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Synthetic Cannabinoids

Laboratories Respond to Demands of Designer Drugs

By Bridgit O. Crews, PhD

Synthetic cannabinoids play a leading role in the cat-and-mouse game between designer drug developers and those charged with protecting the public. Disguised as "herbal incense," mixtures containing these new drugs are sold openly on the Internet, in convenience stores, and in head shops under brand names such as Spice and K2. The products consist of dried plant materials resembling potpourri that have been laced with synthetic cannabinoids.

Although labeled "not for human consumption" to circumvent drug laws, they convey the implicit enticement that they provide a safe and legal alternative to marijuana. But the products are far from safe—users experiencing dangerous adverse effects have caused a spike in hospital emergency department admissions.

While legislators and law enforcement officials are addressing the legal issues to control these new threats, laboratories are developing new tests and methods to detect them. Better detection would help deter their use as well as provide more effective diagnosis and treatment of poisoned patients.

Effects of Synthetic Cannabinoids

Synthetic cannabinoids have been compared with the psychoactive compound, Δ-9-tetrahydrocannabinol (THC), found in marijuana. On the molecular level, they are potent cannabinoid receptor agonists that also may have affinity for other types of receptors. Reported symptoms of toxicity include anxiety, agitation, paranoia, hallucinations, tachycardia, hypertension, excessive sweating, nausea, and vomiting.

Overdoses of synthetic cannabinoids can cause panic attacks and psychosis and lead to tragic results. In 2010, after an Iowa teen smoked K2 with some friends, he reportedly told them he was "going to hell." He then went home, where he shot and killed himself. In another case, a 19-year-old male in Illinois died when his car jumped a retaining wall at an estimated speed of 100 miles per hour, flew 15 feet, and crashed into a house. About 90 minutes before the crash, he told his brother he had been smoking "legal potpourri." In both of these cases, the victims reportedly purchased the synthetic cannabinoids at a local shopping mall.

For people looking to get high, synthetic cannabinoids are readily available, fairly inexpensive, and in many cases, legal to purchase. Naive drug users may incorrectly assume that a product sold at a convenience store and labeled as natural is safe to try. Furthermore, employees, such as transportation workers or military personnel who must undergo random drug testing, may be more likely to use synthetic cannabinoids because they are not detected by standard workplace drug screening programs.

Prevalence

Synthetic cannabinoids originally emerged in Europe in 2006, and by November 2008, the U.S. Drug Enforcement Agency's (DEA) forensic laboratory detected them in products in the U.S. The following year, the American Association of Poison Control Centers (AAPCC) reported 112 calls involving synthetic cannabinoids to poison control centers in 15 states. That number quickly soared. Within 9 months, 49 states plus the District of Columbia recorded 2,700 calls, and by 2011, the number rose to 6,549. In October 2012, AAPCC reported logging an average of 580 calls per month.

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Synthetic Cannabinoids

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Other signs of the growing popularity of synthetic cannabinoids are also evident. In 2010, DEA reported that 30–35% of specimens submitted by juvenile probation departments tested positive for synthetic cannabinoids, and according to the 2011 *Monitoring the Future* survey, sponsored by the National Institute on Drug Abuse, 11% of high school seniors reported smoking synthetic marijuana in the past year, making it one of the most commonly abused drugs in this population—second only to marijuana. Furthermore, researchers recently reported that 4.5% of urine specimens collected from 5,956 U.S. athletes tested positive for synthetic cannabinoids, the highest of all drug classes detected (1). Synthetic cannabinoid use also has spiked among military personnel, and the armed forces are currently conducting a study to determine the prevalence of synthetic cannabinoid use within its ranks.

Classes and Structures of Synthetic Cannabinoids

There are three major categories of synthetic cannabinoids: classical cannabinoids, cyclohexylphenols, and aminoalkylindoles.

One well-known classical cannabinoid is the THC analogue HU-210. This chiral compound takes its name from Hebrew University where it was synthesized by Raphael Mechoulam in the 1980s. HU-210 is a schedule I controlled substance under the Controlled Substances Act. According to the U.S. Customs and Border Protection, it was discovered in January 2009 in herbal incense products in Wilmington, Ohio, where agents seized more than 100 pounds of the product. However, classical cannabinoids are difficult to synthesize and do not appear to be highly prevalent in the market.

Pfizer developed the second category of synthetic cannabinoids, cyclohexylphenols, as analgesics in the late 1970s. Dubbed CP for Charles Pfizer, CP-47,490 and its C8 homologue, cannabicyclohexanol, were among the first synthetic cannabinoids detected in herbal incense. In March 2011, DEA used its emergency scheduling authority to control these two compounds; however, they appear to have been replaced by new designer cannabinoids of the aminoalkylindole variety.

