

Pediatric ADHD Medication Exposures Reported to US Poison Control Centers

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abstract

OBJECTIVES: To describe the characteristics and trends of exposures to attention-deficit/hyperactivity disorder (ADHD) medications among individuals 0 to 19 years old reported to US poison control centers.

METHODS: National Poison Data System data from 2000 through 2014 were retrospectively analyzed to examine pediatric ADHD medication exposures.

RESULTS: From 2000 through 2014, there were 156 365 exposures reported to US poison control centers related to ADHD medications. The overall rate of reported exposures increased 71.2% from 2000 to 2011, followed by a 6.2% decrease from 2011 to 2014. Three-fourths (76.0%) of exposures involved children ≤ 12 years old. Methylphenidate and amphetamine medications accounted for 46.2% and 44.5% of exposures, respectively. The most common reason for exposure was therapeutic error (41.6%). Intentional medication exposures (including suspected suicide and medication abuse and/or misuse) were reported most often among adolescents (13–19 years old), accounting for 50.2% of exposures in this age group. Overall, the majority of exposed individuals (60.4%) did not receive health care facility treatment; however, 6.2% were admitted to a hospital for medical treatment, and there were 3 deaths. The increasing number and rate of reported ADHD medication exposures during the study period is consistent with increasing trends in ADHD diagnosis and medication prescribing. Exposures associated with suspected suicide or medication abuse and/or misuse among adolescents are of particular concern.

CONCLUSIONS: Unintentional and intentional pediatric exposures to ADHD medications are an increasing problem in the United States, affecting children of all ages.



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WHAT'S KNOWN ON THIS SUBJECT: Attention-deficit/hyperactivity disorder (ADHD) is one of the most commonly diagnosed pediatric neurobehavioral disorders in the United States. Most children with ADHD are treated with medication for their condition, and the number of children taking ADHD medications is increasing.

WHAT THIS STUDY ADDS: From 2000 to 2014, 156 365 exposures to ADHD medications were reported to US poison control centers. Sixty percent of exposed individuals did not receive health care facility treatment; however, 6.2% were admitted to a hospital, and there were 3 deaths.

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It is estimated that 6.4 million children in the United States have been diagnosed with attention-deficit/hyperactivity disorder (ADHD).¹ ADHD is the most commonly diagnosed neurobehavioral disorder in children and may be increasing in prevalence.^{2–5} An estimated 69% of children with a current ADHD diagnosis are treated with medication for their condition, and the number of children taking ADHD medications is increasing.^{1,6} Greater use of ADHD medications increases the risk of adverse outcomes from intentional and unintentional exposures. In 2015, US poison control centers (PCCs) received >25 800 calls involving exposures to amphetamine and methylphenidate, which are 2 medications used in the treatment of ADHD.⁷ The number of emergency department visits involving ADHD stimulant medication exposures among individuals of all ages increased 134% from 2005 to 2010.⁸ Researchers of a 2013 study estimated that the annual cost of US hospital admissions because of unintentional ADHD medication exposures is as much as \$24 million.⁹

Medication treatment has been shown to improve the symptoms of ADHD, and stimulant medications are the preferred primary therapy for most children and adults.^{4,10–12} The stimulants methylphenidate and amphetamine are the most frequently prescribed medications for children with ADHD.^{6,13,14} Other drugs commonly used include atomoxetine, a norepinephrine reuptake inhibitor, and modafinil, a stimulant sometimes used off-label for the treatment of ADHD.^{6,13–15} Stimulant medication overdoses can result in a variety of symptoms, including mydriasis, tremor, agitation, tachycardia, hyperreflexia, confusion, hallucinations, hyperthermia, and status epilepticus.^{16–18}

Previous research on ADHD medication exposures among

children has been limited by the medication categories and age groups included, number of years studied, and small sample sizes.^{17–22} With this study, we describe pediatric ADHD medication exposures reported to US PCCs and examine trends over a 15-year period. We also build upon previous studies by examining regional trends in reported ADHD medication exposures.^{1,23,24}

METHODS

Study Design and Case Selection Criteria

With this study, we retrospectively analyze characteristics and trends of ADHD medication exposures that occurred in settings other than a health care facility (HCF) among US individuals <20 years of age using data from the National Poison Data System (NPDS) for the years 2000 through 2014. The American Association of Poison Control Centers (AAPCC) maintains the NPDS, which is used to catalog calls in near-real time from regional PCCs serving the United States and its territories.⁷ PCCs respond to calls regarding potential poison exposures and informational requests and provide free medical advice to health care professionals and the public. The trained poison specialists who answer calls to the PCCs follow-up each exposure on the basis of individual PCC protocol. All PCCs included in this study are nationally accredited and maintain ongoing quality assurance procedures to ensure the accuracy and completeness of the NPDS data.

The AAPCC uses the Micromedex PoisIndex (Micromedex Healthcare Series; Truven Health Analytics, Greenwood Village, CO) database of chemical and household products to code calls received by PCCs.⁷ ADHD medication exposures among individuals <20 years old were obtained from the NPDS database by using the product codes for

ADHD medications (Table 1). Codes for illicit amphetamine and methamphetamine and amphetamine used for weight loss were not included in the query, nor were other drugs sometimes used for ADHD but frequently used for other indications, such as clonidine and guanfacine. Cases were limited to single-substance exposures occurring within the 50 US states and District of Columbia. Cases also were excluded if the medical outcome was categorized as “confirmed non-exposure” or “unrelated effect, the exposure was probably not responsible for the effect(s).”

