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Accidental Amphetamine Ingestion

High Levels of Use for ADHD Raise the Risk of Intoxication in Young Children

By Matthew D. Krasowski, MD, PhD, and Kelly E. Wood, MD

The incidence of diagnosis of attention deficit hyperactivity disorder (ADHD) is increasing in the U.S., with an estimated prevalence of 4–9% in children and 4% in adults (1). The concept of adult-onset ADHD has evolved and was formally introduced into the fifth edition of the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders* in 2013. The diagnostic criteria now allow for an older age of ADHD symptom onset and no longer include the requirement that symptoms cause impairment (2,3).

The U.S Food and Drug Administration (FDA) has approved a number of prescription medications for the management of ADHD (4,5,6). Stimulants continue to be the most common treatment, and ADHD stimulants are derivatives of either amphetamines or methylphenidate. They are available in both immediate-release and extended-action formulations.

Some products contain a single isomer (such as, dextroamphetamine [Dexedrine]), a mixture of isomers (such as, *d*- and *l*-amphetamine; "mixed amphetamine salts" [Adderall]), or pro-drugs of *d*-amphetamine (such as, lisdexamfetamine dimesylate [Vyvanse]). Stimulant medications have been available for decades, and evidence shows that they are safe and effective when used as directed for the management of childhood ADHD (6). In 2004, stimulant medications gained FDA approval for the treatment of adult ADHD (5).

In addition to these medications, clonidine and guanfacine are FDA-approved as adjunct therapy to improve the effectiveness of stimulants in the treatment of ADHD. Several other medications are not specifically approved but have been used "off label" to treat ADHD and its co-morbidities. These medications include bupropion (Wellbutrin), modafinil (Provigil), and tricyclic antidepressants (such as desipramine [Norpramin] and imipramine [Tofranil]).

In terms of regulation, the amphetamines and methylphenidate are classified as Schedule II controlled substances in the U.S. Schedule II drugs are considered to have high abuse potential. Prescriptions for Schedule II drugs typically require extra security measures such as limitations on refills and third parties picking up prescriptions.

Improving Patient Function

Although medications do not cure ADHD, pharmacotherapy can allow the child or adult to improve functioning at home, in school, at work, and in social settings. Some children with ADHD no longer require pharmacotherapy when they reach late adolescence and early adulthood. Table 1 summarizes the stimulants approved for the treatment of ADHD.

Common side effects from stimulants include reduced appetite, sleep difficulties, gastrointestinal discomfort, and social withdrawal (6). Historically, stimulants were thought to cause tics or worsen them, leading to warnings that these medications should not be used in patients with a personal or family history of tic disorders. However, randomized controlled studies found that stimulants had no adverse effects on tics compared with non-stimulant medications in the treatment of ADHD (6).

The increase in ADHD diagnosis in children and adults has been accompanied by significant increases in amphetamine prescriptions, with one study reporting that stimulants were prescribed in over 70% of office visits for ADHD regardless of

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Amphetamine Intoxication

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age (7). From 2010 to 2014, commercially insured adults and children showed increases of amphetamine prescriptions across all age groups, with the greatest increase in adults. Outpatient prescriptions for amphetamine mixed salts exceeded 4.5 million in the U.S. in 2009, leveling off to approximately 3.0 million in 2014 (8). Outpatient lisdexamfetamine prescriptions exceeded 7.5 million in the U.S. in 2014. Thus, total outpatient prescriptions for amphetamine stimulants in the U.S. exceed 10 million per year.

In addition to legitimate prescriptions, prescription stimulants have also been the subject of deceptive direct-to-consumer advertising and Internet sales (6). These products may be counterfeit or generic versions fraudulently labeled as brand-name drugs. There have also been shortages of stimulant medications in the U.S. A variety of factors can lead to pharmaceutical shortages, including restrictions by the Drug Enforcement Administration on stimulant medication production by pharmaceutical companies as a means to limit abuse. Some of the fraudulent counterfeit stimulants are purportedly the exact prescription medication formulations that are in shortage. Poisonings involving counterfeit products can present challenges in the identification of the drug.