Aminoalkylindoles are currently the most prevalent synthetic cannabinoids. Included in this category are the JWH-018, JWH-073, and JWH-200 cannabinoids that DEA recently added to the class I schedule and other indole- and pyrrole-based analogues. Clemson University Professor J. W. Huffmann first developed the JWH series in the late 1990s. These cannabinoid analogues are synthesized in a simple two-step process, and undergraduate summer research students in his lab originally synthesized many of the original JWH analogues. A purification process also is necessary to achieve the final product. Recently, laboratories have detected phenylacetylindoles such as RCS-8, which stands for Research Chemical Suppliers, and benzoylindoles such as AM-694, named for Alexandros Makriyannis, in synthetic cannabinoid products.

Legal Status

Following the DEA's March 2011 temporary emergency ban on the five synthetic cannabinoids described above, in July 2012, President Obama signed the Synthetic Drug Abuse Prevention Act of 2012 (S. 3187) into law. The new law explicitly bans 15 synthetic cannabinoids in addition to 11 other synthetic designer drugs and increases the amount of time an analogue can be temporarily scheduled. At least 41 states also have legislative bans on synthetic cannabinoids.

But manufacturers of herbal incense products are financially motivated to stay one step ahead of such legislation. According to the *Financial Times*, assets for Psyche Deli, the original manufacturer of Spice in the U.K., grew by nearly 1300% from 2006 to 2007. In 2010, manufacturers in the U.S. claimed sales totaling more than $6,000 a day. Furthermore, in police testimony, one major manufacturer stated that if JWH-018 were banned, he would just switch to treating his dried plant products with another legal compound.

In fact, a new synthetic cannabinoid, AM-2201, began appearing in herbal incense products after the 2011 temporary scheduling of JWH-018. This compound is almost identical to JWH-018, except the terminal carbon of the alkyl chain has been changed to fluorine. Anecdotal reports from users posted on the Internet suggest AM-2201 is much more potent than JWH-018.

Pharmacokinetics

Hepatic CYP450 enzymes extensively metabolize the parent drugs of synthetic cannabinoids. For example, more than 20 metabolites of JWH-018 have been identified, including carboxylated, monohydroxylated, dihydroxylated, and trihydroxylated metabolites, that are excreted almost exclusively in urine as glucuronide conjugates (2–4).

Researchers have not detected the parent drugs in urine, and very limited data on detection time win-

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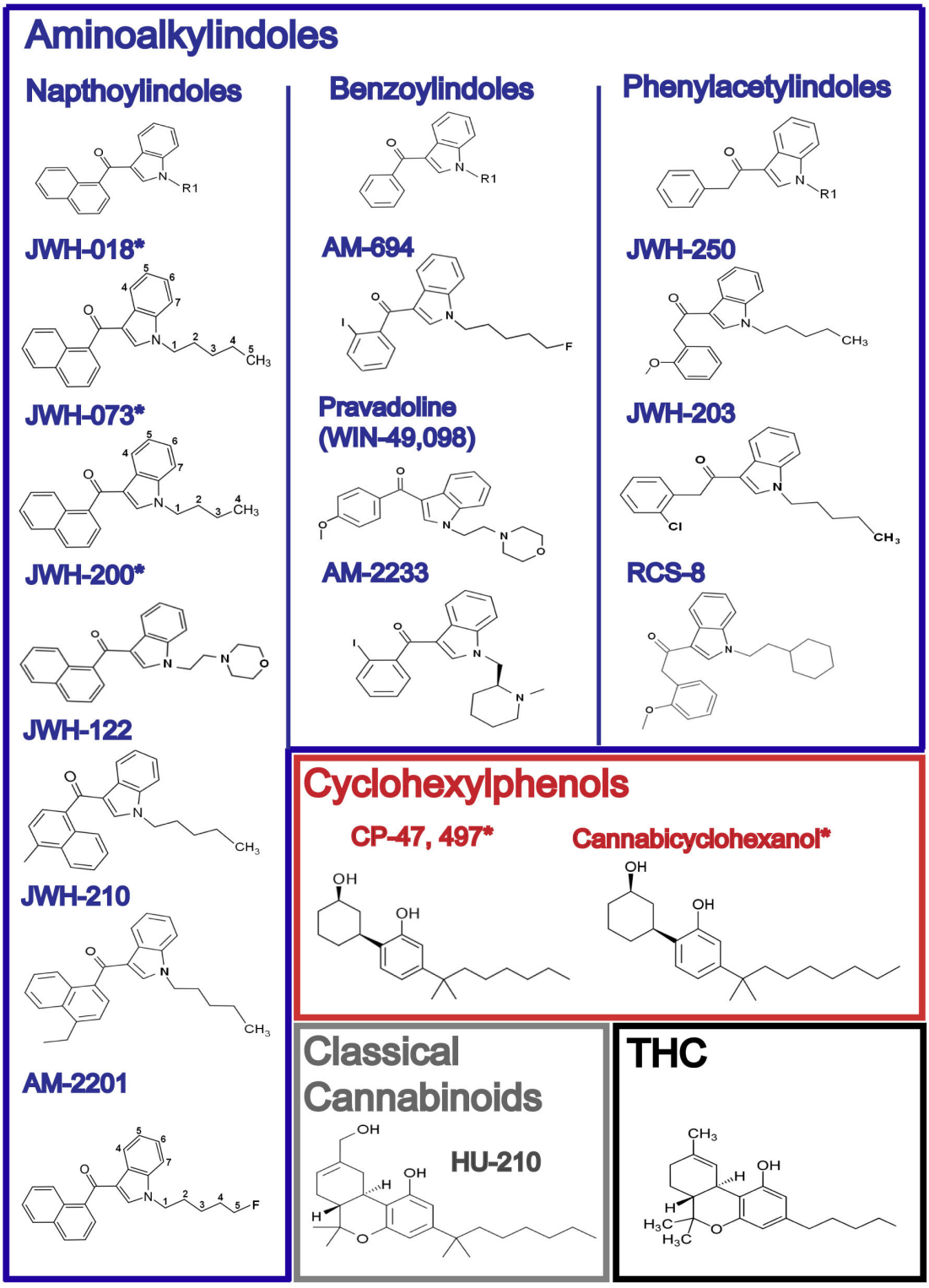