Study Variables

Variables analyzed included year, patient age and sex, medication category, exposure site, reason for exposure, route of exposure, chronicity of exposure, management site, clinical effects, level of health care received, medical outcome, region of the United States where the exposure occurred, and type of therapeutic error.

Patients were grouped by age for analyses (0–5, 6–12, and 13–19 years). Exposure site was categorized as residence (own or other), school, other (public area, workplace, or restaurant), or unknown. Management site was reported as managed on-site (non-HCF), patient already in or en route to an HCF, patient was referred by a PCC to an HCF, other, or unknown. Reasons for exposure were categorized as unintentional (including unintentional general [eg, exploratory behaviors], therapeutic error, other, and unknown), intentional (including suspected suicide, abuse, misuse, and unknown), and other (including adverse reaction, other, and unknown).

Exposure chronicity was reported as acute, acute-on-chronic, or chronic. In the NPDS, exposures are defined as acute if they result from a “single, repeated, or continuous exposure occurring over a period of ≤8 hours.”

TABLE 1 ADHD Medication Product Categories From the NPDS Included in This Study

ADHD Medication Product Categories
Amphetamine
Adderall
Adderall XR
Dexedrine
Dexedrine spansule
Dextroamphetamine
Dextroamphetamine hydrochloride
Dextroamphetamine saccharate, dextroamphetamine sulfate, amphetamine aspartate, and amphetamine sulfate
Dextroamphetamine sulfate
Dextroamphetamine tannate
Lisdexamfetamine dimesylate
Mixed amphetamine salts
Vyvanse
Atomoxetine
Atomoxetine
Strattera
Methylphenidate
Biphentin
Concerta
Daytrana
Dexmethylphenidate
Dexmethylphenidate hydrochloride
Focalin
Focalin XR
Metadate CD
Metadate ER
Methylin
Methylin ER
Methylphenidate
Methylphenidate ER
Methylphenidate hydrochloride
Methylphenidate hydrochloride CD
Methylphenidate hydrochloride LA
Methylphenidate IR
Quillivant XR
Ritalin
Ritalin LA
Ritalin SR
Modafinil
Modafinil
Modafinil and related agents
Nuvigil
Provigil

CD, controlled dose; ER, extended release; IR, immediate release; LA, long acting; SR, sustained release; XR, extended release.

Acute-on-chronic exposure is a “single exposure that was preceded by a continuous, repeated, or intermittent exposure” lasting >8 hours. Chronic exposures are a “continuous, repeated, or intermittent exposure of the same substance” lasting >8 hours.²⁵ ADHD medications were grouped into the following categories: amphetamine (including other amphetamine-related compounds), atomoxetine, methylphenidate (including other methylphenidate-related compounds),

and modafinil (including other modafinil-related compounds; Table 1).

NPDS categories for medical outcome include death, major effect, moderate effect, minor effect, no effect, unable to follow (judged as potentially toxic exposure), not followed (minimal clinical effects possible), and not followed (judged as nontoxic exposure).²⁵ The NPDS defines major effects as symptoms that are life-threatening or result in significant

disability or disfigurement. Moderate effects are more pronounced, prolonged, or systemic than those of minor symptoms and usually require treatment. Minor effects have minimal symptoms and typically resolve quickly.²⁵ In some analyses, moderate effect, major effect, and death were grouped as “serious” medical outcomes. Clinical effects were only included if coded as “related” to the exposure. For regional analyses, the 50 US States and District of Columbia were categorized into 4 groups on the basis of the following US Census Bureau–defined regions: Northeast, Midwest, South, and West.²⁶

Statistical Analysis and Ethical Considerations

Data analyses were conducted by using IBM Statistics SPSS 24.0 (IBM SPSS Statistics, IBM Corporation) and SAS Enterprise Guide 7.11 (SAS Institute, Inc, Cary, NC). National and regional exposure rates were calculated on the basis of intercensal and postcensal estimates for US residents 0 to 19 years old from 2000 to 2014.^{27,28} Piecewise linear regression or simple linear regression was used to analyze trends in the number and rate of exposures associated with ADHD medications. The breakpoints used in piecewise linear regression were determined from Figs 1–3. The estimated slope with the 95% confidence interval (CI) from the regression model was reported, along with the associated *P* value. Statistical significance was established at *P* = .05. This study was determined to be exempt by the institutional review board at the authors’ institution.

