prescription.pdf.
[18] Beck O, Carlsson S, Tusic M, et al. Laboratory and clinical evaluation of on-site urine drug testing. Scand J Clin Lab Invest. 2014; 74(8):681–686.
[19] Nasky KM, Cowan GL, Knittel DR. False-positive urine screening for benzodiazepines: an association with sertraline?: a two-year retrospective chart analysis. Psychiatry. 2009;6(7): 36–39.
[20] Pamukcu GG, Kurtoglu CG, Ersen T, et al. Utility of bedside urine toxicology screening test in emergency department: a retrospective study. Cyprus J Med Sci. 2018;3:98–102.
[21] Tomaszewski C, Runge J, Gibbs M, et al. Evaluation of a rapid bedside toxicology screen in patients suspected of drug toxicity. J Emerg Med. 2005;28(4):389–394.
[22] Mazer-Amirshahi M, Reid N, van den Anker J, et al. Effect of cough and cold medication restriction and label changes on pediatric ingestions reported to United States poison centers. J Pediatr. 2013;163(5):1249–1250.
[23] U.S. Census Bureau, Population Division. Intercensal estimates of the resident population by single year of age and sex for states and the United States: April 1, 2000 to July 1, 2010. [cited 2018 Feb 15]. Available from: http://factfinder2.census.gov.
[24] U.S. Census Bureau, Population Division. Annual estimates of the resident population by sex, single year of age, race, and hispanic origin for the United States: April 1, 2010 to July 1, 2016. [cited 2018 Feb 15]. Available from: http://factfinder2.census.gov.
[25] U.S. Census Bureau, Population Division. Projected population by single year of age, sex, race, and hispanic origin for the United States: 2014 to 2060 [cited 2018 Feb 15]. Available from: http://factfinder2.census.gov.

## Appendix

**Table A1.** Changes in severity of NPDS outcome for benzodiazepine exposure, by year ($p < .001$).

| NPDS Outcome | 2000 | Percent | 2001 | Percent | 2002 | Percent | 2003 | Percent | 2004 | Percent | 2005 | Percent | 2006 | Percent | 2007 | Percent |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Death | 5 | 0.0% | 8 | 0.1% | 3 | 0.0% | 11 | 0.1% | 4 | 0.0% | 10 | 0.1% | 14 | 0.1% | 15 | 0.1% |
| Major or Moderate effect | 1728 | 13.5% | 1949 | 13.9% | 2268 | 14.9% | 2451 | 15.5% | 2575 | 14.8% | 2612 | 14.6% | 3129 | 16.7% | 3455 | 17.1% |
| Potentially toxic exposure | 1075 | 8.4% | 1014 | 7.2% | 1313 | 8.6% | 1372 | 8.7% | 1476 | 8.5% | 1447 | 8.1% | 1507 | 8.1% | 1667 | 8.2% |
| Minor effect, no effect, or not followed | 9838 | 76.7% | 10806 | 77.2% | 11389 | 75.0% | 11750 | 74.5% | 13102 | 75.3% | 13616 | 76.4% | 13816 | 73.9% | 14854 | 73.4% |
| Unrelated effect | 181 | 1.4% | 224 | 1.6% | 221 | 1.5% | 184 | 1.2% | 251 | 1.4% | 145 | 0.8% | 221 | 1.2% | 244 | 1.2% |
| | 2008 | Percent | 2009 | Percent | 2010 | Percent | 2011 | Percent | 2012 | Percent | 2013 | Percent | 2014 | Percent | 2015 | Percent |
| Death | 16 | 0.1% | 29 | 0.1% | 27 | 0.1% | 20 | 0.1% | 24 | 0.1% | 13 | 0.1% | 31 | 0.2% | 23 | 0.1% |
| Major or Moderate effect | 3385 | 16.0% | 3545 | 16.3% | 3730 | 17.4% | 4083 | 19.6% | 4087 | 20.3% | 4136 | 21.2% | 4382 | 22.0% | 4780 | 23.8% |
| Potentially toxic exposure | 1680 | 8.0% | 1535 | 7.1% | 1529 | 7.1% | 1377 | 6.6% | 1271 | 6.3% | 1102 | 5.6% | 1066 | 5.3% | 1046 | 5.2% |
| Minor effect, no effect, or not followed | 15797 | 74.8% | 16400 | 75.5% | 15872 | 74.2% | 15180 | 72.7% | 14523 | 72.1% | 14092 | 72.1% | 14210 | 71.2% | 14019 | 69.7% |
| Unrelated effect | 248 | 1.2% | 227 | 1.0% | 231 | 1.1% | 220 | 1.1% | 234 | 1.2% | 209 | 1.1% | 271 | 1.4% | 238 | 1.2% |