Figure 1. Structures of Synthetic Cannabinoids Detected in U.S. Products as of September 2012
Other cannabinoids found in U.S. products, but not shown, include benzoylindole RCS-4, phenylacetylindole JWH-251, and napthoylindoles JWH-019, JWH-015, JWH-081, JWH-398, AM-1221, and WIN-55,212-2.
* Indicates synthetic cannabinoids scheduled in March 2011.

dows or expected concentrations of metabolites has been published. A study of one drug-naive individual showed the most abundant JWH-018 metabolite, JWH-018-N-pentanoic acid, was present in urine at approximately 0.1 ng/mL approximately 48 hours after a single use (5). Anecdotal evidence, however, suggests chronic users may produce positive urine tests for weeks after they stop using synthetic cannabinoids. In one study, researchers reported concentrations of JWH-018-N-pentanoic acid as high as 27,000 ng/mL in a urine specimen from an individual with an unknown smoking history (6).

The most comprehensive study of synthetic cannabinoids to date included 29 patients in Germany who presented to emergency departments after consuming the drugs (7). Among the patients, toxicity symptoms lasted 4–14 hours and serum concentrations of JWH-018 ranged from 0.38–13 ng/mL. Serum drug concentrations also varied depending on the specific synthetic cannabinoids the individual consumed. It is interesting to note that of the 29 patients, almost 40% had more than one synthetic cannabinoid in their serum. On the other hand, regular users of JWH-018 can have serum concentrations as high as 8 ng/mL without toxic symptoms, suggesting tolerance may develop.

In another study, researchers reported detecting JWH-018 in oral fluid specimens collected from two drug naive individuals following a single smoking session (8). The concentration peaked 20 minutes after the individuals smoked the drug and remained detectable for 5–12 hours at ≤0.5 ng/mL..

Although pharmacokinetic data is beginning to accrue for scheduled analogues such as JWH-018, it remains unclear how this information will translate to modified analogues that manufacturers may produce in the future.

Methods for Detecting Synthetic Cannabinoids

Designing assays that detect synthetic cannabinoids is a challenge for laboratories because the drugs are rapidly moving targets. To avoid detection, illicit drug makers constantly change the structure of the synthetic cannabinoids used in the herbal incense market. In addition, because commercially available THC immunoassays do not cross-react with synthetic cannabinoids, laboratories usually develop their own mass spectrometry-based assays.

Recently, however, Randox introduced an enzyme-linked immunosorbent assay that uses polyclonal antibodies targeted toward different chemical moieties of the aminoalkylindole cannabinoids. Reported sensitivities for the assays are <1 ng/mL, and preliminary data from the manufacturer shows good cross reactivity with metabolites of 11 synthetic cannabinoids. Currently, there is no data on the assay's ability to detect metabolites of emerging synthetic cannabinoids; therefore, screening results generally need to be confirmed with mass spectrometric methods.

