The New Wave of Designer Drugs: A Review for Criminal Justice and Forensic Professionals

By Matthew D. Krasowski and Jerrod Brown

Abstract

In recent decades, synthetic or designer drugs have continuously emerged like weeds. The manufacturers and distributors of synthetic substances are encouraged, at least in part, by the fuzzy legal status and low manufacturing cost of these drugs. Removing the threat of designer drugs has proven problematic for U.S. law enforcement because many of these designer drugs remain legal until the substance's harm can be clearly established. To make matters worse, designer drugs are often not detected by the drug tests commonly utilized in criminal justice and forensic settings. Going forward, greater awareness of designer drugs by forensic, clinical, and law enforcement professionals and sophisticated research are necessary.

Introduction

The last decade has seen increasing growth in novel psychoactive substances that are sometimes termed "designer drugs" (Carroll, Lewin, Mascarella, Seltzman, & Reddy, 2012; Rech, Donahey, Cappiello Dziedzic, Oh, & Greenhalgh, 2015). Two categories of drugs that have captured the public's attention are synthetic cannabinoids (e.g., K2, Spice) and amphetamine-like drugs (e.g., bath salts; Crews & Petrie, 2015). More recently, a new wave of designer opioids (acetylfentanyl, AH-7921,

MT-45, U-47700), methoxetamine, and designer benzodiazepines have entered the illicit drug market. In some cases, these drugs are close chemical analogs of existing drugs. For example, acetylfentanyl is derived from fentanyl by a simple chemical addition. In other cases, the novel drug has a fairly distinct structure from existing drugs (e.g., synthetic designer opioids such as MT-45 and U-47700). Despite the recent emergence of these designer drugs, many were actually discovered decades ago but relatively unutilized in clinical medicine (Carroll et al., 2012). As is common with novel drugs of abuse, the early published literature mostly consisted of case reports on symptoms and fatalities related to use of these chemical compounds. To expand awareness in criminal justice and forensic professionals, this article reviews U.S. drug regulations, highlights some of the newer designer drugs, describes their physiologic and toxicological effects, and considers difficulties with detecting these compounds.

Regulation of Drugs in the United States

Before discussing the specific compounds, it is worth reviewing the regulation of controlled substances in the United States (Rocha, 2013). Within the United States, the Drug Enforcement Administration (DEA) and the Food and Drug Administration (FDA) regulate the sale and distribution of drugs. The Controlled Substances Act of 1970 placed drugs in the five schedules based on their potential for harm and abuse. This scheduling system influences if and under what conditions a drug can be legally prescribed. Schedule I drugs are considered to have very high abuse potential and no accepted medical use. Drugs in this category include heroin, methylenedioxymethamphetamine (i.e., MDMA or ecstasy), marijuana/tetrahydrocannabinol (i.e., THC; although this can vary by state), cathinone (e.g., bath salts), and some hallucinogens (e.g., lysergic acid diethylamide or LSD). Schedule II drugs include amphetamine, cocaine, and many of the commonly prescribed opioids (e.g., fentanyl, hydrocodone, methadone, morphine, oxycodone). Schedule III is an intermediate abuse risk category that currently contains anabolic steroids (used illicitly as performance-enhancing drugs), ketamine (dissociative anesthetic), and dronabinol (Marinol®; purified derivative of THC). Schedule IV contains many sedative-hypnotics such as benzodiazepines (alprazolam, Xanax®; clonazepam, Klonopin®) and zolpidem (Ambien®). Schedule V has drugs with the lowest potential for abuse among the scheduled drugs. Examples include preparations with limited quantities of certain opioids such as codeine.

To avoid violating laws, resourceful chemists can make changes to a wide range of existing chemical structures to create novel compounds with a range of psychoactive properties, all of which remain legal until they are added to the list of scheduled drugs. In light of the ambiguous legal status of novel drugs, many drug dealers take advantage of the situation to distribute these compounds with misleading descriptions such as “not for human use,” “research chemicals,” or “legal/herbal highs.” Adding further incentive to the trafficking of designer drugs, these substances are often cheaper, easier to manufacture, and are typically not detected by standard drug testing (Carroll et al., 2012; Rech et al., 2015; Rocha, 2013).

Designer drugs of abuse present a difficult challenge for the DEA and law enforcement. Although some of the synthetic cannabinoids (e.g., JWH-073) and designer amphetamine-like drugs (e.g., mephedrone, methylone) have been recently added to Schedule I, many of these compounds were not initially on the list of scheduled drugs (Rech et al., 2015; Rocha, 2013). The Federal Analogue Act of 1986 was, at least in part, intended to address this loophole, as it allowed for regulation of compounds very close in structure to existing drugs in Schedule I or II. Nonetheless, this law is difficult to enforce in practice. For example, there are many historic examples of medically useful drugs that are very close in structure to illicit compounds (Rocha, 2013). As such, many designer drugs remain legal until the DEA temporarily places them into a drug schedule, which the agency has regulatory authority to do after the compound’s clear harm has been demonstrated.