RESULTS

General Characteristics

From 2000 through 2014, US PCCs received 156 365 calls related to ADHD medication exposures among individuals <20 years of age that

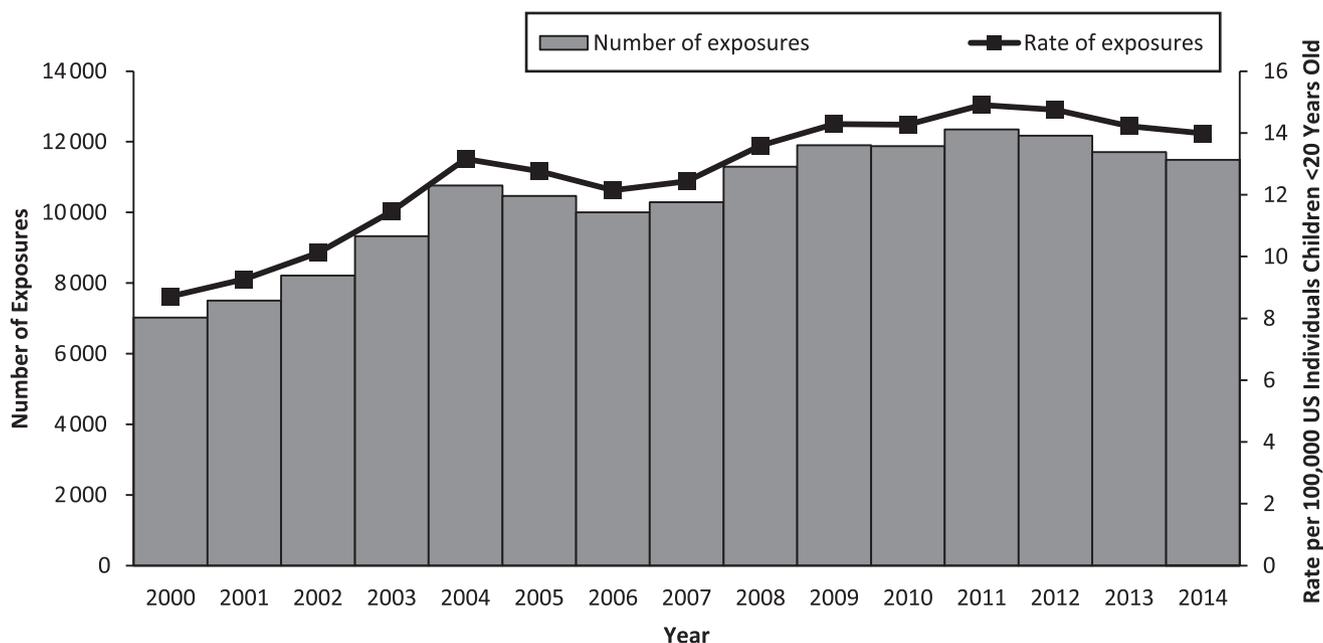


FIGURE 1 Number and rate of ADHD medication exposures among individuals <20 years old reported to PCCs in the United States, NPDS 2000–2014.

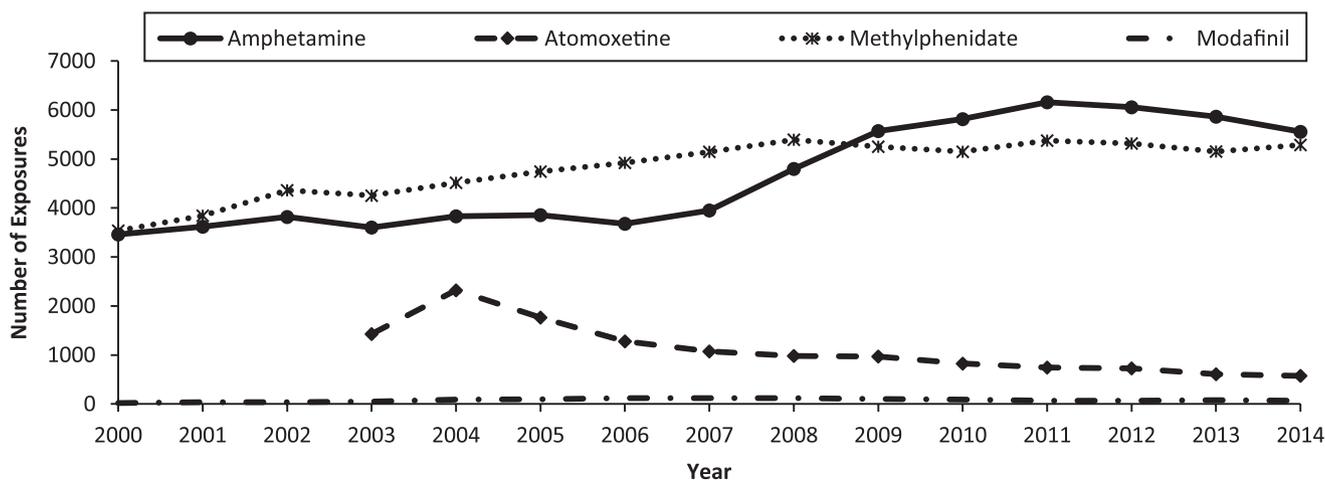


FIGURE 2 Number of ADHD medication exposures among individuals <20 years old reported to PCCs in the United States by medication category, NPDS 2000–2014.