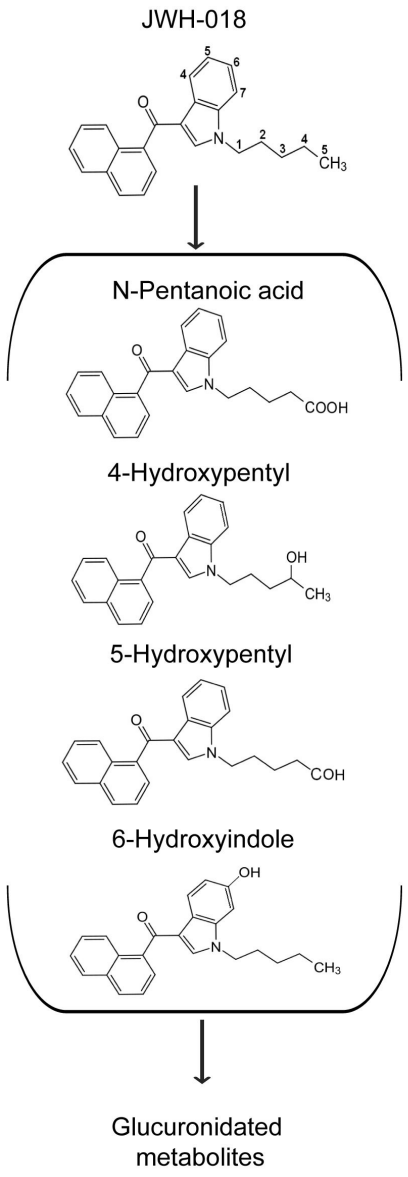

Figure 2. Major Metabolites of JWH-018 Detected in Urine

The best methods for detecting synthetic cannabinoids are liquid chromatography/ tandem mass spectrometry (LC-MS/MS) and gas chromatography/

mass spectrometry. Protocols targeting JWH-018 and JWH-073 metabolites have been described in detail (3–6). Such targeted MS protocols are generally limited by the availability of reference standards, but vendors such as Cayman Chemical offer a wide variety of metabolite standards and deuterated internal standards.

For LC-MS/MS analysis, laboratories usually incubate urine specimens with glucuronidase and extract the sample by liquid-liquid or solid-phase extraction. A 10-minute chromatographic separation is necessary to separate isobaric cannabinoid metabolites and endogenous interferences. Testing saliva and serum is also possible using a modified extraction protocol followed by LC-MS/MS analysis that includes detecting parent synthetic cannabinoids.

The Challenges

As it stands today, laboratories must develop and validate their own methods for detecting synthetic cannabinoids. Furthermore, no guidelines exist to clarify which metabolites should be measured or what cutoffs should be used, and there are no standardized quality control materials or proficiency tests.

This lack of guidance and standardization is keenly illustrated by the following example. In August 2011, the New York State Department of Health identified 12 laboratories that test biological specimens for synthetic cannabinoids, primarily JWH-018 and JWH-073, for healthcare providers in the state (9). None of the laboratories tested for the same panel of metabolites, and the limits of quantitation varied by more than one hundredfold.

While much work still needs to be done to standardize methods for synthetic cannabinoids, cutoff values are a particularly good example of an area that would benefit from more data. One approach some laboratories have taken is to set the limit of detection as low as analytically possible. Considering the current lack of data, extremely low-level positives should be interpreted with caution. Does a urine concentration of 0.1 ng/mL indicate recent use or the slow release of cannabinoids from fat stores of a chronic user who is currently abstaining? Setting cutoffs too high is also detrimental because it can result in misclassifying too many positive specimens as negative. Similar issues exist for interpreting the lipid-soluble THC metabolite, 11-nor-9-carboxy-THC, but cutoffs for screening and confirmation are standardized and based on decades of data.

The bigger issue is keeping pace with the new synthetic cannabinoids that illicit drug makers produce. In 2010, researchers studying herbal products purchased from U.K.-based websites applied a high-resolution MS approach that identified previously unreported synthetic cannabinoids (10). In 2012, two independent groups in the U.S. used a similar approach to profile herbal mixtures they purchased from local stores and on the Internet. One group developed methods for more than 65 different designer drugs using available reference standards (11). The second group incorporated a "mass defect filter," producing a method that does not require reference standards (12). Both groups identified previously undetected and unscheduled synthetic cannabinoids in recently purchased products, again illustrating the rapid evolution of this type of drug.