New Designer Opioids

Opioid analgesics are commonly used in health care, yet they have substantial abuse potential. This danger is emphasized by the fact that opioids are responsible for more than 20,000 overdose deaths per year in the United States (Cheatle, 2015; Martins, Sampson, Cerda, & Galea, 2015). The rise in prescription opioid abuse has fueled a secondary rise in abuse of heroin. Specifically, some patients initially addicted to prescription opioids switch to heroin due to its cheaper cost.

More recently, a new wave of designer opioids has emerged. One example is acetylfentanyl, which is a synthetic analog of fentanyl that is very similar to heroin in color and consistency (Rogers, Rehrer, & Hoot, 2016). Acetylfentanyl was first discovered in the late 1960s, but it never entered clinical use. Acetylfentanyl is much more potent than common opiates, which means that lower doses of acetylfentanyl produce the same effect as larger amounts of morphine or heroin. In 2013, acetylfentanyl emerged on the illicit drug scene with a series of deaths in Rhode Island and Pennsylvania. Around the same time, there was a massive seizure of more than 12,000 pills in a Canadian drug bust. In the case reports on this drug, users often purchased the drug online, where it is typically sold as “synthetic opium” or an additive for electronic cigarettes. On the street, acetylfentanyl may be sold on its own or mixed with heroin or other drugs to allow distributors to increase revenue by lowering the cost of their product.

Several other novel synthetic opioids have also recently appeared on the recreational drug market: AH-7921, MT-45, and U-47700 (Carroll et al., 2012; Helander, Backberg, & Beck, 2014; Katselou, Papoutsis, Nikolaou, Spiliopoulou, & Athanaselis, 2015). These possess potent opioid properties (e.g., euphoria, respiratory depression) comparable to heroin, morphine, and fentanyl but have novel chemical structures. All three of these drugs were originally discovered by pharmaceutical companies in the 1970s, but they never progressed to clinical trials. AH-7921 and U-47700 are isomers of one another (i.e., they have the same chemical formula but a different arrangement of atoms). These three drugs have been reported in multiple fatalities involving users who purchased these compounds on the street or via internet sources (Karinen et al., 2014; Kronstrand, Thelander, Lindstedt, Roman, & Kugelberg, 2014; Papsun, Krywanczyk, Vose, Bundock, & Logan, 2016).

One challenge with the new designer opioids is that they are chemically dissimilar from commonly used opiates like hydrocodone and morphine (Carroll et al., 2012). Although screening tests for fentanyl may detect acetylfentanyl, such tests are not commonly utilized by laboratories. As a result, standard opiate urine drug screens, which commonly use immunoassays (antibody-based assays), are not likely to detect these compounds. This means that detection of the novel opioids requires more sophisticated laboratory testing using methods such as mass spectrometry (MS), gas chromatography/mass spectrometry (GC/MS), and liquid chromatography/tandem mass spectrometry (LC/MS/MS). Because very few hospital laboratories have this capability, this type of costly analysis typically must be done by specialty toxicology reference laboratories.

New Designer Benzodiazepines

Historically, benzodiazepines have been among the most heavily prescribed medications in Western countries (O’Brien, 2005). In the United States, alprazolam (Xanax®), clonazepam (Klonopin®), and lorazepam (Ativan®) are among the most commonly prescribed drugs. Complicating matters, two additional benzodiazepines, etizolam and phenazepam, are legal and marketed in some countries but illegal in others (Rech et al., 2015). These benzodiazepines are typically used for anxiety reduction, antiseizure effect, and sedation. In contrast, diazepam (Valium®), once the most frequently prescribed benzodiazepine (especially in the 1970s and 1980s), has faded in clinical use. Similar to the designer opioids discussed above (e.g., AH-7921, MT-45, and U-47700), previously uncommon benzodiazepines

have appeared on the illicit drug scene—clonazolam, diclazepam, flubromazepam, and pyrazolam—in the last five years (Moosmann, King, & Auwarter, 2015). Again, these designer benzodiazepines were originally discovered decades ago, but they never gained clinical approval. Law enforcement noted an increase over the last several years in internet sources selling these various benzodiazepines as "research chemicals" or other misleading designations (Crews & Petrie, 2015).

A common theme in the case reports of these designer benzodiazepines has been that they are often used in conjunction with other illicit drugs (Nakamae et al., 2008). Nevertheless, there are case reports of fatalities where designer benzodiazepines are the only drugs detected by sophisticated laboratory analysis. Similar to the synthetic opioids discussed above, the detection of designer benzodiazepines faces a similar challenge. Although there is very little literature on this topic, commonly used immunoassay benzodiazepine screens may not detect these designer drugs (Kyle, Brown, Bailey, & Stevenson, 2012). Despite these detection issues, mass spectrometry-based methods can detect these drugs, and there is growing literature on the analytical analysis and metabolic pathways for these benzodiazepines (Meyer, Bergstrand, Helander, & Beck, 2016).