met the study criteria (Table 2). The majority of the calls involved male patients (65.3%) and children ≤ 12 years old (76.0%). Overall, 81.9% of the exposures were unintentional, including unintentional therapeutic error (41.6%) and unintentional general exposure (39.6%). The reasons for exposure varied by age. Among children 0 to 5 years old, most exposures were categorized as unintentional general, whereas exposures among children 6 to 12 years old were most often attributed

to unintentional therapeutic error. Intentional exposures were more frequent among adolescents 13 to 19 years old, accounting for 50.2% of exposures in this age group (Table 2, Fig 4). Most exposures (94.5%) occurred at a residence. Ingestion was the most common route of exposure (99.2%), followed by nasal inhalation (0.5%) and dermal (0.3%). Two-thirds (68.6%) of all exposures were acute, although many exposures among children 6 to 12 years old (47.3%) and adolescents 13

to 19 years old (37.1%) were acute-on-chronic. Methylphenidate and amphetamine medications accounted for the greatest percentage of reported exposures (46.2% and 44.5%, respectively; Table 3). The majority of exposure calls (58.3%) were managed on-site without a referral to an HCF. Almost all (99.9%; $n = 65\,057$) of the 65 105 exposures resulting from therapeutic error had documentation of the exposure scenario, and among these, the most common exposure scenarios

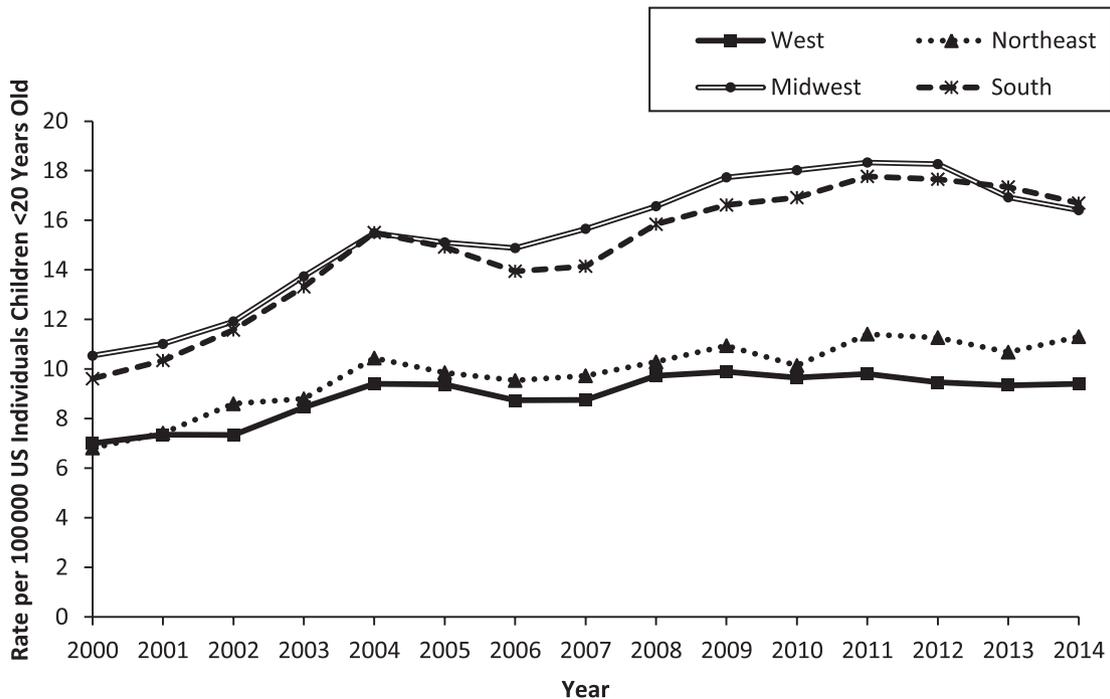


FIGURE 3 Rate of ADHD medication exposures among children <20 years old reported to PCCs in the United States by region of the United States, NPDS 2000–2014.

were ones in which medication was inadvertently taken or given twice (60.1%; $n = 39\,102$), wrong medication was taken or given (10.9%; $n = 7\,108$), and someone else’s medication was inadvertently taken or given (10.1%; $n = 6\,595$).

Exposure Trends

The overall frequency of reported exposures to ADHD medications increased significantly by 76.0% (slope = 458.7; 95% CI: 363.7 to 553.8; $P < .001$) from 7018 in 2000 to 12 351 in 2011, followed by a nonsignificant decline of 7.0% (slope = -398.1 ; 95% CI: -807.9 to 11.7; $P = .056$) during 2011–2014, decreasing to 11 486 in 2014 (Fig 1). Likewise, the overall rate of exposures per 100 000 US children increased significantly by 71.2% (slope = 0.52; 95% CI: 0.41 to 0.64; $P < .001$) from 8.71 in 2000 to 14.91 in 2011 before decreasing to 13.98 in 2014, representing a 6.2% (slope = -0.41 ; 95% CI: -0.91 to 0.10; $P = .103$) decrease during 2011–2014.

During 2000–2006, there were no significant changes (6.3%; slope = 27.6; 95% CI: -33.0 to 88.2; $P = .338$) in the number of reported amphetamine exposures, followed by a 67.4% (slope = 508.4; 95% CI: 438.8 to 578.0; $P < .001$) significant increase during 2006–2011 and then a decrease of 9.8% (slope = -240.1 ; 95% CI: -378.5 to -101.6 ; $P = .003$) during 2011–2014 (Fig 2). Atomoxetine exposures decreased significantly by 59.7% (slope = -124.1 ; 95% CI: -175.4 to -72.7 ; $P < .001$) during 2003–2014. Exposures to methylphenidate increased significantly by 52.5% (slope = 208.1; 95% CI: 180.0 to 236.2; $P < .001$) during 2000–2008 and then increased slightly (2.0%; slope = -19.6 ; 95% CI: -58.4 to 19.2; $P = .293$) during 2008–2014. There were too few modafinil exposures reported to determine a trend.