The Here and Now

Although synthetic cannabinoid testing will likely remain a moving target, developing accurate tests is an important need for laboratories. Having such tests will not only serve as a deterrent to drug makers and users, but it also will aid in diagnosing poisoned patients, monitoring compliance, and identifying patients at risk for drug abuse.

The question facing laboratories today, however, is how to detect these drugs. Laboratories that send out specimens from suspected users for testing should know which synthetic cannabinoids the reference laboratory tests for and what cutoff values are used. On the other hand, laboratories may want to consider developing in-house tests, which also requires keeping up with the constant influx of new synthetic cannabinoids.

Interpreting test results also remains challenging. Laboratorians and clinicians should keep in mind that only very limited pharmacokinetic data exists for just a few synthetic cannabinoids. Furthermore, time windows for detecting these drugs and their concentrations may vary depending on the frequency of drug use and particular flavor of synthetic cannabinoid consumed.

Until more studies are done, laboratorians would be well advised to pay close attention to the analytical methods used for detecting synthetic cannabinoids and to the interpretation of test results.

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The Baby Soap Saga

Nursery–Laboratory Cooperation Solves False-Positive Mystery

By Catherine A. Hammett-Stabler, Ph.D., DABCC, FACB, Steven W. Cotten, Ph.D., DABCC, Carl Seashore, M.D., Daniel Duncan, M.D., and Elizabeth A. Burch, M.S.W.

Recounted by Catherine A. Hammett-Stabler

When the ringing phone interrupted an otherwise quiet afternoon, I did not suspect that the call would lead to our laboratory getting mentioned by Jay Leno and Steven Colbert. A staff member in the newborn nursery unit, Elizabeth "Lizzy" Burch, was on the line with the kind of question I learned to pay attention to long ago: "Has something changed with the urine drug tests for marijuana?"

Lizzy explained that the nursery staff had the impression that a higher percentage of urine screens were not confirming as positive. My mind raced trying to recall the last unconfirmed positive cannabinoid screen. The last one I could remember was more than a year before.

Screening and Confirmation

Our laboratory uses the Vitros 5600 (Ortho Clinical Diagnostics) chemistry analyzer for our urine drug screening, running a standard panel that includes cannabinoids, cocaine metabolite, opiates, benzodiazepines, barbiturates, methadone, and amphetamines. Confirmation of a positive screening result does not happen automatically, but must be ordered by a physician. The most commonly ordered confirmations are for opiates and benzodiazepines, and we perform these in-house to expedite service to our pain clinics and trauma center. We refer other confirmations to Mayo Medical Laboratories, which also performs our meconium testing.

Confirmations are seldom ordered for cannabinoids, in large part because they almost always report back as positive. Furthermore, sending out samples for confirmation from the nursery can be challenging because of their limited specimen volume.

False Positives?

Of course, Lizzy had no reason to know the details of our laboratory procedures. She explained the discrepancy that had sparked her concern: We had recently implemented a revised protocol for newborn screening that increased the number of drug screens ordered by the nursery. And although the number of cannabinoid-positive urine screens had risen, there

was no concomitant increase in positive meconium results. While I considered the differences between the samples, I felt that we needed to take a closer look at the situation.

Lizzy offered to give laboratory personnel access to a shared folder she'd set up within the hospital's electronic medical record system to monitor the drug tests the nursery was ordering so we could pull samples in real time to ensure any sample that screened positive would go out for confirmation.

It took several weeks to accumulate enough data—quite a few samples were returned "quantity not sufficient" for confirmation—and the results were suspicious. Most of the newborn screening results were near the 20 ng/mL cutoff, only a few were substantially above the cutoff, and none of the borderlines confirmed. In contrast, almost all the positive cannabinoid samples from other units, such as the emergency department, family medicine, and pain clinics, confirmed as positive, even those at or just below the cutoff.

Trading Information

Lizzy organized a meeting with nurses, the director of the newborn nursery and other physicians, risk management staff, and several of us from the laboratory. We started by reviewing the concerns and discussing the new protocols the nursery unit had introduced. I gave a 15-minute tutorial explaining the differences between screening and confirmation, particularly in the context of the matrices urine and meconium. I noted that although urine can give an idea of drug use within a window of days to a couple of weeks, meconium can reveal exposure over several weeks, but only if the sample collection is correct and complete.

Not all our newborns are tested for drugs, only those whose maternal histories suggest that they might be at risk of exposure. Considering the implications of a positive test, everyone agreed that all positive urine screens should be confirmed and we would work out the mechanism to do so.