Accidental Ingestion

Accidental ingestion of medications is generally most common in children less than five years old. Toddlers are especially vulnerable because they are curious, mobile, and explore objects by mouthing. Doses that older children and adults can tolerate can produce toxic symptoms in toddlers.

The rise in stimulant prescriptions increases the potential for accidental intoxication in young children, a danger reflected in data from U.S. poison centers (9). For example, U.S. poison control centers reported that 7,113 children 19 years old or younger were exposed to lisdexamfetamine between 2007 and 2012. Of these, 35.8% were less than six years, and 2.3% were younger than one year.

In 2016, the authors published a case report of a previously healthy 10-month-old girl who exhibited a five-hour history of hypertension, tachycardia, dyskinesia, and altered mental status (10). A urine specimen collected about 16 hours after the onset of symptoms was positive by amphetamines immunoassay. Confirmatory analysis by liquid chromatography/tandem mass spectrometry revealed a urine amphetamine concentration of 22,312 ng/mL. The source of exposure was eventually attributed to pills spilled from the grandmother's lisdexamfetamine prescription. The family thought all the pills had been recovered, but evidently the infant ingested one or more.

We then performed a retrospective analysis of data from the University of Iowa Stead Family Children's Hospital from 2008–16 to search for similar cases (10). We discovered a previous case with similar features involving a 15-month-old child with accidental ingestion of amphetamine mixed salts, who presented with tachycardia and other symptoms of sympathetic activation. This child had a positive urine immunoassay for amphetamines; however, no confirmatory analysis was performed.

Another 18 children between the ages of four and eight who presented to our emergency department had positive immunoassay screens for amphetamines. Of these, 16 were explainable by medications prescribed to the child. The remaining two cases involved children who took another child's prescribed amphetamine mixed salts.

Additional Cases

Since this 2016 case report, we have encountered six amphetamine intoxications in young children at our medical center. Three involved lisdexamfetamine, and three involved amphetamine mixed salts. In all these cases, the suspected exposure occurred accidentally from medications in the household, either from older siblings, adult relatives, or another child also being watched by the babysitter. As in the lisdexamfetamine case described above, confirmatory amphetamine analysis found high urine amphetamine concentrations in three of the cases

Table 1. Stimulant Medications Used to Treat Attention Deficit Hyperactivity Disorder

Class	Generic Name	Trade Names
Amphetamines	Mixed amphetamine salts	Adderall; Adderall XR
Amphetamines	Dextroamphetamine	Dexedrine; Dexedrine Spansule
Amphetamines	Lisdexamfetamine dimesylate	Vyvanse
Methylphenidate	Methylphenidate	Concerta, Daytrana (skin patch), Metadate CD, Metadate ER, Methylin, Quillivant XR (liquid), Ritalin, Ritalin LA, Ritalin SR
Methylphenidate	Dexmethylphenidate	Focalin XR

(19,618 ng/mL, 25,533 ng/mL, and 45,751 ng/mL). Common presenting signs included irritability, tachycardia, and movement disorders. Anion gap metabolic acidosis was present in all six cases.

Not surprisingly, there is little pharmacokinetic data on amphetamines in children less than four years, as these medications are generally not prescribed for ADHD until later in childhood. In the children who had confirmatory toxicology analysis, four had urine amphetamine concentrations exceeding 19,500 ng/mL, a urine concentration higher than the maximum achieved in a detailed pharmacokinetic study of amphetamine mixed salts in adults (11). Given that the urine concentrations in these children were derived from single urine collections hours after the suspected ingestion, the peak concentrations were likely much higher.

Symptoms of Overdose

Amphetamines stimulate both the central and sympathetic nervous systems (12). Overdose can produce sympathomimetic toxicity, including hypertension, tachycardia, agitation, altered mental status, aggression, hallucinations, psychosis, and paranoia. Our case series of amphetamine poisonings in young children showed a common feature of irritability (10).