Regional Variation

The overall rate of exposures per 100 000 US children was 15.37 in the Midwest, 14.81 in the South, 9.82

in the Northeast, and 8.92 in the West. The annual rate of exposures increased significantly in the South (84.9%; slope = 0.67; 95% CI: 0.51 to 0.84; $P < .001$) and Midwest (74.0%; slope = 0.72; 95% CI: 0.60 to 0.83; $P < .001$) from 2000 to 2011, followed by a 6.1% (slope = -0.37 ; 95% CI: -1.07 to 0.33; $P = .273$) and 10.5% (slope = -0.84 ; 95% CI: -1.33 to -0.36 ; $P = .003$) decrease, respectively, from 2011 to 2014 (Fig 3). In the West, the rate increased (41.3%; slope = 0.30; 95% CI: 0.20 to 0.40; $P < .001$) during 2000–2009 and then decreased (-5.0 %; slope = -0.13 ; 95% CI: -0.32 to 0.06; $P = .152$) during 2009–2014, whereas the rate in the Northeast increased significantly (65.8%; slope = 0.27; 95% CI: 0.19 to 0.36; $P < .001$) throughout the entire study period (2000–2014).

Clinical Effects, HCF Level of Care Received, and Medical Outcome

Clinical effects were reported for 28.0% ($n = 43\,817$) of ADHD medication exposure calls. The most common clinical effects among all

TABLE 2 Characteristics of ADHD Medication Exposures Among Individuals <20 Years Old Reported to PCCs in the United States, NPDS 2000–2014

Characteristics	Age Group			Total, <i>n</i> (%) ^a
	0–5 y, <i>n</i> (%) ^a	6–12 y, <i>n</i> (%) ^a	13–19 y, <i>n</i> (%) ^a	
Sex				
Male	32 954 (56.0)	46 337 (77.3)	22 859 (60.9)	102 150 (65.3)
Female	25 814 (43.8)	13 574 (22.6)	14 582 (38.9)	53 970 (34.5)
Unknown or missing	123 (0.2)	42 (0.1)	80 (0.2)	245 (0.2)
Medication category				
Methylphenidate	20 983 (35.6)	34 391 (57.4)	16 893 (45.0)	72 267 (46.2)
Amphetamine	32 053 (54.4)	20 328 (33.9)	17 261 (46.0)	69 642 (44.5)
Atomoxetine	5075 (8.6)	5108 (8.5)	3120 (8.3)	13 303 (8.5)
Modafinil	780 (1.3)	126 (0.2)	247 (0.7)	1153 (0.7)
Exposure site				
Residence	57 921 (98.4)	55 729 (93.0)	34 151 (91.0)	147 801 (94.5)
School	650 (1.1)	3892 (6.5)	2293 (6.1)	6835 (4.4)
Unknown	131 (0.2)	117 (0.2)	866 (2.3)	1144 (0.7)
Other	189 (0.3)	215 (0.4)	211 (0.6)	615 (0.4)
Reason for exposure				
Unintentional	57 879 (98.3)	52 918 (88.3)	17 322 (46.2)	128 119 (81.9)
Therapeutic error	5436 (9.2)	44 717 (74.6)	14 952 (39.8)	65 105 (41.6)
General	52 249 (88.7)	7586 (12.7)	2013 (5.4)	61 848 (39.6)
Other	165 (0.3)	514 (0.9)	301 (0.8)	980 (0.6)
Unknown	29 (0.0)	101 (0.2)	56 (0.1)	186 (0.1)
Intentional	164 (0.3)	4038 (6.7)	18 832 (50.2)	23 034 (14.7)
Suspected suicide	27 (0.0)	905 (1.5)	8975 (23.9)	9907 (6.3)
Abuse	16 (0.0)	418 (0.7)	5364 (14.3)	5798 (3.7)
Misuse	75 (0.1)	1849 (3.1)	3110 (8.3)	5034 (3.2)
Unknown	46 (0.1)	866 (1.4)	1383 (3.7)	2295 (1.5)
Other	848 (1.4)	2997 (5.0)	1367 (3.6)	5212 (3.3)
Adverse reaction	703 (1.2)	2461 (4.1)	876 (2.3)	4040 (2.6)
Other	69 (0.1)	117 (0.2)	125 (0.3)	311 (0.2)
Unknown	76 (0.1)	419 (0.7)	366 (1.0)	861 (0.6)
Region				
Northeast	6732 (11.4)	7769 (13.0)	6246 (16.6)	20 747 (13.3)
Midwest	16 079 (27.3)	15 699 (26.2)	10 058 (26.8)	41 836 (26.8)
South	26 203 (44.5)	26 771 (44.7)	14 501 (38.6)	67 475 (43.2)
West	9877 (16.8)	9714 (16.2)	6716 (17.9)	26 307 (16.8)
Chronicity				
Acute	55 392 (94.1)	29 881 (49.8)	21 960 (58.5)	107 233 (68.6)
Acute-on-chronic	3182 (5.4)	28 381 (47.3)	13 923 (37.1)	45 486 (29.1)
Chronic	250 (0.4)	1567 (2.6)	1013 (2.7)	2830 (1.8)
Unknown	67 (0.1)	124 (0.2)	625 (1.7)	816 (0.5)
Total	58 891 (37.7)	59 953 (38.3)	37 521 (24.0)	156 365 (100.0)