I asked the nurses to clarify how they collected urine samples from the babies. I'd been told that they collected them by squeezing the diaper, but this was clearly impossible with the brands the nursery used. Some nurses said they put cotton balls or gauze in the diaper, some turned the diaper inside out and wiped it, and some used collection devices. The collection process was anything but standardized, which was understandable given that each baby's situation was different.

Then one of us asked what happened between birth and the collection. Again, each situation was different. Some babies were cleaned using wipes; others were bathed. At that point, I suggested that a pathology resident (Daniel Duncan) and a clinical chemistry fellow (Steven Cotten) from the laboratory visit the nursery the next day to shadow the nurses and see what takes place. They would gather samples of everything that touched the babies between birth and urine collection.

The nursery staff members enthusiastically agreed.

A Visit to the Nursery

The next afternoon, Dr. Duncan and Dr. Cotten obtained quite a bit of material: cotton balls, gauze, three types of diapers, a collection device, lotions, gels, wipes, soap, and more. After setting up experiments incubating the solid materials with drug-free urine, they turned to adding a small amount of each liquid to a urine sample and testing it. Minutes later, they all but ran to my office with the news that one item had yielded a positive cannabinoid result—the baby soap. No other drug class was positive. No other liquid agent was positive, only the baby soap.

Dr. Cotten reminded us that these preliminary results needed repetition and confirmation. We sketched out a series of experiments and I offered to stop by a pharmacy on the way home to purchase other baby soap brands.

Over the next few weeks, the evidence mounted that baby soap was the cause of our false-positive cannabinoid screening results. For every brand of baby soap we tried, increasing the amount of soap increased the apparent cannabinoid concentration (Figure 1). The cannabinoid assay was the only test affected.

We sent blinded samples to nearby colleagues at Duke University Medical Center and UNC Rex HealthCare, who used other screening methods. Samples spiked with baby soap elicited a positive response, although to a lesser degree than with the Vitros reagents.

We tested four active ingredients: cocamidopropyl betaine, polyquaternium 11, sodium lauryl sulfate, and a polyethylene glycol (PEG 80) sorbitan laurate-cocamidopropyl betaine-sodium lauryl sulfate mixture. Of these, only sodium lauryl sulfate had no effect, the other three yielded a positive cannabinoid screening result when added to drug-free urine. In fact, we saw positive results with all the soaps and washes used throughout the hospital except for hand soaps.

But, importantly, incubating drug free urine with any of the wipes, including those used in the adult clinics to acquire clean-catch urine samples, did not cause any positive results. However, we did note a loss of signal when positive cannabinoid samples

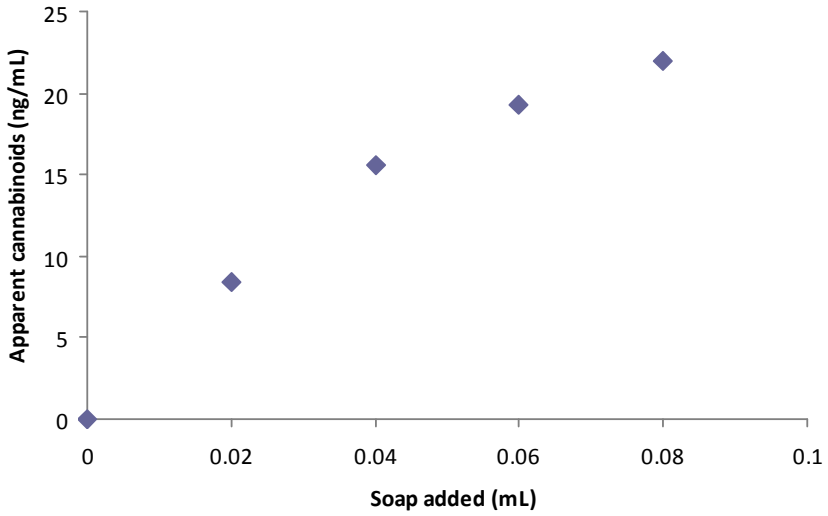

Figure 1. Dose Response Curve of Soap in Drug-Free Urine

For every brand of soap tested, increasing the amount of soap in a urine sample increased the apparent cannabinoid concentration in a classic dose response curve.

were incubated with wipes and textiles (gauze, cotton balls, and diapers), likely because the drug and metabolites adsorbed onto the materials.

Surprising Results

We found these false-positive screening results to be particularly interesting because of the notoriety soaps have had historically in causing the opposite finding, false-*negative* results, in workplace drug testing (1, 2). In a review of adulterants, Warner reported that the addition of small amounts of Joy dishwashing detergent to urine produced both false-negative and false-positive results depending on the screening assay used (3).