**Table A2a.** Prevalence of co-ingestant(s) by year, ages 0–17 ($p < 0.001$).

| Co-ingestant(s) | 2000 | Percent | 2001 | Percent | 2002 | Percent | 2003 | Percent | 2004 | Percent | 2005 | Percent | 2006 | Percent | 2007 | Percent |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| BZD exposure only | 5982 | 47% | 6290 | 45% | 6875 | 45% | 7160 | 45% | 7896 | 45% | 8059 | 45% | 8551 | 46% | 9112 | 45% |
| BZD exposure AND one or more co-ingestants | 6845 | 53% | 7711 | 55% | 8319 | 55% | 8608 | 55% | 9512 | 55% | 9771 | 55% | 10136 | 54% | 11123 | 55% |
| | 2008 | Percent | 2009 | Percent | 2010 | Percent | 2011 | Percent | 2012 | Percent | 2013 | Percent | 2014 | Percent | 2015 | Percent |
| BZD exposure only | 9474 | 45% | 9844 | 45% | 9523 | 45% | 9171 | 44% | 8486 | 42% | 8024 | 41% | 7660 | 38% | 7690 | 38% |
| BZD exposure AND one or more co-ingestants | 11652 | 55% | 11892 | 55% | 11866 | 55% | 11709 | 56% | 11653 | 58% | 11528 | 59% | 12300 | 62% | 12416 | 62% |

BZD: Benzodiazepine.

**Table A2b.** Prevalence of co-ingestant(s) by year, ages 12–17 ($p < 0.001$).

| Co-ingestant(s) | 2000 | Percent | 2001 | Percent | 2002 | Percent | 2003 | Percent | 2004 | Percent | 2005 | Percent | 2006 | Percent | 2007 | Percent |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| BZD exposure only | 1511 | 28% | 1582 | 26% | 1820 | 27% | 1768 | 25% | 2050 | 27% | 1903 | 25% | 2009 | 25% | 2268 | 26% |
| BZD exposure AND one or more co-ingestants | 3911 | 72% | 4506 | 74% | 4990 | 73% | 5196 | 75% | 5582 | 73% | 5608 | 75% | 5941 | 75% | 6468 | 74% |
| | 2008 | Percent | 2009 | Percent | 2010 | Percent | 2011 | Percent | 2012 | Percent | 2013 | Percent | 2014 | Percent | 2015 | Percent |
| BZD exposure only | 2211 | 25% | 2168 | 25% | 2065 | 24% | 2083 | 23% | 1935 | 22% | 1744 | 20% | 2018 | 21% | 2182 | 21% |
| BZD exposure AND one or more co-ingestants | 6670 | 75% | 6671 | 75% | 6490 | 76% | 6900 | 77% | 6823 | 78% | 6847 | 80% | 7806 | 79% | 8261 | 79% |

Abbreviations: Benzodiazepine (BZD).

**Table A3.** Reported reason for benzodiazepine exposure, by year ($p < .001$).

| NPDS Outcome | 2000 | Percent | 2001 | Percent | 2002 | Percent | 2003 | Percent | 2004 | Percent | 2005 | Percent | 2006 | Percent | 2007 | Percent |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Intentional (e.g., overdose, abuse suicide) | 4752 | 37.0% | 5283 | 37.7% | 5965 | 39.3% | 6164 | 39.1% | 6764 | 38.9% | 6676 | 37.4% | 7075 | 37.9% | 7735 | 38.2% |
| Unintentional (e.g., accidental ingestion, incorrect dose) | 7787 | 60.7% | 8357 | 59.7% | 8864 | 58.3% | 9237 | 58.6% | 10224 | 58.7% | 10762 | 60.4% | 11174 | 59.8% | 12023 | 59.4% |
| Adverse reaction | 103 | 0.8% | 150 | 1.1% | 158 | 1.0% | 161 | 1.0% | 171 | 1.0% | 154 | 0.9% | 193 | 1.0% | 184 | 0.9% |
| Other | 72 | 0.6% | 65 | 0.5% | 59 | 0.4% | 67 | 0.4% | 102 | 0.6% | 80 | 0.4% | 70 | 0.4% | 64 | 0.3% |
| Unknown reason | 113 | 0.9% | 146 | 1.0% | 148 | 1.0% | 139 | 0.9% | 147 | 0.8% | 158 | 0.9% | 175 | 0.9% | 229 | 1.1% |
| | 2008 | Percent | 2009 | Percent | 2010 | Percent | 2011 | Percent | 2012 | Percent | 2013 | Percent | 2014 | Percent | 2015 | Percent |
| Intentional (e.g., overdose, abuse suicide) | 7991 | 37.8% | 7888 | 36.3% | 7795 | 36.4% | 8101 | 38.8% | 7919 | 39.3% | 7770 | 39.7% | 9044 | 45.3% | 9590 | 47.7% |
| Unintentional (e.g., accidental ingestion, incorrect dose) | 12714 | 60.2% | 13361 | 61.5% | 13109 | 61.3% | 12354 | 59.2% | 11792 | 58.6% | 11277 | 57.7% | 10492 | 52.6% | 10008 | 49.8% |
| Adverse reaction | 151 | 0.7% | 200 | 0.9% | 146 | 0.7% | 145 | 0.7% | 193 | 1.0% | 232 | 1.2% | 187 | 0.9% | 184 | 0.9% |
| Other | 59 | 0.3% | 85 | 0.4% | 79 | 0.4% | 87 | 0.4% | 47 | 0.2% | 68 | 0.3% | 74 | 0.4% | 86 | 0.4% |
| Unknown reason | 211 | 1.0% | 202 | 0.9% | 260 | 1.2% | 193 | 0.9% | 188 | 0.9% | 205 | 1.0% | 163 | 0.8% | 238 | 1.2% |