^a Percentages may not sum to 100.0% because of rounding error.

exposures included agitation and/or irritability (11.3%; *n* = 17 636), tachycardia (10.0%; *n* = 15 621), drowsiness and/or lethargy (3.1%; *n* = 4804), hypertension (2.9%; *n* = 4535), and vomiting (2.3%; *n* = 3568). Most exposures (60.4%) were not treated at an HCF, and 24.6% were treated or evaluated and released; however, 3.4% of individuals were admitted to a noncritical care unit, 2.8% were admitted to a critical care unit, and 1.8% were admitted to a psychiatric care facility (Table 3). A greater percentage of amphetamine

exposures were admitted to a critical or noncritical care unit (7.8%), compared with other ADHD medication categories. Serious medical outcomes were reported for 9.4% of exposure calls (Table 3). Among adolescents 13 to 19 years old, 18.4% (*n* = 6896) of ADHD medication exposures resulted in serious medical outcomes, compared with 8.0% (*n* = 4725) of exposures among children 0 to 5 years old and 5.3% (*n* = 3148) of exposures among children 6 to 12 years old. The 3 reported deaths resulted from exposures to amphetamine (*n* = 2)

and methylphenidate (*n* = 1), and all were from intentional exposures among adolescents 13 to 19 years old (intentional abuse, *n* = 2; intentional suspected suicide, *n* = 1).

DISCUSSION

On average, there were ~10 400 ADHD medication exposures among individuals <20 years old reported annually to PCCs in the United States during 2000–2014, with the number of exposures ranging from 7018 in 2000 to 12 351 in 2011. The average annual rate of exposures over the

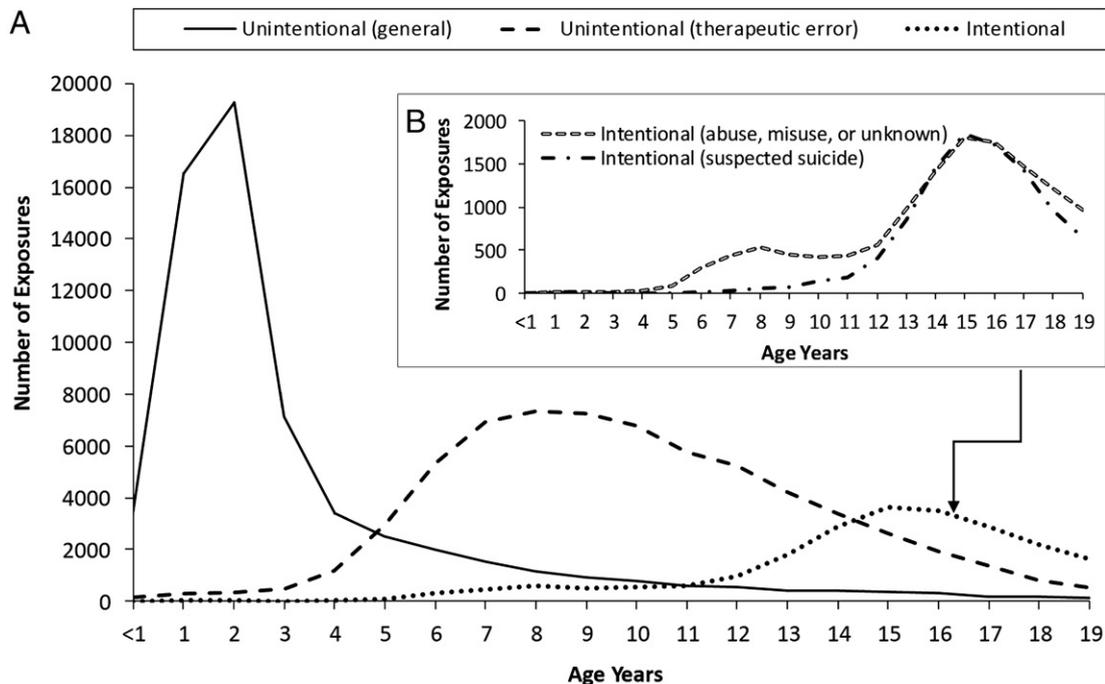


FIGURE 4

Number of ADHD medication exposures among individuals <20 years old reported to PCCs in the United States by reason for exposure, NPDS 2000–2014. A, Unintentional (general), unintentional (therapeutic error), and intentional reasons for exposures. B, Intentional (abuse, misuse, or unknown) and intentional (suspected suicide) reasons for exposures.

study period was 12.67 per 100 000 US children. Exposure frequencies and rates increased significantly by >70% from 2000 to 2011, followed by a nonsignificant decline during 2011–2014. The initial increase is consistent with previous studies in which researchers identified similar increases in ADHD diagnoses and prescribing of treatment medications during this time.^{1,2}