Amphetamine toxicity can also cause movement disorders, including dyskinesia and dystonia, with some reports documenting symptoms in children even 48 to 72 hours after overdose (12). Chorea (jerky involuntary movements) has been described in both adults and children. Ford et al. reported two pediatric cases of sudden-onset chorea involving an eight-month-old who accidentally ingested a sibling's mixed amphetamine prescription and a 10-year-old who inadvertently received an extra dose of lisdexamfetamine (13). Ataxia, teeth grinding, tics, and tremors have also been reported in pediatric amphetamine intoxications (12–14).

Diagnosis

The differential diagnosis of a young child presenting with toxic sympathomimetic symptoms can be challenging because a number of drug exposures can present similarly (15). The possibility must also be considered that the symptoms are due to a medical condition such as epilepsy. Of possible drug causes, methamphetamine should always be considered because there have been many reports of toxicity in young children (15–18).

A presumptive-positive drug screen for amphetamines can help narrow down possible causes. In these cases, it is important to know whether the drug screen can differentiate between amphetamine and methamphetamine (19). In addition, overdoses of other drugs, such as bupropion and aripiprazole, can also cause positive screens on some amphetamine immunoassays and may present with signs and symptoms that resemble amphetamine toxicity (20–22). Confirmatory toxicology analysis can help in definitive identification of a specific drug.

Lisdexamfetamine dimesylate presents some special considerations because of its prolonged duration of action. Lisdexamfetamine was the first prodrug stimulant developed for treatment of ADHD and first appeared on the U.S. market in 2007 (9,23). It is converted to its active form, *d*-amphetamine, by red blood cell hydrolysis. Its therapeutic effect after a single dose can extend over 12 hours in both children and adults (24,25). It is thus not surprising that effects can last longer in very young children who were previously naïve to this drug (10,13,14).

Summary

With the increasing therapeutic use of stimulant medications in children and adults, clinicians and toxicologists should consider accidental stimulant ingestion in infants and young children presenting with sympathomimetic toxicity and/or movement disorders. A thorough history of prescription medications present in the household can help. Ingestion of long-acting drugs such as lisdexamfetamine dimesylate can result in protracted symptoms. Confirmatory toxicology analysis can be valuable in distinguishing accidental prescription stimulant ingestion from other drugs such as methamphetamine.

Learning Objectives

After reading this article, the reader will be able to identify the amphetamine medications commonly used to treat attention deficit hyperactivity disorder. The reader will also be able to recognize the common signs and symptoms of amphetamine overdose and the role of toxicology analysis in diagnosis.

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Matthew D. Krasowski, MD, PhD, is a clinical professor and vice chair of clinical pathology and laboratory services in the department of pathology at the University of Iowa Hospitals and Clinics. E-mail: mkrasows@healthcare.uiowa.edu. Kelly E. Wood, MD, is a clinical associate professor of pediatrics and medical director of newborn nursery and pediatric hospitalist services at the University of Iowa Stead Family Children's Hospital. E-mail: kelly-wood@uiowa.edu.

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U-47700
Novel Psychoactive Opioid Grows In Use and Leads to Fatalities

By Janetta Bryksin, PhD, and James Ritchie, PhD

Worldwide, the past decade has been marked by unprecedented use of opioids. In the U.S., opioids have become the most common drug of addiction. In October, President Donald Trump declared a public health emergency to fight the deadly U.S. opioid epidemic. In addition to traditional opioids, the use of novel synthetic opioids, including fentanyl analogs and new non-fentanyl compounds such as U-47700, has surged.

Sold under the street names pink, synthetic cocaine, and U4, U-47700 is a structural analog of AH-7921 (an opioid discovered in the 1970s that was never sold for a medical use and has been classified as a Schedule 1 drug in the U.S.). U-47700 was developed by Upjohn Company scientists in 1978 but was never approved for medical use.