Since our report of these findings (4,5), numerous others have come forward with similar cases. In addition, following their own investigation of discordant urine screening and confirmation cannabinoid results, Barakauskas et al. suggested that perhaps newborns and neonates produce different urinary cannabinoid metabolites (6). We agree and look forward to their identification of the metabolic profile for these patients.

Collaborative Success

Our published results also received attention from local and national media, with late-night comedians cracking jokes about babies with the munchies.

But for us the best part of this project was the collaboration between the laboratory and nursery staff to resolve this issue as a part of patient care. The teamwork that went into the discussion, identification, and resolution of the problem demonstrates the importance of such collaboration and monitoring of the total testing process.

Some colleagues within the forensic arena have made critical comments that false-positive results from unsuspected causes are not surprising and support more aggressive requirements for confirmation testing. While we agree in principle that more confirmation testing is sometimes desirable, the cost of such testing can be significant when budgets are already stretched and longer turnaround times can delay patient care. More importantly, challenges like this demonstrate the need to educate those who perform the tests and those who use the results about the methods' limitations so they can both make appropriate decisions.

Table 1. Items Tested for Cannabinoid Reactivity

Liquids

- Head-to-Toe Foaming Wash (Johnson & Johnson, New Brunswick, N.J.)
- Johnson's Bedtime Bath (Johnson & Johnson)
- Baby Magic: Hair and Body Wash (Naterra Inc., Flower Mound, Texas)
- Night-Time Baby Bath (CVS Caremark Corp., Woonsocket, R.I.)
- CVS Baby Shampoo (CVS Caremark Corp.)
- Aveeno Soothing Relief Creamy Wash (Johnson & Johnson)
- Aveeno Wash Shampoo (Johnson & Johnson)

Textiles

- Medichoice Baby Wipes (Owens & Minor, Mechanicsville, Va.)
- Kendall Curity Gauze Sponge (Covidien, Mansfield, Mass.)
- Cotton Ball X-large (Custom Hospital Products, Portland, Ore.)
- Huggies Newborn Diapers (Kimberly-Clark Corp., Neenah, Wis.)
- Huggies Preemie Diapers (Kimberly-Clark Corp.)
- U-Bag Urine Collection Preemie (Briggs Healthcare, Waukegan, Ill.)
- U-Bag Urine Collectors Newborn (Briggs Healthcare)
- Cleansing Towelette (PDI Inc., Orangeburg, N.Y.)

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Watch for the next issue of *CFTN* in June

Attention Deficit Hyperactivity Disorder

Abuse of Drugs for Treatment Rising

By Michael A. Wagner, Ph.D.

Attention deficit hyperactivity disorder (ADHD) is characterized by a neurological imbalance that leads to behavioral impulsiveness, inattention, hyperactivity, or a combination of these symptoms. ADHD is typically diagnosed during childhood, affecting 8–12% of children worldwide. But treatment often continues into adulthood, with some 4% of adults worldwide taking drugs for the condition.

The number of prescriptions issued for treatment has grown greatly in recent years: Prescriptions for patients under 19 years old increased by 80% over five years, from the 6.5 million in 2004 to 11.8 million in 2009 (1).

The drugs used to treat ADHD include the stimulants methylphenidate (Ritalin, Concerta), amphetamine/dextroamphetamine (Adderall), dexmethylphenidate (Focalin), and dextroamphetamine (Dexedrine). When used as directed they provide effective medical management, but their side effects include excitability, insomnia, dizziness, cardiovascular effects, and psychiatric effects.

Increase in Adverse Reactions

Abuse of these stimulants has increased steadily since their introduction. Between 2005 and 2010, emergency department (ED) visits related to ADHD drug misuse increased by 134% (2). Males tend to report to the ED more often than females; however, female rates of abuse increased at a significantly higher rate over this period (Figure 1).

Further evaluation of the abuse demographics reveals that, for the 5-to-17 age group, the number of ED visits for abuse or adverse drug reactions remained relatively constant from 2005 to 2010. In 2005, the average number of ED visits for this age range was approximately 3000, compared with 3600 in 2010.

The 18-to-25 age group recorded the greatest increase in number and the greatest percentage increase. In 2005, 2131 cases were recorded; in 2010, that number was 8148, a 282% increase. The 35-and-older age group recorded the second highest number of ED cases (7957) as well as the second highest percentage increase (215%). The 26-to-34 age group showed the third largest increase (6094 cases and 71% increase).

In 2010, 50% of the ED visits recorded for ADHD stimulant abuse involved nonmedical use.

The other half resulted from adverse drug reactions or other reasons (2).