The US Food and Drug Administration (FDA) issued a series of public health advisories related to ADHD medications during the study period, but it is unclear how and to what degree they may have influenced the trends observed in the current study. In August 2004, labeling changes were required for Adderall XR (amphetamine and dextroamphetamine) to advise consumers of the increased risk of adverse cardiovascular events among individuals with existing heart defects.²⁹ This was followed by an FDA public health advisory

in February 2005, which was used to highlight this risk among individuals using Adderall XR, as well as Adderall, the immediate-release formula of the drug.²⁹ In September 2005, the FDA issued an advisory warning of possible sudden death or suicidal ideation associated with the use of atomoxetine and required a revised patient medication guide and boxed warning on the product label.³⁰ In February 2007, the FDA issued a public health advisory warning of the risk of adverse cardiovascular and psychiatric symptoms associated with the use of ADHD medications.³¹ Authors of 1 study in which the impact of this series of public health advisories was examined observed that market shares for Adderall and Adderall XR and atomoxetine declined between 2004 and 2008 but that physician prescribing of ADHD medications for children and adolescents remained stable.³² In November 2011, the FDA announced the results of a large cohort study finding that ADHD medications were

not associated with increased risk of adverse cardiovascular events among children and adolescents.³³ The fluctuations observed in the current study may have been influenced by these FDA advisories and may also reflect the introduction of new ADHD medications and formulations into the consumer market at different points during the study period.

All regions of the United States experienced increases in the rate of reported exposures early in the study period, and every region except the Northeast observed decreases later. Throughout the study period, the South and Midwest maintained higher rates of exposure than the Northeast and West. Authors of other studies have identified similar patterns of regional variation in rates of ADHD prevalence and prescribing of ADHD medications.^{1,23,24} The regional differences in the current study may be attributable, in part, to variations in ADHD diagnosing,

TABLE 3 Management Site, Level of Health Care Received, and Medical Outcome of ADHD Medication Exposures Among Individuals <20 Years Old Reported to PCCs in the United States, NPDS 2000–2014

Characteristics	ADHD Medication Category				Total, <i>n</i> (%) ^a
	Methylphenidate, <i>n</i> (%) ^a	Amphetamine, <i>n</i> (%) ^a	Atomoxetine, <i>n</i> (%) ^a	Modafinil, <i>n</i> (%) ^a	
Management site					
Managed on-site (non-HCF)	46 045 (63.7)	35 347 (50.8)	9 130 (68.6)	663 (57.5)	91 185 (58.3)
Patient already in or en route to an HCF ^b	13 748 (19.0)	17 628 (25.3)	1 967 (14.8)	231 (20.0)	33 574 (21.5)
Patient was referred by PCC to an HCF	10 759 (14.9)	15 323 (22.0)	1 982 (14.9)	246 (21.3)	28 310 (18.1)
Other	1 335 (1.8)	920 (1.3)	172 (1.3)	6 (0.5)	2 433 (1.6)
Unknown	380 (0.5)	424 (0.6)	52 (0.4)	7 (0.6)	863 (0.6)
Level of health care received					
Treated or evaluated and released	15 272 (21.1)	20 366 (29.2)	2 569 (19.3)	309 (26.8)	38 516 (24.6)
Patient lost to follow-up or left AMA	2 686 (3.7)	3 862 (5.5)	456 (3.4)	56 (4.9)	7 060 (4.5)
Admitted to noncritical care unit	2 054 (2.8)	2 949 (4.2)	218 (1.6)	35 (3.0)	5 256 (3.4)
Admitted to critical care unit	1 798 (2.5)	2 457 (3.5)	136 (1.0)	20 (1.7)	4 411 (2.8)
Patient refused referral or did not arrive at HCF	1 443 (2.0)	2 136 (3.1)	270 (2.0)	44 (3.8)	3 893 (2.5)
Admitted to psychiatric care facility	1 254 (1.7)	1 181 (1.7)	300 (2.3)	13 (1.1)	2 748 (1.8)
No HCF treatment received	47 760 (66.1)	36 691 (52.7)	9 354 (70.3)	676 (58.6)	94 481 (60.4)
Medical outcome					
Death	1 (0.0)	2 (0.0)	0 (0.0)	0 (0.0)	3 (0.0)
Major effect	169 (0.2)	302 (0.4)	10 (0.1)	0 (0.0)	481 (0.3)
Moderate effect	5 778 (8.0)	7 974 (11.4)	451 (3.4)	82 (7.1)	14 285 (9.1)
Minor effect	10 465 (14.5)	12 232 (17.6)	1 799 (13.5)	162 (14.1)	24 658 (15.8)
No effect	20 948 (29.0)	21 439 (30.8)	4 670 (35.1)	492 (42.7)	47 549 (30.4)
Unable to follow, toxic ^c	3 630 (5.0)	5 019 (7.2)	590 (4.4)	73 (6.3)	9 312 (6.0)
Not followed, minimal clinical effects ^d	27 745 (38.4)	20 196 (29.0)	5 009 (37.7)	285 (24.7)	53 235 (34.0)
Not followed, judged nontoxic exposure ^e	3 531 (4.9)	2 478 (3.6)	774 (5.8)	59 (5.1)	6 842 (4.4)
Total ^f	72 267 (46.2)	69 642 (44.5)	13 303 (8.5)	1 153 (0.7)	156 365 (100.0)

AMA, against medical advice.

^a Column percentages may not sum to 100.0% because of rounding error.

^b Patient already in or en route to HCF when PCC called.

^c Judged as potentially toxic exposure.