Reports of Abuse

The abuse of U-47700 was first reported in Sweden in 2014. Since then it has been found throughout Europe. It was first reported to the U.S. National Forensic Laboratory Information System in October 2015, and its use quickly spread. By 2016, there had been at least 46 overdose deaths related to U-47700

consumption, with most occurring in New York and North Carolina (1). There were 320 law enforcement seizures of this drug in the U.S. by 2016.

In November 2016, the U.S. Drug Enforcement Administration declared U-47700 as well as its isomers, esters, and ethers to be illegal and placed them under temporary Schedule I.

Effects, Administration, and Dosage

U-47700 has been reported to be used on its own and in combination with other opioids. Although U-47700 is 10 times less potent than fentanyl, it is seven to eight times more potent than morphine. It acts as an agonist and has a high binding affinity for the μ-opioid receptors, much higher than for the δ- and κ-opioid receptors.

Several routes of administration have been reported, including nasal, oral, intrarectal, intravenous, and by insufflation. Users report that U-47700 induces euphoria, analgesia, sedation, and an urge to re-dose. Reported side effects include constipation, respiratory depression, itching, tachycardia, decreased mental status, drowsiness, nausea, anxiety, and abdominal pain. The administration of naloxone can reverse the effects (2).

The common dose of U-47700 is 7.5–15 mg and up to 25 mg in strong users (3). When consumed orally or by insufflation, the onset of action is in 15 minutes. When injected intravenously, onset is within a minute. The duration of drug action is five to seven hours for oral consumption; three to four hours for insufflation; and one to two hours for intravenous injection. The effects last for one to four hours independent of the route of administration.

Fatalities

Of the 46 reported fatalities involving U-47700 in the U.S., only a handful have been attributed to U-47700 alone. The rest involved other drugs as well, including various opioids, amphetamine, tramadol, etizolam, alprazolam, and ethanol. Some users might not have been aware that they were consuming U-47700 because dealers add it to drugs such as heroin or substitute it for another compound.

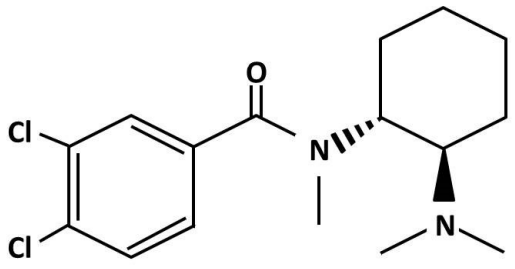

Figure 1. Chemical structure of U-47700 ($C_{16}H_{22}Cl_2N_2O$; IUPAC name: 3,4-dichloro-*N*-[(1R,2R)-2-(dimethylamino) cyclohexyl]-*N*-methylbenzamide)

In fatalities involving U-47700 alone, the femoral blood concentrations ranged from 0.24 to 0.40 mg/L. When U-47700 was combined with other drugs, its concentrations were lower (2). Pulmonary edema is the most common finding in lethal cases.

The use of psychoactive synthetic substances continues to rise, including synthetic cannabinoids, synthetic cathinones, tryptamines, piperazines, benzofurans, phencyclidine and other ketamine-type compounds, and opioids. Indeed, high-potency opioids, such as U-47700, AH-7921, and MT-45, add to the opioid public health threat due to their toxicity and abuse potential. The medical and toxicological communities would benefit from more research into the pharmacokinetic properties of these drugs.

Learning Objectives

After reading this article, the reader will be able to describe the physiological effects of U-47700 and the circumstances of some fatalities caused by its consumption.

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Janetta Bryksin, PhD, DABCC, is assistant clinical director of core and POCT laboratories at Emory Healthcare in Atlanta. Email: janetta. bryksin@emoryhealthcare.org. James Ritchie, PhD, DABCC, is a professor in the department of pathology and laboratory medicine and director of the core and special chemistry laboratories at Emory University in Atlanta. Email: jritchi@emory.edu.

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FDA Issues Warning on Use of Opiate Substitute Plant Kratom

The U.S. Food and Drug Administration (FDA) issued a warning in November against the use of the herb kratom, which has effects similar to those of narcotics like opioids.