Methoxetamine

Methoxetamine is a new designer drug chemically related to ketamine and phencyclidine (PCP; Craig & Loeffler, 2014). Ketamine is a dissociative anesthetic mostly used in hospital settings for general anesthesia and sedation whereas PCP is a Schedule I drug in the United States. The history of this class of medications dates back to the 1920s. Since then, large series of PCP derivatives have been synthesized and evaluated, providing potential for several PCP-related compounds to be used as designer drugs (Carroll et al., 2012).

The discovery of methoxetamine has been credited to an underground pharmaceutical scientist who created the drug in the late 2000s (Craig & Loeffler, 2014). Methoxetamine appeared on the illicit drug scene in 2010. By 2012, methoxetamine was one of the top five most common designer drugs sold in European online shops. The symptoms resemble those caused by PCP and ketamine, and thus similar clinical management is applied. Users of methoxetamine report ketamine-like dissociative effects including sensory deprivation, derealization, and sometimes an experience akin to a near-death experience. Other users report vivid hallucinations or intense euphoric effects. Defining the toxicity of methoxetamine has been difficult given that users often simultaneously use other psychotropic drugs. Acute toxic effects have included agitation, waxing and waning consciousness, amnesia, and aggression. Methoxetamine is not currently detected by any commonly used drug screens. Mass spectrometry-based analysis is required for its detection (Craig & Loeffler, 2014).

Resources for Law Enforcement

As noted above, designer drugs present a tough problem for law enforcement officers. The ever-increasing number of designer drugs makes it very difficult to keep current. The DEA maintains several resources that can aid in the understanding of designer drugs. The DEA fact sheets (https://www.dea.gov/druginfo/factsheets.shtml) include detailed information on emerging drugs of abuse including the designer drugs. The DEA also publishes news releases on designer drugs (accessible via https://www.dea.gov/pr/top_story_archives.shtml) and maintains the National Clandestine Laboratory

Registry (https://www.dea.gov/clan-lab/clan-lab.shtml) that contains lists of addresses where law enforcement agencies have reported chemicals or other items that indicate the presence of clandestine drug laboratories of dumpsites.

Law enforcement officials should be aware of designer drugs and consider them as possibilities in cases of unusual toxicity or fatalities. For example, many of the published case reports of fatalities from synthetic opioids indicate that the causative drug was challenging to uncover, but ultimately investigators sought out specialized resources when the findings were not explained by typical drugs of abuse. Some of the case reports were drug users who migrated from common drugs of abuse (e.g., heroin or methamphetamine) to designer drugs, often obtained from internet sources (Karinen et al., 2014; Kronstrand, Thelander, Lindstedt, Roman, & Kugelberg, 2014; Papsun, Krywanczyk, Vose, Bundock, & Logan, 2016). In some cases, law enforcement or paramedics find drug material labeled with its identity (e.g., AH-7921) at the scene, or there may be a history from witnesses that the user purchased an unknown drug from an internet source or other supplier. Designer drugs have caused waves of fatalities, as described above with acetylfentanyl. Unusual patterns of drug overdoses should be reported to the DEA or a similar agency that can assist with investigation and/or with referral to specialized toxicologic analysis, if indicated. Within the armed forces, there are resources such as the U.S. Army Criminal Investigation Laboratory (http://www.cid.army.mil/dfsc-usacil.html#sec3).

Conclusion

The coming years will undoubtedly see more designer drugs emerge on the illicit drug scene. Thus, the forensic, clinical, and law enforcement communities must be aware of the existence of these drugs. When the clinical symptoms resemble a known class of drugs such as opioids and benzodiazepines but no positive detection by standard toxicology testing is present, designer drugs should be considered as a possibility. To this end, case studies and research on the toxicology and clinical symptoms of designer drugs are valuable to publish where appropriate.

Biographies

Matthew D. Krasowski, MD, Ph.D., is a pathologist and Vice Chair of Clinical Pathology and Laboratory Services in the Department of Pathology at the University of Iowa Hospitals and Clinics. He has interest in the pharmacology and analytical toxicology of drugs of abuse. He has published multiple articles and book chapters on pharmacology and drugs of abuse.

Jerrod Brown, M.A., M.S., M.S., M.S., is the treatment director for Pathways Counseling Center, Inc. Pathways provides programs and services benefiting individuals impacted by mental illness and addictions. Jerrod is also the founder and CEO of the American Institute for the Advancement of Forensic Studies (AIAFS), and the Editor-in-Chief of Forensic Scholars Today (FST) and the Journal of Special Populations (JSP). Jerrod holds graduate certificates in Autism Spectrum Disorder (ASD), Other Health Disabilities (OHD), and Traumatic-Brain Injuries (TBI). Jerrod is certified as a Youth Firesetter Prevention/Intervention Specialist, Thinking for a Change (T4C) Facilitator, Fetal Alcohol Spectrum Disorders (FASD) Trainer, and a Problem Gambling Treatment Provider. Jerrod is currently in the dissertation phase of his doctorate degree program in psychology.

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