Category combination rules.
Intentional – Includes: Intentional Abuse, Intentional Misuse, Intentional Suspected Suicide, and Intentional Unknown.
Unintentional – Includes: Unintentional Therapeutic Error, Unintentional Misuse, Unintentional Bite/Sting, Unintentional Environmental, Unintentional Food Poisoning, Unintentional General, Unintentional Occupational, and Unintentional Unknown.
Adverse reaction – Includes: Adverse Reaction Drug, Adverse Reaction Food, and Adverse Reaction Other.
Other – Includes: Other Contamination / tampering, Other Malicious, and Other Withdrawal.
Unknown Reason – Includes: Unknown reason.

**Table A4.** Distribution of benzodiazepine exposure by age group ($p < .001$).

| Age Group (years) | 2000 | Percent | 2001 | Percent | 2002 | Percent | 2003 | Percent | 2004 | Percent | 2005 | Percent | 2006 | Percent | 2007 | Percent |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Age 0 to <2 | 2244 | 17.5% | 2275 | 16.2% | 2456 | 16.2% | 2469 | 15.7% | 2803 | 16.1% | 3082 | 17.3% | 3192 | 17.1% | 3603 | 17.8% |
| Age 2 to < 6 | 4193 | 32.7% | 4676 | 33.4% | 4905 | 32.3% | 5281 | 33.5% | 5924 | 34.0% | 6154 | 34.5% | 6357 | 34.0% | 6829 | 33.7% |
| Age 6 to <12 | 968 | 7.5% | 962 | 6.9% | 1023 | 6.7% | 1054 | 6.7% | 1049 | 6.0% | 1083 | 6.1% | 1188 | 6.4% | 1067 | 5.3% |
| Age 12 to <18 | 5422 | 42.3% | 6088 | 43.5% | 6810 | 44.8% | 6964 | 44.2% | 7632 | 43.8% | 7511 | 42.1% | 7950 | 42.5% | 8736 | 43.2% |
| | 2008 | Percent | 2009 | Percent | 2010 | Percent | 2011 | Percent | 2012 | Percent | 2013 | Percent | 2014 | Percent | 2015 | Percent |
| Age 0 to <2 | 3693 | 17.5% | 3959 | 18.2% | 3930 | 18.4% | 3515 | 16.8% | 3501 | 17.4% | 3392 | 17.3% | 3229 | 16.2% | 3056 | 15.2% |
| Age 2 to < 6 | 7336 | 34.7% | 7748 | 35.6% | 7785 | 36.4% | 7222 | 34.6% | 6589 | 32.7% | 6353 | 32.5% | 5705 | 28.6% | 5495 | 27.3% |
| Age 6 to <12 | 1216 | 5.8% | 1190 | 5.5% | 1119 | 5.2% | 1160 | 5.6% | 1291 | 6.4% | 1216 | 6.2% | 1202 | 6.0% | 1112 | 5.5% |
| Age 12 to <18 | 8881 | 42.0% | 8839 | 40.7% | 8555 | 40.0% | 8983 | 43.0% | 8758 | 43.5% | 8591 | 43.9% | 9824 | 49.2% | 10443 | 51.9% |