Kratom is a plant that grows naturally in Thailand, Malaysia, Indonesia, and Papua New Guinea, and is seeing increasing use in the U.S.

Kratom is taken recreationally by users for its

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Counterfeit Opioid Pills

Drug Users Play Russian Roulette In Utah and across the Nation

By Kamisha L. Johnson-Davis, PhD

More than 100 individuals die from an opioid overdose each day in the U.S. Exacerbating the problem, a growing number of counterfeit pills are being manufactured. These counterfeit pills contain fentanyl and other synthetic compounds, such as furanyl-fentanyl and U-47700, so are more potent than prescription medications. These compounds are put in pill presses to resemble prescription pain medications, like oxycodone, with similar color and stamped trademark symbols (1). Disguised as prescription opioid pills or heroin, they are sold on the street or on the Internet.

Individuals who purchase these pills may have no idea that the pills are counterfeit. Noteworthy, the investigators of the overdose death the musician Prince discovered counterfeit pills in his residence. The pills resembled the prescription drug Vicodin, but contained fentanyl (2).

Higher Profits

The compounds in the counterfeit pills are dangerous because of their potency. U-47700 has seven times the potency of morphine, and fentanyl is 50 to 100 times more potent. Table 1 highlights the potency of various opioid compoumds in comparison to morphine.

The street value of oxycontin ranges from $50 to $80 per pill. Counterfeit opioid and benzodiazepine pills are cheaper to create, so increase profits (3). Fentanyl powder can be ordered on the dark web from China and shipped by mail. A kilogram of fentanyl costs $3,000 to $5,000. When combined with cutting agents, it can produce up to 1 million pills, potentially generating a multimillion dollar profit (4,5). The pill presses can produce thousands of pills per hour (6).

The dose of fentanyl in these counterfeit pills varies greatly and can be dangerously high. These highly potent counterfeit pills have spread across the U.S. and are increasing the risk of opioid overdose, leading to respiratory depression, organ failure, stroke, and death (1).

Opioids in Utah

According to the Centers for Disease Control and Prevention, there were over 33,000 opioid-related deaths nationwide in 2015 (7). The state of Utah, where six to 10 people die from opioid overdoses each week, exemplifies the problem. The state ranks seventh in the nation for the number of drug overdose deaths (8). The presence of synthetic opioids in Utah gained attention in September 2016, when two teenage boys in Park City died from an overdose of "pink" or U-47700 (9). Federal agents busted a drug operation where thousands of counterfeit pills were being pressed in a home facility in Cottonwood Heights in November 2016. The pills were being dispersed across the U.S. (4,5).

Additional drug busts have occurred in the state in the past few years, in cities like Sandy and West Jordan, where millions of counterfeit pills have been confiscated (4,5). According to the Utah Department of Health Office of the Medical Examiner, opioid-related deaths increased from 139 in 2000 to 409 in 2015 (10). Moreover, there were 127 fentanyl-overdose deaths from 2012 to 2016 (11). The state has responded with a drug awareness initiative called "Stop the Opidemic" (11). On the federal level, President Donald Trump declared the opioid epidemic a public health emergency in October.

Table 1. Opioid Potency in Comparison to Morphine (12)

Opioid	Dose (mg)	Potency
Morphine	10	1
Meperidine	80	0.125
Codeine	40	0.25
Oxycodone	6.66	1.5
Hydrocodone	6.66	1.5
Oxymorphone	3.33	3
Methadone	2.5	4
Heroin	2	5
Hydromorphone	1.5	6.67
U-47700	1.33	7.5
Alfentanil	0.75	13.33
Furanyl Fentanyl	0.5	~20
Buprenorphine	0.3	~33.33
Fentanyl	0.1	100
Remifentanil	0.05	200
Sufentanil	0.01	1000
Etorphine	0.01	1000
Carfentanil	0.001	10000

Learning Objectives

After reading this article, the reader will be able to recognize the dangers of counterfeit opioid pills made from potent synthetic compounds such as fentanyl.