Factors Contributing to Abuse

One probable factor contributing to the increase in the abuse of these drugs is the previously mentioned increase in prescriptions. As prescriptions increase, the potential for drug diversion increases as well. Although there is a correlation between the increase in prescriptions issued and the increase in reported abuse cases, more data may be needed to prove causation.

Worth noting, this correlation has been seen before with drugs such as opiates (methadone, hydrocodone, and oxycodone) and benzodiazapines (alprazolam, lorazepam, and clonazepam). Another factor is that some drugs are more prone to abuse. The amphetamine/dextroamphetamine combination shows a higher rate of abuse (47%) than methylphenidate (37%).

Abuse of these drugs is associated with severe health risks. Increased blood pressure, heart rate, and body core temperature; insomnia; suppressed appetite; and malnutrition are typical signs of stimulant abuse. Elevated drug concentrations and repeated drug use can lead to paranoia, cardiovascular collapse, and stroke (1,3).

Abuse of Other Drugs

Both statistical correlations and anecdotal testimony link ADHD drug abuse with abuse of other drugs. Of the ED visits involving ADHD drugs in 2010, 25% involved one other drug and 38% involved two or more other drugs. Some 45% of the total visits involved other pharmaceuticals, with 26% being anti-anxiety medications and 16%, narcotic pain relievers. Some 21% of the 2010 ED cases also involved drugs of abuse, with marijuana the most common at 14%. Marijuana is seen most often in the 15-to-17 age group. One-fifth of all the cases involve the use of ethanol, with the 18-to-25 age group the most frequent alcohol users (2).

Nonscientific interviews with and testimonials from students reveal that these medications are readily obtained on college campuses. The drugs are passed among friends for free and for purchase because they are popular aids for studying, particularly when cramming for exams.

Testing Methods

Testing for the amphetamine analogues involves immunoassay screening and confirmation by gas chromatography/mass spectrometry (GC/MS). Methylphenidate cannot be detected by immunoassay, so hybrid chromatographic analyses are used for screening and confirmation. GC/MS and electrospray ionization-liquid chromatography/tandem mass spectrometry with multiple reaction monitoring meet the forensic criteria needed (4).

As the number of ADHD diagnoses increases, so does the potential for abuse. An accurate medical history coupled with comprehensive laboratory testing are keys for addiction management and emergent care. Future drug development may lead to effective drugs that minimize the abuse profile.

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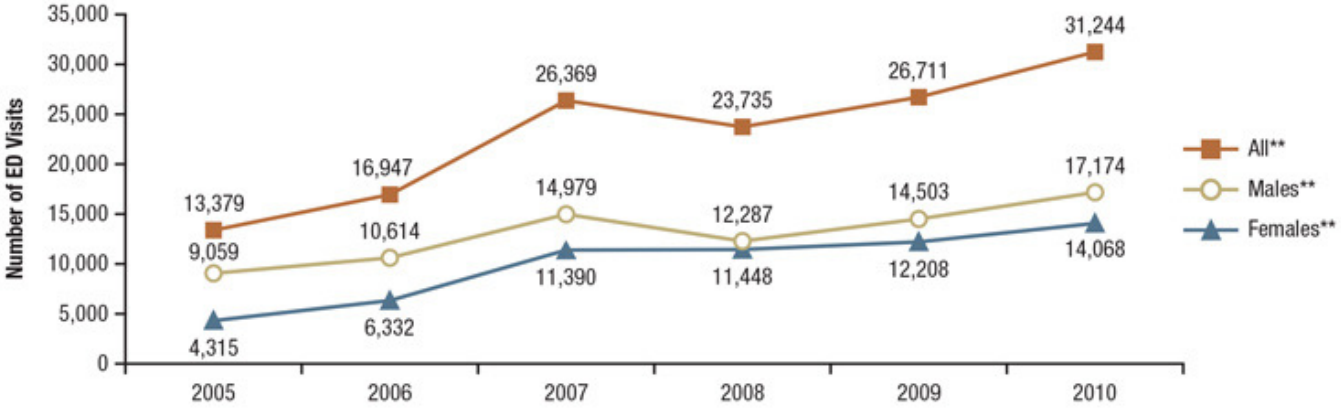

Figure 1. Emergency Department (ED) Visits Related to Attention Deficit Hyperactivity Disorder Stimulant Medication by Gender

* Because gender is unknown in some visits, numbers for males and females do not add up to the total.

** The change from 2005 to 2010 is statistically significant at the .05 level.

Source: 2005 to 2010 SAMHSA Drug Abuse Warning Network (DAWN)

Reprinted from http://www.samhsa.gov/data/2k13/DAWN073/sr073-ADD-ADHD-medications.htm

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