^d Minimal clinical effects possible (no more than minor effects possible).

^e Judged as nontoxic exposure (clinical effects not expected).

^f Row percentages may not sum to 100.0% because of rounding error.

ADHD medication treatment practices, and reporting to poison centers.^{34,35}

Three ADHD medication–related deaths were reported; however, most exposures did not result in serious medical outcomes. Most reported clinical effects involved the cardiovascular or neurologic systems and included agitation and/or irritability, tachycardia, and hypertension, which is consistent with the known mechanisms of action of stimulant medications.¹⁶ Although less common, drowsiness and/or lethargy was reported for ~3% of cases; the sedative effects of low doses of stimulants have been reported previously in the literature.³⁶ Serious medical outcomes, including the 3 deaths,

were associated with amphetamine and methylphenidate. Although both medication categories are psychostimulants, their mechanisms of action and pharmacokinetics differ.¹⁶ Atomoxetine and modafinil had far fewer reported exposures, which is likely, in part, because of the less frequent prescribing of these medications. Although, with this study, we did not include exposures to clonidine and guanfacine, which are sometimes prescribed for treatment of ADHD, authors of a previous study in which the NPDS was used found that a greater percentage of reported exposures to those drugs resulted in moderate or major effects (19.9% and 13.7%, respectively) compared with the medications included in the current study.³⁷

The majority of intentional exposures were among adolescents, a concern that has been identified in previous research.^{21,22} In addition, all deaths in this study resulted from intentional exposures among adolescents. Although stimulant medications are recommended for treatment of ADHD, they also have potential for abuse, misuse, and diversion to other individuals. Authors of a recent study found that among 12th-graders who reported using amphetamine without a doctor’s prescription, most obtained the drugs from a friend.³⁸ Authors of 1 study found that adolescents’ nonmedical use of stimulants was directly correlated with the number of prescription users in their school.³⁹ High school students report nonmedical use of stimulants for a variety of reasons,

including to help with concentration, increase alertness, get high, or experiment.⁴⁰ ADHD medication exposures among adolescents are increasing, and exposures among this age group are more likely to result in serious outcomes.^{17,21} To help prevent prescription drug abuse and misuse among adolescents, safe storage and disposal of unused medications are recommended. Parents who believe their child has been abusing prescription medications should seek help from their pediatrician or family physician.

Among children 6 to 12 years old, unintentional therapeutic error was the most common reason for exposure, whereas exposures among children <6 years old were most frequently attributed to general unintentional causes, such as accessing improperly stored medications. This is consistent with the findings of others.⁴¹ Pediatric poisonings by medications are an ongoing problem.⁴² Efforts to eliminate unintentional medication exposures should encompass both parental education and packaging modifications to prevent child access and reduce the risk of therapeutic errors.⁴³ Parental education regarding safe storage of medications may help to prevent exploratory ingestions among younger children. Packaging changes, such as the use of unit-dose packaging (eg, blister packs) instead of pill bottles for daily medications, may be used to assist parents and caregivers in remembering whether a medication has already been administered. Unit-dose packaging can also be used to put an additional barrier between children and medications and has been shown

to be effective in reducing serious poisoning.⁴⁴

Medications, particularly stimulants, are considered a first-line therapy for most children with ADHD (excluding preschool-aged children).⁴ However, combining stimulant therapy with behavioral therapy may decrease the amount of medication needed for treatment.^{4,12} In turn, this may reduce the risk of adverse medication effects and decrease the availability of stimulants in the home that could result in the types of intentional and unintentional pediatric exposures described in this study.

This study has several limitations. The number of ADHD medication exposures among children and adolescents reported in this study is an underestimate of the true frequency in the population, because we excluded clonidine and guanfacine, and because not all exposures are reported to PCCs. Some ADHD medication exposures may go unrecognized, and others may result in a call to a primary care physician or receive treatment in an HCF that does not result in a call to a PCC. Some exposures included in this study may have been associated with stimulant medications prescribed to individuals with narcolepsy or obstructive sleep apnea and not ADHD. NPDS data are based on self-report from the caller and cannot be fully verified by the PCCs or AAPCC. Not every exposure represents an overdose or poisoning, and only single-substance exposures occurring in a non-HCF setting were evaluated in this study. Despite these limitations, the NPDS provides high-quality national data on ADHD

medication exposures among children in the United States.

CONCLUSIONS

With this study, we provide a comprehensive investigation of pediatric ADHD medication exposures reported to PCCs in the United States. Overall, the number and rate of ADHD medication exposures increased significantly during the study period, although there were 2 periods of slight decline, most recently from 2011 to 2014. The majority of calls involved children 12 years of age and younger; however, exposures with the most serious outcomes were intentional exposures among adolescents. Regional variations in reported ADHD medication exposures in this study correlate with regional variations in ADHD diagnosis and medication prescribing identified in previous studies. Strategies to prevent these exposures include education of parents, caregivers, and adolescents; safe storage of medications; use of unit-dose packaging; and increased use of nonpharmacologic interventions for ADHD.

ABBREVIATIONS

AAPCC: American Association of Poison Control Centers
ADHD: attention-deficit/hyperactivity disorder
CI: confidence interval
FDA: US Food and Drug Administration
HCF: health care facility
NPDS: National Poison Data System
PCC: poison control center

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