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Kamisha L. Johnson-Davis, PhD, DABCC, is an associate professor in the department of pathology at the University of Utah and medical director of clinical toxicology at ARUP Laboratories in Salt Lake City. She chairs the board of editors of Clinical & Forensic Toxicology News.

The author has nothing to disclose.

Nationwide Perspective on Counterfeits

A recent *Washington Post* article provides a perspective on how counterfeit pills are affecting other states: "Counterfeit opioid pills are tricking users—sometimes with lethal results," by Katie Zezima. Nov. 19, 2017. https://www. washingtonpost.com/national/counterfeit-opioid-pills-are-tricking-users--sometimes-with-lethal-results/2017/11/19/d34edb14-be4b-11e7-8444-a0d4f04b89eb_story.html?utm_term=.1e6fe4aa9ea7

FDA Issues Kratom Warning

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euphoric effects, but it carries similar risks to opioids of abuse, addiction, and in some cases, death.

"At a time when we have hit a critical point in the opioid epidemic, the increasing use of kratom as an alternative or adjunct to opioid use is extremely concerning," said FDA Commissioner Scott Gottlieb, MD. Gottlieb expressed particular concern "that patients believe they can use kratom to treat opioid withdrawal symptoms. There is no reliable evidence to support the use of kratom as a treatment for opioid use disorder."

"There's clear data on the increasing harms associated with kratom," Gottlieb said. "Calls to U.S. poison control centers regarding kratom have increased tenfold from 2010 to 2015, with hundreds of calls made each year. The FDA is aware of reports of 36 deaths associated with the use of kratom-containing products. There have been reports of kratom being laced with other opioids like hydrocodone. The use of kratom is also associated with serious side effects like seizures, liver damage, and withdrawal symptoms."

The statement notes that proponents argue that kratom is safe largely because it's a plant-based product, so people are using it to treat conditions like pain, anxiety, and depression. "There are currently no FDA-approved therapeutic uses of kratom. Moreover, the FDA has evidence to show that there are significant safety issues associated with its use. Before it can be legally marketed for therapeutic uses in the U.S., kratom's risks and benefits must be evaluated as part of the regulatory process for drugs that Congress has entrusted the FDA with," Gottlieb said.

"The FDA has exercised jurisdiction over kratom as an unapproved drug, and has also taken action against kratom-containing dietary supplements. We are working to actively prevent shipments of kratom from entering the U.S. At international mail facilities, the FDA has detained hundreds of shipments of kratom. Kratom is already a controlled substance in 16 countries, including two of its native countries of origin, Thailand and Malaysia, as well as Australia, Sweden, and Germany. Kratom is also banned in several states, specifically Alabama, Arkansas, Indiana, Tennessee and Wisconsin and several others have pending legislation to ban it," Gottlieb said.

For more information, see the March 2016 *Clinical & Forensic Toxicology News*, "Kratom: Herb Gains Popularity as a Gentler Opiate Substitute."

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- International Federation of Clinical Chemistry
- National Registry in Clinical Chemistry
- States of California, Florida, Louisiana, Montana, Nevada, North Dakota, Rhode Island, and West Virginia

Learning Objectives

Learning objectives vary by article, but in general, after reading *CFTN*, the reader will be able to:

- Describe emerging and changing drug-abuse trends.
- Identify potential analytes of clinical significance.
- Evaluate methodologies' utility and limitations.
- Discuss relevant regulations.
- Explain analytical and regulatory issues.
- Describe the medical implications of drug abuse.

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A new proficiency testing program from the College of American Pathologists will focus on trace metals in whole blood. Analytes will include aluminum, arsenic, chromium, cobalt, copper, manganese, mercury, selenium, thallium, and zinc. For information: https://estore.cap.org/OA_HTML/xxCAPibeCCtpItmDspRte.jsp?section=10410&item= 503254&sitex= 10020:22372:US

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